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Abstracts from the 1st World Congress on Epidermolysis Bullosa

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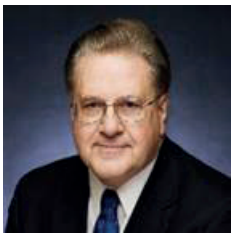
Caroline Collins
Research Director, DEBRA UK



Jouni Uitto
Thomas Jefferson University, Philadelphia, USA

Jemima Mellerio
St John's Institute of Dermatology Guy's & St. Thomas' NHS Foundation Trust, London, UK

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Contents of this Abstract Book

PROGRAMME

Monday 20th January 2020 - Plenary

8.30 Opening of the Congress

Jouni Uitto and Jemima Mellerio

8.35 – 8.40 *Jouni Uitto:* Challenges and unmet needs - the breadth of preclinical work ongoing (OP1)
8.40 – 8.55 *Cristina Has:* EB classification and updates from the 2019 classification meeting (OP2)
8.55 – 9.30 **Current dilemmas – a debate – The complexity of EB. Chair: Jo-David Fine**
Johann Bauer: EB as a systemic disease – implications for research (OP3)
Leena Bruckner-Tuderman: Modelling EB in the research environment (OP4)
John McGrath: Curative vs disease modifying strategies (OP5)
10.00–11.05 **The challenges of EB skin. Chair: Peter Marinkovich**
Sabine Eming: Wound healing mechanisms – macrophages (OP6)
Josefine Hirschfeld: Immune function and bacterial challenge (OP7)
Maria Jose Escamez: Clinical research (OP8)
David Abraham: Learnings from other diseases (cell inflammation) (OP9)
11.05–12.25 Inflammation, fibrosis & therapeutics, Chair: Leena Bruckner-Tuderman
Alexander Nyström: Fibrosis in EB – mechanisms and anti-fibrotic strategies (OP10)
Dimitra Kiritsi: Losartan for RDEB trial – results and international perspectives (OP11)
Giovanna Zambruno: miRNA in DEB (OP12)
Oral poster presentations
Esteban Chacon-Solano: Novel players in the establishment and progression of fibrosis in recessive dystrophic epidermolysis bullosa (P112)
Liat Samuelov: Skin microbiome characteristics of dystrophic epidermolysis bullosa patient (P25)
1.25–3.10 **Cancer & cancer therapeutics, Chair: Johann Bauer**
Kevin Harrington: **KEYNOTE: Precision medicine for SCC (OP13)**
Andy South: Genetic overview/current RDEB knowledge (OP14)
Leena Bruckner-Tuderman: Interdisciplinary management and therapies for EB associated cancers (skin, mucosal, internal) (OP15)
Jemima Mellerio: RDEB-SCC protocols (rigosertib, pembrolizumab, cetuximab & nivolumab, SCC cream) (OP16)
Oral poster presentations
Angela Filoni: Morphological and morphometrical analysis of cutaneous squamous cell carcinoma in patients with recessive dystrophic epidermolysis bullosa: a prospective study (P73)
Jasbani Dayal: Heterogeneous addiction to TGFβ signalling in life threatening cutaneous squamous cell carcinomas arising in recessive dystrophic epidermolysis bullosa (P128)
3.40–4.20 **Therapeutics**, Chair: Jouni Uitto
Thomas Magin: EBS target and treatment options/targeting EB as an inflammatory disease (OP17)
David Woodley: Read-through therapeutics: drug re-purposing for EB patients (OP18)
Dedee Murrell: Topical treatments – an update (OP19)
4.20–4.55 **Natural history – implications for clinical trial design, Chair: Jouni Uitto**
Jemima Mellerio: PEBLES (OP20)
Anna Bruckner: The EB clinical characterization and outcomes database (OP21)

Monday 20th January 2020 – Oral poster station presentations

Christina Guttmann-Gruber: The impact of low-dose calcipotriol ointment on wound healing, pruritus and pain in patients with dystrophic epidermolysis bullosa (P34)
Hannah Mumber: Biallelic JUP Mutation in Families with Arrhythmogenic Right Ventricular Cardiomyopathy and Skin Fragility in the Form of Epidermolysis Bullosa Simplex: Naxos Disease (P137)
Vicki Chen: Understanding ocular disease in the DEB mouse model: challenges of asymmetry and survival (P107)
Subhanitthaya Chottianchaiwat: A case series of six paediatric cases with laryngo-onycho-cutaneous syndrome (LOC) (P10)

Tuesday 21st January, 2020 - Plenary

8.30–8.40 *Jemima Mellerio:* From theory to practice – translational medicine into clinical trials (OP22)
8.40–10.25 **Cell manipulation and therapies: Chair: John McGrath**
Jakub Tolar: Combining approaches – BMT & systemic treatment (OP23)
Su Lwin: Fibroblast gene therapy (OP24)
Katsuto Tamai: HMGB1 peptide (OP25)
Dennis Roop: State of the art iPSCs (OP26)
Oral poster presentations
Joanna Jackow: Efficient genome editing for correction of recessive dystrophic epidermolysis bullosa in iPS cells using CRISPR/Cas9 RiboNucleoProtein complexes (P115)
Martin Barbier: Self-assembled skin substitutes and retroviral gene therapy for the permanent treatment of recessive dystrophic epidermolysis bullosa (P7)

10.55–1.25 **Gene manipulation and therapies: Chair: Jakub Tolar**
Fernando Larcher: State of the art gene editing (OP27)
Alain Hovnanian: EBGRAFT and advances in skin grafting using improved vectors (OP28)
Laura de Rosa: Hologene projects (OP29)
Jouni Uitto: Next generation sequencing applications for mutation detection in EB (OP30)
Peter Marinkovich: Gene therapy for RDEB (ex-vivo vs in-vivo) (OP31)
Peter van den Akker: Exon skipping for RDEB (OP32)
Ulrich Koller: COL17A1 editing using CRISPR/Cas9 (OP33)
Mark Sumeray: Non-viral gene therapy (OP34)
Oral poster presentations
Jose Bonafont Arago: CRISPR/Cas9-based gene editing strategies for clinically-relevant *ex vivo* correction of Recessive Dystrophic Epidermolysis Bullosa (P81)
Hiroyuki Morisaka: Possible application of broad and unidirectional genome editing using the novel CRISPR-Cas3 system for autosomal dominant Epidermolysis Bullosa (P86)

2.25–4.10 **Clinical trials & research programmes: Chair: Johann Bauer**
Johann Bauer: Introduction – clinical trial design (OP35)
Jean Tang: Large wounds: an update on natural history data and EB101 (OP36)
Theresa Podrebarac: Recombinant collagen 7: a systemic approach to RDEB therapy (OP37)
Mary Spellman: A tale of two therapeutic approaches - an update on clinical studies in diacerein and FCX-007 (OP38)
Suma Krishnan: B-VEC off the shelf topical gene therapy for DEB (OP39)
Kathrin Dieter: ABCB5+ mesenchymal stem cells for the treatment of recessive dystrophic epidermolysis bullosa – from bench to bedside (OP40)

Break

4.40–4.50 *Brett Kopelan:* Partnerships - charities, regulators and industry (OP41)
4.50–5.00 *Sharmila Collins:* Partnership approach to research funding (OP42)
5.00–5.45 **Current dilemmas – a debate - Measurement and Research - Chair: Jouni Uitto**
Dedee Murrell: EB relevant endpoints (OP43)
Elena Pope: Quality of life measures (OP44)
Brett Kopelan: Regulatory perspectives and challenges (OP45)
Catriona Crombie: Planning for clinical translation (OP46)
Mauro Perretti: Innovative therapeutic development (OP47)

Tuesday 21st January 2020 – Oral poster station presentations

Karen Snelson: Guidelines for the care of adults with EB undergoing clinical and surgical procedures (P6)
Cristina Has: Molecular and mutational signatures of squamous cell carcinomas in epidermolysis bullosa (P2)
Ashjan Alheggi: Treatment of multifactorial anaemia in adults with severe epidermolysis bullosa using intravenous ferric carboxymaltose: a single institution, observational, retrospective study (P39)
Vicki Chen: Anterior segment spectral domain optical coherence tomography in epidermolysis bullosa (P120)

Wednesday 22nd January 2020 - Plenary

8.30–8.40 *Sophie Kitzmueller:* Update - EB-CLINET (OP48)
8.40–8.50 *Anna Martinez:* Clinical challenges of EB skin - inside and out (OP49)
8.50–9.00 *Cristina Has:* Advances in diagnostics/phenotyping (CPG) (OP50)
9.00–9.35 **Current dilemmas – a debate - Funding Challenges - Chair: Al Lane**
Leena Bruckner-Tuderman: Individualised therapies (OP51)
Johann Bauer: Allocation of research funds (OP52)
Al Lane: Funding for EB research (OP53)
Peter Marinkovich: Costs and accessibility (OP54)

9.35–12.25 **Update on clinical management strategies: Chairs: Anna Martinez & Ignacia Fuentes**
Eli Sprecher: Superficial EBS/peeling skin syndromes (OP55)
Katie Plevey: Wound care (JEB) (OP56)
Anna Bruckner: Oesophageal management (OP57)
Joe Curry: Gastrostomy (OP58)
David Albert: ENT (OP59)
Susanne Kramer: Oral health (OP60)
Michael Baertschi: Eye (OP61)
Antonia Reimer: Growth patterns (OP62)
Irene Lara-Corrales: Anaemia (OP63)
Gill Smith: Hand surgery – management strategies (OP64)
Catina Bernardis: Surgery for SCC (OP65)
Tariq Khan: Podiatry (OP66)

1.25–1.55 **Clinical and management case histories: Chairs: Eli Sprecher/Hana Buckova**
Anna Bruckner: CASE REPORT: SCC management and response (OP67)
Pavel Rotschein: CASE REPORT: SCC management and response (OP68)

1.55–2.50 **Quality of life (pain & itch): Chair: Marieke Bolling**
Nic Schrader: Cannabinoids — pain and itch (OP69)
Margarita Calvo: Small fibre neuropathy (OP70)
Boris Zernikow: Prevention and treatment of pain (OP71)
Hagen Ott: Pruritus in EB (OP72)

3.20–4.45 **Support models: Chairs: Anna Martinez and Anja Diem**
Jemima Mellerio: Multidisciplinary team best practice (GSTT) Rare Disease Centre (OP73)
Ravi Hiremagalore: Managing EB in a resource limited setting (OP74)
Danielle Greenblatt: Telemedicine (OP75)
Bahar Dasgeb: EB-associated SCC: The Jefferson Adult EB and Complex Skin Cancer Clinic (OP76)
Christine Bodemer: Educational programmes (OP77)
Godfrey Fletcher: International EB patient registry (OP78)
Michael Hund: Innovation in patient data platforms (OP79)

4.45–6.15 **Strategies for care – status update: Chairs: Anna Martinez and Anja Diem**
Erik Gerner: A potential new therapeutic approach targeting wound infection – disrupting bacterial communication (OP80)
Mark Sumeray: Development of two topical approaches to wound healing in EB. An update on progress with Oleogel-S10 and AP 103 (OP81)
Gilles Brackman: The impact of antimicrobial resistance on topical treatment selection (OP82)
Rachel Torkington-Stokes: The role of Hydrofiber dressings in EB wound management (OP83)

Wednesday 22nd January, 2020 – Oral poster station presentations

Catherine Miller: Hand Contracture Development in Children with Recessive Dystrophic Epidermolysis Bullosa (P42)
Mark O'Sullivan: The effect of rocker bottom footwear on foot biomechanics and the development of plantar blisters in patients with epidermolysis bullosa simplex; a pilot study (P93)
Suma Krishnan: Results from a Phase I/II study of a topical gene therapy (bercolagene telserpavec, B-VEC) in patients with recessive dystrophic epidermolysis bullosa (RDEB) (P52)
Tobias Zahn: Losartan for EB, or 'It takes a village to raise a child' (P47)

Thursday 23rd January 2020 – Plenary

9.05–9.40 **A global approach to EB: Chair: Brett Kopelan**
Evanina Morcillo Makow: DEBRAs around the world – a 40 year history (OP84)
Brett Kopelan/Jimmy Fearon: DEBRA International/ co-ordination and collaboration (OP85)

9.40–10.55 **Updates in EB research: Chair: Jouni Uitto**
Su Lwin: Research update (cell therapy) (OP86)
Peter Marinkovich: Research update (gene and protein) (OP87)
Jemima Mellerio: Cancer & cancer therapeutics (OP88)
Anna Martinez: Advances in clinical management strategies (OP89)
Brett Kopelan: Biotech commercial development (OP90)

11.35–12.15 **Current dilemmas – a debate - Patients in clinical trials - Chair: Jouni Uitto**
Gabriela Petrof: Clinical trials explained (OP91)
Sharmila Collins & Lena Riedl: Patient and parent perspectives (OP92)
Christine Prodinger: Challenges of clinical trial design (OP93)
Godfrey Fletcher: Using registries and big data (OP94)

12.15–1.15 **Living with EB: Chairs: Anja Diem & Anna Martinez**
Natasha Harper & Assya Shabir: Quality of life – clinician and patient working together (OP95)
Brett Kopelan & Simone Bunting: Family and community (OP96)
Sam Geuens: Education and family support/care & social services (OP97)

2.30–3.55 **Updates in EB clinical care: Chairs: Jemima Mellerio & Agnes Schwieger-Briel**
Kattya Mayre-Chilton: Clinical practice guidelines, patient versions and EB infographics updates (OP98)
Amy Price: The importance of exercise in EB (OP99)
Jennifer Chan: Occupational therapy in EB (OP100)
Petra de Graaf: Psychosocial guidelines (OP101)
Danielle Greenblatt: EB and pregnancy (OP102)
Lynne Hubbard: Nutrition (OP103)
Susanne Kramer: Oral health (clinical guideline in EB) (OP104)

4.40–5.25 **EB community open forum – ask the panel: Facilitator: Jemima Mellerio**
Rachel Box, Jane Clapham, Lynne Hubbard, Susanne Kramer, Susana Morley Mark Popenhagen

5.30 Close of the Congress
Jouni Uitto and Jemima Mellerio

ORAL LECTURE ABSTRACTS

OP1
CHALLENGES AND UNMET NEEDS - THE BREADTH OF PRECLINICAL WORK ONGOING

Jouni Uitto
Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College, and Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA USA

No abstract supplied

OP2
CONSENSUS RE-CLASSIFICATION OF INHERITED EPIDERMOLYSIS BULLOSA AND OTHER DISORDERS WITH SKIN FRAGILITY

Cristina Has
Department of Dermatology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

Several new genes and clinical subtypes have been identified since publication in 2014 of the report of the last international consensus meeting on epidermolysis bullosa (EB). In April 2019, in the most recent consensus expert meeting we re-classified the disorders with skin fragility, with a focus on EB, based on new clinical and molecular data. We introduce the concept of genetic disorders with skin fragility, of which classical EB represents the prototype. Other disorders with skin fragility, where blisters are a minor part of the clinical picture or are not seen because skin cleavage is very superficial, are classified as separate categories. These include peeling skin disorders, erosive disorders, hyperkeratotic disorders, and connective tissue disorders with skin fragility. Because of the common manifestation of skin fragility, these "EB-related" disorders should be considered under the EB umbrella in terms of medical and socioeconomic provision of care.

The proposed classification scheme should be of value both to clinicians and researchers, emphasizing both clinical and genetic features of EB. A reliable tool for identification of splicing errors.

OP3
EB AS A SYSTEMIC DISEASE – IMPLICATIONS FOR RESEARCH

Johann Bauer
Department of Dermatology, EB House Austria, University Hospital Salzburg

The primary gene defect discovered in variants of EB leads to deficiencies in epithelial structures of the body. Several promising approaches to local therapies on the stratified epithelium have been investigated recently. Systemic symptoms can be defined as direct consequence of the adhesion defect in the esophageal, bronchopulmonary and urogenital epithelial systems. The inflammation processes leading to those sequelae can affect the whole body via metabolic and epigenetic consequences. Thus systemic delivery of medication that is recreating lost gene expression or suppressing secondary features of EB has been evaluated. In this regard cell therapies and several small molecules have been studied in patients. Other approaches targeting the systemic nature of EB should be an important target of research to uncover novel aspects of pathophysiology and possible novel therapeutic applications.

OP4
MODELLING EB IN THE RESEARCH ENVIRONMENT

Leena Bruckner-Tuderman
Freiburg Institute for Advanced Studies School of Life Sciences, Freiburg, Germany

No abstract supplied

OP5
CURATIVE VS DISEASE MODIFYING STRATEGIES

John McGrath
St John's Institute of Dermatology, King's College London, London

No abstract supplied

OP6
WOUND HEALING MECHANISMS – THE ROLE OF MACROPHAGES

Sabine Eming
Department of Dermatology, University of Cologne, Cologne, Germany

The skin provides a life-sustaining structural and immunological outer barrier of the body and has intrinsic mechanisms that protect the organism from diverse external threats including infections and mechanical injuries. Skin injury extending into the dermis induces a complex, dynamic cellular program proceeding in sequential stages of inflammation, tissue growth and differentiation. Cells of the monocyte/macrophage lineage are an integral component of the body's innate ability to restore tissue function after injury. Blood monocytes that are recruited to the side of tissue damage sense a variety of environmental cues of injured tissue and integrate those into a host protective wound healing response. Given that inappropriate macrophage activation underlies a broad range of pathological processes, from chronic inflammatory skin diseases, type 2 diabetes and cancer, macrophages have emerged as an important target to treat disease. The molecular determinants that precisely control the dynamics of macrophage functional plasticity during healing progression are largely unknown and are just beginning to emerge. We are interested to understand signalling pathways and transcriptional networks in macrophages that coordinate their functional plasticity during the sequential phases of the physiological repair response. Further, we aim to understand the role of myeloid cell activation at the interface of disturbed wound healing and epidermal carcinogenesis in patients with RDEB. We uncovered a fundamental role of type 2 cytokine-activated wound macrophages in controlling the development of bone-like type collagen fibril crosslinks in skin fibrosis. Emerging evidence indicates that these specific type collagen fibril crosslinks play also a critical role in carcinogenesis. We postulate a functional role for the interplay between type 2-activated macrophages and collagen fibril crosslinks in excessive scarring and carcinogenesis in patients with RDEB. We will present findings that indicate that targeting and shaping monocyte/macrophage activation, specifically type-2 activation, impacts the outcome of the healing response and could offer a new approach to pharmaceutically target impaired wound healing conditions, including perturbed wound healing in RDEB patients.

OP7

IMMUNE FUNCTION AND BACTERIAL CHALLENGE

Josefine Hirschfeld
Birmingham Dental School & Hospital, Birmingham, UK

Epidermolysis bullosa (EB) encompasses a group of rare genetic disorders characterised by recurrent blister formation. This may lead to infective sequelae, delayed healing and scarring. Understanding the inflammatory-immune response in these patients is a fundamental prerequisite for developing novel antimicrobial and/or healing therapies. Neutrophils are the most abundant type of immune cell and the first responders at sites of infection and during biological wound debridement in healing. They exhibit a range of antimicrobial mechanisms crucial to host defence and healing. It is known that dysfunctional neutrophils have detrimental effects on tissue health, in particular when they release excess reactive oxygen species (ROS), cytokines or proteases, or have abnormal apoptosis rates. Therefore, one of the key aims of this ongoing observational study is to characterise, for the first time, the immune function of systemic neutrophils in EB patients. Dystrophic, junctional EB, and EB simplex patients were enrolled based upon frequency and location of blistering. Age- and gender matched healthy controls are currently being recruited. Peripheral blood neutrophils were isolated by density gradient centrifugation and analysed by fluorescence- and luminescence-based assays, to monitor neutrophil antimicrobial mechanisms as well as cell death, in response to physiological and experimental stimuli. Preliminary data analysis revealed that EB patients display marked heterogeneity of neutrophil responses, ranging from hypo- to hyper-reactive. Clustering of data was noted for junctional and dystrophic EB with regard to higher ROS release and higher apoptosis rates, respectively, rendering them different from EB simplex patients and healthy controls. Neutrophil dysfunction during immune responses and healing can cause considerable damage to host cells and tissues. This collateral tissue damage may contribute to delayed wound healing and scar formation in EB patients, particularly in those with dystrophic and junctional EB. Completion of this study should further refine the above outcomes.

OP8

CLINICAL RESEARCH

María José Escámez
Department of Biomedical Engineering-Carlos III University (UC3M), Spain

Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a systemic disease with multiorgan involvement in which, fibrosis, infection and inflammation play a relevant role in the progression and burden of the disease. Mesenchymal stromal cells (MSCs), isolated from different tissues, have shown to be able to attenuate these processes. It is not clear whether the ones derived from adipose tissue (ADMSC) are therapeutically superior. Long-term systemic pharmacologic treatment –H2 antagonists, opioid analgesics, tramadol, proton pump inhibitor and antidepressant- was barely managing the symptoms. Oral ulcers were refractory to a variety of local treatments (topical corticosteroids, anesthetic lidocaine, intralesional injection of platelet-rich plasma and hyaluronic acid gingival application). ADMSC were administered with the objective to provide a safe and efficient treatment to a RDEB patient with a high disease burden and a poor quality of life mainly due to painful intraoral lesions and constant itching. The cell-based treatment was provided as a compassionate use exception after ethical approval and permission from the Spanish Agency of Medicines (AEMPS). Three separate intravenous injections of 1 million ADMSC per kilo were administered every 21 days. Tolerability and efficacy were evaluated over a period of 2 years by vital signs and physical examination, biochemical testing and the use of specific clinimetric scales for cutaneous pathology (EBDASI and BEBSS), pain (VAS), itching (LIS) and the impact on the quality of life (QoL-5D). The patient experienced transient benefits that improved her overall condition including her quality of life without major adverse reactions. The significant improvement in the muco-cutaneous condition correlated with a decrease in the EBDASI, BEBSS, LIS and pain-VAS scores. Simultaneously, the drug medication doses were reduced. Understand the possible impact of ADMSC in the inflammatory and immunologic status of the patient was the secondary aim of this study. Altered circulating levels of positive and negative acute phase reactants were moderated/normalized after the ADMSC-treatment. Blood leukocyte populations (PBLs) were analyzed by flow cytometry. Interestingly, changes in PBLs memory T cells, CD56bright natural killer, non-classical monocytes and granulocytes- correlated with the health improvement. In conclusion, we provide the first proof of concept about use of adipose tissue as a source of MSC for the safe and transiently efficacious treatment of RDEB in a systemic fashion. Results suggest that is critical to explore the effect of MSCs in the modulation of the patient's immune cells to improve their therapeutic rational use.

OP9

LEARNINGS FROM OTHER DISEASES

David Abraham
Department of Inflammation, Division of Medicine, University College London

Evidence from clinical and laboratory studies places cell inflammation as a key process in the pathogenesis of autoimmune diseases. The prominent role of inflammation arises from several overlapping studies including those focusing on genetics and transcriptomics, and in the disease context, the clear links with autoantibodies and associated clinical endotypes. Dysregulation of the immune system (innate and adaptive) and allied changes in immune cell phenotypes and cytokine, chemokine and growth factor profiles have also emphasized critical mediators and modulators of important pathogenic events. Innate immunological studies in the autoimmune disease scleroderma have built upon previous observations on the role of monocytes/macrophages in initiating and perpetuating disease pathology. Candidate gene, GWAS and genome sequencing has begun to identify genes associated with susceptibility to disease or disease subphenotypes. Recent studies exploring isolated monocyte-derived macrophages have identified changes in the scleroderma macrophage transcriptome signature significantly enriched for genes implicated in disease pathogenesis including the upregulation of glycolysis, hypoxia, and cell signaling and modulation of IFNγ response pathway. A new and potentially exciting area of study of T cell biology has recently emerged that is highly relevant to T cell function in immune-mediated diseases. This research relates to the observation of the role of intracellular complement signaling (complosome) regulating Th1 responses. Deep phenotyping and assessment of cytokine expression by resting and activated T cells identified a pathological CD4+ T cell complosome signature in scleroderma. Upon activation, these cells exhibited elevated levels of IL-6 and IL-17 and altered IFNg:IL-10 ratios. This data is especially pertinent to T cell function, and in addition proposes the complosome for patient stratification as well as importance in pathogenesis and a target for intervention. The increasing understanding of B cell subpopulations in immune-mediated disease has highlighted their role in the development of specific hallmark autoantibodies in scleroderma. These studies have also revealed altered distribution of B cell subsets (transitional B cells), and their increased production of IL-6 and IL-8. This, in concert with their reduced ability to produce IL-10 when stimulated through innate immune pathways, may underlie the failure to suppress the emergence of B cells that

produce scleroderma specific autoantibodies. Studies on biological mechanism(s) driving cell inflammation are paramount to delineate and assess common or shared features underlying autoimmunity across diseases and to define aspects that are likely to be specific or selective for certain autoimmune diseases, useful as biomarkers and/or tractable for the development of effective therapeutics.

OP10
FIBROSIS IN EB – MECHANISMS AND ANTI-FIBROTIC STRATEGIES

Alexander Nyström
Department of Dermatology, Medical Faculty, Medical Center – University of Freiburg, Freiburg, Germany

Genetic loss of type VII collagen causes dystrophic epidermolysis bullosa (DEB), a monogenic disease characterized by chronic skin fragility, impaired antibacterial immunity and progressive soft tissue fibrosis. In its most severe form – generalized severe recessive DEB (RDEB) – the combination of these events results in high propensity for early-onset, metastasizing cutaneous squamous cell carcinomas. Previous work has shown that targeting disease mechanisms secondary to loss of type VII collagen can skew a severer form to a milder form of RDEB. However, to improve the efficacy of symptom-relief therapies detailed knowledge of disease mechanisms at play in RDEB is needed. I will discuss recent advances in the understanding of fibrotic disease progression in RDEB. In addition, I will present data and lessons learned from preclinical evaluation of novel symptom-relief therapies for RDEB designed to interfere with specific events during the progression of dermal fibrosis.

OP11
LOSARTAN FOR RDEB TRIAL – RESULTS AND INTERNATIONAL PERSPECTIVES

Dimitra Kiritsi
Department of Dermatology, Medical Center-University of Freiburg, Faculty of Medicine, Freiburg, Germany

RDEB is characterized by life-long skin fragility and multi-organ involvement. Severe progressive fibrosis follows skin blistering and wound healing, which favours development of highly aggressive squamous cell carcinomas. Among the many symptoms, joint contractures and mitten deformities of hands and feet cause severe disability. No cure exists for RDEB, and the unmet medical need remains very high. We propose an evidence-based approach to alleviate RDEB symptoms by targeting excessive TGFβ activity. This is based on our preclinical research that uncovered a key role of TGFβ in mediating injury-driven inflammation, generating the fibrotic phenotype and facilitating skin cancer progression in RDEB. The phase I/II clinical trial REFLECT on the use of losartan in children with RDEB was initiated in June 2017. The objective of the trial is to evaluate safety and tolerability of losartan in children with RDEB aged 3-16 years, but also to gain first data on the efficacy of the drug. Although losartan would not be a cure for RDEB, we expect an amelioration of the disease manifestations and a delay in the progress. We performed an interim analysis after 18 patients completed the trial. No severe complications resulting in a serious safety concerns were observed during the trial. The data on safety and tolerability of losartan in RDEB were positive. We present first data on the efficacy of losartan in reducing inflammation and fibrosis, by showing different scoring systems to assess all RDEB-related clinical manifestations. In addition, initial data on fibrotic and inflammatory markers in the circulation are presented. Based on the promising data of the interim analysis, a phase II/III trial to assess the efficacy of losartan in RDEB is currently being planned. For this trial a pediatric formulation for losartan is being designed, since this is currently not in the market.

OP12
MIRNA IN DEB

Giovanna Zambruno
Laboratory of Molecular and Cell Biology, IDI-IRCCS, Rome, Italy

No abstract supplied

OP13
PRECISION MEDICINE FOR SQUAMOUS CELL CANCER OF THE HEAD AND NECK

Kevin J. Harrington
Targeted Therapy Team, The Institute of Cancer Research, London

There has been huge progress with the development and implementation of novel targeted and immunotherapies for head and neck cancer (HNC) in the 15 years. The anti-EGFR monoclonal antibody, cetuximab, is part of standard-of-care treatment of locally-advanced disease in combination with radiotherapy1 and of relapsed/metastatic (R/M) disease in combination with cytotoxic chemotherapy2. More recently, immune checkpoint-inhibitory antibodies that block interactions between the anti-programmed death-1 receptor and its ligand have been shown to improve outcomes in R/M HNC in both second-line (platin-refractory)3,4 and first-line settings5. Both nivolumab and pembrolizumab have received FDA and EMA approvals for use in patients with relapsed/metastatic HNC within the last 5 years. Ongoing research seeks to build on these platform therapies, by adding novel combination agents, including: cancer vaccination (against private tumour-specific mutations or viral antigens); innate immune activators (toll-like receptor agonists, stimulator of interferon gene (STING) agonists); oncolytic virotherapies (herpes simplex virus, Newcastle disease virus, vaccinia virus); and novel antibodies which provide antagonistic (anti-LAG3, anti-TIM3, anti-NKG2A) or agonistic (anti-CD137, anti-GITR, anti-CD40, anti-OX40) signals. A range of these novel therapy opportunities in HNC will be discussed. Our recent advances in patients with relapsed/metastatic disease have underpinned the development of treatment approaches in which either anti-EGFR/anti-HER or immunotherapies have been used in the context of regimens delivered with curative intent. Induction/neoadjuvant, concomitant and adjuvant strategies (and combinations of such approaches) are all potentially feasible and have theoretical bases of efficacy. For anti-EGFR/anti-HER therapies, the basis of potential efficacy rests on the concept of oncogene addiction and the premise that prolonged blockade of a pathway that is needed for cancer survival and growth will, ultimately, lead to permanent growth arrest or cancer cell death. For anti-EGFR/anti-HER-targeted therapies, data from studies involving the anti-EGFR/anti-HER2 agent, lapatinib6, and the pan-HER inhibitor, afatinib7, have been largely negative and these approaches do not appear to have the potential significantly to improve outcomes for patients with HNC. In contrast, the use of adjuvant immunotherapy is based on the notion of enhanced anti-cancer immunosurveillance at a time when only minimal residual disease is present. The designs of key registrational trials in this area (JAVELIN-100 head and neck [NCT02952586]8, KEYNOTE-412 [NCT03040999] and ImVoke-10 [NCT03452137]) will be presented with specific reference to their differences and the possible implications for future use of anti-PD1/anti-PD-L1 drugs in concomitant/adjuvant regimens. Specific immunization against antigens expressed on the surface of cancer cells can also be viewed as a powerful approach to improving disease control in this context. The role of adjuvant anti-cancer vaccines will be discussed by reviewing available data from patients with R/M HNC and considering how this might influence practice in both HPV-positive and HPV-negative HNC in the setting of curative treatment regimens.Finally, issues relating to the toxicities of novel therapies, especially as they relate to cutaneous effects, will be considered.

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OP14
GENETIC OVERVIEW/CURRENT RDEB KNOWLEDGE

Andrew South
Thomas Jefferson University, Philadelphia, USA

Squamous cell carcinoma (cancer) arising in the skin of patients with epidermolysis bullosa (EB) is a major, life threatening, complication. Cancer is especially important in patients with the recessive dystrophic sub-type of EB (RDEB) who are at increased risk. Recent work characterizing the genetics of RDEB cancers has shown that mutations in "driver-genes", so-called because they are frequently detected in many separate cancers and are thought to play a role in cancer development, are similar when compared with other squamous cell carcinoma (SCC) found in skin and the oral mucosa. These observations suggest that many of the mechanisms which lead to cancer are not unique to RDEB and that new and emerging therapies, such as immune based approaches that show promise in treatment of other types of SCC, may also have benefit in RDEB. In particular, therapies that are approved for treatment of patients with SCC in the oral mucosa, so-called head and neck cancer, should be made available for trials in patients with RDEB. Genetic analysis has also identified a group of endogenous enzymes that have been subverted in RDEB away from their normal role in the immune system to attack skin cells' DNA and cause mutations that lead to cancer. Work is ongoing to understand how these enzymes, collectively called "APOBEC" enzymes, are subverted to cause cancer and whether their activity can be inhibited with drugs such that cancer can be delayed or even prevented. Finally, in addition to identifying similarities between RDEB and other SCC cancers, research has identified fibrosis as a major mediator of cancer progression in RDEB patients, and work is ongoing to identify therapeutic targets which may reduce fibrosis and cancer development. In this context therapies being developed to prevent fibrosis with the goal of reducing disease burden and symptoms may also show benefit to patients by delaying or even preventing cancer.

OP15
INTERDISCIPLINARY MANAGEMENT AND THERAPIES FOR EB ASSOCIATED CANCERS

Leena Bruckner-Tuderman
Freiburg Institute for Advanced Studies School of Life Sciences, Freiburg, Germany

No abstract supplied

OP16
RDEB-SCC PROTOCOLS (RIGOSERTIB, PEMBROLIZUMAB, CETUXIMAB & NIVOLUMAB)

Jemima Mellerio
St John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust, London

The development of aggressive cutaneous squamous cell carcinomas (SCCs) remains one of the biggest challenges for individuals with recessive dystrophic epidermolysis bullosa (RDEB), particularly the severe generalised form. Tumours tend to arise from adolescence onwards with increasing frequency with age, arise at sites which may be challenging anatomically for surgical removal, and with most developing multiple primaries. Despite surgical clearance, SCCs behave aggressively and metastasize readily, making this the leading cause of death for adults with this form of EB. In addition, RDEB SCCs are usually very poorly responsive to conventional chemotherapy agents and radiotherapy, making newer targeted therapies attractive and an imperative area for further study. A handful of publications detail the response of EB-related SCCs to the EGFR inhibitor, cetuximab: results have been mixed and generally disappointing, although there may be a tendency for greater impact on tumour growth with earlier initiation of treatment. Given in weekly intravenous (IV) cycles, access may be an issue in EB and wound healing at other sites may be impaired during treatment. Programmed death-1 (PD-1) antibodies have been a major development in the armoury against many different cancers. They have also become an area for more recent consideration in EB SCCs although the number of published reports is, at present, limited. Anecdotally, pembrolizumab, nivolumab and cemiplimab may result in disease stabilisation or partial regression in advanced EB SCCs but formal clinical trial data is lacking. These drugs have variable side effect profiles although seem to be generally well-tolerated but require IV infusion every 2 or 3 weeks. Identification of the polo-like kinase-1 (PLK-1) inhibitor, rigosertib, which has preferential toxicity for EB SCC cells *in vitro* and in an *in vitro* mouse chimera model has paved the way for a clinical trial of oral or IV use in advanced RDEB SCCs which should be starting recruitment in coming months. There are significant challenges to identifying new therapeutic targets for EB SCCs; being a rare complication of a rare disease means that formal clinical trials can be fraught with difficulties with small and disparate patient cohorts. The aggressive nature of these tumours and the potential short time span between presentation and advance can compromise rapid approval and commencement of therapy, with significant geographical variability in access to new and expensive immunotherapy drugs. However, repurposing of agents approved for a number of other cancer ty-

pes, and preclinical research identifying EB SCC-specific agents brings us closer than ever to finding potential new anti-cancer treatments. It is imperative that the EB medical community share their experiences and strive, where possible and feasible, to establish formal clinical trials.

OP17
EBS TARGET AND TREATMENT OPTIONS/ TARGETING EB AS AN INFLAMMATORY DISEASE

Thomas M. Magin
Institute of Biology, Division of Cell & Developmental Biology, Leipzig University, Germany

Most EBS forms are caused by missense mutations in KRT5 and KRT which cause the collapse of the keratin cytoskeleton into cytoplasmic aggregates. These render keratinocytes highly susceptible and result in extensive cell/tissue fragility. Moreover, keratin mutations compromise cell adhesion, increase inflammation and contribute to itch. Based on our understanding of keratin aggregation mechanisms, we are developing a therapy approach aiming to prevent or revert aggregation, using chemical compounds that can be applied as a cream or orally to improve the quality of EBS skin. Using EBS keratinocytes expressing K14R125C, we performed a high content screen of ~5.500 chemical compounds and used artificial intelligence to identify cells in which the number and size of aggregates were reduced. To examine whether candidate compounds not only reduced aggregation but improved cell adhesion, we performed epidermal sheet assays (ESA). We have identified several compounds which target protein phosphorylation, inflammation and chaperoning. I present compound C1 which significantly reduces keratin aggregation and strengthens intercellular adhesion in ESA assays. Given that C1 is already in clinical use for treatment of other diseases, clinical studies should be in reach. We expect that compound C1 or relatives might be suitable for the local or systemic treatment of EBS, in particular in young patients.

OP18
READ-THROUGH THERAPEUTICS: DRUG RE-PURPOSING FOR RDEB

David T. Woodley
The Keck School of Medicine, University of Southern California, Los Angeles, California

Recessive dystrophic epidermolysis bullosa (RDEB) is a life-threatening, blistering disease for which there is no current curative treatment. RDEB patients lack functional type VII collagen (C7) and anchoring fibril structures (AFs) at the interface between the main two layers of skin, the epidermis and dermis, which causes marked skin fragility, skin blisters, and erosive wounds that heal with exuberant scarring. Over 300 mutations in the gene encoding for C7 (the COL7A1 gene) have been described, but about 25 – 30% of these mutations are nonsense mutations. Aminoglycoside antibiotics have been shown to be able to read-through nonsense mutations in patients with Hailey-Hailey Disease, Cystic Fibrosis and Duchenne's' Muscular Dystrophy. We sought to determine if aminoglycosides such as gentamicin could read-through nonsense mutations in the COL7A1 gene and safely produce new full-length C7 leading to new AFs. We placed RDEB keratinocytes and fibroblasts into culture and showed that these cells did not synthesize full-length C7. However, the addition of increasing doses of gentamicin and two other aminoglycosides to these cultures readily generated full-length, functional C7. With this *in vitro* data in hand, we then performed a blinded, vehicle controlled, clinical study on five RDEB patients with COL7A1 nonsense mutations who had little or no C7 in their skin. Gentamicin 0.1% ointment or vehicle was applied to erosive wounds 3 times a day for 2 weeks. In the same patients, gentamicin or a saline vehicle were injected into intact skin sites for 2 days. At 1 month and 3 months after treatment, the treatment sites were biopsied and the expression of C7 and AFs evaluated by immunofluorescence (IF) staining with anti-C7 antibodies and immuno-electron microscopy (IEM), respectively. In all 5 patients, gentamicin generated new C7 between 20% and 165% of that observed in normal skin. No new C7 was observed in placebo-treated sites. Pre-treatment and placebo-treated test sites had few or no AFs, while new AFs were observed at sites treated by gentamicin topically or by intradermal injections. Gentamicin-treated wounds, but not placebo-treated wounds, exhibited improved wound closure and decreased new blister formation. Despite the formation of new C7 in the patients' skin, the patients did not generate anti-C7 auto-antibodies in their blood or skin. No alterations in hearing (audiograms), laboratory values or renal function were observed. In another on-going clinical trial in which the results are still pending, we administered intravenous gentamicin (7.5 – 10 mgs/kg) to similar RDEB patients daily for 2 weeks or twice weekly for 3 months. In these 7 patients, there were no alterations in their audiograms, renal function or laboratory tests after treatment. Taken together, these studies suggest that gentamicin may be safely administered to RDEB patients topically, intradermally or intravenously and generate new C7 and AFs in their skin. Other non-aminoglycoside, read-through drugs such as amlexanox, may also have a similar potential to gentamicin, but have not yet been tested in a clinical trial.

OP19
TOPICAL THERAPIES FOR EPIDERMOLYSIS BULLOSA

Dedee F. Murrell
Dept Derm, St George Hospital, UNSW and University of Sydney, Australia

Topically applied therapies for EB can work by several mechanisms, including targeting downstream inflammation, specific targeting of EB genes and targeting recessive forms of EB by misreading premature termination codon (PTC) mutations. The types of evidence include case reports, independent and sponsored randomized controlled trials (RCTs). Topical therapies have had profound impacts in other rare blistering diseases, such as bullous pemphigoid. In such studies, it is important to reduce the placebo effect by keeping dressings the same, using validated objective and subjective outcome measures, including scoring inflammation separately from longer term damage; short term studies can measure changes in disease activity/inflammation (erythema, blisters, erosions) whilst longer term studies may show changes in damage/scarring. The studies that will be reviewed include topical vs intralesional gentamicin for RDEB, which has been published. Topical sirolimus for EB simplex – the methodology; topical allantoin 6% RCT vs vehicle for all forms of EB, and why there were issues with the placebo effect in this trial; topical oleogel vs vehicle phase III RCT for JEB and DEB which is in the final stages of recruitment. There are other topical therapies in trial but time will not allow discussion of all of these.

OP20
PEBLES

Jemima E. Mellerio
St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK

The Prospective Epidermolysis Bullosa Longitudinal Evaluation Study (PEBLES) has been running since November 2014, collecting a broad and comprehensive set of data covering objective, subjective, laboratory and health economic data from adults and children with different forms of recessive dystrophic EB (RDEB). In addition to gathering baseline data, the study involves data cap-

ture at regular intervals (6-monthly in under 10 year olds, thereafter annually) establishing intra-individual data throughout life, with the aim to identify potential clinical end points for future clinical studies in EB. In addition, comparison of different variables, clinical, subjective or laboratory, may reveal surrogate markers or prognostic indicators that are relevant for clinical management. Granular analysis of the costs of care can highlight the economic burden of caring for EB and serve as a highly relevant and useful indicator to justify the development of new, potentially costly treatments for EB. To date, PEBLES has recruited 60 children and adults with RDEB. Initial data analysis has focussed on itch and pain, quality of life and costs of care. Itch is an extremely common symptom in all RDEB subtypes with a negative impact on different aspects of life including sleep, mood and concentration. Despite this, the majority of individuals are not taking any medication for itch, probably highlighting the lack of efficacy of current therapies. Pain was also very common, both background and procedural, particularly in generalised severe RDEB (RDEB-GS) who also experienced greatest sleep disturbance from pain. Adult quality of life was assessed with the QOLEB tool; individuals with RDEB-GS had greatest impact on QOL, predominantly from physical rather than emotional functioning. A similar trend was reported from parents and children using the PedsQL tool but with smaller numbers of participants. This may reflect psychological adjustment of individuals to their RDEB. Analysis of costs of dressings and retention garments in different forms of RDEB revealed a median of £85,156 pa (SD £68,875) in RDEB-GS, £10,112 pa (SD £19,414) in RDEB generalised intermediate, and £1,699 pa (SD £2,800) in RDEB inversa. Costs for paid care were also greatest in RDEB-GS; combined with dressings costs the mean annual total was £97,943. Future areas for analysis of the PEBLES data include bone health and gastrointestinal disease and complications. Our aim is to continue UK recruitment, to expand to international EB centres to gather data from as many individuals with RDEB as possible, and longer term, to expand the study to other EB subtypes.

OP21
EPIDERMOLYSIS BULLOSA CLINICAL CHARACTERIZATION AND OUTCOMES DATABASE

Anna Bruckner
University of Colorado School of Medicine, Children's Hospital Colorado

The Epidermolysis Bullosa Clinical Research Consortium (EB-CRC) is a North American multisite research network. Formed in 2010, it now includes 20 sites in the US, Canada, and Mexico. The EB Clinical Characterization and Outcomes Database (CCOD) is the primary research project of EBCRC. The overall goals of the CCOD are: 1) to identify well-described patient cohorts that may participate in future studies and therapeutic trials; and 2) to gather longitudinal data on the course, complications, and clinical interventions of EB in order to develop and refine guidelines for best clinical practice. Enrollment in the CCOD started in 2011 when the database was based at Stanford University. In 2015, the CCOD moved to University of Colorado, the current data coordinating center. Patients are enrolled and reviewed when they present for scheduled, routine care. Baseline data includes demographics, diagnostic information, and objective, initial clinical events (called Milestone events), such as gastrostomy tube placement, first esophageal dilation, first squamous cell carcinoma, etc. A summary of patients enrolled through June 30, 2017 was recently published (Feinstein J et al. Assessment of the Timing of Milestone Clinical Events in Patients With Epidermolysis Bullosa From North America. JAMA Dermatol. 2019;155(2):196-203). Ongoing data collection includes clinical features and management, laboratory test results, and patient reported symptoms and outcomes. These data enable EBCRC investigators to better understand EB, as evidenced by recent collaborative studies on skin care practices, wound microbes, diagnostic testing, and patient reported outcomes.

OP22
FROM THEORY TO PRACTICE – TRANSLATIONAL THERAPY INTO CLINICAL TRIALS

Jemima Mellerio
St John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust, London

Advances in our understanding of the patho-mechanisms underlying different forms of epidermolysis bullosa (EB) have gathered momentum over recent decades. From Pearson's ultrastructural work in the 1960s delineating the main types of EB based on the plane of blister formation at the basement membrane zone (BMZ), the introduction of monoclonal antibodies against BMZ antigens in the diagnosis of EB, gene discovery from the start of the 1990s through to the current state of understanding with over 20 genes implicated in different subtypes of EB with application of this knowledge to diagnostics, prenatal and preimplantation genetic diagnosis, counselling and prognostication, a tremendous amount has been learnt and applied in clinical practice. However, the last 5 to 10 years has witnessed fresh drives to apply this to new translational therapies offering for the first time opportunities for much more effective treatments and the potential for a cure for EB. Specifically, efforts in the areas of cell and gene therapy, gene editing, protein replacement and drug treatments are reaching the early phase clinical trial stage. In parallel, and acknowledging the pressing need for better symptomatic treatments, trials are being developed to address pain, itch, wound care and fibrosis. Paramount to the success of clinical trials in EB is the development of a fuller understanding of the natural history of the disease and clinically meaningful endpoints. Collaboration between clinicians, researchers, patients, industry and support organisations and charities is key to reaching potential benefits across the spectrum of approaches currently being explored.

OP23
COMBINING APPROACHES: BMT AND SYSTEMIC TREATMENT FOR EB

Jakub Tolar
Blood and Marrow Transplantation, Department of Pediatrics, University of Minnesota, USA

Using bone marrow transplant (BMT) to treat severe variants of epidermolysis bullosa (EB) has not been curative, but it has led to the discovery and development of systemic therapies that have the potential to improve quality of life for these patients. Each EB patient's disease presentation is unique and evolving, as the impact of infection, inflammation, and scarring are cumulative over time. In the absence of a cure, personalized therapy that combines several approaches offers significant benefits. BMT is the only current therapy that can impact internal tissues. Milder transplant conditioning regimens make BMT safer, and the ability to use haplotype-matched donors increases the pool of available donors. The acquired immune tolerance of the patient allows the donor to provide additional cellular products, like epidermal grafts or mesenchymal stem/stromal cells. Using the patient's own genome-edited or naturally revertant cells to create bio-engineered grafts or to inject into chronic wound sites is another option. Additional therapies include local topical treatments, ABCB5 protein coding, nutritional support, and protective bandaging. We can offer patients improved pain relief and slower progression of disease by combining therapeutic approaches tailored to their unique disease stage and treatment goals.

OP24

FIBROBLAST GENE THERAPY FOR RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Su Lwin
St John's Institute of Dermatology, King's College London, London, UK

Recessive dystrophic epidermolysis bullosa (RDEB) is a severe form of skin fragility disorder due to mutations in COL7A1 encoding basement membrane type VII collagen (C7), the main constituent of anchoring fibrils (AFs) in skin. We developed a self-inactivating lentiviral platform encoding a codon-optimized COL7A1 cDNA under the control of a human phosphoglycerate kinase promoter for phase I evaluation. In this single-center, open-label phase I trial, 4 adults with RDEB each received 3 intradermal injections (~1 × 106 cells/cm2 of intact skin) of COL7A1-modified autologous fibroblasts and were followed up for 12 months. The primary outcome was safety, including autoimmune reactions against recombinant C7. Secondary outcomes included C7 expression, AF morphology, and presence of transgene in the injected skin. Gene-modified fibroblasts were well tolerated, without serious adverse reactions or autoimmune reactions against recombinant C7. Regarding efficacy, there was a significant ($P<0.05$) 1.26-fold to 26.10-fold increase in C7 mean fluorescence intensity in the injected skin compared with noninjected skin in 3 of 4 subjects, with a sustained increase up to 12 months in 2 of 4 subjects. The presence of transgene (codon-optimized COL7A1 cDNA) was demonstrated in the injected skin at month 12 in 1 subject, but no new mature AFs were detected. To our knowledge, this is the first human study demonstrating safety and potential efficacy of lentiviral fibroblast gene therapy with the presence of COL7A1 transgene and subsequent C7 restoration *in vivo* in treated skin at 1 year after gene therapy. These data provide a rationale for phase II studies for further clinical evaluation.

OP25

DEVELOPMENT OF HMGB1 PEPTIDE DRUG FOR REGENERATING EPIDERMAL STEM CELL NIEHCES IN RDEB SKIN

Katsuto Tamai
Department of Stem Cell Therapy Science, Graduate School of Medicine, Osaka University, Japan

Recessive dystrophic epidermolysis bullosa (RDEB) patients continuously deplete epidermal stem cell populations due to repetitive blistering all over the skin. RDEB patients eventually destroy the dermal microenvironments by severe scar formation. To recover functional skin, both the epidermal and dermal components of the epidermal stem cell niches must be regenerated. We have developed HMGB1 peptide drug as a regeneration-inducing medicine, which induces accumulation of bone marrow-derived circulating mesenchymal stem cells in the necrotic injuries such as RDEB skin and promotes regeneration of both mesenchymal and epidermal components. With these scientific backgrounds, we started investigator-initiated phase II clinical trial of the HMGB1 peptide drug for promoting regeneration of the RDEB skin lesions. Nine RDEB patients are involved in the phase II clinical trial of the HMGB1 peptide. Prior to administering the HMGB1 peptide, we evaluated total area of the RDEB skin lesions (blisters, erosions and ulcers) in each RDEB patients once a month for two months (three times) to determine the baseline of the lesion area. We then systemically administered the HMGB1 peptide drug to the RDEB patients at a dose of 1 mg/kg by 30 minutes' drip infusion once a day, 4 days in the first week, followed by 2 days in the 2nd, 3rd, and 4th weeks, totally 10 times administration in a month. As a primary endpoint, we evaluated change rate of the total lesion area from the baseline once a month after the drug administration for 6 months (7 evaluation points). Currently, we are evaluating efficacy and safety of the HMGB1 peptide drug in the RDEB patients.

OP26

STATE OF THE ART IPSCS AND ALTERNATIVE METHODS FOR DELIVERING CELLS DERIVED FROM GENE-EDITED IPSCS

Dennis Roop
Department of Dermatology, Director, Gates Center for Regenerative Medicine, University of Colorado

To reduce the number of steps associated with the generation of genetically corrected iPSCs, we have combined our previously reported high-efficiency RNA-based reprogramming protocol together with RNA-based CRISPR/Cas9-mediated correction into a one-step procedure which can be performed within 5-6 weeks. To test the robustness of this protocol, we produced genetically corrected iPSCs from three RDEB patients sharing the founder c.7485+5G>A (IVS98+5G>A) mutation in the COL7A1 gene. We observed correction efficiencies as high as 5% and all characterized iPSC lines were karyotypically normal and had no observable off-target genetic modifications. All corrected iPSC lines successfully differentiated into keratinocytes and expressed Col7 protein, as detected by immuno-staining. Although epidermal grafts may be the fastest path forward to demonstrate safety and efficacy of an iPSC-based therapy for RDEB patients, the time required to generate these grafts from genetically corrected iPSCs is lengthy and consequently expensive. Therefore, we are currently evaluating a "spray-on-skin" delivery system developed by Avita Medical, for delivering skin cells differentiated from gene-edited RDEB iPSCs as a more straightforward alternative to epidermal grafts. If successful, the "spray-on-skin" delivery system would decrease the time to patient application vs. the time and cost it takes to grow epidermal grafts and would potentially produce superior outcomes for RDEB patients due to the lower risk of inflammation and scarring. While gene-corrected iPSC-derived keratinocytes may correct the cutaneous phenotype in RDEB patients, these cells will not be effective in treating the severe gastrointestinal manifestations associated with RDEB, which often require the use of feeding tubes. Therefore, we are currently assessing if the systemic delivery of gene-corrected-iPSC-derived mesenchymal stem cells (MSCs) can facilitate wound healing in internal epithelia.

OP27

STATE OF THE ART GENE EDITING

Fernando Larcher
Epithelial Biomedicine Division, CIEMAT-CIBERER, Department of Bioengineering, UC^{3}M, Madrid, Spain

Mutations in COL7A1 are the cause of RDEB. The main goal of our research is to achieve highly effective and precise correction of pathogenic mutations in COL7A1 gene by means of different genome editing tools. Recently, we have shown a one-step NHEJ-based correction protocol consisting of dual gRNA/Cas9 complexes delivered by electroporation, achieving highly efficient mutation-containing COL7A1 exon removal in primary patient keratinocytes. COL7A1 Exon 80 was chosen as a target because a frame-shift mutation in this exon is highly prevalent in Spain an other Latin American countries. More recently, we have designed a marker free HDR-based strategy for RDEB correction, using Cas9 as RNP to create double stand breaks in the DNA and a donor template-carrying AAV, aiming to precisely correct the gene. With the NHEJ approach, we achieved efficiencies of exon removal close to 90% in primary RDEB keratinocytes, with practically every cell in the bulk population expressing functional C7 while, the HDR-based gene correction strategy showed efficiencies over 40% in primary keratinocytes, producing C7 protein levels, comparable to those detected in normal carrier keratinocytes, sho-

wing that these are feasible strategies to restore dermal-epidermal adhesion in regenerated skin. Both genome editing tools offer a remarkable gene correction efficiency able to support a normal healthy skin regeneration when transplanted onto nude mice. NHEJ-based approach offers a therapeutic option that could be applied to other mutation-containing exons suitable for exon removal. Otherwise, HDR-based strategy offers a precise gene correction covering a wider number of mutations. The use of gene corrected bulk keratinocytes, enables the easy translation of both approaches to the clinic.

OP28
EBGRAFT AND ADVANCES IN SKIN GRAFTING USING IMPROVED VECTORS

Alain Hovnanian and EBGRAFT partners
Department of Genetics, Laboratory of genetic skin diseases, INSERM UMR 1163 Imagine Institute, University of Paris, Necker hospital for sick children, Paris, France

EBGRAFT is an international *ex vivo* gene therapy phase I/II trial aiming at grafting adult subjects with recessive dystrophic epidermolysis bullosa (RDEB) using autologous skin equivalents genetically corrected with a COL7A1-encoding SIN (Self INactivating) retroviral vector (Orphan drug). It is a single-center open-label proof-of-concept study aiming at evaluating safety and efficacy of this treatment. We have identified eight subjects from France and the UK with optimal clinical and biological features. Subjects have moderate to severe RDEB, low levels of detectable type VII collagen (C7), absence of circulating neutralizing antibodies against C7, multiple sites suitable for grafting and no history of skin cancer. Three subjects will be initially grafted. The two first subjects have already been enrolled. Each subject will receive up to 300 cm^2 of COL7A1-modified autologous skin equivalent grafts made of genetically corrected keratinocytes and genetically fibroblasts into a fibrin gel to treat chronic or recurrent wounds according to subject's preference and demand. The GMP genetically corrected skin equivalents will be generated in the department of Gene therapy at Niño Jesus Hospital in Madrid. Subjects will be referred from France and the UK and grafted in the department of Hematology at Necker hospital for sick children in Paris. The primary endpoints are safety, knowing that pre-clinical studies showed a safe integration profile. Secondary outcomes include efficacy (clinical assessment, C7 expression, anchoring fibril morphology, presence of transgene in the grafted skin) and immune tolerance by detection of C7 antibodies and T-cell response to C7. The subjects will be followed for 12 months (at M1, M2, M3, M6 and M12) with a 4-year additional long term follow-up period. This study holds the promise of a safe and efficient *ex vivo* gene therapy approach for permanent treatment of RDEB, allowing improved quality of life and prevention of skin cancer.

OP29
HOLOGENE PROJECTS

Laura De Rosa
Holostem Terapie Avanzate S.r.l., Center for Regenerative Medicine "Stefano Ferrari", Modena, Italy

Cell therapy is an emerging therapeutic strategy aimed at replacing or repairing severely damaged tissue with cultured cells. Since surface epithelia experience a continuous self-renewal process during life, the success of keratinocyte-mediated cell therapy requires the cultivation and transplantation of epithelial stem cells. Under the appropriate culture conditions, epithelial stem cells can be cultivated and generate autologous sheets suitable for transplantation ensuring long-lasting clinical efficacy. Cultured keratinocytes are currently used to restore severe epithelial defects such as thermal or chemical burns of the ocular and skin surface damage irreversibly. When the cell therapy meets the gene therapy a skin genetic disease can be deal, this is the case of Junctional and Dystrophic Epidermolysis Bullosa. Junctional epidermolysis bullosa (JEB) is a severe and often lethal genetic disease caused by mutations in genes encoding the basement membrane component laminin-332. We show here full phenotypic correction of the adhesion properties of stratified epithelium obtained from epidermal stem cells isolated from three patients suffering from laminin-5-deficient JEB and transduced *ex-vivo* with a gamma retroviral vector expressing the ß3 chain of laminin-5. The last patient treated demonstrated: (i) the feasibility and possibility of cultivating and transplanting large areas of the epidermis, (ii) the availability of surgical protocols for grafting large skin areas;(iii) the demonstration of sustained transgene expression and stable gene correction in epidermal stem cells from JEB-patients. These evidences prompt us to propose the implementation of a pivotal clinical trial aimed at ex-vivo gene therapy of selected JEB-LAMB3 patients. Based on these studies, what can be envisioned for the future is a patient-oriented strategy, built on the specific features of the individual and genetic mutation. In this context arises the HOLOGENE projects aimed at cell and gene therapy platform for the treatment of Epidermolysis Bullosa.

OP30
NEXT GENERATION SEQUENCING APPLICATIONS FOR MUTATION DETECTION IN EB

Jouni Uitto
Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College, and Jefferson Institute of Molecular Medicine, Thomas Jefferson University, Philadelphia, PA USA

Epidermolysis bullosa (EB) is currently known to be associated with mutations in as many as 21 distinct genes expressed in the cutaneous basement membrane zone and in the epidermis. Identification of mutant genes and pathogenic sequence variants is important for confirmation of the diagnosis with subclassification, and allowing prognostication of the disease severity and the overall outcome. Knowledge of the genetic defects also forms the basis for prenatal testing and preimplantation genetic diagnosis. Moreover, the information of the mutant genes and specific mutations is a prerequisite for allele-specific treatments currently under development for this group of intractable disorders. Mutation detection strategies in EB have largely focused on DNA analysis by next-generation sequencing techniques (NGS), including use of gene-targeted sequencing panels as well as whole-exome and whole-genome sequencing. Genome-wide homozygosity mapping, based on DNA polymorphism, has also assisted in identification of candidate genes in families with consanguinity. However, DNA-based analyses failed to identify many of the mutations, particularly those impacting on splicing and gene expression at RNA levels. Thus, combination of whole-transcriptome sequencing by RNA-Seq with other NGS-based technologies improves the diagnostic yield significantly. We have recently applied whole-transcriptome sequencing by RNA-Seq on families with different forms of EB, with appropriate bioinformatics analytical steps. RNA-Seq allowed variant calling and homozygosity mapping similar to DNA-based approaches, but could also be used for identification of mutations and their consequences on transcriptome expression as quantitated by heatmap analysis, and altered splicing patterns of RNA as visualized by Sashimi plots. As an example, RNA-Seq identified synonymous-exonic and deep-intronic sequence variants resulting in aberrant splicing; these mutations were undetectable by DNA-based sequencing approaches. Thus, "clinical RNA-Seq" extends molecular diagnostics of rare genodermatoses, and it can provide a reliable first-tier diagnostic approach to extend mutation databases in heritable skin diseases, such as EB.

OP31
GENE THERAPY FOR RDEB (EX VIVO VS *IN VIVO*)

M. Peter Marinkovich
Department of Dermatology and Program in Epithelial Biology, Stanford University School of Medicine, Stanford CA, USA

Our group has been active in studying a group of early phase clinical trials employing several promising new techniques in the molecular correction of RDEB. In total 26 RDEB patients have been treated with gene therapy at Stanford so far, including 7 pediatric patients. 7 adults have been treated with *ex vivo* COL7A1 treated autologous epidermal monolayer grafts (6 grafts per patient = 42 grafts total). 5 adults and one pediatric patient have been treated with *ex vivo* COL7A1 treated autologous fibroblasts which are injected into both intact skin and chronic wounds. The advantages of *ex vivo* gene therapies are that they have demonstrated the longest track record of efficacy and safety and studies are now entering pivotal phase 3 trials. Drawbacks include a theoretical risk of insertional oncogenesis due to the vectors that are employed, however having the gene transfer occur *ex vivo* limits the systemic risk of this and no cancers have yet been detected. In addition, each approach requires a manufacturing run on each patient, applications to patients requires hospitalization including placement either in operating room or day procedure unit, and the timing of shipping and cell production needs to be tightly coordinated. An alternative approach is *in vivo COL7A1* gene therapy for RDEB. Stanford has participated in two such approaches. The first involves a topical gel containing oligonucleotides which act at the RNA level to induce exon 73 skipping, and production of a slightly truncated by still functional collagen VII protein. In this approach, 4 patients have been treated, 3 at Stanford, including 2 pediatric and two adult patients. The other approach involves a topical gel containing a replication incompetent HSV-1 - COL7A1 vector (B-VEC) which has been used in 10 patients, 4 of which are pediatric. While the exon skipping data are still blinded and unavailable, interim reports of the B-VEC therapy indicates robust molecular correction, positive effects on durable wound healing without safety issues even upon repeated reapplication. Disadvantages of the *in vivo* approach would be that while the risk of insertional oncogenesis is not present, these therapies would theoretically not be expected to be as durable as the *ex vivo* therapies described above. Advantages would be ease of application as a wound dressing gel, ultimately in a home setting, as well as off the shelf shipping of the products without the need for biopsies, with the potential to reach many RDEB patients worldwide who do not have access to specialized settings. The B-VEC therapy is also approaching the pivotal phase 3 clinical trials stage. In total, the progress with gene therapy of RDEB has been fast paced and exciting, and will continue to pick up speed in the near future with groups in europe entering new trials, including one in France who will be employed gene corrected epidermal and fibroblast autologous skin equivalents, and a group in Italy/Austria who are building on progress from JEB epidermal autografts achieved in recent years. It is quite possible that these *ex vivo* and *in vivo* gene therapies may be complementary or synergistic, however this remains to be tested.

OP32
EXON SKIPPING FOR RDEB

Peter C. van den Akker
University Medical Center Groningen, Departments of Genetics and Dermatology, Groningen, the Netherlands

Exon skipping uses antisense oligonucleotides (ASOs; synthetic, chemically modified RNA-molecules) to block exonic splice-signals in order to exclude in-frame exons harboring null mutations from the mature mRNA. That way, mutations are bypassed and protein production reinitiated. The ultimate aim of exon skipping is to ameliorate the most severe RDEB phenotypes due to biallelic null mutations. Previously, we demonstrated successful proof-of-concept for *COL7A1* exon 105 skipping *in vitro* and in a xenograft mouse model. To determine the potential therapeutic effect of exon skipping, we studied the phenotypes of DEB patients carrying mutations that lead to natural exon skipping from the Dutch EB Registry and literature. We identified 27 *COL7A1* variants that induced natural exon skipping, of which 15 acted dominantly and 12 required a second variant *in trans* to cause RDEB. The phenotypes associated with the dominant natural exon skipping variants were within the spectrum of DDEB caused by glycine substitutions. We therefore concluded that it is questionable whether exon skipping has a future as systemic therapy for DDEB. Phenotypes in patients carrying recessive natural exon skipping variants ranged from generalized severe to localized acral phenotypes. As seen in our previous study on RDEB for wildtype type VII collagen, the higher the expression of the skipped protein, the less severe the phenotype. Hence, exon skipping has the potential to ameliorate the most severe RDEB phenotypes caused by biallelic null mutations, provided considerable expression levels of the skipped protein can be reached. We are currently studying the delivery and efficacy of exon skipping ASOs in intact human skin using a novel *ex vivo* skin model. Preliminary data suggest that our ASOs can indeed induce skipping of specific *COL7A1* exons in intact human skin after intradermal injection. These data demonstrate that exon skipping may also work in non-blistered RDEB skin, which is a prerequisite for further systemic ASO-development.

OP33
COL17A1 EDITING USING CRISPR/CAS9

Ulrich Koller
EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology, University Hospital of the Paracelsus Medical University Salzburg,

Type XVII collagen (C17) is a transmembrane protein essential for maintaining the connection between the plasma membrane of basal keratinocytes and the lamina lucida of the basement membrane zone. *COL17A1* mutations typically lead to a reduced or absent expression of C17 in junctional epidermolysis bullosa (JEB) patients. Aiming at the CRISPR/Cas9-mediated correction of a frameshift mutation responsible for JEB, we treated primary JEB patient keratinocytes with paired nicking ribonucleoproteins (RNPs). Pairing of Cas9 nickases is associated with a reduced off-target activity and no impairment of on-target gene editing. Upon nucleofection-mediated RNP delivery into JEB keratinocytes, we maintained a highly efficient allele-specific gene disruption efficiency of > 80%. Further, an efficient *COL17A1* restoration was shown at the RNA (> 38% efficiency) and protein level (> 49% efficiency) in bulk treated samples. FACS analysis of samples revealed a C17 restoration efficiency of > 50%, without selection. However, using FACS we were able to isolate *COL17A1* reframed JEB keratinocytes, thereby accumulating the C17 positive cell population. Restored C17 was detectable via immunofluorescence, western blot and flow cytometric analysis of unsorted and sorted RNP-treated primary JEB keratinocytes. These studies demonstrate the development of an *ex vivo* gene editing therapy for JEB, using CRISPR/Cas9 paired nicking to permanently treat the genetic basis of the disease without the need for single cell expansion.

OP34
NON-VIRAL GENE THERAPY FOR EPIDERMOLYSIS BULLOSA

Mark Sumeray
Amryt Pharmaceuticals DAC, Dublin, Ireland

Gene therapies to treat EB are being tested in preliminary clinical trials, both as cell-based therapeutics and direct to patient topical applications. All but one (a topical RNA therapy) use a viral vector

to deliver the therapeutic gene. The challenge to deliver therapeutic DNA by non-viral methods is currently being researched academically by a range of different methods. These include, in broad terms, physical force, inorganic particles and synthetic engineered molecules. Of these three types, synthetic molecules show the most promise for delivery of DNA to the skin of patients with EB. Highly branched poly(β-amino esters) (HPAEs) are a synthetic polymer complexed with the therapeutic gene needed to treat Dystrophic EB, COL7A1. This complexation forms the non-viral gene therapy for RDEB currently in development by Amryt Pharmaceuticals DAC as AP103. The AP103 polyplexes were applied to RDEB patient cells *in vitro* to test efficacy and tolerability. Following in-vitro testing the AP103 polyplexes were tested *in vivo* in a murine model grafted with human RDEB skin. Three topical applications were applied to the RDEB grafts, or the grafts were pre-treated with the AP103 polyplexes and then also received three topical applications. Approximately 5-fold more type VII collagen is expressed in RDEB keratinocytes after a single AP103 delivery compared with normal keratinocyte endogenous levels of type VII collagen. RDEB fibroblasts express approximately 3.5-fold more type VII collagen compared with normal fibroblast levels. Topical AP103 application leads to type VII collagen detection in grafted RDEB skin cultures 2 weeks after treatment. Of a total of 18 treated animals, 10 were positive for type VII collagen. When outliers removed a significant difference was detected between EB control and pre-transfected group. AP103 has not shown any toxicity when applied to RDEB cells *in vitro* or *in vivo*. It has also shown it can successfully return type VII collagen along the basement membrane zone of RDEB skin after topical applications. As a non-viral gene vector HPAE shows significant promise as a topical therapy for RDEB.

OP35
INTRODUCTION TO CLINICAL TRIAL DESIGN

Johann Bauer
Department of Dermatology and Allergology, Paracelsus Medical University Salzburg

Clinical research in rare diseases (RD) like Epidermolysis bullosa (EB) faces many challenges, to include (1) limited insights into pathogenic disease traits, natural course and potential targets/mechanisms of intervention, with subsequent difficulties to define endpoints, effect size and outcome measures; (2) sample size restrictions and recruitment failures compromising statistical power while increasing trial duration and costs; (3) heterogeneity of the diseased study cohort with increased random imbalance in covariates further limiting data validity and generalizability; (4) ethical concerns to use placebo controls as well as to conduct research in children; or (5) increasing trial complexity due to methodological, logistical and regulatory challenges that critically impairs trial feasibility. Approaches to overcome these hurdles comprise e.g. a close collaboration between sponsor, academia, regulatory agencies and patient groups to encourage a patient-centric trial design. This involves affected individuals and their caregivers in decision on study length, target population, in-/exclusion criteria, outcomes and measurements procedures as well as information policy, which also aims at reducing the patients‘ trial burden (e.g. in terms of time, travel, extent of scheduled visits and invasive investigations, literacy, personal financial expenditures and compatibility with occupational obligations). Administrative support needs accurate resources to ensure quality and professionalism. Likewise, global regulatory strategies and operational execution, harmonization of regulatory and funder requirements as well as institutional policies are major issues to foster the RD research agenda via research networks/consortia. Another key strategy in RD trials is to use the limited available information as efficiently as possible. This includes e.g. usage of multiple/composite endpoints and multiple treatment arms; incorporation of interim data review; or formal synthesis of previously collected data (e.g. Bayesian statistical methods). Likewise, alternative clinical trial designs (such as series of n-of-1 trials design; response-adaptive study design; randomized withdrawal design; factorial designs) hold some promise to increase trial acceptability, optimize randomization procedures and mitigate effects of clinical heterogeneity, as well as to decrease sample size requirements by applying statistical methods to adapt the significance level in small populations.

0P36
LARGE RDEB WOUNDS: AN UPDATE ON NATURAL HISTORY DATA AND EB101

Jean Tang
Department of Dermatology, Stanford University

RDEB patients have mutations in the COL7A1 gene, thus lacking functional type VII collagen (C7). We have shown that two types of RDEB wounds exist: chronic open wounds (which never heal), and recurrent wounds (which are dynamic – healing and re-opening within weeks). Chronic wounds are larger, more painful and more pruritic. In 2013, our group initiated a Phase 1/2a clinical trial of keratinocyte-based autologous gene therapy in 7 adult subjects to treat these wounds. Six chronic wounds were treated in each subject, with molecular correction seen for up to 2 years in the form of C7 and anchoring fibrils, wound healing for up to 6 years, and no serious adverse events or systemic retrovirus detection. A larger, phase 3 study is forthcoming.

OP37
RECOMBINANT COLLAGEN 7: A SYSTEMIC APPROACH TO RDEB THERAPY

Theresa Podrebarac
Phoenix Tissue Repair, Boston, USA

No abstract supplied

OP38
A TALE OF TWO THERAPEUTIC APPROACHES – AN UPDATE ON CLINICAL STUDIES IN DIACEREIN AND FCX-007

Mary Spellman, MD
Castle Creek Biosciences

The expression of interleukin-1β (IL-1β), a pro-inflammatory cytokine, is implicated in the pathogenesis of epidermolysis bullosa simplex (EBS). Diacerein 1% ointment, an inhibitor of IL-1β, has been shown to reduce blistering in patients with EBS. A randomized, double-blind, vehicle-controlled, Phase 2 study randomized 54 patients with moderate to severe EBS to apply diacerein 1% ($n=28$) or vehicle ointment ($n=26$) once daily for 8 weeks. The primary endpoint, a ≥60% reduction in the surface area of EBS lesions, and the key secondary endpoint, at least a 2-point reduction in the Investigator’s Global Assessment (IGA) score for the assessed area at Week 8. The proportion of patients who achieved ≥60% reduction in the surface area of EBS lesions was numerically greater in the diacerein 1% group (57.12%) than in the control group (53.8%), but not significantly ($p=0.9666$). The proportion of patients who achieved success on the IGA endpoint was higher in the diacerein 1% group (42.9%) compared with the control group (26.9%), but not significantly ($p=0.2861$). An IGA score of clear/almost clear was reported for 39.3% of the diacerein 1% group and 23.1% of the control group. Diacerein 1% ointment was generally safe and well tolerated. Mutations in the COL7A1 gene encoding type VII collagen (COL7) cause dermal-epidermal separation in patients with dystrophic epidermolysis bullosa (RDEB).In an ongoing Phase1/2 study, 6 patients (5 adults, 1 child; ages 9 to 38 years) with severe generalized RDEB received injections of genetically-corrected,COL7-expressing autologous human dermal fibroblasts (FCX-007) at targeted chronic wounds

(confirmed present for 12 weeks or longer in a monitored period). All 6 patients received FCX-007 at baseline, and 4 patients received a second injection (52, 25, 12, and 4 weeks post-baseline). FCX-007 was well tolerated up to 52 weeks post-administration with no antibody response to COL7 and no replication-competent lentivirus (RCL) detected. At 12 weeks following the initial injection of FCX-007, 8 of 10 (80%) treated wounds were evaluated as completely healed; no paired and untreated wound was completely healed. Positive wound healing trends, associated with COL7 expression in local tissues, have been observed up to 52 weeks following the injection of FCX-007.

OP39
B-VEC OFF THE SHELF TOPICAL GENE THERAPY FOR DEB

Suma Krishnan
Krystal Biotech, Pittsburgh, USA

No abstract supplied

OP40
ABCB5+ MESENCHYMAL STEM CELLS FOR THE TREATMENT OF RDEB – FROM BENCH TO BEDSIDE

Kathrin Dieter
RHEACELL GmbH & Co. KG

While several treatment strategies for RDEB have been tested in preclinical and clinical trials, effective therapies remain to be developed. Currently much research focuses on curative strategies to correct the genetic defect at the DNA, mRNA or protein level. However, due to complex challenges, curative treatments will not become available until in years. Other approaches focus on disease-modifying, symptom-relieving pathways, addressing the accumulating evidence that inflammatory pathomechanisms significantly contribute to RDEB disease phenotype and severity. Recently, the ATP-binding cassette transporter ABCB5 has been found to identify a novel immunomodulatory mesenchymal stem cell (MSC) population in human skin, showing marked inflammation-dampening and tissue-healing effects involving several pathways. In a Col7a1−/− mouse model of RDEB, ABCB5+ MSCs markedly extended the animals' lifespans via reduced skin infiltration of inflammatory myeloid derivatives (Webber et al., 2017). To develop ABCB5+ MSCs for cell-based treatment of RDEB, we have established a GMP-conform manufacturing process to isolate the MSCs from donor skin tissue and process them to a highly functional homogenous cell population formulated as an advanced-therapy medicinal product. Having shown a convincing preclinical safety and tolerability profile, this ATMP is currently tested in an international phase I/IIa clinical trial (NCT03529877). Patients are successively enrolled into 5 age cohorts (adult/12-18/5-12/1-5/0-1 years) to receive 2×106 cells/kg i.v. on days 0, 17 and 35. Efficacy (overall symptom improvement) is monitored for 12 weeks, safety for 24 months. As of now, 13 patients (7 adults; 4 12-18 years; 3 5-12 years) have been treated. Ten of them have completed efficacy follow-up with reductions in EBDASI activity by 14.6% and 23%, iscorEB clinician by 28.2% and 17.7%, and itch by 25% and 8.7% (adults and 12-18 years, respectively) vs. baseline. So far, evaluation by the data monitoring committee has not raised any safety concerns. These results support our ATMP as promising potential candidate for symptom-alleviating treatment of RDEB.

OP41
PARTNERSHIPS – CHARITIES, REGULATORS AND INDUSTRY

Brett Kopelan
Debra of America, New York, USA

No abstract supplied

OP42
PARTNERSHIP APPROACH TO RESEARCH FUNDING

Sharmila Collins
Cure EB, London

EB was first described by Ferdinand Ritter von Hebra in Austria in 1870, but it was only in the 1960's and 70's that transmission electron microscopy allowed differentiation of EB into 3 main categories. Antigen mapping in the 80's brought us the ability to diagnose and differentiate EB subtypes but it was in 1991 that the first EB genes were discovered and with them an indication of where the battle lines would be drawn in the fight towards treatments and cures. In the early days of EB research the partnerships needed to conduct it were simpler. You needed a dedicated researcher and a funding source but after decades of fabulous research, in the midst of treatment trials the relationships are more complex and diverse. The areas of EB research have expanded from fundamental research into the genetics and biology of EB to the development of therapies but also attempts to ameliorate symptoms and tackle the most severe consequences of EB, chronic wounds, fibrosis and of course malignant skin cancer. So where do the partnerships lie now? We have the same researchers and funders as before, with brand new ones but also have the international regulatory bodies, ethics committees and industry all hovering around the EB community who wait patiently for treatments. Their willingness to participate in trials, however unlikely to cause lasting change is a testament to the desperation felt. But how can we address their need and maximise the impact of funding and make sure that areas of research are covered adequately? Forming effective partnerships in EB research is an essential objective if we're going to get better treatments into clinic but the very nature of those partnerships is really determined by what's hot in the research arena and what bit of translational research looks most promising, and therefore picking the best research priorities is fundamentally at the core of all effective partnerships. So what research priorities should one focus on…..

OP43
EPIDERMOLYSIS BULLOSA RELEVANT ENDPOINTS – A DEBATE

Dedee F. Murrell
Dept Derm, St George Hospital, UNSW and University of Sydney, Australia

The ideal clinical endpoint score for any skin disease should be valid, reliable, responsive and feasible. In terms of the EB toolbox, we have subjective measures that have been validated: the quality of life in EB or QOLEB, the EB-BOD score for family QOL and the functional foot health status questionnaire (FHSQ). For objective clinical scores we have the EBDASI (EB disease activity and scarring index), the BEBS (Birmingham EB score) and an oral score; blister counts and an IGA score for EB simplex. In such studies, it is important to reduce the placebo effect by keeping dressings the same, using validated objective and subjective outcome measures, including scoring inflammation separately from longer term damage; short term studies can measure changes in disease activity/inflammation (erythema, blisters, erosions) whilst longer term studies may show changes in damage/scarring. There are some lab parameters but none are specific to EB; finally there is one mixed score, the iSCOREB (subjective (QOL and function), objective and lab together). Ideally, outcome measures in studies should not be composite/mixed scores. Each of these scores will be reviewed briefly. A comparison study of EBDASI and iSCOREB has been conducted in Australia by 6 assessors and is being presented at this meeting by honours student Clare Rogers as a poster. This found significant advantages for EBDASI over iSCOREB. Outcome

measures should be subjected to COSMIN analysis such that each instrument should have good inter and intra-rater reliability, responsiveness to change, minimum clinically important difference (MCID), content and construct validity, feasibility and severity cutoffs. When the EB outcome measures are assessed in this standardized way, only the EBDASI fulfills all of these criteria. In comparison, the iSCOREB has 4 of these 8 parameters but dose not assess damage and BEBS has 5 but is unable compare activity and damage separately. To progress this field it would be ideal if DebRA sponsored a consensus meeting led by independent experts on outcome measures, such as Hywel Williams, Sinead Langan or Victoria Werth, to address the different outcome measures above in an unbiased manner.

OP44
QUALITY OF LIFE MEASURES
Elena Pope
Paediatric Dermatology, The Hospital for Sick Children, Toronto, Canada

No abstract supplied

OP45
REGULATORY PERSPECTIVES AND CHALLENGES
Brett Kopelan
Debra of America, New York, USA

No abstract supplied

OP46
PLANNING FOR CLINICAL TRANSLATION
Catriona Crombie
LifeArc, UK

No abstract supplied

OP47
INNOVATIVE THERAPEUTIC DEVELOPMENT
Mauro Perretti
Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK

No abstract supplied

OP48
EB-CLINET - A CLINICAL NETWORK TO HELP IMPROVE CARE FOR EB PATIENTS
Sophie Kitzmüller
EB House Austria, Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University Salzburg, Salzburg, Austria

Epidermolysis bullosa (EB), as a rare and phenotypically diverse disease, requires specialized medical attention. Patient's needs have to be addressed by multidisciplinary care. To build up expertise about disease mechanisms and best treatment options it is therefore important to share knowledge. EB-CLINET built up a network of health care professionals working in the field of EB. We aim to facilitate connection, collaboration and communication between professionals and institutions. We also train and instruct medical specialists so that they can act as EB specialists in their national centers. Our members get informed about worldwide training options, meetings and EB-related events, on recent developments regarding treatments and research and updates on clinical trials, or calls for the recruitment of collaborators. We want to find more partners and include more countries into our network, as EB affects patients all around the world. Together we can make a difference and increase the quality of life for EB patients.

OP49
CLINICAL CHALLENGES OF EB SKIN-INSIDE AND OUT
Anna E. Martinez
Great Ormond Street NHS Foundation Trust

The clinical challenges of EB skin change over time. Patients with RDEB progress though 4 distinct phases.
Phase 1, from birth to 18 months, is often described as a honey moon period where there can be minimal skin signs. This is can be mirrored by normal systemic inflammatory markers reflecting very little if any internal involvement. Around 18 months, the first signs of internal disease manifest, with reduced weight gain and anaemia. Phase 2, from 18 months to 10 years, sees a steady increase in severity with more extensive skin involvement which, due to chronic inflammation, begins to affect four main internal pathways: growth, bone health, iron metabolism and puberty. Interventions at this stage such as gastrostomy placement can be highly beneficial, and anti-inflammation therapies such as intravenous stem cell therapy also appear to be beneficial. Phase 3, from 10-20 years, shows a faster progression in severity both in the skin and internally with continued massive high levels of chronic inflammation. Systemic anti-inflammatory therapies appear to be less affective from this phase onwards. Phase 4, from the age of 20 years, often results in a rapid decline of the skin with the onset of squamous cell carcinoma or progressive deterioration of both the skin, and internal complications are exacerbated. The importance of knowing EB skin inside and out will be discussed.

OP50
ADVANCES IN DIAGNOSTICS/PHENOTYPING (CPG)
Cristina Has
Department of Dermatology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, German

We have developed a clinical practice guideline (CPG) for EB Laboratory diagnosis based on a systematic review of the literature. Sixty-four papers were appraised according to the Critical Appraisal Skills Programme and Scottish Intercollegiate Guidelines Network quality rating. Based on the literature, both genetic testing and IFM should be performed to allow complete molecular characterization of EB, at both the DNA and protein levels. These methods provide complementary information that enables prediction of the consequences of novel sequence variants and genotype–phenotype correlations. Genetic testing by NGS, either as targeted EB gene panels or as whole exome with targeted filtering for EB genes is able to solve the vast majority of cases and is therefore recommended to save time and resources. When no pathogenic variant is found, additional techniques (e.g.multiplex ligation-dependent probe amplification, reverse-transcriptase PCR, quantitative real-time PCR, RNA-Seq, SNP arrays or Western blotting) should be exploited. In particular, RNA-Seq has been proved to be a reliable tool for identification of splicing errors.

OP51
INDIVIDUALISED THERAPIES
Leena Bruckner-Tuderman
Freiburg Institute for Advanced Studies School of Life Sciences, Freiburg, Germany

No abstract supplied

OP52
ALLOCATION OF RESEARCH FUNDS

Johann Bauer
Department of Dermatology/EB House Austria, University Hospital Salzburg

The last ten years of research into pathophysiology and therapy of EB have advanced our understanding of how adhesion deficiency leads to disease and how we can combat this loss of adhesion. Basic research that has contributed in this area is the classical and successful model of funding. In this case the involved research party retains control over the further progress. Early studies on cell-based therapies and other late-stage clinical studies have shown that these studies are rather expensive. Thus the usual model is to out-license academic research to biotechnology companies. Inevitably academic institutions and patient organisations tend to loose control over the progress of these ventures. Mixed models, in which unrestricted funding comes with in-kind and cash contributions of applicants might be able bridge this gap between basic research and company-driven late stage approval –directed work.

OP53
FUNDING FOR EB RESEARCH

Alfred Lane
Professor of Dermatology and Pediatrics, Emeritus, Stanford University School of Medicine

Before requesting research funding you must know what you want to do and what you are capable of accomplishing. Funding support is approved because of both the requesting research goals and the requesting individual. Successful completion of previous efforts greatly supports future requests. Research funding request often are submitted to multiple funding sources in order to obtain funding. Once funding is obtain, you can withdraw or modify other submitted requests. Precisely follow the funder's application directions. Never plan more than you can accomplish as well as realizing that you will usually take 2 or 3 times longer than what you plan. Look for funding sources in your community as well as through many outside sources of research support. Continue to obtain preliminary data while you are formulating a plan and completing your applications. Include flexibility in your budget, research is always more expensive than you think. Good Luck.

OP54
COSTS AND ACCESSIBILITY

M. Peter Marinkovich
Department of Dermatology and Program in Epithelial Biology, Stanford University School of Medicine, Stanford CA USA

As several gene therapies are now moving into pivotal phase 3 trials, issues of commercialization, costs and accessibility of these treatments are now arising. This talk addresses the hurdles which impact patient access to these emerging therapies. Manufacturing and clinical supply issues vary from therapy to therapy. Ex vivo therapies require manufacturing runs derived from autologous patient biopsies, performed at specialized facilities then transported to specialized medical centers for placement to EB patients in the OR or day hospital unit. This requires tight coordination of manufacturing, shipping, and clinical care. In vivo therapies in general do not require autologous cell manufacturing or biopsies and instead can be shipped off the shelf as needed to various locations and applied under more basic less specialized conditions. Reimbursement is another potential hurdle to patient access. In general all of these therapies are expected to be expensive, and existing reimbursement practices within healthcare systems many not easily accomodate the potential outstanding value and risk profile of potential curative or disease modifying therapies. Labeling is dependent on establishment of primary and secondary objectives negotiated between FDA and the investigators, during design of pivotal trials. The farther that primary and secondary objectives of these new molecular therapies extend beyond the benefits of currently available non-genetic therapies such as allogenic cell treatments, the greater an argument and justification can be made to payers and insurance companies. This also can impact the access of these therapies to patients.

OP55
SUPERFICIAL EBS/PEELING SKIN SYNDROMES

Eli Sprecher
Division of Dermatology, Tel Aviv Medical Center, Tel Aviv, Israel

Inherited disorders featuring supra-basal intraepidermal separation must be considered in the differential diagnosis of classical forms of epidermolysis bullosa (which are associated with intrabasal or sub-basal blister formation). These rare genodermatoses feature extensive genetic heterogeneity and range in severity from mild isolated cutaneous disorders to life-threatening complex diseases. Peeling skin syndromes are of particular interest as they often directly or indirectly result from abnormal expression of corneodesmosin, suggesting that interventions targeting this adhesion molecule may benefit most patients affected with these conditions.

OP56
WOUND CARE (JEB)

Katie Plevey
Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

No abstract supplied

OP57
ESOPHAGEAL MANAGEMENT: CLINICAL UPDATE

Anna Bruckner
University of Colorado School of Medicine, Children's Hospital Colorado, USA

The esophageal manifestations of epidermolysis bullosa (EB) include blisters and erosions, strictures, webs, and in rare cases, perforation or rupture of the esophagus. Strictures are primarily associated with recessive dystrophic EB (RDEB). Data from the National EB Registry show that 50% of patients with severe RDEB will develop a stricture by age 5, and more recent data from the EB Clinical Research Consortium show the most common age for a patient's first esophageal dilation procedure is 3 to 4 years of age. A single, proximal esophageal stricture is characteristic in RDEB. These strictures are best treated with fluoroscopy-guided balloon dilation, which has a low risk of adverse events in the hands of experienced operators. Recurrence after dilation is common. There is little evidence to guide current management on how to prevent or delay the onset of esophageal strictures and how to prevent or delay re-stricture after a dilation procedure.

OP58
GASTROSTOMY

Joe Curry
Great Ormond Street Hospital NHS Foundation Trust, London, UK

No abstract supplied

OP59
ENT

David Albert
Great Ormond Street Hospital NHS Foundation Trust, London, UK

No abstract supplied

OP60
ORAL HEALTH (DENTAL TREATMENT IN EPIDERMOLYSIS BULLOSA)

Susanne Marie Krämer
Special Care Dentistry Unit, Faculty of Dentistry, Universidad de Chile, Santiago, Chile

The first Guideline commissioned by Debra International on Oral Health Care for people living with EB was published in 2012. New evidence has become available and a revised version will be published later in 2020. This conference was based on the 15-year clinical experience of the Universidad de Chile Dental Reference Center for Rare Diseases, where ~250 people living with EB are looked after. In the cohort of patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB) aged 0 to 6 years, severity of caries decreased from 10.2 teeth affected in 2006 to 1.8 teeth affected in 2016. The oral care program is based on early referral and continuous dental care throughout life focused on education, prevention and patient-clinician partnership. The patient and his family commits to oral hygiene with appropriate toothbrushes, patient specific fluoride scheme and alternatives to manage oral ulcers; and the clinician provides early diagnosis and oral hygiene instructions aided by plaque disclosing solutions, fluoride varnishes, fissure sealants and a variety of remineralization and carries arrest strategies to minimize dental disease. Specific challenges in RDEB include: (1) Microstomia, which can be approached with exercises and stricture release surgery, depending on the severity and patients age. (2) Tooth crowding can be managed by patient specific analysis considering serial extractions during mixed dentition and fixed orthodontics in permanent dentition. Patients with severe generalized RDEB might need some adaptations, such as removing hooks from brackets if they cause ulcers, or vestibuloplasty to release the lip. (3) Adults with RDEB who have not had access to preventive care might be edentulous. Dental implants have a 98.6% 1-year osseointegration success rate in RDEB, improving patient's quality of life through enhanced oral functioning, aesthetics and comfort. Specific challenges in Junctional EB: patients present with generalized enamel hypoplasia, varying form pits and fissures to severely hypoplastic enamel. This can cause tooth sensitivity, attrition or failure to erupt. Depending on the severity of the enamel abnormality, teeth should be covered to prevent secondary damage. As EB is a rare and highly variable condition, each patient presents an unique challenge. International collaboration among research and reference centers is key for improving the care of patients with this skin condition.

OP61
EYE: THERAPEUTIC CONTACT LENSES FOR EPIDERMOLYSIS BULLOSA

Michael Baertschi
Department of specialized Contact Lenses and Optometry, eyeness AG, Bern, Switzerland

The ocular surface of mainly dystrophic and junctional EB patients is often affected by recurrent and painful corneal erosions, scarring and reduced vision with an incidence rate of about 40-51%. As an attempt to reduce the occurrance of these erosions in less severe cases, moisturizing eye drops and creams are being employed. However, in more severe cases, sepcialized bandage contact lenses have shown to be more effctive in permanently reducing pain sensation, exessive tearing and chronic ocular inflammation. They were able to restore vision and dicreased the occurance of new formed neovascularisation and scar tissue. In clinical practice bandage contact lenses made out of extreme high oxygen permeable and deposit resistant soft silicone-hydrogel material or from extreme high oxygen permeable hard material with over all diamter between 11 to 16mm were used since 2006. The lenses are mainly worn in an extended or constant wear mode of 24h/7d or 24h/30d. The use of protective contact lenses are helpful to minimize recurrent superficial corneal lesions and consequently increased the patient's quality of life sustainably and effectively.

OP62
GROWTH PATTERNS IN EPIDERMOLYSIS BULLOSA

Antonia Reimer
Department of Dermatology, Medical Center – University of Freiburg

Despite epidermolysis bullosa (EB) being a skin disease, extracutaneous manifestations are common in severe subtypes. Among these, failure to thrive is a major complication in severe dystrophic EB, while individuals with EB simplex are at risk for obesity. This talk focusses on the recently described growth patterns of children with recessive dystrophic EB (RDEB). Weight is the best prognostic measure for growth development in RDEB. Stagnation of weight gain begins within the second year of life and correlates with the amount of collagen VII in the skin, presence of anaemia, low albumin, deficiencies of vitamin D and zinc, and inflammation. In conclusion, the following recommendations for patient management are given: 1) Measuring children with EB every 3 months and use of disease-specific growth charts for clinical follow-up, 2) starting nutritional intervention <2 years, and 3) continuous nutritional supplementation in RDEB.

OP63
ANEMIA IN EB

Irene Lara-Corrales
Hospital for Sick Children, Toronto, Canada, Department of Pediatrics, University of Toronto, Canada

Anemia is a common problem encountered in patients with epidermolysis bullosa (EB). Prevalence of anemia in EB patients is higher than in the general population. Literature on this topic is scarce, but few manuscripts report up to 100% of patients, particularly with severe forms of EB, suffer from anemia. There are many factors that lead to anemia in EB, like blood loss from wounds, decreased iron absorption, decreased oral intake, inflammation, among many others, making this a multifactorial problem. Diagnosing anemia in EB patients may be challenging as it is not only difficult to obtain blood from EB patients, but also there are special considerations that need to be taken into account when interpreting blood test results. The second challenge faced with anemia in EB is its treatment. For optimal management multiple factors need to be addressed, like putting in place interventions to improve nutritional status, decrease inflammatory state, as well as giving oral or intravenous iron supplements or considering other interventions such as blood transfusions. As part of the Debra International initiative to create clinical practice guidelines, anemia guidelines were created. A modified Delphi methodology was used in the process and 20 statements were approved for this guideline. Statements address diagnosis, monitoring, treatment and outcomes of anemia in EB patients.

OP64
HAND SURGERY – MANAGEMENT STRATEGIES

Gill Smith
Great Ormond Street Hospital NHS Foundation Trust, London, UK

No abstract supplied

OP65
SURGERY FOR SCC

Catina Bernardis
Guy's & St. Thomas' NHS Foundation Trust, London, UK

No abstract supplied

OP66

PODIATRY

Tariq Khan
Marigold Clinic, Royal London Hospital for Integrated Medicine, University College London Hospitals NHS Foundation Trust

EB is a group of rare heritable skin fragility disorders, typically presenting as blistering of the skin from minor trauma (DEBRA UK 2018). Ninety percent of EB patients have one or more podiatric manifestations, including blistering, hyperkeratosis, flat feet, nail dystrophy or structural abnormality affecting foot positioning, (Khan 2010; Khan 2012). EB requires specialised podiatric care but because of its rarity many podiatrists have limited knowledge of the disorder. Furthermore there is a dearth of evidence regarding podiatric care of EB and management decisions are usually based on experience and expert opinion. To provide service providers and users, with an evidence based set of current best practice guidelines for people and their families and carers, living with EB. A systematic literature review relating to the podiatric care of patients with Epidermolysis bullosa (EB), was undertaken. Articles relating to podiatric treatment were identified as early as 1979 to present day. The Scottish Intercollegiate Guidelines Network (SIGN) methodology was used. The resulting document went through an external review process by a panel of experts, other health care professionals, patient representatives and lay reviewers. Following an EB community international survey the outcomes indicated six main areas which the community indicated as a priority to foot management. These included blistering and wound management; exploring the most suitable footwear and hosiery for EB; Management of dystrophic nails; hyperkeratosis (Callus); maintaining mobility; and fusion of toes (Pseudosyndactyly).
Evidence here is limited but several interventions currently practised by podiatrists show positive outcomes.

OP67

CASE REPORT: A WOMAN WITH RDEB AND METASTATIC SCC MANAGED WITH NIVOLUMAB

Anna Bruckner
University of Colorado School of Medicine, Children's Hospital Colorado, USA

A 40-year-old woman with recessive dystrophic epidermolysis bullosa (RDEB) presented with a rapidly enlarging tumor on her left forearm. Three biopsies of the tumor confirmed the clinical suspicion of squamous cell carcinoma (SCC). Pathology showed well to moderately differentiated SCC in one area and moderate to poorly differentiated SCC in the other two. Workup revealed SCC in the axillary lymph nodes on the affected side. Surgery was refused, and cetuximab x 5 cycles and radiation therapy to the forearm and axilla (45 Gy over 15 fractions) were given. Marked improvement was seen, but six months after treatment ended, recurrence of the tumor was apparent. The patient underwent below the elbow amputation and lymph node dissection, which were complicated by lymphedema and poor healing of the axillary incision. Six months later, the patient sustained a pathologic fracture of the left humerus due to metastatic SCC. She underwent forequarter amputation of the left arm. Two months later, metastatic SCC affecting her cervical lymph nodes and chest wall was found. The PD-1 inhibitor nivolumab was started, and rapid involution of the tumors occurred. Subsequent clinical examinations and imaging suggested remission of the SCC. Nivolumab was continued for over three years and was well-tolerated except for fatigue. The patient has been stable off therapy for four months at the time of this presentation. As this is a single case report, generalizability is limited. This woman with RDEB has survived for over five years since her initial presentation with primary and metastatic SCC, which was treated with cetuximab, radiation therapy, complex surgeries, and nivolumab.

OP68

CASE REPORT: SCC MANAGEMENT AND RESPONSE IN RDEB AR GENERALIZED FORM

Pavel Rotschein
University Hospital Brno, Czech Republic

A 43-year-old woman with RDEB AR generalized severe was treated at the Department of Pediatric Dermatology in Children's Hospital in Brno since birth. The initial diagnosis was based on the electron microscopy examination of skin and was later confirmed by genetic analysis with the finding of COL7A1 mutations (c.425A>G p.(?)/c.6146G>A p.(Gly2049Glu)). In adolescence she voluntarily interrupted the regular check-ups and visited the National EB Center in Brno after ten years at the age of 28. She had a chronic wound on the right foot lasting for over a year and she was affected by diffuse skin affections including erosions, hemorrhagic vesicles, crusts, atrophic lesions and depigmentation with pruritus, as well as mouth and teeth lesions, onychodystrophy, mild contraction of the fingers and dysphagia. Total excision of the wound on the foot revealed squamous cell carcinoma (SCC) overlapping the margins. Staging and evaluation of lymph nodes ruled out metastatic disease. Amputation of the limb was recommended by the multidisciplinary EB team as the treatment of choice. Advantages favoring this treatment were non-blistering skin of the upper calf and close cooperation with a prosthetic. The patient refused the surgery at first, but for excessive pain and strong odor eventually agreed to it. The EB plastic surgeon in cooperation with EB physiatrist prepared the patient for the below the knee leg amputation which was executed within half a year from the diagnosis. There were observed no complications in the healing of the stump and the patient started early weight bearing using specially manufactured prosthesis. Over the next years she followed the recommendation of regular check-ups including restaging in the EB Center. She was able to graduate college, return back to work and start a family. 15 years after the surgery the patient is in complete remission with improved signs of EB and a high quality of life.

OP69

CANNABINOID-BASED MEDICINES FOR PAIN AND PRURITUS IN EB

Nicholas Schräder
Center for Blistering Diseases, Department of Dermatology, University Medical Center of Groningen, The Netherlands

Cannabinoid-based medicines (CBMs) are gaining increasing attention in the scientific and clinical realms with regard to our growing understanding of the endocannabinoid system in health and disease. The endocannabinoid system found in humans contains an abundance of receptors, which bind cannabinoid-like ligands, and provides a basis to understanding the potential effect of CBM therapies. Research has largely focused on the effect of CBMs on top-down symptoms such as pain and pruritus from various aetiologies, and anecdotal CBM-use in the EB patient population is emerging. Two case series in The Netherlands and the United States described improved pain, pruritus and wound healing in patients treated with sublingually administered CBM-oil (comprising tetrahydrocannabinol and cannabidiol, both plant derived cannabinoids) and topically applied CBMs (comprising cannabidiol), respectively. As symptomatic treatment for EB is often inadequate, there there is an imperative to investigate novel or repurposed treatments, such as CBMs – and objectively scrutinize the role they may play in the treatment of the symptoms affecting daily life in EB. A collaboration between the Stanford (US) and Groningen (NL) EB centers will collect international data on the use of CBMs in EB in order to identify research avenues. The Groningen EB center, after being awarded a DEBRA grant, will investigate a sublingually administered CBM-oil in the setting of

a controlled clinical trial with the aim to objectify its effect on quality of life in patients with EB.

OP70
SECONDARY SMALL FIBRE NEUROPATHY IN RDEB

Margarita Calvo, MD, MSc, PhD
Pontificia Universidad Catolica de Chile

Skin innervation consists of large diameter/highly myelinated fibres that innervate mechanosensors in the dermis, and small/unmyelinated fibres that cross the dermo-epidermal border and transduce pain from the epidermis. We recently showed that RDEB patients have a decreased epidermal innervation that leads to neuropathic pain and itch (Brain 2017). In this study we aim to understand the mechanisms behind this RDEB-induced painful small fibre neuropathy with special emphasis on the role of neurotrophic factors in epidermal axonal regeneration after injury.
A 3mm punch biopsy was obtained at 10 days after skin lesion in RDEB adult patients and matched controls. Neurotrophins were investigated using qPCR and WB. Rat sensory neurons were grown *in vitro* at the same time as primary human keratinocytes from patients and controls. Conditioned media from the latest was tested for neurotrophin secretion after injury and were used to treat sensory neurons. Axon regeneration was measured. We found that there is an increase in NGF and GDNF transcripts in the skin of healthy volunteers after skin lesion, but this response is abolished in RDEB patients. We are confirming these results using ELISA. We also observed that primary keratinocytes from healthy volunteers secrete NGF after an *in vitro* scratch lesion but RDEB keratinocytes do not. Conditioned medium from primary keratinocytes from healthy volunteers induced an increase in axonal regeneration in rat sensory neurons, while conditioned medium from RDEB keratinocytes was unable to induce axonal regeneration. In summary, after skin lesion, epidermal axons are severed and suffer degeneration. The skin of healthy volunteers was shown to secrete neurotrophic factors that induces nerve regeneration. However, keratinocytes from RDEB patients do not secrete these neurotrophins and their intraepidermal axons do not regenerate following skin damage. Investigating the role of neurotrophins in axonal regeneration after skin damage will allow us to identify targets for treatment of small fibre neuropathy in RDEB patients which will hopefully lead to a relief in neuropathic pain symptoms.

OP71
PREVENTION AND TREATMENT OF PAIN

Boris Zernikow
Children`s Pain Therapy and Paediatric Palliative Care Witten/Herdecke University, Faculty of Health, School of Medicine, Germany

Pain in Epidermolysis bullosa (EB) is caused by the disease itself, its treatment and various medical procedures.
Especially the daily dressing change is highly bothersome for the children. The use of dressing materials in the context of a dressing change and the use of psychological technics to support the child are key issue for parents and affected children. Several education materials have been developed to support parents. An education movie with English subtitles (Movie with English subtitles (https://www.deutsches-kinderschmerzzentrum.de/en/eb-video/) as well as other helpful information can be downloaded in German, English and Italian free of charge (https://kinderpalliativzentrum.de/downloads/). In the future those materials will be embedded into educational workshops and translated into other languages. Regarding the child's development, parents are continually confronted with new challenges and must adapt their old, or develop new, support strategies.

OP72
PRURITUS IN EPIDERMOLYSIS BULLOSA

Hagen Ott
Children's Hospital Auf der Bult, Hannover, Germany

Defined as the unpleasant sensation leading to the need to scratch, pruritus also occurs in patients with epidermolysis bullosa (EB) in whom it has even been described as one of the most bothersome complications. In all EB subtypes, healing wounds and/or certain body sites such as the legs and feet are the itchiest affected areas. However, itch profiles differ significantly according to EB subtype. Whereas pruritus scores in EB simplex are mild to moderate in most patients, other forms of EB are associated with higher itch severity, frequency and duration. Of note, patients with recessive dystrophic EB seem to be most severely affected suffering from the highest itch burden. The pathophysiology of pruritus in EB is very complex mostly involving non-histaminergic and, far less frequently, histaminergic pathways. Additionally, EB pruritogenesis involves keratinocytes, immune cells, sensory nerves as well as spinal cord and brain cells. Their itch signals are transmitted by extensive tissue crosstalk through cytokines, neuropeptides, proteases and a multitude of other mediators. For decades, pruritus treatment in children and adults with EB has been performed with established or "historical" therapies also used in the context of other chronic pruritic diseases such as atopic dermatitis or prurigo (e. g. topical glucocorticosteroids, emollients, sedating or non-sedating oral antihistamines, gabapentinoids). However, novel therapeutic agents have been repurposed for itch treatment in EB patients with chronic pruritus. Apremilast, an oral phosphodiesterase-4 inhibitor licensed for treatment of psoriasis, has recently been shown to alleviate inflammatory pruritus in generalized severe EB simplex. Moreover, a humanized monoclonal IgG4 antibody (Dupilumab) approved for subcutaneous treatment of atopic dermatitis, has successfully been used to reduce itch and prurigo-like skin lesions in dystrophic EB pruriginosa. Likewise, the oral Neurokinin-1 receptor antagonist Serlopitant has been investigated in a first randomized trial revealing small, but clinically relevant effects on itch severity and a good safety profile in patients with dystrophic EB. Finally, the oral μ-opioid receptor antagonist Naltrexone, previously used off-label in cholestatic and uremic pruritus, has been reported to reduce pruritus and pruritic skin lesions in an adult with dystrophic EB pruriginosa. In summary, pruritus represents a still undertreated, yet highly significant complication in all EB subtypes. While established therapeutic strategies are known to have little impact on itch intensity and pruritic skin lesions, novel and promising therapeutic agents have been used in preliminary case studies or small clinical trials. Hence, further controlled investigations of these agents including sizeable patient numbers are urgently needed.

OP73
MULTIDISCIPLINARY TEAM BEST PRACTICE (GSTT) RARE DISEASE CENTRE

Jemima Mellerio
St John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust, London

Guy's and St Thomas' NHS Foundation Trust has hosted an adult EB service for many years. Funded by the National Health Service as one of 2 adult EB centres in England, it provides multidisciplinary (MD) care for individuals with all forms of EB in both outpatient and inpatient settings. Historically, there were challenges around providing care for a large EB cohort (currently c. 480 patients) with very variable clinical needs; clinics had been hosted in many different areas throughout the hospital without a dedicated space specifically designed for the

needs of people with EB in mind. Conceived initially in 2009, the idea of specific clinical space for the GSTT EB service took many years and various iterations before funding was secured, a space identified and refurbishment completed. Joining forces with other rare disease services meant that the project was feasible and deliverable economically and in terms of maximising clinical space, as well as enabling a combined sense of purpose between services with many commonalities. Patient engagement was a key element in the design of the space with practical considerations for all stakeholder groups. An emphasis on making the space as relaxing and non-clinical as possible, also highlighting the need to be able to socialise with others was key. A garden providing a calm, contemplative space for patients and carers has been central to this concept. In November 2017, the Rare Diseases Centre, the first of its kind for adults and children in the UK, opened its doors to the adult EB service. The RDC has enabled great flexibility in the types of clinics that run, depending on patient need and the different specialists that need to be seen. Full MD and mini-MD clinics run monthly for individuals with the highest level of need, enabling access to the full MD team in one clinic with biopsies, blood tests, infusions and other tests available as a one stop shop. For those with less complex needs, a monthly outpatient clinic sees 30-40 patients each clinic, with additional nurse-led clinics running weekly. Moving to the RDC has led to weekly EB podiatry clinics and newly established Skype clinics to save on patient travel. Ad hoc reviews are an essential part of the service, especially for biopsies of potential skin cancers without delay. Establishing a bespoke centre for the care of individuals with rare, lifelong, complex medical conditions such as EB can present many challenges. However, taking opportunities to join forces with other similar services, patient engagement from the outset, and clinic design that is flexible around patient need with the provision of a one stop shop experience where possible are key.

OP74
MANAGING EB IN A RESOURCE LIMITED SETTING

Ravi Hiremagalore
Centre for Human Genetics, Manipal Hospital, Bangalore

Epidermolysis bullosa is common in India. However, population heterogeneity, huge land area and limited funding for rare diseases by the government poses great challenges in providing care for these patients. The journey began with referrals from individual doctors and adhoc patient care to multi-disciplinary clinics with a focus on establishing diagnosis on the subtype of EB and wound care management. Approach to diagnosis was targeted based on the immunofluorescence antigen mapping findings and then genetic testing. This approach costed about $250, which is a reduction of cost by 50 percent. Wound care management was based on a cafeteria approach. We distributed EB kits with samples of available dressings and allowed the patients to choose the one that suited best. Likewise, we chose locally available materials for mouth opening issues and finger splinting. We created a hub-and-spokes model to reach out and reach far. The following link was periodically sent to pediatricians and dermatologists to seek referral. It is https://chgregistryapp.appspot.com/register/chg upon receipt of referral; our team would liaise with the referring clinician to conduct an EB clinic through telemedicine. This reduced the costs of travel to Bangalore for regular care. Crowd sourcing strategies was used to raise funds to specific interventions in individual patients. This is very useful where state funding and philanthropy are limited particularly in rare diseases like EB.

OP75
TELEMEDICINE

Danielle Greenblatt
St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

Telemedicine allows healthcare professionals to assess, diagnose and treat patients remotely, using telecommunications technology. Since the 1990's, this model of care has gradually gained pace, and is starting to transform the way in which many services are being delivered in the UK. Use of teledermatology in the management of EB presents a compelling format for improving access to specialist care, reducing patient travel times and delivering cost efficiencies for both patient and hospitals. We discuss our experience of running a live interactive video conferencing clinic in EB.

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OP76
EB-ASSOCIATED SCC: THE JEFFERSON ADULT EB AND COMPLEX SKIN CANCER CLINIC

Bahar Dasgeb
Thomas Jefferson University, Philadelphia, USA

No abstract supplied

OP77
EDUCATION PROGRAMMES

Christine Bodemer
Department of Dermatology, French national centre for genodermatoses (MAGEC), Hôpital Necker-Enfants Malades, Paris France

Therapeutic Patient Education (TPE) enables people with chronic diseases to manage their illness and yields benefits in both health and financial terms (World Health Organization). In our centre for EB patients, we take care of patients from birth until Adult period. More than 400 EB patients are regularly manage. The birth of an EB neonate is an intense familial traumatism, "a true tsunami. In our experience, TPE is the most rigorous and efficient strategy to help the patients to live and not only to survive with their EB. TPE objectives are to: - permit a sustainable improvement of the quality of life, the autonomy, the understanding of therapeutic recommendations; -avoid/decrease relapses and complications, with a constant patient-based approach (how to do (cognitive dimension), how to be (emotional dimension). TPE is also a synergistic and reciprocal education between caregivers and patients/families. The tasks for the health care providers are to understand: the disease, the patient, and also the person with his (her) own familial, sociocultural, emotional characteristics. TPE needs are: 1- team trained in TPE; 2-a concise program; 3-educational tools, adapted to each period of life. In our centre (MAGEC-Necker), a multi professional team (11 medical and paramedical staff members) graduated in TPE since 2009, has set up a concise program for EB patients , certified by the Health Ministry, with an involvement of patients. The program includes 4 steps: -Step 1: the educational diagnosis for each patient: it means with the help of a questionnaire to analyse for each patient: needs, expectations, daily life, psychosocial environment; -Step 2: a patient centred approach. It means to list all the competencies that have to be mastered for: the best self-management, prevention

of avoidable complications, secure lifestyle, organized awareness for a psychosocial adaptation; -Step3: implementation of a practical TPE program for each patient. 12 sessions (1hour session) are offered: -2 concerns the skin, the EB forms, the genetic, -8 to 10 concern the wounds and nursing, -2 concern the systemic involvement; Step 4: the evaluation of the acquired competencies. The objective is to adjust the program on the basis of continuous assessment. Education tools have been created adapted to each group of ages. In our experience, TPE is a gradual experience: the trust between patients/families and caregivers is strengthened; the context of a program encourages speech, allows a break in isolation with a mutual aid; the design of a collective tool covering all areas of the patients' experience and, therefore, all the necessary multidisciplinary medical and paramedical management, has led the care providers to "educate" themselves in the techniques and expectations of their colleagues and to better understand the disease in all its dimensions.

OP78
INTERNATIONAL EB REGISTRY

Godfrey Fletcher
National & International Skin Registry Solutions CLG

The concept of an International EB Registry has been under discussion for a number of years. The "State of Play" document has been updated and is available from Debra International. Output from initial meetings in Dublin (2016) and Salzburg (2017) resulted in a minimal common dataset and the formation of a Registry Committee. A registry needs to be sustainable, it requires funding that covers the platform development and ongoing maintenance and operational costs. Due to the lack of funding, Ireland will make the core technology that they have developed for their own National Registry available to other countries and available as the core technology for the International Registry. This will save considerable development costs. Localisation costs would have to be carried by each centre wishing to take advantage of this offer. Actions: Convene a meeting of the International Registry Executive Committee with the following agenda items to be agreed upon: 1) Finalise the minimal dataset that is feasible to be collected from each of the participating centres. 2) Undertake a data harmonisation exercise for each of the agreed variables. If definitions are not agreed then the output from any analysis of a common international dataset would be meaningless. 3) GDPR compliance. 4) Development of Standard Operating Procedures for the input of data and transfer of data to the International Registry.

OP79
INNOVATION IN PATIENT DATA PLATFORMS

Michael Hund
EB Research Partnership, New York, USA

No abstract supplied

OP80
A POTENTIAL NEW THERAPEUTIC APPROACH TARGETING WOUND INFECTION – DISRUPTING BACTERIAL COMMUNICATION

Erik Gerner
Department of Biomaterials, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg & Mölnlycke Health Care AB

Chronic EB wounds are generally colonized by microorganisms and suffers from a high pro-inflammatory status. Infections of EB wounds are typically treated with antibiotics. However, due to the ever-increasing problem of antibiotic resistance, alternative treatment strategies are urgently called for. Interfering with the bacterial communication system (quorum sensing, QS), which is important for the overall pathogenicity/virulence of the bacteria, has been proposed as an alternative option. The target of such treatment is to make bacteria less pathogenic allowing the immune system to better perform its role in clearing or preventing the infection. The aim of this study was to *in vitro* evaluate the activity of sodium salicylate (NaSa) as a QS inhibitor to be used in the prevention or treatment of wounds infected by Pseudomonas aeruginosa. It was found that NaSa effectively interfered to a different extent with three interconnected QS systems in P. aeruginosa, each regulating a subset of important virulence factors. Treatment with NaSa resulted in reduced levels of the toxin pyocyanin and iron-binding siderophores, both important factors in persistent wound infections, without inhibiting bacterial growth. Supernatants from bacterial cultures with NaSa were not toxic towards human dermal fibroblasts, whereas the opposite was seen for cultures without NaSa. Addition of NaSa to differentiated and lipopolysaccharide-stimulated monocytes resulted in decreased NF-κB activity. This work presents the proof-of-concept on NaSa anti-QS activity, resulting in less bacterial toxin production, improved fibroblast survival and reduced activity of the pro-inflammatory transcription factor NF-κB, which encourages further evaluation of NaSa as an anti-infectious agent using *in vivo* infection models.

OP81
DEVELOPMENT OF TWO TOPICAL APPROACHES TO WOUND HEALING IN EB – AN UPDATE ON PROGRESS WITH OLEOGEL-S10 AND AP103

Mark Sumeray
Amryt Pharmaceuticals DAC, Dublin, Ireland

Birch bark has long been known to have wound healing properties. Oleogel-S10 (AP101) is a specially formulated gel preparation of sunflower oil with triterpene extract (TE) from birch bark consisting of betulin (72%–88%), betulinic acid, lupeol, oleanolic acid and erythrodiol. Amryt Pharma is developing this gel as a potential treatment for epidermolysis bullosa. The mode of action is under investigation, but the extract is already known to have activities that cause transient upregulation of inflammatory mediators important to the wound healing process. These include Interleukin (IL) 6, IL-8 and cyclooxygenase. In addition, TE promotes keratinocyte migration via Rho-activated kinases, and keratinocyte differentiation into terminal phase skin cells via upregulation of involucrin, keratin 10 and transglutaminases. Clinical studies of Oleogel-S10 have shown accelerated wound healing in patients with split-thickness graft wounds and burns. Oleogel-S10 has been studied in an initial proof-of-concept study in EB (Schwieger-Briel 2017) and is being assessed in the largest global phase III study in ~250 EB patients (with junctional, dystrophic EB and kindler syndrome), known as EASE (EudraCT No. 2016-002066-32; NCT 03068780). Expectations are that EASE will provide efficacy data in 2020. Amryt Pharma is also investigating a non-viral gene therapy, AP103, for the treatment of recessive dystrophic epidermolysis bullosa. AP103 enables skin cells to express fully functional type VII collagen via topical applications. AP103 has potential as a therapy for recessive dystrophic epidermolysis bullosa were there is a mutation in COL7A1. Oleogel-S10 and AP103 are the cornerstones of the commitment of Amryt Pharma to the development of new treatments for EB. Amryt Pharma are aiming to develop a range of treatments not only to help manage EB but also address the underlying cause in the hope of a potential cure.

OP82
THE IMPACT OF ANTIMICROBIAL RESISTANCE ON TOPICAL WOUND TREATMENT SELECTION

Gilles Brackman
Flen Health

In all forms of EB, skin fragility may result in bacterial colonisation which can negatively impact wound-healing, the quality

of life and result in increased healthcare costs. When managing infected wounds and wounds at risk of infection, attention needs to be given to the potential of antimicrobial resistance (AMR) development. In this study, we investigated the potential of AMR development towards a patented antimicrobial enzyme-system consisting of glucose-oxidase, lactoperoxidase and guaiacol applying different microbiological, phenotypic and genomic analysis. In contrast to what is observed for e.g. Silver nanoparticles, no changes in susceptibility were observed in any of the micro-organisms when exposed to sub-optimal concentrations of the antimicrobial enzyme-system. No changes in MIC, MBC or in the number of persister cells were observed during any of the >50 cycles. Additionally, no significant phenotypic changes were expected to be observed between populations exposed to one or repeated treatments with the antimicrobial enzyme-system. Defining a rational use of systemic and topical antimicrobials is an important tool to limit and control the development of microbial resistance in wound care. All systemic and topical antimicrobial agents used in wound care should be assessed at an early stage for their potential for selection of resistance. Our results indicate that pathogens commonly reported to infect wounds do not evolve resistance towards the antimicrobial enzyme-system consisting of glucose-oxidase, lactoperoxidase and guaiacol.

0P83
THE ROLE OF HYDROFIBER® DRESSINGS IN EB WOUND MANAGEMENT

Rachel Torkington-Stokes
ConvaTec, UK

Wound management in EB is complex as it is influenced by multiple co morbidities (underlying genetic defect, poor nutritional status, anaemia, pain and pruritus…) and the fragility of the skin. Dressing management is specific to the type of EB, presence of infection or critical colonisation, levels of exudate, availability of products and personal preference[1]. Where do Hydrofiber® dressings fit? Denyier[1] offers general guidance of selection of the correct dressing for management of EB wounds. The 4 key attributes are protecting the peri-wound skin, avoiding skin stripping, addressing the bio-burden and exudate management. To meet this challenge, wound dressings need to be underpinned by a well-constructed and responsive technology. Hydrofiber® Technology is derived from a high purity cellulose and is found in the AQUACEL® family of dressings. Ability of Hydrofiber® dressings to 'lock in', 'contour' & 'respond' offers optimal wound management and patient benefits. 'Locks in' is the ability of the dressing to absorb and most importantly retain wound fluid/exudate. As the fibers swell the fluid and its contents (bacteria, inflammatory cells and enzymes), are trapped and held within the dressing. This bacteriostatic action stops bacteria from reproducing. Hydrofiber® dressings with silver are bacteriocidal thus not only inhibit reproduction but kill bacteria locked within the dressing. This Technology not only supports management of the bio-burden but by retaining the fluid in the dressing also reduces the risk of periwound maceration. Hydrofiber® Technology has the ability to closely 'micro-contour' to the wound bed. This means that there is no or very little dead space between the wound surface and the dressing where fluid may accumulate and bacteria may proliferate, again supporting optimal management of the bio-burden. Characteristics of Hydrofiber® to 'respond' to wound conditions initiates the formation of a cohesive gel. The gel helps maintains a moist wound environment, aids autolytic debridement and supports the healing process without damaging newly formed tissue, hence avoiding skin stripping.As is widely accepted, the type of EB dictates skin and wound care. Several case reports were presented to illustrate the wound and patient benefits Hydrofiber® Technology can offer.

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OP84
DEBRAS AROUND THE WORLD – A 40-YEAR HISTORY

Evanina Morcillo Makow
DEBRA, Spain

In 1963, a girl called Debra, with EB, was born. Little was known about EB; Her mum, Phyllis, was told that there was nothing that could be done for Debra and to take her home and look after her until she died. Phyllis ignored this advice and instead looked for ways to treat Debra's skin using cotton dressings. Years later, in 1978, when Debra was 15, her mum Phyllis was contacted by a woman who wanted help and advice following the birth of her baby who had been born with EB. Phyllis was shocked and saddened that nothing had changed in 15 years – and nothing would unless she and other parents took action. Phyllis wrote to magazines, radio stations, celebrities, and hospitals to organise the first meeting for parents of children with EB. 78 people attended the meeting, which was held in Manchester. This was a meeting that led to DEBRA UK being formed – the world's first EB patient support group. Sadly, on the 21st of November 1978, the year the charity was founded, Debra passed away. The original aims of the charity were to stimulate knowledge of, and interest in, EB for the benefit of those with the condition and their families, and to fund medical research into EB. From those humble, brave and inspirational origins, DEBRA has grown significantly and is now international in scope. Over the past 40 plus years, we have seen the establishment of more than 50 national groups in countries around the world. Europe, North America, and Australasia have been well represented since the 1980s and 1990s. The 2000s and 2010s saw an increasing number of DEBRAs established throughout Asia, and Central and South America. With an average of one new group established per year, we look forward to seeing what this new decade, and indeed the next 40 years, holds for the development of the international DEBRA group network.

OP85
DEBRA INTERNATIONAL/ CO-ORDINATION AND COLLABORATION

Brett Kopelan/Jimmy Fearon
Debra of America, New York, USA

No abstract supplied

OP86
RESEARCH UPDATE (CELL THERAPY)

Su Lwin
King's College London, UK

No abstract supplied

OP87
RESEARCH UPDATE (GENE AND PROTEIN)

M. Peter Marinkovich
Department of Dermatology and Program in Epithelial Biology, Stanford University School of Medicine, Stanford CA USA

Our group has been active in studying a group of early phase clinical trials employing several promising new techniques in the molecular correction of RDEB. In total 26 RDEB patients have been treated with gene therapy at Stanford so far, including 7 pediatric patients. 7 adults have been treated with *ex vivo* COL7A1 treated autologous epidermal monolayer grafts (6 grafts per patient=42 grafts total). 5 adults and one pediatric patient have been treated with *ex vivo* COL7A1 treated autologous

fibroblasts which are injected into both intact skin and chronic wounds. The advantages of *ex vivo* gene therapies are that they have demonstrated the longest track record of efficacy and safety and studies are now entering pivotal phase 3 trials. Drawbacks include a theoretical risk of insertional oncogenesis due to the vectors that are employed, however having the gene transfer occur *ex vivo* limits the systemic risk of this and no cancers have yet been detected. In addition, each approach requires a manufacturing run on each patient, applications to patients requires hospitalization including placement either in operating room or day procedure unit, and the timing of shipping and cell production needs to be tightly coordinated. An alternative approach is *in vivo* COL7A1 gene therapy for RDEB. Stanford has participated in two such approaches. The first involves a topical gel containing oligonucleotides which act at the RNA level to induce exon 73 skipping, and production of a slightly truncated by still functional collagen VII protein. In this approach, 4 patients have been treated, 3 at Stanford, including 2 pediatric and two adult patients. The other approach involves a topical gel containing a replication incompetent HSV-1 - COL7A1 vector (B-VEC) which has been used in 10 patients, 4 of which are pediatric. While the exon skipping data are still blinded and unavailable, interim reports of the B-VEC therapy indicates robust molecular correction, positive effects on durable wound healing without safety issues even upon repeated reapplication. Disadvantages of the *in vivo* approach would be that while the risk of insertional oncogenesis is not present, these therapies would theoretically not be expected to be as durable as the *ex vivo* therapies described above. Advantages would be ease of application as a wound dressing gel, ultimately in a home setting, as well as off the shelf shipping of the products without the need for biopsies, with the potential to reach many RDEB patients worldwide who do not have access to specialized settings. The B-VEC therapy is also approaching the pivotal phase 3 clinical trials stage. In total, the progress with gene therapy of RDEB has been fast paced and exciting, and will continue to pick up speed in the near future with groups in europe entering new trials, including one in France who will be employed gene corrected epidermal and fibroblast autologous skin equivalents, and a group in Italy/Austria who are building on progress from JEB epidermal autografts achieved in recent years. It is quite possible that these *ex vivo* and *in vivo* gene therapies may be complementary or synergistic, however this remains to be tested. In addition, exciting new developments are occurring in the area of protein therapy for RDEB. Currently a phase 1/2 trial of intravenous delivery of purified collagen VII to RDEB patients is taking place with several patients now being dosed and studied for safety, molecular correction, and well as wound healing at Stanford University, with other sites expected to participate in the near future. Results are currently blinded/ unavailable and studies are still ongoing.

OP88
CANCER AND CANCER THERAPEUTICS

Jemima Mellerio
St John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust, London

Epidermolysis bullosa (EB), notably generalised severe recessive dystrophic EB (GS-RDEB), is associated with the development of mucocutaneous squamous cell carcinomas (SCCs). In GS-RDEB, patients develop cancers from adolescence or early adulthood and often get multiple primaries. Tumours behave aggressively and arise predominantly at sites of repeated trauma, wounding and scarring. SCC is the leading cause of death in this form of EB with a median survival from diagnosis of first SCC of 2.5-5 years (Fine et al. 2009; Kim et al 2018). Current treatments often have limited benefit and highlight a desperate need for improved therapies; recent research into the pathogenesis of these cancers is identifying potential areas for targeted treatment. Genetic analysis has demonstrated that genes mutated in RDEB and ultraviolet (UV)-induced SCCs in non-EB patients are essentially the same e.g. HRAS, NOTCH1, CDKN2A, TP53 (SansDeSanNicolas et al. 2018). However, whereas UV-associated SCCs carry a high UV mutation signature, this is much lower in GS-RDEB cancers. In contrast, in GS-RDEB tumours, there is a high level of APOBEC enzyme signature mutations not seen in UV SCCs (Cho et al. 2018). Interestingly, APOBEC genes are upregulated in inflamed tissue surrounding EB SCCs (Cho et al. 2018). In RDEB, pro-inflammatory cytokines and growth factors drive dermal fibroblasts to a myofibroblast-like phenotype with a transcriptome similar to cancer-activated fibroblasts in UV-associated SCCs, which increases extracellular matrix stiffness and may provoke a stroma-led predisposition to SCC in EB (Guerra et al. 2017). Loss of collagen VII releases thrombospondin which in turn increases TGF-b levels, and decorin, an endogenous inhibitor of TGF-b, is reduced in RDEB mouse models and also correlated inversely with clinical severity in RDEB patients (Odorisio et al 2014; Anatosova et al 2019; Cianfarani et al 2019). Recent research has also identified specific miRNAs which are upregulated in RDEB and have a pro-fibrotic effect (Condorelli et al 2019). Inflammation in GS-RDEB correlates with disease severity. Interleukin 6 (IL-6), in particular, has been identified as having a role in other fibrotic diseases, and is elevated in collage VII null mice and RDEB patients (Esposito et al 2016; Liao et al 2018). It is also related to aggressiveness and metastatic potential in other cancer types, so may also contribute to the behaviour of EB-associated SCCs. Microbial colonisation has also been highlighted as a contributor to EB SCC development (Hoste et al 2015). Toll-like receptor-5 (TLR-5) is a receptor for bacterial flagellin which may have a direct and indirect role in RDEB SCCs. Loss of collagen VII in the spleen and lymph nodes leads to increased bacterial bioburden in RDEB through abolition of macrophage and neutrophil mobilisation via cochlin processing, which may contribute to the increased microbial colonisation been in RDEB, leading further to SCC predisposition (Nyström et al 2018). The innate immune system has also been identified as a potential factor in EB SCC development; RDEB SCCs show upregulation of complement 1s and 1r, with knockdown of both in SCCs showing reduced cell viability and increased apoptosis (Riihilä et al 2019). Current treatment modalities for EB SCC include surgery, chemotherapy, radiotherapy and newer immunotherapy agents. Recent discoveries highlighted above, however, may provide potential new targets for EB cancer therapies. For example, drugs to target APOBEC enzymes, TGF-b, thrombospondin, IL-6, TLR5, miRNAs or complement may prove to be clinically relevant and useful against these aggressive and difficult to treat tumours.

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OP89
ADVANCES IN CLINICAL MANAGEMENT STRATEGIES

Anna E. Martinez
Great Ormond Street NHS Foundation Trust

Whilst it can sometimes feel like we have made little progress in the day to day management of patients with all types of EB,

reviewing the morbidity and mortality of children with RDEB from 2000 to 2020 shows an overall reduction in the burden of disease. Improvements in wound care have lead to a reduction in back ground chronic inflammation, the incidence of osteoporosis and vertebral fractures and anaemia. Young people with RDEB have better growth and ascertainment of puberty. The 4 phases of RDEB are still present but the gradient of the severity curve has reduced. Whilst intravenous anti-inflammatory therapies such as MSC's have some short-term benefit in children under 10 years with RDEB, their affects are much harder to detect in older children. In addition, there appears to be no reduction yet in the incidence squamous cell carcinoma in phase 4 of the disease. Perhaps this will be observed as the younger cohort transition into the adult services with better very early care.

OP90
BIOTECH COMMERCIAL DEVELOPMENT

Brett Kopelan
Debra of America, New York, USA

No abstract supplied

OP91
CLINICAL TRIALS EXPLAINED

Gabriela Petrof
Dermatology Department, Great Ormond street Hospital NHS Foundation Trust

Interventional medicinal clinical trials are complex and one can view their pathway as a maze with countless obstacles. Unfortunately, this can be true and regulatory bodies internationally have taken that on board and are working towards simplifying some of the rules which should hopefully reduce the cost as well. Clinical trials consist of three main parts. The first part is securing funding for the clinical trial. Over the years industry has shown major interest in EB and there are currently 90 studies worldwide in EB across all ages, 38 of which are commercially funded. This is compared to 16 registered trials, 3 of which were commercial studies back in 2010. The second part of a clinical trial is the design. The design depends on the question you want answered, if this is primarily safety or efficacy. When looking at efficacy, the gold-standard design is a double-blind, placebo-controlled clinical trial, but this is also one of the most challenging design for a trial in EB trials as it is in other rare diseases. The most popular model for drug approval in the EU is the decentralised route where manufacturers can apply simultaneously for approval in more than 1 EU member state. Finally selecting clinical trial endpoints poses great challenges and selecting the right ones could be the fine line between a successful trial and one which fails to meet its primary outcome. The most important component of a clinical trial after finding the money is finding the patients. As patients typically cannot participate in more than one study at the same time, the increase in the number of studies has resulted in some competition among studies for patients. The limited number of patients that can participate in studies present a significant challenge in carrying out clinical trials, and emerging clinical trials that require specific genetic mutations face an even greater challenge in recruiting patients. There is increasing interest in endpoints that refer to direct, clinically meaningful outcome measures that patients experience in their daily life. These are known as patient reported outcome measures and regulatory bodies acknowledge that and accept them as primary outcome. An interesting concept is also rather than listing outcome points when you may see improvement in one but no change in another, in a disease as heterogeneous as EB, is to define success and efficacy from the start giving an overall picture.

OP92
PATIENT AND PARENT PERSPECTIVES

Lena Riedl[1], Sharmila Collins[2]
[1]Salzburg, Austria, [2]Cure EB, London

Patient View: Lena Riedl

The biggest challenge I faced taking part in a clinical study was not things like giving skin or blood samples, travelling to the study side a lot of times – because I knew that I will have to do these things and I understood why it is important. But the hardest thing for me was going through this clinical study without any psychological help. Without anyone taking my hand, answering all the questions I had and also those I did not even know I had. I did not know what I was putting myself through. I did not know that even though I told myself, that this might not work, that this will not be the cure, that it is just a trial, I built up hopes and expectations. This was happening subconsciously. So, what I personally would have needed was someone to guide me through that whole process. Preparing me for it, helping me throughout the trial and also help me process after the study ended.

Parent View: Sharmila Collins

1. Potential benefits VS risks - before enrolling your child in a trial you will have to make an assessment of what the potential benefits could be against the risks of taking part. A more invasive therapy is likely to carry larger risks. It is important that you are happy that the potential benefit is worth it. With a small child these decisions will be made by parents. As a child gets older the potential risks can be discussed amongst you but always make sure you question the doctors in charge so that you fully understand the procedures that will be undertaken.
2. Learning about the trial-You will be given detailed information regarding the trial. If your child is old enough they will get a 'child's' version. Do make sure you read it carefully and ask questions if there are elements that you do not understand. Trials also often require extra blood tests and perhaps skin biopsies. These are often traumatic for small children in particular. Be prepared to ask about the frequency of these interventions to better prepare yourselves and your child.
3. Logistics - Participation in clinical trials is time consuming. There are many visits from assessing suitability to participate to follow up visits after the trial. Travelling to the centres also takes time and you may have to stay overnight for some. When you decide to participate make sure you know the commitment you are making both for your family and the trial sponsors.
4. Emotional Support- However practical you are, however much you try and minimise the hopes you attach to participating in a trial you may end up being disappointed which can have a big emotional toll on both yourself and your child. It is perhaps advisable to seek emotional support throughout the trial process. This might be best from a regular psychologist if your child has one. Someone who your child knows and is comfortable with and who can guide them through this extra stress.
5. Follow up - What happens now? The trial has ended and the treatment has helped. Is there an option to continue on the treatment or does it just stop whilst the analysis takes place? Some trials just stop and there is no opportunity to continue on the treatment. If there has been improvement but you know the effects will wear away in time it is very difficult to appreciate that you are likely to see a deterioration in your child's condition. Be prepared!

Last comment - It is wonderful that treatment trials are happening. Do try and participate because everyone leads to better understanding and gets us a little step further but make sure it is right for your child and your family before signing up.

OP93
CHALLENGES OF CLINICAL TRIAL DESIGN

Christine Prodinger
Paracelsus Medical University Salzburg, Austria

No abstract supplied

OP94
USING REGISTRIES & BIG DATA

Godfrey Fletcher
National & International Skin Registry Solutions CLG

Registry data can play a significant role in patient advocacy. Most governmental bodies have limited access to patient demographics particularly for patients with rare diseases. Registries can provide relevant data that can support the interaction between patients and their health providers when motivating for improved facilities and treatments. Registries can assist in the identification of patient cohorts suitable for clinical trials. This can have extra relevance when patients of a particular rare genotype can be identified across multiple countries. Once new drugs have been identified registries can support the Heath Technology Assessment process by providing the data required to support the cost and outcome benefits of new drugs or treatments. New high tech drugs are expensive so health bodies want to see improved patient outcomes for their investment and regulatory bodies such as the EMA require data to support Post Authorisation Safety Studies. International collaboration between national registries makes it possible to benchmark a country's outcomes against another country or against an International average. Registries can be used for Quality of Life studies particularly if a patient portal is deployed. When it comes to the sharing of international data, data harmonisation is vital. When undertaking an international collaboration of national registries focus on a minimal data set, "if you take care of the pennies the pounds will look after themselves"

OP95
QUALITY OF LIFE IN EPIDERMOLYSIS BULLOSA: PATIENT AND CLINICIAN WORKING TOGETHER

Natasha Harper[1] & Assya Shabir[2]
[1]Adult Epidermolysis Bullosa Service, University Hospitals Birmingham, [2]Patient

The World Health Organisation defines Quality of Life (QoL) as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Studies have shown that all types of Epidermolysis Bullosa (EB) have a significantly detrimental effect on QoL. Factors to be taken into account include pain, itch, mobility and other physical limitations, time needed for dressings, side-effects of medication, psychological symptoms, reproductive issues, social isolation, and difficult family relationships, amongst many others. There are four EB specialist centres in England and these clinics aim to provide multidisciplinary services which can help to improve many aspects of patients' QoL, including podiatry, dietetics, psychology, pain specialists, genetic testing, gastroenterology, liaison with dental teams, social work, and most importantly, dedicated nursing teams. However, EB is an extremely heterogenous group of conditions and therefore a highly individualised approach is essential. The most important aspect of clinical care is good communication between the patient and clinician in order to identify the key issues and priorities for that particular individual. The clinical team should be approachable, flexible and resourceful, and ensure that their service offers valuable, holistic support to all of their patients. Over time, an effective therapeutic relationship can be built, based on trust and respect, allowing the patients and clinicians to work together towards the common goal of improving patients' QoL.

OP96
FAMILY AND COMMUNITY

Brett Kopelan and Simone Bunting
Debra of America, New York, USA, DEBRA UK

No abstract supplied

OP97
EDUCATION AND FAMILY SUPPORT/CARE & SOCIAL SERVICES

Sam Geuens
University Hospital Leuven, Belgium

Epidermolysis Bullosa (EB) is a medical condition with an enormous impact on the psychosocial development of children who suffer from it. Because of this disease, they may struggle with a lot of issues during their childhood and adolescence. However, as for any child, it is important they can complete the different developmental stages of psychosocial development. The complex consequences of EB can put the achievement of every developmental goal under stress. Therefor it is important that psychosocial support can be implemented from a young age to guide the child into adulthood in different phases of development and different contexts. This presentation will address some topics that social services should focus on at home and at school. De diagnose of EB is for parents a really hard burden to deal with. This can have an enormous impact on their own wellbeing and psychological health. Beside those feelings, they have to cope with a great amount of care for their child. Wound care and a lot of practical issues are not the only issues. They can also be confronted with atypical and complex behaviour of their child. Raising a child with a severe chronical condition like EB can be very challenging. A healthcare professional with experience in EB can give advice during those difficult periods about how to handle behaviour during wound care or how to cope with an anxious child. Sometimes there can be a need for respite or extra help during a certain period. Social services should focus on how to support those families at any way and encourage and empower parents to take care of themselves.

Going to school is from great importance for every child, so also a child with EB. It doesn't only serve academic achievement, but it is also a place where children can experiment with social skills, meet friends and explore the world. However, there can be a lot of barriers for children with EB to attend school. Social support can help to prevent or to tackle these barriers and make it possible for a child to attend school as frequent as possible. Psychosocial support and social services should work together with parents in order to optimize psychosocial development in a child with EB.

OP98
CLINICAL PRACTICE GUIDELINES, PATIENT VERSIONS, AND EB INFOGRAPHICS UPDATES

Kattya Mayre-Chilton
DEBRA International CPG Coordinator

DEBRA International is undertaking a long-term initiative to develop clinical practice guidelines (CPG) for Epidermolysis bullosa (EB) in order to improve the clinical care of people with the condition. The CPG development cycle requires a dissemination and implementation stage, the patient versions (PVs) support this stage thus improving healthcare. To ensure that key recommendations remain consistent in all settings and to help patients to participate more actively in their care no matter where they live, DI's EBWB team have been developing EB infographics; a visual summaries of the CPGs. Although an unusual undertaking for a patient organisation, it is unlikely that CPGs, PVs, or EB infographics would have been developed without the drive of patients. The composition of the working panels and support teams are recruited from the DI CPG network (N = 340+). This network

of international EB clinical and social experts, researchers and people living with EB volunteer their time, knowledge, expertise and experiences to develop the following project. In 2019 DI completed five CPGs in the clinical fields of "laboratory diagnosis", "podiatry", "constipation", "psychosocial", and "occupational therapy"; four were published open access. We received seven CPG applications and five have been awarded funding and are ready to start: "neonatal care", "palliative care", "enteral and parenteral nutrition", "transition", and "anaesthesia and clinical procedures". In 2020 we expect six CPGs to be published and PVs developed in the areas of "physiotherapy", "sexuality", "anaemia", "hand surgery and hand therapy", and "pregnancy, childbirth and aftercare". Since 2018, the development of eleven PVs of CPGs recently published was undertaken with the aim to launch in 2020. The clinical areas were "laboratory diagnosis", "podiatry", "fundamentals of wound care", "psychosocial" and "occupational therapy". All will be available for free downloads from the DEBRA International website. Since 2017, eight EB infographic booklets are planned. In 2019, "The Health Body and Skin: EB Infographics" was clinically piloted and direct patient feedback was obtained. These booklets, to support people living in low resource countries, are aimed for full international launch in 2020. The project far exceeded its initial goals and over its course considerable steps were taken to progress and strengthen plans for many individual CPGs, PVs, and EB infographics for different aspects of EB clinical care.

OP99
THE IMPORTANCE OF EXERCISE IN EB

Amy Price
EB patient, UK

No abstract supplied

OP100
OCCUPATIONAL THERAPY IN EB

Jennifer Chan
Lucile Packard Childrens Hospital Palo Alto, California, USA

Historically occupational therapy (OT) practice for persons with EB has been based on anecdotal care, clinical expertise and trial and error with collaboration between caregiver and patient. Intervention based on research has been needed to establish a foundation of knowledge to guide practitioners. In 2016, an international panel of 11 members was co-ordinated through DEBRA International with the goal of creating a clinical practice guideline for OT. In 2017, a scoping survey was created and focused on topics relevant to OTs working with patients with EB in an effort to prioritize the outcomes. Five outcomes were determined by survey of persons with EB, caregivers, and experienced healthcare professionals. The outcomes include independence in activities of daily living, independence in instrumental ADL, maximization of hand function (non-surgical), fine motor development and retention, and oral feeding skills. Literature was gathered using a systematic format. The search identified 70 articles, of these 56 articles were specific to the EB population. Articles were appraised by the panel using standardized methodology. Post appraisal 27 articles were chosen for the final recommendations. Additional files by expert panel members were added to supplement the recommendations to further guide practitioners. Occupational therapy for epidermolysis bullosa: clinical practice guidelines was published by Orphanet Journal of Rare Diseases, https://doi.org/10.1186/s13023-019-1059-8, (2019)14:129. Direct link: https://rdcu.be/bFQ4c. It is anticipated that a literature search for new evidence pertaining to the provision of OT in EB will be undertaken every 3–5 years after publication in order to update the guidelines. There are limitations of high quality evidence based literature in patients with EB, requiring OT services. These guidelines also serve to reveal areas needing further research.

OP101
PSYCHOSOCIAL GUIDELINES

Petra de Graaf
UMCG Netherlands

Epidermolysis Bullosa (EB) is a group of rare genetic disorders resulting in skin fragility and other symptoms. Commissioned by DEBRA International and funded by DEBRA Norway, evidence-based guideline has been made to provide recommendations to optimise psychosocial wellbeing in EB. An international multidisciplinary panel of social and health care professionals (HCP) and people living with EB was formed. A systematic international literature review was conducted by the panel following the Scottish Intercollegiate Guidelines Network (SIGN) methodology. The resulting papers underwent systematic selection and critique processes. Included papers were allocated to 6 different outcome groups to allow data synthesis and exploration: quality of life, coping, family, wellbeing, access to HCP and pain. Based on the evidence in those papers, recommendations were made for individuals living with EB, family and caregivers and HCP working in the field. General recommendations can be made. People and families living with EB need access to multidisciplinary support, including psychological guidance, in order to improve quality of life and psychosocial wellbeing. Interventions should stimulate social participation to prevent isolation. People with EB and their families should be able to access a supportive network. HCP should be well supported and educated about the complexity of EB. They should work collaboratively with those around the individual with EB to provide psychosocial opportunity and care. Directions for research are indicated.

OP102
EB AND PREGNANCY

Danielle Greenblatt
St John's Institute of Dermatology, St Thomas' Hospital, London

We report on the development of clinical guidelines in pregnancy, childbirth and aftercare in the context of EB. This domain has received little attention in the medical literature to date and this work intends to address a gap in expert consensus and evidence-based recommendations. We discuss the results of a systematic literature review and how this may translate into concise and patient-centred recommendations for women living with EB as well as healthcare professionals internationally.

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OP103
NUTRITION IN EPIDERMOLYSIS BULLOSA

Lynne Hubbard
St Thomas' Hospital, London

To optimise nutritional intake we need to identify with the patient what are the barriers to eating which may be physiological e.g. oesophageal stricture, constipation, blistered mouth, painful dental caries or psychological e.g. reduced pleasure from eating as eating alone, eating different things to peers, taking too long to eat. Wherever possible we need to find solutions for these barriers. Part of the consultation needs to be educational so patients become experts in the role of different nutrients in optimising their health.

It is well understood that for those with severe types of EB and large wounds a diet high in energy, protein, vitamins and minerals is needed. Of equal importance is considering bone health. Optimising calcium, vitamin D, protein, mobility, attaining puberty and achieving a BMI above 18.5kg/m^2 can lead to improvements in bone density in people with EB reducing the risk of fracture in spite of inflammation. Wider research into the role of vitamin D shows it is important in muscle strength, inflammation and immunity. All patients with EB are at risk of low vitamin D as they often cover their skin reducing synthesis from sunlight. Correction using soluble vitamin D or sprays has proved to be effective and acceptable to patients with swallowing problems. Anaemia is a common problem in EB. If the cause is dietary then advice on soft foods high in iron can be given or soluble iron. However iron medication can result in constipation and the anaemia of chronic inflammation may not be responsive to oral iron. Under these circumstances the use of Ferinject (ferric carboxymaltose) intravenously has been found to be an effective treatment. Gastrostomy placement can be helpful if a patient : has faltering growth, oral supplementation has been tried and failed, puberty may be jeopardised, has intractable painful defaecation, refuses all oral medication or the child and family have become intolerably stressed at meal times. However it needs to be performed in a centre with experience of gastrostomy tube placement ideally using a laparascopic technique. It needs to be fully consentual even if this discussion takes time. Many patients are on multiple medications to treat pain, reflux or infections. This can become a burden and side effects versus the benefits need to be considered e.g. iron and opiates result in constipation, Pregabalin can cause weight gain, proton pump inhibitors can reduce absorption of iron and calcium. We also need to consider offering weight management support to adults with EBS where mobility can be reduced due to hyperkeratosis, blistering and pain. In conclusion by working with a person who has EB to set joint goals it is possible to optimise nutrition, enjoy eating as a social activity and this can contribute to quality of life.

OP104
ORAL HEALTH (CLINICAL GUIDELINE IN EB)

Susanne Marie Krämer
Special Care Dentistry Unit, Faculty of Dentistry, Universidad de Chile, Santiago, Chile

Since the publication of the first Clinical Practice Guideline (CPG) on Oral Health Care for individuals with Epidermolysis Bullosa (EB) in 2012, new evidence has been published, patients' priorities have changed, and the methodologies have been updated. It became necessary to update the guideline considering emerging topics. The original Oral Health CPG is now divided into a series of three sections focused on:

1. Oral health care in EB. This section follows a standard methodology based on a systematic review. The consensus recommendations developed by an international panel of 33 volunteers from 13 countries. It highlights the importance of early referral to the dentist, and the establishment of a preventive protocol with continuous follow up.
2. Dental implants in patients with recessive dystrophic EB (RDEB). This section follows a standard methodology based on GRADE methodology with 24 PICO questions. This was developed by an international panel of 24 volunteers from 10 countries. It provides guidance on techniques, and highlights the impact of a successful implant based oral rehabilitation on the patient's quality of life.
3. Sedation and anaesthesia for patients with EB undergoing dental treatment. This section was developed by an international panel of 25 volunteers from 11 countries. It will assist clinicians in managing the challenges of skin fragility before, during and after surgery based on available evidence and expert consensus. Furthermore, this section considers the different stages of patient preparation and details a list of non-adhesive wound care products that will aid patients care.

As EB is a rare disease, international collaboration among reference centers is key for improving the care of patients with this skin condition. The new guidelines will be published in the next few months.

POSTERS

P1
A RARE CASE OF RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA AND TYPE 1 DIABETES

K.E. Plevey, G. Petrof, A.E. Martinez
Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

Introduction and objectives: *Case report - please see results. Materials & methods:* Case report - please see results. *Results:* Symptoms of type 1 diabetes are normally recognisable in well children. However, children with RDEB are likely to already present with: Poor weight gain; Irritability/Fatigue; Delayed wound healing. Therefore the signs are easily missed. This case study demonstrates an 11 year old girl with severe RDEB, who developed Type 1 diabetes in 2018. She presented with abdominal pain (common in EB) at her local hospital and was found to be in DKA. Problems have since arose with monitoring blood sugar levels, administering Novo rapid and securing her Libra pump – due to extensive skin fragility/poor wound healing. Previously she preferred to graze, rather than eat full meals. Previously also required an overnight feed. This has been adjusted under the advice of the endocrinology team with support from EB dietetics to avoid sugar hits, however to promote effective weight gain. 1. DKA corrected locally with administration of IV fluids. Bowels opened once electrolytes stable. 2. BMs originally obtained via ears as fingers/ heels severely affected. 3. LIBRA pump fixed to right arm (on unaffected skin) Standard EB dressing not used due to the importance of staying in place. Advised how to remove safely with SMARs. 4. Effective dietetic plan – stop overnight feed. Bolus feeds given at mealtimes if patient unable to eat. Insulin given at these times. Low carb snacks introduced (such as cheese or yoghurt) 2 daily. 5. 2 monthly home visits from CNS/joint Endo reviews. Joint management between teams of complex patient. 6. Dressing management/cleansing regime changed by EB CNS for slow healing wounds. 1. Patient discharged home once stable and parents taught Diabetic care. Regular contact with EB team. 2. Pain and wounds developed on ears. Anxiety formed around BMs. Libra pump reduced the need for ear pricks. 3. Patient gained 4kg in 4 months once dietetic plan in place. Patient happier, excelling in school. 4. Effective inter professional working between teams demonstrated. 5. Wound originally improved, however have recently deteriorated – difficult to attain whether this is a result of the impact of her diabetes. Wound management in EB is challenging at best, combined with another complex condition, this case study remains ongoing. It is likely that originally her wound healing improved as a result of better nutrition. However she must be continually monitored and information must be shared between endocrinology and EB to ensure optimal management. Introduction of Libra pump beneficial for skin cares and emotional health. *Conclusions:* Case report - please see results.

P2
MOLECULAR AND MUTATIONAL SIGNATURES OF SQUAMOUS CELL CARCINOMAS IN EPIDERMOLYSIS BULLOSA

Sisi Lu[1], Maria E. Hess[2], Antonia Reimer[1], Daniele Castiglia[3], Yinghong He[1], David Rafei-Shamsabadi[1], Dagmar V. Bubnoff[1], Hauke Busch[4], Frank Meiss[1], Melanie Boerries[2], Cristina Has[1]
[1]Department of Dermatology, Medical Center - University Medical Center Freiburg, [2]Institute of Medical Bioinformatics and System Medicine, Faculty of Medicine, Freiburg, Germany, [3]IDI-IRCCS, Rome, Italy, [4]Lübeck Institute for Experimental Dermatology, Germany

Introduction and objectives: Squamous cell carcinomas (SCC) are major complications of epidermolysis bullosa (EB), and one of the most common causes of death. *aterials & methods:* Here, we analysed molecular and mutational signatures of 48 SCC obtained from patients with EB, ten with recessive dystrophic epidermolysis bullosa (RDEB), seven with Kindler syndrome (KS) and one patient with junctional epidermolysis bullosa (JEB). *Results:* Although we observed significant tumour heterogeneity, some common characteristics emerged. All EB SCC samples showed high EGFR and COX-2 expression, and expression of at least one immune checkpoint, CTLA-4, PD-1 or PD-L1. CTLA-4, PD-L1 and IDO expressions were significantly higher in RDEB SCC compared to KS SCC. The molecular biomarker expression was higher in tumor samples compared to non-tumor samples in RDEB patients. Based on these findings, considering the high expression of immune biomarkers in EB SCC, combination therapies of immune checkpoint inhibitors, EGFR inhibitors and the COX-2 anti-inflammatory drug could be potential treatments for EB SCC patients. The signatures of somatic mutations in EB SCC were heterogeneous with widely varying numbers of alterations. All mutational signatures of EB SCC were similar to those of head and neck SCC and UV SCC. KS SCC showed higher tumour mutational burden as compared to RDEB SCC and JEB SCC. The mutational profiles of RDEB SCC and JEB SCC were similar, while KS SCC was distinct. We found recurrently altered genes (TP53, CDKN2A, NOTCH1/2 and KNSTRN) but also a wide spectrum of oncogenic mutations affecting cell cycle, DNA damage response, tyrosine kinases, PI3K-AKT-mTOR and RAF-MEK-ERK pathways in all EB SCC. *Conclusions:* Taken together, we have immunohistochemically and genetically characterized SCC in a cohort of patients with EB and identified diverse arrays of immune signatures and oncogenic alterations that can guide future studies and potential treatments of this disease.

P3
REVIEW OF URGENT PATIENT CONTACTS AND EMERGENCY ADMISSIONS IN CHILDREN WITH SEVERE GENERALISED RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB)

C Prodinger[1], S Chottianchaiwat[2], L Holland[2], M Laimer[1], G Petrof[2], AE Martinez[2]
[1]Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, [2]Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

Introduction and objectives: Routine clinical appointments for individuals with RDEB are carefully documented but there is no defined system for capturing unscheduled and emergency contacts related to their EB. Our aim was to review all urgent contacts and emergency admissions to our paediatric EB service in order to identify the causes and to put measures in place to better support our patients. *Materials & methods:* The hospital Electronic Patient Record database and EB nurse records from 20 severe RDEB children were reviewed over a period of 12 months (04/2018-04/2019). We included all parent-initiated contacts outside their regular or scheduled clinical appointments and procedures including emergency hospital admissions. *Results:* Twenty patients sought urgent advice on 102 occasions (mean 5.1 contacts per patient per year). Twenty-four contacts (23.5%) required admission to hospital. The majority of contacts were made via email or telephone call to the EB nurses ($n=92$, 94%) followed by contacts during home visits ($n=3$, 3%) and directly to the palliative/symptom care team ($n=3$, 3%). The most common reason was acute dysphagia ($n=27$, 26.5%) which led to oesophageal dilatation (OD) in 90%

(n=24/27) of cases. Other reasons for contact were suspected skin infection (n=16, 15.7%), uncontrolled pain (n=16, 15.7%) and eye problems (n=12, 11.8%). The majority of contacts (mean 7 per patient) involved children under 2 years old, followed by children aged 11 and above (mean 5.8 per patient). *Conclusions:* The low number of contacts during the 12-month period demonstrates a good level of patient/family education about the condition and adequate provision of standard medical care. The higher need for urgent advice in younger children and those above 11 years is likely to reflect the newer families having less experience and the increase in incidence of symptoms such as pain and itch with age. Reported symptoms of oesophageal strictures, such as dysphagia, were extremely reliable with 90% of patients going on to have an OD with confirmed strictures. We have now supplied all patients with severe RDEB with two doses of dexamethasone for acute symptomatic treatment whilst waiting for an OD. Further actions addressing identified issues included the setup of 12-weekly telephone pain management clinics, implementation of a standardized procedure for suspected skin infection and the introduction of an 'emergency eye card' for patients. This retrospective study has led to the generation of symptom-orientated measures to empower families to manage RDEB-related complications with the aim to reduced emergency contacts and hospital admissions.

P4

WHEN THE GENETIC RESULT SURPRISES THE CLINICAL DIAGNOSIS: SPLICING VARIANTS LEADING TO ATYPICAL PHENOTYPES ARE MORE COMMON THAN THE SUPPOSED IN EPIDERMOLYSIS BULLOSA

Luiza Monteavaro Mariath[1], Juliana Tosetto Santin[1], Jeanine Aparecida Frantz[2,3], Maria Juliana Rodovalho Doriqui[4], Ana Elisa Kiszewski[5,6], Lavínia Schuler-Faccini[1,7]

[1]Federal University of Rio Grande do Sul, [2]Regional University of Blumenau, [3]DEBRA-Brazil, [4]Dr. Juvêncio Mattos Children's Hospital, [5]Federal University of Health Sciences of Porto Alegre, [6]Santa Casa de Misericórdia of Porto Alegre Hospital, [7]National Institute on Population Medical Genetics (Inagemp), Brazil

Introduction and objectives: In low and middle income countries, such as Brazil, exams to subclassify Epidermolysis Bullosa (EB) patients are difficult to access and also frequently inaccurate. We have developed a panel of 11 genes that was able to detect the causal mutation allowing correct EB classification in 94.2% of the analysed patients. Our objective here is to compare the prior clinical hypothesis and the genetic diagnosis of a sample of EB Brazilian patients. *Materials & methods:* A total of 76 index-cases were included in the analysis. All patients were subjected to clinical examination performed by dermatologists with expertise in genodermatoses, who inferred the type of EB. The genetic analysis was performed through a next-generation sequencing multigene panel including the 11 genes implicated in most EB cases (KRT5, KRT14, PLEC, TGM5, LAMA3, LAMB3, LAMC2, COL17A1, ITGB4, COL7A1, and FERMT1). Bioinformatic tools were used to analyse and classify the genetic variants. *Results: A* concordance between a priori clinical hypothesis and definitive genetic result was identified in 49 from the 76 index-cases (64.5%). In eight (10.5%) index-cases there was a clinical-genetic discordance. In nine (11.8%), the main EB type (Dystrophic EB) was correctly indicated, but the subtype (dominant or recessive) was incorrectly inferred. Finally, ten index-cases (13.2%) presented Localized Dystrophic EB, subtype whose dominant and recessive forms are clinically indistinguishable, making the final classification not possible. Therefore, in 27 index-cases the surprising genetic result proved to be essential for the correct diagnosis. Of them, 20 (74%) carry pathogenic variants predicted to alter the correct gene splicing. Although a notable phenotypic variability has been demonstrated in patients carrying this type of variant, this mechanism of pathogenesis appears to be more frequent in EB than the supposed before. *Conclusions:* Our study demonstrated that clinical evaluation does not solve all EB cases. In low and middle income countries, such as Brazil, in which exams such as immunofluorescence mapping and electron microscopy are not accessible to most patients, it is difficult to correctly diagnose and classify EB and to provide proper follow-up steps and genetic counseling for patients. The proposed gene panel proved to be an effective tool for EB diagnosis, providing EB type determination and inheritance pattern. Clinical phenotypes varying from classical EB types, previously considered rare, appear to be more frequent than presumed. Additional investigations regarding splicing variants and its respective effects are important for a better comprehension on the genetic background involved in EB.

P5

REVIEW OF HAIR DISORDERS AND ALOPECIA IN EPIDERMOLYSIS BULLOSA DISEASE GROUP: A NEGLECTED AREA OF CARE

Danica Xie[1,2], Asli Bilgic[1,2,3], Nada Abu Alrub[2], Dédée F Murrell[1,2]

[1]Department of Dermatology, St George Hospital, Kogarah, [2]Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia, [3]Antalya Training and Research Hospital, Dermatology Clinic, University of Health Sciences, Antalya, Turkey

Introduction and objectives: Epidermolysis Bullosa (EB) is a group of inherited blistering diseases characterized by increased mechanical fragility of skin and mucous membranes resulting in easily repeated blisters, erosions, poor healing and scarring, dystrophy of nails and systemic problems. The main problem is gene mutations involved in encoding adhesion proteins within the epidermis or the basement membrane zone. These adhesion proteins are also present in normal hair follicles. Thus, scalp alopecia and hair disorders are a complication of EB. However, hair disorders have generally been overlooked and there is no consensus about the natural history, clinical manifestations and treatment or follow-up guidelines for alopecia and hair disorders in EB to allow potential intervention. This study aimed to review the current literature in order to provide information about the epidemiology, pathogenesis, and clinical presentations of hair disorders in EB. *Materials & methods:* We searched for all relevant case reports and studies in Medline, PubMed, and EMBASE electronic databases from January 1950 up to August 2019 in any language. To maximize sensitivity, search terms including "alopecia or hair loss or baldness or hair disorders" "epidermolysis bullosa," and "vesiculobullous skin diseases" and "skin fragility syndromes" and "lethal acantholytic epidermolysis bullosa" were used. First abstracts, then full texts of identified records were reviewed. Furthermore, additional records were identified through scanning the bibliographies that had cited these eligible records. *Results:* Forty reports detailed 64 patients with all clinical subtypes of EB (as defined by Fine et al. Inherited epidermolysis bullosa: Updated recommendations on diagnosis and classification) were identified with demographic and clinical manifestations of hair disorders. The most common patterns were patchy scalp alopecia and diffuse alopecia along with short, sparse and fragile hair or woolly hair. Although nonscarring alopecia was more common especially in patients with EB simplex (EBS), scarring alopecia was seen in all dystrophic EB (DEB) patients. Specific hair structure patterns (short, sparse and fragile hair or woolly hair) were seen in patients with skin fragility syndromes. *Conclusions:* Although some forms of EB are quite mild and just cause blistering with mechanical trauma on acral sites, others like recessive DEB and JEB can result in hair abnormalities and scarring alopecia by causing loss of normal architecture. There is no universal validated alopecia scoring system and evaluation guide for alopecia in EB.

P6
GUIDELINES FOR THE CARE OF ADULTS WITH EB UNDERGOING CLINICAL AND SURGICAL PROCEDURES

Karen Snelson
Advanced Nurse Practitioner, Guy's & St Thomas' NHS Foundation Trust, London, UK

Introduction and objectives: Guidelines previously published by the author in 2011 were reviewed and updated to reflect current practice and recommendations. The aim was to produce more easily accessible and widely available guidance to ensure high quality patient care based on best practice and up to date evidence. *Materials & methods:* Recommendation and best practice requires that all guidelines should be reviewed 3 yearly, therefore updating of this guidance was overdue. There was anecdotal evidence that the previous guidelines (2011) were not regularly accessed by clinicians; this was perceived to be because they were not aware of the existence of the guidelines or how to obtain these.
The author works in a specialist environment where EB patients undergo clinical and surgical procedures on a weekly basis, therefore the experience upon which the recommendations are based is extensive. A literature search was carried out and articles reviewed. Existing guidelines (2011) were updated by the author and new recommendations produced based on current practice, including the addition of photographs to aid explanation and understanding. Guidelines (2019) were peer reviewed, including by anaesthetist colleagues, for accuracy prior to publication. *Results:* Literature on this subject remains scarce; a small number of previously unseen published articles were reviewed and no significant changes to recommended practice or case studies were identified. The content of previous guidelines (2011) was found to reflect safe practice and the recommendations currently advised by the author's specialist environment. Some minor changes in practice, dressings and equipment recommended were introduced. Guidelines will be made freely available and signposted to clinicians on various platforms. *Conclusions:* Recommendations for safe practice are outlined in the new guidance. The addition of photographs to aid explanation and understanding is intended to improve patient experience when being cared for by clinicians less familiar with EB. Clinicians are the target audience and the aim is to provide an educational resource to inform and guide practice. Improved accessibility to updated guidelines (2019) and increased awareness of the existence of guidance is ultimately intended to improve patient experience and ensure patient safety. The updated guidance (2019) will next be reviewed in 2022.

P7
SELF-ASSEMBLED SKIN SUBSTITUTES AND RETROVIRAL GENE THERAPY FOR THE PERMANENT TREATMENT OF RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Martin Barbier[1,3], Andréanne Cartier[1,3], Angela Dakiw Piaceski[1,3], Alex Larose[1,3],Sébastien Larochelle[1,3], Danielle Larouche[1,3], Karim Ghani[2,3], Véronique Moulin[1,3], Elena Pope[4], Manuel Caruso[2,3], Lucie Germain[1,3]
[1]Centre de recherche en organogénèse expérimentale de l'Université Laval/LOEX, [2]Centre de recherche sur le cancer de l'Université Laval, [3]CHU de Québec-Université Laval Research Centre, Québec, [4]Hospital for Sick Children and University of Toronto, Toronto, Canada

Introduction and objectives: Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic disease in which minor mechanical stress in the skin causes the formation of blisters and erosions. RDEB is caused by mutations in the COL7A1 gene – encoding type VII collagen (Col7), which leads to defective anchoring fibrils or their absence at the dermal-epidermal junction (DEJ) ultimately resulting in a loss of adhesion between the epidermis and the dermis. Production of autologous skin substitutes from the patient's cells genetically corrected for Col7 expression, and their subsequent graft, is a new strategy for the development of a suitable permanent treatment to the skin lesions of RDEB patients. *Materials & methods:* RDEB patient's fibroblasts and keratinocytes lacking Col7 expression were transduced using a SIN COL7A1 retroviral vector. Transduction efficacy was assessed through flow cytometry. Transduced stem cell keratinocytes were quantified using keratin 19 as a stem cell marker. These corrected cells were used to produce skin substitutes with the self-assembly approach and analyzed by immunofluorescence as well as transmission electronic microscopy. The adhesion of the epidermis to the dermis was measured by a mechanical peeling test. Skin substitutes were grafted onto athymic mice for 28 days. *Results:* We observed that viral particules transduced 40% of keratinocytes and 70% of fibroblasts of this RDEB patient. Up to 80% of keratin 19-expressing keratinocytes were successfully transduced and maintained in culture. Skin substitutes were produced from the transduced cell populations and we observed the restoration of Col7 at the DEJ as well as the presence of anchoring fibril-like structures. Moreover, 60% of keratin 19-expressing keratinocytes produced Col7 in the skin substitutes. The adhesion of the epidermis to the dermis was also restored compared to skin substitutes produced from RDEB cells. It was comparable to skin substitutes produced from healthy donor cells. Finally, Col7 localization at the dermal-epidermal junction was maintained 28 days after grafting. *Conclusions:* We developed an efficient method to restore Col7 production in keratinocytes and fibroblasts of a RDEB patient using a SIN COL7A1 retroviral vector. Skin epithelial stem cells were effectively transduced and observed in the epidermal layer of the skin substitutes. Adhesion of the epidermis to the dermis was also restored compared to controls. In conclusion, our results indicate that this method might be suitable for the permanent treatment of RDEB skin lesions.

P8
OUTCOMES AND PREDICTORS FOR RE-STENOSIS OF ESOPHAGEAL STRICTURE IN EPIDERMOLYSIS BULLOSA: A MULTICENTER COHORT STUDY

Elena Pope, MD, MSc[1], Anne Lucky, MD[2], Irene-Lara Corrales, MD, MSc[1], Carmen Liy Wong, MD[1], Julio Salas-Alanis, MD[3], Francis Pallison, MD[4], Anna Martinez, MD[5], Jemina Mellerio, MD[6], Dedee Murrell, MD[7], Mauricio Torres Pradilla, MD[8]
[1]Section of Dermatology, Division of Paediatric Medicine, The Hospital for Sick Children, University of Toronto, [2]Cincinnati Children's Hospital, [3]University of Monterrey, Mexico, [4]Debra Chile Foundation, Santiago, Chile, [5]Great Ormond Street Hospital, London UK, [6]Guys Hospital, London, UK, [7]St George Hospital, University of New South Wales Australia, University of Bogota

Introduction and objectives: Esophageal strictures are the common gastrointestinal complications in patients with epidermolysis bullosa (EB) requiring dilation. There is limited information on the best type of intervention, outcomes and predictors for re-stenosis. We aimed to investigate the frequency, clinical presentation of esophageal strictures in EB patients and to ascertain the predictors of re-stenosis. *Materials & methods:* We conducted a retrospective, multicenter cohort study involving 7 specialized, international EB centers on patients who were 0-50 years of age. Descriptive statistics and hazard risks for re-stenosis were calculated. *Results:* We identified 125 patients with 497 esophageal stricture episodes over a mean period of observation of 17 (SD=11.91) years. Dilations were attempted in 90.74% of episodes, using guided fluoroscopy 45.23%, retrograde endoscopy 33.04% and antegrade endoscopy 19.07%. Successful dilation was accomplished in 99.33% of attempts. Patients experienced a median of 2 (IQR:1-7)

stricture episodes with a median interval between dilations of 7 (IQR:4-12) months. Predictors for re-stenosis included: number of strictures {2 vs 1 stricture: $\chi^2 = 4.293$, $p = 0.038$, HR = 1.294 (95%CI: 1.014, 1.652 and 3 vs 1 stricture:$\chi^2 = 7.986$, $p = 0.005$, HR = 1.785 (95%CI: 1.194, 2.667)} and a long (>1 cm) segment stricture ($\chi^2 = 4.599$, $p = 0.032$, HR = 1.347 (95%CI: 1.026, 1.769). Complications were more common with the endoscopic approach (8/86- antegrade endoscopy, 2 /149- retrograde endoscopy versus 2/204- fluoroscopy, $\chi^2 = 17.39$, p value<0.000). *Conclusions:* We found excellent dilation outcomes irrespective of the dilation procedure, however with higher complications in the endoscopic approach. Long (>1cm) segment involvement and multiple locations were predictive of stricture reoccurrence.

P9

DIACEREIN 1% OINTMENT FOR EPIDERMOLYSIS BULLOSA IN A RANDOMIZED CONTROLLED PILOT STUDY

Chu-Han Huang[1], Jing-Yi Lee[1], Huang-Ling Hsu[1], Yu-Hsiang Liao[1], Chao-Kai Hsu[2,3,4], Chao-Chung Yang[2,4], Wei-Ting Tu[2,4], Ya-Ju Hsieh[5], Wei-Shu Lu[1], I-Yin Lin[1], Yiumo Michael Chan[1], Chih-Kuang Chen[1]

[1]TWi Biotechnology, Inc., Taipei, [2]Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, [3]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, [4]International Center for Wound Repair and Regeneration (iWRR), National Cheng Kung University, Tainan, [5]Hsinchu Mackay Memorial Hospital, Hsinchu, Taiwan

Introduction & objectives: Epidermolysis bullosa (EB) is a group of inherited skin disorders characterized by skin fragility, recurrent blistering on skin and mucous membranes. Currently, there are no FDA-approved therapies. The main objectives of this study (ClinicalTrials.gov Identifier: NCT03468322) are to evaluate the efficacy and safety of diacerein ointment 1% in EB patients. Diacerein is a novel NLRP3 inflammasome inhibitor that suppresses pro-inflammatory IL-1b production, which is thought to play an important role in pathogenesis of EB Simplex (EBS). *Materials & methods:* Patients with clinical diagnosis and laboratory confirmation of EB were enrolled. Two comparable EB lesion areas in terms of body surface area (BSA) (1 – 5% each) and severity were selected on each patient. One selected lesion area was treated with diacerein 1% ointment and the other with placebo ointment. Patients were treated for 8 weeks and followed for additional 4 weeks. *Results:* Nine patients from age 4 to 36 were enrolled, consisting of five dystrophic or junctional EB (DEB/JEB) and four EBS patients. Diacerein was well tolerated throughout the study period and there were no drug related adverse events (AEs). At the end of treatment period (Week 8), mean blister numbers were reduced by 56% and 34% from baseline in diacerein and placebo treated areas, respectively. Diacerein treated areas also demonstrated improvement in mean Investigator's Global Assessment (IGA) score from 2.4 to 1.9, and in mean Pruritus Visual Analogue Scale (VAS) score from 54 to 27, but the difference was not significant from placebo treated areas. During the follow-up period, the mean IGA score for diacerein treated areas decreased by 0.1 from Week 8 whereas placebo treated areas increased by 0.8; and the number of subjects with IGA score equals to 0 or 1 with at least 2-point reduction from baseline was 3 and 0 for diacerein and placebo treated areas, respectively. Similarly, the mean total lesion surface area (LSA) at Week 12 increased slightly from Week 8 by 12% in diacerein treated areas but significantly by 99% in placebo treated areas. *Conclusions:* Overall, diacerein ointment 1% is safe and well-tolerated. During treatment period, diacerein treated areas demonstrated modest improvement in IGA and blister numbers. When treatment stopped, diacerein but not placebo treated areas showed noticeable sustained improvement in IGA, suggesting a durable effect of diacerein. This study was the first time diacerein was intended to treat different EB subtypes, possibly expanding its potential indication beyond EBS.

P10

A CASE SERIES OF SIX PAEDIATRIC CASES WITH LARYNGO-ONYCHO-CUTANEOUS SYNDROME (LOC)

C. Prodinger[1], S. Chottianchaiwat[2], J.E. Mellerio[3], J.A. McGrath[3], L. Liu[4], W. Moore[5], M. Laimer[1], G. Petrof[2], A.E. Martinez[2]

[1]Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, [2]Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, [3]St. John's Institute of Dermatology, King's College London, Guy's Hospital, London, [4]Viapath, Guy's and St Thomas' NHS Foundation Trust, London, [5]Department of Ophthalmology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Materials & methods: We reviewed our current paediatric EB database to identify alive children with genetically confirmed LOC. Demographic data, clinical features, medical history, skin immunofluorescence, genetic analysis as well as laboratory parameters were retrieved from the hospital electronic patient records. *Results:* We identified six children with a diagnosis of LOC, with mean age 5.4 years (range 2–8). All of them were female and two were siblings. Skin fragility was the earliest presenting sign and occurred at birth or within the first 2 months of life. Periungual overgranulation of finger and toenails occurred with a mean onset at 1.7 months, followed by appearance of laryngeal stenosis at 10.7 months, dental abnormalities and ocular granulation tissue formation at 11.8 months. Severe anaemia was noticed in 5 out of 6 children with mean onset at 18.7 months. Skin immunofluorescence revealed near-normal or normal intensity in laminin-332 staining compared to control skin in 5 children. One child had total absence of laminin-332 on a skin biopsy with a biallelic mutation in LAMB3, both in peripheral blood and skin, which predicted a severe phenotype. An additional heterozygous loss-of-function mutation in exon 39 of LAMA3 was detected in DNA from the skin, which was not present in the blood. In addition, two, previously unreported mutations, were identified in LAMA3. *Conclusions:* This retrospective study of 6 children with LOC syndrome delineates the disease course with classical symptoms appearing very early in life. Skin fragility starts within the first 2 months of life, followed by overgranulation of the nails and skin wounds. Thereafter, laryngeal stenosis and ocular granulation tissue appear before 1 year of age. Hypoplastic teeth with sharp edges appear after delayed tooth eruption. The interpretation of skin immunolabelling and molecular diagnostics can be challenging. Beside the "typical" LOC-specific insertional mutation in exon 39 of LAMA3 (c.151insG), we identified a further novel mutation (p.Leu3055fs in exon 33) and a 6-bp deletion in exon 52 both in LAMA3. Early diagnosis is essential to reduce morbidity and mortality. Our findings provide additional phenotypic and genotypic insights into LOC syndrome and highlight the importance of expert-led, multidisciplinary care.

P11

CASE STUDY: THE APPLICATION OF A HYDROACTIVE COLLOID GEL ON TO THE SKIN OF A CHILD WITH EPIDERMOLYSIS BULLOSA SIMPLEX GENERALISED SEVERE

Katie White

Results: 3 year old boy. Epidermolysis Bullosa Simplex Generalised Severe (previously known as Dowling Meara). Genetic condition resulting in a Keratin 5 mutation. No cure- conservative wound management and pain relief only. Oral morphine given

every 4 hours. Chronic Anaemia. Active child with delayed gross motor skills due to diagnosis. Not walking or crawling. *Wound Description*: Widespread blisters all over body, down to the dermis level due to extreme skin fragility. Multiple open wounds from sheering and friction. *Wound location:* All over body..*Duration of wound & cause:* wounds typically take 3-5 days to heal depending on size and depth however will then re-blister and the cycle will start again repetitively. The cause is from everyday friction and occasional trauma due to Epidermolysis Bullosa causing there to be no attachment of the epidermis layer. *On-going medical treatment:* Wound care is performed twice daily- all blisters are lanced, and fluid expelled. Intact blisters have baby powder applied and covered with non-adherent foam dressings which are secured with either soft wipes or tubular retention dressings, depending on the location. *Size of wound:* Wounds all vary in size- they can expand the full length of a limb. *Physical appearance:* Intact blisters are fragile with surrounding erythema and painful. Open wounds are shallow and granulating. When the intact blisters are in the healing phase they form thin scabs. *Aim of treatment*: Quick healing, reduce erythema and inflammation, see a reduction in re-blistering and reduce his pain. Provide good moisture balance, prevent infection and facilitate roof of blister re-attachment. Hydroactive Colloid gel application twice daily, then if needed cover with non-adherent foam for protection. *Provide rationale for choice:* optimal moist healing environment. Speed up healing, debride dry skin (which causes more blisters) and reduce pain. *Clinical outcome*: Over the course of 10 days blisters healed and the dry skin was debrided quicker which meant re-blistering also reduced. You can see from the images that the erythema has reduced. Length of treatment: 10 days but plan to continue with this due to positive results. Pain reduced due to reduction of re-blistering. The Hydroactive Colloid gel was quick and easy to apply. No pain experienced on application- minimal friction caused. Improved the speed of healing considering there was some very large blisters at the start of the treatment. These would usually de-roof but they didn't. Dead skin debrided well which in turn reduced blisters. Whilst there are many variables as to why the skin of an EB patient fluctuates I found there to be an overall improvement. Further long-term application is needed to ensure this is the work of the gel. *Clinical benefits*: Providing optimum healing environment (good moisture balance) and debridement of dry skin from healing Blisters. Reduced inflammation and improved pain.

P12
TESTING GASTROINTESTINAL IRON ABSORPTION WHEN TREATING ANEMIA IN PATIENTS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Bret D. Augsburger, BA, CCRP, Anne W. Lucky, MD, Kalyani Marathe, MD, MPH, Cristina Tarango, MD
Epidermolysis Bullosa Center, Cincinnati Children's Hospital, and the University of Cincinnati College of Medicine, Departments of Dermatology and Pediatrics, Cincinnati, Ohio, USA

Introduction & objectives: The purpose of this study was to determine whether iron was being enterally absorbed in patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB) who had anemia. *Materials & methods:* Ten patients with RDEB who had anemia refractory to or poor adherence to oral or gastrostomy-given iron completed 12 iron absorption challenges. Subjects were given a dose of 2 mg elemental iron/kg by mouth or via gastrostomy tube in the form of ferrous sulfate liquid. Baseline serum iron as well as hematologic, inflammatory, and nutritional markers were collected before and after intervals of two to four hours. Successful iron absorption was defined as a two to three-fold increase of serum iron level or a rise to above 100 mcg/dL two hours after the challenge. *Results:* Nine of the 12 iron challenges showed inadequate iron absorption. One patient initially demonstrated an ability to absorb iron, while 19 months later no longer could. Another patient twice demonstrated a lack of iron absorption. Only three of the ten subjects at any point demonstrated normal iron absorption. All patients had elevated sedimentation rate (ESR) and C Reactive Protein (CRP), low serum albumin, and low hemoglobin levels (7.3-11.2 gm/dl). Ten challenges were in patients with elevated soluble transferrin receptor (STFR) levels. The three challenges with normal iron absorption all had increased STFR (1.9-2.3 mg/l, normal 0.76-1.76). They also had elevated ESR (29-75 mm/hr, normal 0-15) and CRP (1.2 -4.9 mg/dl, normal < 0.40), but these inflammatory markers were in general less elevated than those in non-absorbers (ESR 34-115 mm/hr and CRP 5.8-13.5 mg/dl). *Conclusions:* Oral iron is routinely prescribed for patients with RDEB who have anemia. Anemia is usually due to a combination of iron deficiency and chronic inflammation. Adherence to enteral iron tends to be unreliable due to bad taste and abdominal pain, constipation and/or nausea. Thus, EB patients prescribed enteral iron may not be receiving the intended benefits. Enteral iron absorption tests are relatively non-invasive and appear to be well-tolerated. We have shown that poor gastrointestinal iron absorption may be an important factor in failure to treat anemia in RDEB enterally. It may be prudent to test patients with RDEB who are anemic and not responding well to conventional iron supplements with iron absorption tests and to consider replacement of enteral with intravenous iron.

P13
FOOD ALLERGY AS COMORBID CONDITION IN CHILDREN WITH EPIDERMOLYSIS BULLOSA. THE RESULTS OF THE OBSERVATIONAL STUDY

S.G. Makarova[1,2], N.N. Murashkin[1], R.V. Epishev[1], O. Ereshko[1], T.R. Chumbadze[1], E.T. Ambarchian[1]
[1]FSAI 'National Medical Research Centre of the Children's Health' of the Ministry of Health of the Russian Federation, [2]Pirogov Russian National Research of Medical University

Introduction & objectives: Epidermolysis bullosa (EB) refers to a group of rare inherited disorders characterized by severe damage of skin and mucosa. Children with severe EB are one of the most nutritionally compromised group of patients. Food sensitization in these patients has not been studied, and, given the nutritional deficiency in these patients and the difficulties in the formation of the adequate diet, the study of this problem is important. To evaluate the clinical manifestations of food allergy (FA) and IgE-response to food proteins in children with EB. *Materials & methods:* 82 patients with EB aged from 2 months to 16 years were entered this open non-randomized observational prospective study, including 20 patients with simple form of EB and 62 patients with dystrophic form of EB. We analyzed allergic history and clinical manifestations of the FA in all the patients. Every patient in this study underwent of determination of the concentration of total serum IgE and specific serum IgE to the most important food allergens, as well as to mixtures of household allergens (UniCAP System, Phadia AB). *Results:* FA (clinical manifestations) was identified in 20.7% of children with EB (in 10% of cases with simple form of EB and in 24.2% - with dystrophic form of EB). Products containing cow's milk protein, cereals, and eggs were identified as etiologic factors of FA in most cases. Within the group of children with comorbidity FA and EB high and very high levels of total IgE (> 1,000 kUA/l) were detected most frequently. We discovered a positive correlation between such indexes as Body surface area of denuded/ulcerated skin(%), skin infection (%) and the presence of FA ($p < 0.05$) and the level of total IgE ($p < 0.05$). *Conclusions:* Comorbidity with FA is high in patients with dystrophic form of EB and may be caused by a violation of the protective properties of the skin and mucous barrier. The presence of the FA should be

identified actively and taken into account in the treatment and as well as in the diet recommendations and choice of special nutrition for this severe category of patients.

P14
INCIDENCE OF SQUAMOUS CELL CARCINOMA IN PATIENTS WITH DYSTROPHIC EPIDERMOLYSIS BULLOSA – EXPERIENCE OF CLINIC OF DERMATOVENEREOLOGY IN BELGRADE, 1975-2019

J. Lalosevic[1], M. Gajic-Veljic[1,2], L. Medenica[2], M. Nikolic[1,2]
[1]Division of Pediatric Dermatology, Clinic of Dermatovenereology, Clinical Center of Serbia, [2]University of Belgrade School of Medicine, Belgrade, Serbia

Introduction & objectives: Epidermolysis bullosa (EB) is a heterogeneous group of skin disorders manifesting with widespread blisters, erosions and chronic wounds. There are three main subtypes: EB simplex (EBS), junctional EB (JEB), and dystrophic EB (DEB), based on ultrastructural levels of skin cleavage, with Kindler syndrome as a relatively recently added EB subtype. EB-associated SCCs tend to arise at sites of chronic skin blistering, wounds and scarring, particularly in Hallopeau-Siemens Recessive Dystrophic Epidermolysis Bullosa (HS-RDEB). Tumors in HS-RDEB patients generally behave more aggressively than SCCs in general population, and they carry very significant morbidity and mortality. Patients with HS-RDEB usually die from metastatic SCC by the age of 40 years. In general population, SCC commonly develops between 70 and 80 years of age, 1.5-2.2 times more frequently in men than in women, predominantly on sun-exposed areas. In RDEB, SCC usually develops between the ages of 35 and 40 years, with no gender preponderance, predominantly on the extremities, and are generally histopathologically well differentiated. *Materials & methods:* The data were obtained from 108 patients with hereditary EB diagnosed and followed at the Clinic of Dermatovenereology, Clinical Center of Serbia, from 1975 to 2019. Clinical diagnoses were confirmed by transmission electron microscopy. The diagnosis of SCC was confirmed histopathologically. In EB patients, the analyzed parameters were: age, gender, tumor localization, tumor differentiation by histopathology, age at the time of SCC diagnosis. *Results:* Of 108 patients, 95 had dystrophic EB, 12 had EB simplex, and one patient had Kindler syndrome. Of 95 DEB patients, 46 had the most severe form, HS-RDEB. Eleven patients with HS-RDEB were diagnosed with SCC. The most common localization of tumors were lower extremities. SCC was slightly more frequent in females than in males (F:M=6:5). Patients' age at the time of SCC diagnosis was 26.7±2.6 years. Seven patients died of metastatic SCC, at the age of 27.4±2.6 years. The most common type was poorly differentiated SCC (7 patients), while moderately differentiated SCC was diagnosed in 4 patients. *Conclusions:* Given the highly aggressive nature of RDEB-SCCs, its high incidence and mortality rate, regular follow-up of every RDEB patient is imperative. The early diagnosis and timely surgical treatment of SCC may improve the prognosis in EB patients.

P15
IDENTIFYING POTENTIAL NEW AND REPURPOSED DRUGS FOR IMPROVING MANAGEMENT OF CHRONIC WOUNDS IN RDEB

Alexandros Onoufriadis[1], Chrysanthi Ainali[1], Denis Torre[2], Laura Proudfoot[1], Ellie Rashidghamat[1], Jemima E. Mellerio[1], Avi Ma'ayan[2], John A. McGrath[1]
[1]St John's Institute of Dermatology, School of Basic and Medical Biosciences, King's College London, London, UK, [2]Department of Pharmacological Sciences, Mount Sinai Center for Bioinformatics, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

Introduction & objectives: One of the main disease burdens of recessive dystrophic epidermolysis bullosa (RDEB) is chronic wounds. Frustrated attempts at tissue repair result in poorly healing inflamed wounds, mutilating scars, digital fusion and a significantly increased risk of squamous cell carcinoma. At present, management and treatment options for chronic RDEB wounds are limited. In keeping with a major research priority of people living with RDEB, this project investigates the genes and tissue signalling pathways that go awry in RDEB wounds with a focus on using these data to try to identify new or repurposed therapies that could improve symptoms. *Materials & methods:* Following ethics approval and informed consent, we collected 4mm punch biopsies of whole skin from the edge of chronic wounds in RDEB subjects (EBw), 6 samples from intact/normal skin from the same RDEB individuals (EBn), and 6 samples from healthy controls (HC) matched for age, sex, ethnicity and body site. Samples were homogenised using a hand-held Polytron in lysis buffer and RNA extracted and quantified. Gene expression profiling was performed using the Illumina whole-genome expression array HumanHT-12 v4.0 Expression BeadChip. *Results:* To assess gene expression and gene pathways that may be differentially expressed in EB wounds, we compared the expression levels of the genes from the wounded skin (EBw) versus normal (EBn) or control skin (HC). Bioinformatic analysis using a p-adjusted value of <0.01 and logFC>+/- 2 identified 2388 transcripts differentially expressed (DE) between the EBw vs EBn samples and 2685 DE transcripts between the EBw and HC samples. Most of the DE transcripts (2324) were shared between the two comparison groupings. Next, we implemented a comprehensive functional pathway enrichment analysis using GAGE and GSVA packages. Both analyses showed that dysregulated genes were enriched in signalling pathways, with cytokine-cytokine interactions signalling and Toll-like receptor signalling pathways being highlighted as key players in EB wounds. Predictions for compounds that mimic or reverse the gene expression signatures were performed using L1000FWD, which is a web application that provides interactive visualization of over 16,000 drug and small molecule induced gene expression signatures. This analysis identified 50 compounds that opposed the signatures of DE genes between normal and wounded skin in EB patients. *Conclusions:* Our study provides a comprehensive analysis of differentially expressed genes and pathways in RDEB chronic wounds and provides opportunities for drug repurposing. Next, functional validation will be required to assess potential therapeutic relevance.

P16
PAIRED SPCAS9 D10A RNPS PRODUCE THE SUBSTRATE FOR EFFICIENT GENE REPAIR VIA HOMOLOGOUS RECOMBINATION IN RDEB PATIENT KERATINONOCYTES

Thomas Kocher[1], Toni Cathomen[2], Simone Haas[2], Anna Hoog[3], Dirk Strunk[3], Johann W Bauer[1,4], Ulrich Koller[1]
[1]EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology, University Hospital of the Paracelsus Medical University Salzburg, Austria, [2]Institute for Transfusion Medicine and Gene Therapy, Medical Center – University of Freiburg, Freiburg, Germany, Center for Chronic Immunodeficiency, Medical Center – University of Freiburg, Freiburg, Germany, [3]Cell Therapy Institute, SCI-TReCS, Paracelsus Medical University, Salzburg, Austria, [4]Department of Dermatology, University Hospital of the Paracelsus Medical University Salzburg, Austria

Introduction & objectives: Several approaches for CRISPR/Cas9-based correction of RDEB have been described so far. Dependent upon the presence or absence of a homologous repair template, these approaches may result in non-homologous end joining

(NHEJ) or homologous recombination (HR). HR can lead to precise correction of mutations, and is thus highly preferable. A caveat, however, is the generally low efficiency of HR compared to NHEJ. *Materials & methods:* We established and optimized a selection-free correction strategy, using paired SpCas9 D10A ribonucleoproteins (RNPs) and rationally designed single- and double-stranded repair templates with 5´overhangs. RNPs and repair templates were delivered into RDEB keratinocytes via electroporation and gene editing efficiencies were analyzed via next generation sequencing (NGS), western blotting and immunofluorescence staining. *Results:* Electroporation of our paired SpCas9 D10A RNPs into RDEB keratinocytes, carrying a homozygous splice site mutation in exon 3 of the COL7A1 gene (c.425A>G/c.425A>G), results in high on-target cutting efficiency and a very heterogeneous repair outcome (insertions and deletions) observed via T7 Assay. However, the addition of repair templates into this approach results in increased HR and correction efficiency of >20%, analyzed via NGS. DNA cleavage and precise HR between repair template and endogenous COL7A1 led to the correction of the mutation, and thus to accurate C7 restoration and secretion in treated RDEB patient cells. *Conclusions:* Cas9/sgRNA ribonucleoproteins (RNPs) are generally associated with higher targeting and gene editing efficiencies accompanied with a shorter persistence in the nucleus than Cas9 proteins expressed from plasmids. This results in a larger number of edited cells and reduced off-target activity. Improved HR efficiencies and predictable repair outcomes are pivotal for advancing experimental gene therapies into a clinical setting. We believe that combining RNP delivery with double-nicking and optimized repair templates will comprise an improved approach for precise correction of COL7A1 mutations with high efficiency and lower adverse off-target effects.

P17
TWO SIBLINGS WITH DESMOPLAKIN DEFICIENCY LEADING TO END STAGE HEART FAILURE

S. Chottianchaiwa[1], C. Prodinger[2] ,R. Andrews[3], M. Fenton[4], G. Petrof[1], A.E. Martinez[1]

[1]Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [2]Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, [3]Department of Cardiology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [4]Department of Cardiothoracic, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

Results: We report two siblings with skin fragility, palmoplantar keratoderma and wooly hair with compound heterozygous nonsense/frameshift mutations in the DSP gene leading to desmoplakin deficiency. The older sibling successfully underwent heart transplantation while the younger sibling had an implantable cardioverter defibrillator (ICD) inserted while awaiting transplantation. The siblings were referred to our center at age 2 and 3 years respectively with a diagnosis of severe eczema. Examination revealed skin fragility, palmoplantar keratoderma and sparse hair raising the possibility of a desmosomal disorder. Desmoplakin gene (DSP) testing revealed a nonsense mutation, c.2131-2132delAG, p.S711fsX4, in exon 16 and a frameshift mutation, c.7756 C>T, p. R2586X, in exon 24. The mother was carrier of the nonsense mutation while the father was carrier for the frameshift mutation. This particular frameshift mutation is associated with cardiomyopathy. Therefore, cardiac monitoring was initiated with 6 monthly echocardiograms along with cardiac biomarkers. By the age of 9 the older sibling had developed left ventricular (LV) dilatation and impaired systolic function with multifocal ventricular ectopic beats. Her heart disease progressed despite treatment including Lisinopril, Spironolactone, Furosemide, Digoxin and Carvedilol. By age 13 she had biventricular cardiomyopathy with end stage heart failure and was admitted for full inotropic support. She was moved to the urgent transplant waiting list. Due to further deterioration with significant fluid overload and end organ failure, she had a ventricular assist device (VAD) inserted. Surgery and the device were tolerated with minimal skin breakdown at the site. A donor heart became available and she was successfully transplanted one week later. She has made an excellent recovery with no signs of graft rejection. Her brother first developed moderate LV dilatation with reduced systolic function at age 8. He is now 13 years old and has recently developed arrhythmogenic ventricular cardiomyopathy. The latest echocardiogram has shown a severely dilated LV with severely impaired biventricular systolic function. He had an implantable cardioverter defibrillator (ICD) and is on the cardiac transplant waiting list. In conclusion, individuals with desmoplakin deficiency present early with skin fragility, wooly hair and subsequent palmoplantar keratoderma. The need for regular cardiac monitoring is vital due to a very high risk of cardiomyopathy. ICD insertion, VAD insertion and cardiac transplant should be considered as treatment options despite the skin fragility as these were well tolerated in our patients.

P18
MIRNA-10B MARKS AGGRESSIVE SQUAMOUS CELL CARCINOMAS IN RDEB

Monika Wimmer[1], Roland Zauner[1], Michael Ablinger[1], Josefina Piñón-Hofbauer[1], Christina Guttmann-Gruber[1], Manuela Reisenberger[1], Thomas Lettner[1], Norbert Niklas[2], Johannes Proell[2], Mila Sajinovic[3], Paul De Souza[3], Stefan Hainzl[1], Eva M. Murauer[1], Johann W. Bauer[1], Dirk Strunk[4], Julia Reichelt[1], Albert S. Mellick[3], Verena Wally[1]

[1]EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, [2]Center for Medical Research, Medical Faculty, Johannes-Kepler-University, Linz, Austria, [3]Medical Oncology, Ingham Institute for Applied Medical Research, [1] Campbel Street, Liverpool NSW [217]0, Australia, [4]Institute of Experimental & Clinical Cell Therapy, Paracelsus Medical University, Salzburg, Austria

Introduction: Previously, it has been shown that squamous cell carcinomas (SCCs) in patients with a comorbid condition of the monogenic skin disease recessive epidermolysis bullosa (RDEB) present particularly aggressive. However, the specific molecular and cellular events in malignancy still remain relatively undefined. Small RNAs have been linked to cellular and developmental changes associated with the aggressive spread of tumour cells in a range of other malignancies. *Objectives*: Investigate the small RNA profile in RDEB-SCCs and assess a functional relevance of dysregulated miRNAs. *Materials & methods:* Affymetrix miRNA 4.0 microarray was performed on miRNAs isolated from RDEB-SCC and cSCC without RDEB background derived cultured cells as well as respective primary keratinocyte controls. All data were analysed in statistical software R. TaqMan qPCR and miRNA fluorescence in situ hybridization (FISH) was applied to validate differential expression in cultured cells and FFPE tissue sections. Migration assays and 3D spheroid formation assays were conducted to assess functional impact of miR-10b overexpression in keratinocytes. *Results:* In this work, we first identified small RNAs differentially regulated in RDEB-SCCs, compared with keratinocytes from RDEB patients, and normal skin. This allowed us to identify the miR-10b, as upregulated in SCC. These changes were validated by specific qPCR analysis, and with an adapted version of a combined ISH-fluorescent protocol applied to archival skin biopsies. In agreement with the hypothesis that there is a strong link between RDEB SCC malignancy and miR-10b expression in RDEB tissues, an increase in miR-10b expression was observed

in SCC as well as in an RDEB-SCC lymph-node metastasis. To further investigate this link between miR-10b and malignancy in RDEB, we performed functional assays. Unexpectedly, increased expression of miR-10b in RDEB keratinocytes lead to impaired motility in RDEB KCs. To examine the ability of miR-10b to confer a malignant phenotype to RDEB keratinocytes we next examined cells expressing miR-10b for properties associated with tumor initiating cells (cancer stem cells). Following 3D spheroid studies showed that miR-10b confers the cancer stem cell like ability of anchorage-independent aggregation to keratinocytes.

P19
INCIDENCE OF OBESITY IN PEOPLE WITH EBS AND IMPACT ON MOBILITY

Lynne D Hubbard
Department of Nutrition and Dietetics, St Thomas' Hospital, London, SE[1] 7EH

Introduction & objectives: People with epidermolysis bullosa simplex (EBS) are known to have hyperkeratosis and foot-blistering, resulting in reduced mobility and pain. Reduced mobility may have an impact on body weight and an increased body mass index (BMI) may further affect mobility. The aim of the study was a) to identify the incidence of obesity in people with EBS and b) to establish whether patients felt that obesity impacted on mobility and whether a bespoke dietary advice service would assist them. *Materials & methods:* Data was collected on the height, weight and BMI of all patients with EBS attending EB clinics between January and November 2018. BMI was recorded as normal - 18.5 kg/m^2; overweight - 25.1-29. 9 kg/m^2; obese - 30-39.9 kg/m^2; and morbidly obese -≥40 kg/m^2. Between February and August 2019 patients attending clinic who were obese were asked to complete a survey that asked them to rate the impact of their EBS on their mobility (1-10 with 10 "mobility limited, feet extremely blistered most of the time"). It also asked if weight impacted on mobility and other areas of their body, if they wanted help in weight management and, if so, what help was required. *Results:* Data was collected on BMI in 90 patients: 2 (5%) were underweight, 41 (45.5%) were a normal BMI, 19 (21%) were overweight, 19 (21%) were obese and 9 (10%) were morbidly obese (total=31%). Fifteen questionnaires were completed. The mean score for the impact of EBS on mobility was 7.3, 13 felt their body weight impacted negatively on their mobility. All 15 identified their feet as affected by their EBS and obesity, with 9 identifying bra line, 3 inner thighs, 2 groin, 6 waist and 1 sock line as also affected. All fifteen wanted dietary advice mainly as one to one consultations or in group EBS sessions with additional local support. *Conclusions:* The incidence of obesity for patients in this survey was 31% compared with 26% for adults in the UK. Patients identified obesity as negatively impacting on their mobility and skin folds. We now plan to begin a pilot study to establish a supportive weight management programme for people with EBS and evaluate both weight loss and impact on mobility.

P20
NUTRITIONAL STATUS AND BONE MINERAL DENSITY IN CHILDREN WITH EPIDERMOLYSIS BULLOSA

Nataliya Balatska[1,3], Inna Gedeon[3], Lyudmyla Derevyanko[2], Tetyana Zamorska[4]
[1]Bogomolets National Medical University, [2]Kyiv Medical University, [3]Okhmatdyt National Children's Specialized Hospital, [4]Debra-Ukraine

Introduction & objectives: Epidermolysis Bullosa (EB) is a group of inherited diseases that are characterized by skin and mucosal fragility and blister formation. The various complications such as malnutrition, anemia, growth retardation, esophageal stenosis, and deformities may develop. Low bone mass and fractures recognized as complications of dystrophic forms of EB. To study the frequency of chronic protein-energy malnutrition in children with Epidermolysis Bullosa (EB) and its influence on bone mineral density. *Materials & methods:* 26 EB patients of age 5 to 20 years were carried out at the EB cabinet in Ukrainian National Children's Specialized Hospital «OKHMATDYT». Anthropometric data (height, weight, body mass index), child medical and nutrition history were obtained. BMD was measured by "Discovery wi". Short stature was diagnosed in 19.2% examined. Height adjustment (HAZ) formula was used for recalculating BMD Z-score for the total body and lumbar spine. *Results:* Chronic protein-energy malnutrition was found in 34.6 %. Low BMD was registered in 57 % of children; three of them (7.7. %) had osteoporosis with multiple vertebral fractures. Children with chronic protein-energy malnutrition had significantly lower Z-score at the total body (-3.21 ± 1.15 vs -1.18 ± 0.70 SD, $p<0.001$) and L1-L4 (-3.51 ± 1.96 vs -0.95 ± 0.86 SD, $p<0.001$). Furthermore, low BMD was found in each child in a group with chronic protein-energy malnutrition while in a group without malnutrition it was registered only in 18.7 %. Also, we found a significant correlation between body mass index and Z-score at the level L1-L4 ($r=0.61$, $p<0.01$) and total body ($r=0.65$, $p<0.01$). Likewise, body mass index influenced on the trabecular bone score ($r=0.48$, $p<0.025$). *Conclusions:* Chronic protein-energy malnutrition is one of the factors that have a great influence on bone mineral density in EB children. Therefore it is important for early diagnosis and ensures appropriate treatment approach.

P21
GAIT PATTERNS AND THE ROLE OF JOINT HYPERMOBILITY IN CHILDREN WITH EPIDERMOLYSIS BULLOSA

M.Wood[1] G Petrof[2], A.E.Martinez[2]
[1]Clinical Specialist Paediatric Physiotherapist, [2]Paediatric Dermatology Consultant, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Introduction & objectives: Background: In the literature, there is no evidence surrounding the incidence of altered gait patterns and the role of hypermobility in children with epidermolysis bullosa (EB). The aim of this study was to define the altered gait pattern and identify possible causes for it in this patient group. Our hypothesis was that gait kinetics are different from the age-normalised population and that hypermobility can affect the gait in these children. *Materials & methods:* We conducted a retrospective review of our EB database to identify children referred to our tertiary service since 2009 with at least one physiotherapy assessment noting an altered gait pattern. The GaitRite system (electronic pressure sensitive walkway) was used for assessment of gait; this equipment requires the patient to walk independently at their preferred speed allowing specific gait characteristics to be studied. The total contact area of the foot with the floor was analysed, areas of decreased force transmission identified and gait velocity and step length studied. *Results:* We identified 48 children out of 59 referrals (22M: 26F) with an altered gait pattern. 23 (48%) had RDEB, 17(36%) had EBS, 5(10%) JEB and 3 (6%) DDEB. The pathomechanical altered gait patterns were characterised by: altered load-bearing surface in contact with the floor (63%), short shuffling pattern with high cadence and decreased single support (42%) and equinovarus (toe walking) (6%). Hypermobility (as defined by the Beighton score) was present in 67% .Of these: 43% of RDEB, 88% of EBS, 100% of JEB and 67% of DDEB. 23% had orthotic footwear, which were well tolerated. There was a trend towards decreased velocity compared with age-matched equivalents in all groups. *Conclusions:* Children with all types of

EB commonly present with an altered gait pattern. This is multifactorial, often due to pain, bulky dressings, open wounds and scarring which leads to movement restriction and contractures. In our cohort, we also observed a high percentage of altered weight bearing in a pattern not previously recognised: pronation due to joint hypermobility. Although this is commonly associated with EBS, in our cohort it has also been noted across all subtypes of EB. Healthcare professionals should be aware of joint hypermobility and its effect on gait in the paediatric EB cohort. Assessment for orthotics and supportive footwear when tolerated; should be considered to improve foot posture, promote efficiency of the gait pattern and ultimately improve functional mobility.

P22
A UNIQUE COMBINATION OF CLINICAL AND GENOMIC FINDINGS IN A CHILD WITH LARYNGO-ONYCHO-CUTANEOUS SYNDROME: A CASE REPORT

S. Chottianchaiwat[1], C. Prodinger[2] ,G. Petrof[1], A.E. Martinez[1]
[1]Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [2]Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria

Introduction & objectives: An infant with typical features of laryngo-onycho-cutaneous syndrome (LOC) was referred to our EB service at 6 months old. LOC is a rare subtype of Junctional Epidermolysis Bullosa (JEB). Its hallmark is aberrant granulation tissue formation in the skin, larynx and eyes, which can lead to delayed wound healing, laryngeal obstruction and blindness. It is caused by mutations in the LAMA3A gene. We report a unique combination of clinical and genomic findings in a child with LOC which may provide some insight into disease pathology. *Materials & methods:* A skin biopsy from the right thigh was taken for immunofluorescence (IMF) staining and DNA extraction. In addition, blood for DNA extraction was collected from the child and both parents. The biopsy was examined by immunofluorescence microscopy using antibodies against laminin-332 (GB3 clone), type VII collagen (LH7.2 clone) and type IV collagen (COL94 clone). Staining was repeated on three separate occasions. *Results:* There was no major blistering at the dermo-epidermal junction on skin IMF. The major finding was severely reduced staining for laminin 332. Sanger sequencing of the LAMB3 gene revealed a single nucleotide insertion, c.1823insG, in exon 14, which was present as a homozygous finding in both genomic DNA and the skin of the patient. Both parents carried the same mutation in their genomic DNA. Unexpectedly, in DNA extracted from the skin of this child there was an additional loss-of-function single-allele heterozygous mutation, c.151insG, in the LAMA3 exon. This mutation was not presented in genomic DNA from the individual and parents. We report a 3-year old child with clinical features of LOC with absent laminin 332 expression in the skin and a homozygous mutation in LAMB3, both in peripheral blood and skin, which predicted a severe phenotype of JEB. An additional heterozygous mutation in LAMA3 was detected in DNA extracted from skin which was not present in the blood, and is characteristically associated with the LOC phenotype. Our patient is currently 3 years of age, she has much less severe skin involvement than we would expect to see in patients with JEB-severe generalised and extensive granulation tissue in the airway and eyes is much more characteristic of LOC syndrome. *Conclusions:* We report a child with a homozygous mutation in LAMB3 and an additional single heterozygous mutation of LAMA3 in the skin resulting in the clinical phenotype of LOC rather than JEB-severe generalised. This is the first report of this unique combination of clinical and genomic findings.

P23
CIRCULATING CELL-FREE MIRNA SCREENING FOR RDEB-SCC BIOMARKER IDENTIFICATION

R. Zauner[1], M. Wimmer[1], M. Ablinger[1], T. Lettner[1], S. Atzmüller[2], J. Pröll[2], J.W. Bauer[1], V. Wally[1]
[1]EB House Austria, EB Research, Department of Dermatology and Allergology, Salzburger Landeskliniken (SALK), Paracelsus Medical University Salzburg (PMU), [2]Center for Medical Research, Medical Faculty, Johannes-Kepler-University, Linz, Austria

Introduction & objectives: Contrary to UV induced skin cancer (UV SCC) patients suffering from the monogenetic skin disease recessive dystrophic epidermolysis bullosa (RDEB) are prone to developing particularly aggressive RDEB-SCC, which are considered as the main drivers in rising the mortality rate up to 80% by age 55 in RDEB patients. Currently no approved causal treatment other than tumor resection is available to EB patients. Early diagnostics of RDEB-SCCs is of high clinical significance, but is impaired in the context of RDEB by the fact that primary tumors predominantly arise in chronic non-healing wounds, rendering them hard to detect by visual inspection only. The diagnostic gold standard – histological screening of skin punch biopsies - represents a major burden for patients, therefore a sensitive low-invasive liquid biopsy alternative is of great relevance. Tumors have been reported to release short non-coding miRNAs into to the blood stream representing very stable biomarker molecules. Therefore we conducted a candidate biomarker profiling of serum derived, sequenced miRNome in a pilot study. *Materials & methods:* Illumina MiSeq miRNA sequencing was performed on libraries (Qiagen UMI) generated from miRNAs isolated from RDEB patients ($n=3$) diagnosed with SCC ($n=3$) and non-EB healthy control ($n=3$) serum samples. miRNAs were combined to form pairs in an auto-normalization approach. Machine learning algorithms were trained on serum miRNA-pairs and their performance evaluated. *Results:* Unsupervised principal components analysis (PCA) of normalized (rlog) and batch compensated (surrogate variable analysis, SVA) serum miRNAs demonstrated an inherent informative profile able to cluster samples with positive SCC diagnosis. Differential expression filtering comparing RDEB-SCC with RDEB was performed based on fold-change and significance. In an auto-normalization approach 58 miRNA-pairs were formed by combining 29 up with one down-regulated and one stable miRNA. A consensus serum signature derived from three machine learning algorithms reflected tumor presence and partially a tumor intrinsic miRNA profile. *Conclusions:* In summary we report the feasibility of a cell-free circulating miRNA based tumor prediction in serum samples with the current limitation of low sample size, which requires further validation studies in larger cohorts.

P24
RESULT OF SCREENING RUSSIAN EB PATIENTS BY WHOLE EXOME SEQUENCING

Julia Kotalevskaya[1,2], Natalia Marycheva[2,3] and Margarita Geht[2]
[1]Moscow Regional Clincal Research institue, Russian, [2]DEBRA Russia, [3]Moscow Scientific and Parctical Centre of Dermatology and Cosmetology

Introduction & objectives: Epidermolysis Bullosa (EB) is a group of rare genetic disorders associated with extreme skin fragility caused by mutations in 19 genes that coding for various components of the cutaneous basement membrane zone. There are four main types of EB: simplex (EBS), junctional (JEB), dystrophic (DEB) and Kindler syndrome. EB has autosomal dominant (D) and autosomal recessive (R) inheritance. Due to the clinical/genetic heterogeneity of the disease, the current methods available for diagnosing EB involve immunohistochemistry of skin samples

followed by single candidate gene by Sanger Sequencing, which are labour intensive and expensive diagnostics. Next-Generation Sequencing (NGS) of many genes represents a proper method for reducing the processing time and costs of EB diagnostics. *Materials & methods:* We included 27 patients from 26 unrelated families, previously clinically diagnosed with EB. There were 10 EBS patients, 3 dominant DEB (DDEB) patients and 14 recessive DEB (RDEB) patients. Genomic DNA was extracted from fresh peripheral blood samples using the QIAamp DNA Mini Kit, (Qiagen, USA), then to prepare genomic libraries for mass parallel sequencing we used KAPA Library Preparation Kit (Illumina, Roche). Nucleotide sequence was determined on a sequencer (HiSeq 1500, Illumina). Sequencing data reads were mapped to human reference genome (GRCh37/hg19). *Results:* We have tested samples from 27 patients using WES. Significant mutations were identified in all 27 probands. We found 18 earlier known mutations and 10 mutations didn't to have been previously reported. Genotype-phenotype correlation gives us opportunity to consider that 10 founded mutations are causative in our EB cases. Also the prediction of causality was performed using the in silico bioinformatics tool. The results of the prediction programs showed causality for our new variants as damaging. We identified 8 cases of EBS, 1 case of recessive EBS, 1 case of JEB, 2 cases of uncertain subtype of DEB, 1 case of DDEB, and 14 cases of RDEB. In total, we identified significant mutations in KRT5, KRT14, LAMB3, COL7A1 genes. We also found 29 variants of uncertain clinical significance that didn't appear to provide primary diagnoses in 12 additional EB genes (PLEC, ITGA3, ITGB4, ITGA6, DST, EXPH5, DSP, LAMA3, LAMC2, COL7A1, COL17A1, PKP1) in 20 of the 27 probands we tested. *Conclusions:* This study presents the implementation of a new diagnostic method for DNA diagnostics of EB that provides more comprehensive diagnosis than classical genetic approaches using PCR and direct sequencing in a gene-by-gene approach. NGS allows fast and cost-effective identification of gene mutation(s) and facilitates clinical prognosis and genetic counseling for a patient's family.

P25
SKIN MICROBIOME CHARACTERISTICS OF DYSTROPHIC EPIDERMOLYSIS BULLOSA PATIENTS

Samuelov Liat[1], Bar Jonathan[1], Sarig Ofer[1], Lotam-Pompan Maya[2,3], Dassa Bareket[4], Miodovnik Mor[1], Weinberger Adina[2,3], Segal Eran[2,3], Sprecher Eli[1,5]

[1]Division of Dermatology, Tel Aviv Medical Center, Departments of Computer Science and Applied Mathematics[2], Molecular Cell Biology[3] and Bioinformatics Unit, Life Sciences Core Facilities[4], Weizmann Institute of Science, Rechovot, Israel, [5]Department of Human Molecular Genetics and Biochemistry, Sackler Faculty of Medicine, Tel Aviv University

Background and objectives: The human microbiome project addresses the relationship between bacterial flora and their human host, in both healthy and diseased conditions. The skin is an ecosystem with multiple niches, each featuring unique physiological conditions, thus hosting different bacterial populations. The skin microbiome has been implicated in the pathogenesis of many dermatoses. We aimed at characterizing the skin microbiome of dystrophic epidermolysis bullosa (DEB) patients compared to healthy controls, using next generation sequencing, with the aim to develop novel therapeutic approaches targeting normal and abnormal bacterial populations within EB-associated wounds.
Patients and methods: Nine patients with confirmed DEB were sampled. Samples were taken from an untreated wound, perilesional skin and normal (uninvolved) skin. Age-matched controls were sampled from normal skin. Samples were taken under sterile conditions using dedicated sampling swabs. We used a special DNA extraction protocol to isolate microbial DNA which was then analyzed using next generation microbial 16S DNA sequencing and advanced bioinformatics tools. *Results:* We found increased staphylococci species in DEB patients lesional and perilesional skin, compared to their uninvolved, intact skin. Uninvolved skin of DEB patients displayed increased staphylococcal content when comparing to control skin. Furthermore, the uninvolved skin of DEB patients featured significantly different microbiome diversities (other than staphylococci) when compared to control skin. *Conclusions:* These findings suggest the existence of a DEB-associated unique skin microbiome which may be targeted by specific pathogen-directed therapies.

P26
NATURAL HISTORY OF EPIDERMOLYSIS BULLOSA SIMPLEX: PLANTAR KERATODERMA IS A MAJOR DETERMINANT OF THE CLINICAL COURSE

Antonia Reimer[1], Moritz Hess[2], Leena Bruckner-Tuderman[1] & Cristina Has[1]

[1]Department of Dermatology and EB Center Freiburg, [2]Institute of Medical Biometry and Statistics,Medical Faculty and Medical Center – University of Freiburg, Germany

Introduction & objectives: Among the four main epidermolysis bullosa (EB) types, EB simplex (EBS) is mostly regarded as the mildest one. However, disease burden is high even in localised EBS. The objective was to identify the major determinants of this disease burden. *Materials & methods:* In this retrospective study, all individuals with EBS presenting to a national reference center between February 2003 and July 2019 and with results of genetic testing available were included. Weight and height, presence of plantar keratoderma (PK), palmoplantar hyperhidrosis, pain, infection, use of analgesics, requirement of a wheelchair and information on working life were retrieved. Data analysis was performed using descriptive statistics, correlation of variables was assessed using mixed log-linear models and fixed effect models. *Results:* A total of 157 individuals were included in the study, thereof 76 (48.4%) with localised, 11 (7%) with intermediate and 38 (24.2%) with severe EBS. Rare subtypes included EBS with mottled pigmentation ($n=8$), EBS due to KLHL24 deficiency ($n=7$), EBS Ogna ($n=6$), EBS autosomal recessive ($n=6$), EBS with muscular dystrophy ($n=3$) and EBS with circinate erythema ($n=2$). In 75.8%, PK was observed. The frequency and appearance of PK (focal vs. diffuse) differed between EBS subtypes. While infants mainly showed plantar blisters and no PK yet, the mean age of transition to PK was as early as 4.3 years. Obesity and overweight were features of adults with EBS localised and severe. Pain occurred in all EBS subtypes, but was most common and intense in localised and severe subtypes. A third of patients ($n=52$) reported severely reduced mobility with blister-free walking distances shorter than 600 m and even less during summer months. Strikingly, 8.2% ($n=13$) of our cohort required a wheelchair occasionally or constantly. The need for a wheelchair was more common when PK was present ($P=0.0356$). The presence of PK correlated significantly with local infections, pain, obesity and requirement of a wheelchair. We suggest that these factors are linked in a vicious circle. *Conclusions:* The perception of EBS as a mild disease is outdated: both personal and socioeconomic burden are high. Early and thorough prevention and treatment of PK could be a therapeutic key in breaking the vicious circle of EBS.

P27
WHICH OUTCOME MEASURES ARE THE BEST FOR CLINICAL TRIALS IN EPIDERMOLYSIS BULLOSA?

Clare L Rogers[1,2], Matthew Gibson[1,2], Johannes S. Kern[3,4], Linda

Martin[5], Susan Robertson[6], Benjamin S Daniel[1,2], John C. Su[6,7], Dedee F Murrell[1,2]
[1]Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia, [2]Department of Dermatology, St George Hospital, Sydney, NSW, Australia, [3]Faculty of Medicine, University of Melbourne, Melbourne, VIC, Australia, [4]Department of Dermatology, Royal Melbourne Hospital, Melbourne, VIC, Australia, [5]Department of Dermatology, Sydney Children's Hospital, Sydney, NSW, Australia, [6]Department of Dermatology, The Royal Children's Hospital, Melbourne, VIC, Australia, [7]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia

Introduction & objectives: Background: The success of clinical trials in Epidermolysis Bullosa (EB) is dependent upon the availability of a valid and reliable scoring tool that can accurately assess and monitor the severity of disease. The Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) and Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa (iscorEB) were independently developed and validated against the Birmingham Epidermolysis Bullosa Severity (BEBS) score, but have never been directly compared. To compare the reliability, convergent validity and discriminate validity of the EBDASI and iscorEB scoring tools, to determine which is best for use in clinical trials in Epidermolysis Bullosa. *Materials & methods:* An observational cohort study was conducted in 15 patients with EB. Each patient was evaluated by 6 dermatologists with expertise in EB using the EBDASI and iscorEB-c scoring tools. Quality of life was assessed using the iscorEB-p and QOLEB measures. *Results:* The intraclass correlation coefficients (ICC) for inter-rater reliability were: EBDASI 0.942 and iscorEB-clinician (iscorEB-c) 0.852. The ICC for intra-rater reliability was 0.99 for both scores. The two tools demonstrated strong convergent validity with each-other. Both tools could discriminate between EBS and JEB, EBS and RDEB and DDED and RDEB. In addition, the EBDASI could discriminate between EBS and DDEB. *Conclusions:* Both scoring tools demonstrate excellent reliability. The EBDASI appears to better discriminate between EB types and disease severities.

P28
CLASSIFICATION OF TWO DISTINCT WOUND TYPES IN RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA: A NATURAL HISTORY STUDY

Claudia Eva Teng, BA[1], Daniel C. Solis, MD[1], Melissa Barriga, MSc[1], Shufeng Li, M. Peter Marinkovich, MD[1,3], Jean Y. Tang, MD, PhD[1]
[1]Dept. of Dermatology, Stanford University School of Medicine, Stanford, CA, [2]Invitae, San Francisco, CA Corresponding author: Jean Tang, MD PhD tangy@stanford.edu

Introduction & objectives: Characterizing the natural history of wounds in patients with recessive dystrophic epidermolysis bullosa (RDEB) is crucial as a comparison for future clinical trials. This study aimed to define and characterize two distinct types of RDEB wounds: chronic open wounds and recurrent wounds. *Materials & methods:* Two groups of RDEB participants were enrolled: one group had serial wound photographic assessments and another group reported on their wound type, wound size, pain, and itch in a survey. Wounds in the photograph cohort were traced and wound area was measured. Medical records were reviewed to determine wound type (chronic versus recurrent). In the survey group, participants self-identified wound type and estimated wound size in comparison to known objects (e.g. grapes, apples). A subset of patients completed both assessments. *Results:* 251 wounds were evaluated in 65 participants: 62 wounds were serially photographed in 25 participants for up to 72 weeks, 189 wounds were reported by 40 participants. 93 chronic open wounds (wounds that remained open for at least 12 weeks) and 158 recurrent wounds (wounds that healed within 12 weeks but re-blistered) were evaluated. Chronic open wounds were significantly larger at baseline (photographed group: 118.4 cm^2 versus 26.0 cm^2 recurrent wounds, $p<0.01$; survey group: chronic open wounds 66.3 cm^2 versus 44.7 cm^2 recurrent wounds, $p<0.01$). Chronic open wounds were significantly more painful (5.0 versus 2.4, $p=0.02$) and tended to be more pruritic (2.4 versus 1.5, Itch Man scale, $p=0.07$). Larger wounds were associated with more severe subtypes (e.g. generalized severe) and location on the posterior trunk. 22 participants with wound photographs also completed the wound survey. These participants were able to correctly classify their wounds (Kappa=0.5, 95% CI=0.3–0.8) and accurately estimate wound surface area (Kappa=0.6, 95% CI=0.4–0.8). *Conclusions:* This natural history study defines two RDEB wound types: chronic open wounds and recurrent wounds. These two wound types are important to differentiate when selecting target wounds in clinical trials, given their differing clinical course and patient reported outcomes. However, larger studies are needed to further examine these two wound types.

P29
RELATIONSHIPS BETWEEN WOUND SIZE, CLINICAL MANIFESTATIONS, AND QUALITY OF LIFE IN RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA: A GLOBAL CROSS-SECTIONAL SURVEY

E.S. Gorell[1], V. Eng[1], D. Solis[1], S. Choi[1], J. Nazaroff[1], M. de Souza[2], D. Murrell[3], M.P. Marinkovich[1], J.Y. Tang[1]
[1]Stanford School of Medicine, [2]deSouzaTech, [3]University of New South Wales

Introduction & objectives: A spectrum of skin disease severity exists in patients with recessive dystrophic epidermolysis bullosa (RDEB). The objective was to characterize how self-reported skin disease severity relates to wound characteristics, comorbidities, medication burden and quality of life (QOL) in RDEB patients. *Materials & methods:* RDEB patients were surveyed online through the global EBCare Registry. Patient self-reported outcomes included skin disease severity, wound characteristics, pain, itch, extra-cutaneous symptoms, and medications. QOL was measured using the validated Quality of Life in Epidermolysis Bullosa (QOLEB) instrument. *Results:* 85 RDEB patients reported on 1,226 wounds. 937 were recurrent wounds (classified by participants as "areas that are difficult to heal"), all of which healed within 12 weeks. 289 were chronic open wounds (classified by participants as "areas that have not healed for weeks/months"), none of which healed in 12 weeks. 52% of recurrent wounds and 30% of chronic open wounds were 40 cm^2. Overall skin disease severity was self-reported as mild (26%, 22/83), moderate (48%, 40/83), or severe (25%, 21/83). Worsening skin disease severity was significantly associated with larger wounds ($p<0.01$), history of squamous cell carcinoma ($p=0.04$), routine use of gabapentin ($p=0.02$), and routine use of opiates ($p=0.02$). Participants with more severe skin disease were more likely to use analgesics during dressing changes ($p=0.03$), including opiates ($p=0.02$). 85% of all participants reported itch; there were not significant differences in itch based on disease severity. Extracutaneous manifestations including history of anemia ($p<0.01$), gastrostomy tube use ($p=0.02$), and osteoporosis ($p=0.03$) were significantly associated with increased self-reported skin disease severity. The average QOLEB score (completed by 39 participants) was 20.0 ± 9. Larger wound size was associated with worse quality of life scores ($p=0.02$). *Conclusions:* This study shows clinically important correlations between larger wound size and worse QOL in RDEB. These larger wound areas were seen more in chronic open wounds, however recurrent wounds were reported more frequently, similar to findings in separate studies. This study supports the existence of these two

wound types and shows that patients understand their existence. Larger wounds correlated with self-reported disease severity and key clinical manifestations including history of squamous cell carcinoma, anemia, osteoporosis, and gastrostomy tube use. This study also revealed increased opiate usage routinely and during dressing changes in patients with more severe skin disease.

P30
TSP1 SECRETION IS DEPENDENT ON TYPE VII COLLAGEN IN DERMAL FIBROBLASTS

Qingqing Cao[1], Julio C. Salas-Alanis[2], Andrew P. South[1]
[1]Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [2]Instituto Dearmatologico de Jalisco, Guadalajara, Mexico

Introduction & objectives: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a severe skin fragility disorder caused by mutations in the COL7A1 gene, encoding type VII collagen (C7). C7 is a large extracellular matrix (ECM) protein and the main component of anchoring fibrils that attaches dermis and epidermis. Defective C7 in RDEB patients results in diminished dermal-epidermal adhesion leading to excessive scarring and fibrosis. Furthermore, RDEB patients with chronic fibrosis carry a high risk of metastatic squamous cell carcinoma (SCC) with more than 80% mortality by age 50, which makes RDEB a life-threatening disease. This work aims to investigate the mechanisms of thrombospondin-1 (TSP-1) driven TGFβ signaling leading to skin fibrosis in RDEB. *Materials & methods:* We utilized proximity ligation assay (PLA) and western blotting to measure TSP-1 localization and expression, and we investigated whether TANGO1 participates in TSP-1 secretion in both normal human fibroblasts and RDEB fibroblasts *Results:* TSP-1 secretion is dependent on TANGO1, a transmembrane protein facilitating bulky protein transport from ER to Golgi, which is disrupted by dysfunctional C7. *Conclusions:* TSP-1 secretion to ECM is directed by C7 and the disruption of which, when C7 is absent, will result in abnormal TSP-1 secretion contributing to a fibrotic and tumor promoting ECM.

P31
CEMIPLIMAB FOR METASTATIC SQUAMOUS CELL CARCINOMA IN EPIDERMOLYSIS BULLOSA

G.M. O'Sullivan[1], J. Clapham[1], C. Mackenzie[1], D.T. Greenblatt[1], C. Bernardis[2], S. Papa[3], J.E. Mellerio[1]
[1]St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust.[2]Department of Plastic Surgery, Guy's and St Thomas' NHS Foundation Trust,[3]Department of Oncology, Guy's and St Thomas' NHS Foundation Trust

Results: A twenty-eight year old female with recessive dystrophic epidermolysis bullosa (RDEB) gave a 2 week history of a rapidly enlarging mass on the right upper chest wall. She had previously had squamous cell carcinomas (SCCs) excised from the right side of the neck one and three years previously. On examination there was a 3cm fluctuant mass on the right upper chest wall. An urgent ultrasound-guided fine needle aspirate confirmed the mass to be a subcutaneous SCC deposit. An urgent MRI demonstrated a 4.3 x 2.9 x 4 cm mass on the right upper chest wall, abutting the right pectoralis muscle. The case was discussed at the skin cancer multidisciplinary team meeting; she was not felt to be a suitable candidate for curative surgery or radiotherapy, but it was felt that she might benefit from electrochemotherapy and cemiplimab therapy. Over the next few weeks the SCC metastasis enlarged and began to ulcerate. She had debulking surgery and electrochemotherapy. She subsequently went on to have intravenous cemiplimab every three weeks and has now had eight doses of cemiplimab. To date no cemiplimab related adverse events have occurred. Treatment is well tolerated, requirement for analgesia has significantly reduced and sleep has improved. Radiologic stable disease has been achieved with clinical evidence of reduction in tumour bulk. Cemiplimab is a monoclonal antibody immune checkpoint inhibitor (CPI) that binds the inhibitory checkpoint receptor programmed death-1 (PD-1). It is the first CPI to receive a license for the treatment of locally advanced or metastatic cutaneous SCC [1]. In the registration phase II trial, 47% (95% CI, 34 to 61) of patients with metastatic cutaneous SCC had an objective response [2]. There are no published reports of the use of cemiplimab in EB-associated SCC, however. To date our patient has had stabilisation of rapidly progressing disease, with clear symptomatic improvement and no adverse events.

P32
ELECTROCHEMOTHERAPY FOR METASTATIC SQUAMOUS CELL CARCINOMA IN EPIDERMOLYSIS BULLOSA

G.M. O'Sullivan[1], J. Clapham[1], C. Mackenzie[1], D.T. Greenblatt[1], C. Bernardis[2], A.D. MacKenzie Ross[2], J.E. Mellerio[1]
[1]St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, [2]Department of Plastic Surgery, Guy's and St Thomas' NHS Foundation Trust

Results: We describe our experience of electrochemotherapy (ECT) in 3 patients with advanced cutaneous squamous cell carcinomas (SCCs) associated with recessive dystrophic epidermolysis bullosa (RDEB). ECT involves electroporation and the delivery of chemotherapy to tumours. A recent systematic review of ECT in the management of a variety of cutaneous metastases found it was effective for palliative treatment and was generally well tolerated [1]. Patient 1 was a 23 year old female who presented with an ulcerated area over the left knee at a site of a previously excised SCC. She had ECT to help with management of pain and to impede tumour growth. She received bleomycin systemically and 303 sequences with a linear electrode. She had short term pain following ECT, but there was no significant change in the size of the tumour. She subsequently required an above knee amputation but developed metastatic deposits in the left inguinal lymph nodes and passed away 3 months later. Patient 2, a 24 year old male presented with a nodule on the left hand at the site of a previously excised SCC. This was excised and SCC confirmed on histology. He developed a further recurrence with in transit and axillary metastases. He had a left below elbow amputation and axillary lymph node dissection. He developed a further recurrence on the amputation stump and opted for ECT after multidisciplinary discussion. He had bleomycin systemically and 500 sequences with a linear electrode. After ECT he became septic, requiring admission and intravenous antibiotics. Following this acute episode his pain control and sleep improved, however his local disease progressed and he passed away 2 months later. Patient 3, a 28 year old female presented with a rapidly enlarging nodule on the right chest wall. She had previous SCCs excised from the right neck. A fine needle aspirate confirmed SCC. She had debulking surgery followed by bleomycin systemically and 61 sequences to the wound with a linear electrode. ECT was well tolerated, pain control improved and tumour growth slowed. She has now commenced cemiplimab with disease stabilisation. ECT treatments were performed according to the 2006 standard operating procedure [2]. To our knowledge, there is only one published report describing ECT in 3 EB patients with advanced SCC [3]. Our experience suggests it may be useful for debulking and palliation in locally advanced RDEB-associated SCC although further experience of this modality is required to more fully assess its potential role in these tumours.

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P33

EPIDERMOLYSIS BULLOSA (EB) WITHOUT BORDERS: A SUCCESSFUL EXAMPLE OF INTERNATIONAL COLLABORATION

James D, Hiremagalore R, George S*, Moss C, Ogboli M*
*Birmingham Women's and Children's NHS Foundation Trust and *Manipal Hospitals, Bangalore & Centre for Human Genetics, Bangalore*

Results: All of us working with EB are very conscious that care and facilities are spread unevenly around the globe. Despite the extensive reach of Debra International, many countries remain unaffiliated, with medical professionals working with minimal resources and patients struggling to fend for themselves. The UK is a melting pot of different nationalities and our city in particular has a rich diversity of cultures. This has encouraged us to look outwards and establish links with medical professionals in resource-limited settings. After several years of individual visits between our countries sharing knowledge, a unique and ambitious project was developed, involving the whole EB multiprofessional team from our Hospital visiting a centre in India, and organizing a 2 day educational event with the local team, sharing the stage with colleagues from across the continent The conference was widely advertised in India, and EB professionals from other centers were able to attend. The program consisted of presentations on various aspects of EB clinical features and management given jointly by the relevant healthcare professionals from the two countries. The meeting was facilitated by Debra's EB Without Borders. The visitors were self-funded with limited Debra travel grants for nurses and therapists. On the third day we held an EB Family support meeting - the first to be held in India. Patients travelled many miles to be there and enjoyed presentations and one-to-one discussions with the professionals. The feedback was overwhelmingly positive. All the health professionals from both countries found the experience informative, enriching and rewarding on both professional and personal levels. Patients were thrilled to meet other affected families and expressed the view that they didn't want the day to end. The event has been followed by further exchanges and information-sharing. This event demonstrated the deep commitment felt by those working with EB and renewed our determination to provide the best possible care for all patients wherever they live. We wholeheartedly recommend such visits to our colleagues.

P34

THE IMPACT OF LOW-DOSE CALCIPOTRIOL OINTMENT ON WOUND HEALING, PRURITUS AND PAIN IN PATIENTS WITH DYSTROPHIC EPIDERMOLYSIS BULLOSA

Christina Guttmann-Gruber[1], Josefina Piñón Hofbauer[1], Birgit Tockner[1], Victoria Reichl[1], Peter Hofbauer[2], Martin Wolkersdorfer[2], John E. Common[3,4], Anja Diem[5], Katharina Ude-Schoder[5], Wolfgang Hitzl[6], Florian Lagler[7], Julia Reichelt[1], Johann W. Bauer[8], Roland Lang[8] and Martin Laimer[8]**
*[1]EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, [2]Landesapotheke Salzburg, Department of Production, Hospital Pharmacy, Salzburg, Austria, [3]Institute of Medical Biology, A*STAR, [8]A Biomedical Grove, Immunos #0[6]-0[8], Singapore, Singapore, [4]Skin Research Institute of Singapore, A*STAR, [8]A Biomedical Grove, Immunos #0[6]-0[6], Singapore, Singapore, [5]EB House Austria, Outpatient Unit, Department of Dermatology and Allergology, Paracelsus Medical University, Salzburg, Austria, [6]Research Office Biostatistics, Paracelsus Medical University, Salzburg, Austria, [7]Institute for Inborn Errors of Metabolism and Department of Pediatrics, Paracelsus Medical University, Salzburg, Austria, [8]Department of Dermatology and Allergology, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria;*equally contributing authors*

Introduction & objectives: Vitamin D3 (VD3) is an essential factor for skin homeostasis and proper wound healing, facilitating the ability of keratinocytes to recognize and respond to injury and infection by enhancing pathways of tissue repair and antimicrobial defense. Consistently, own previous *in vitro* studies using 100 nM of the VD3 analogue calcipotriol demonstrated augmented microbial defense and accelerated wound closure in 2D cell culture models of dystrophic epidermolysis bullosa (DEB). Importantly, the same concentration of calcipotriol exhibited significant antineoplastic effects against tumor cells. Based on this favorable data as well as evidence revealing VD3 deficiency to be highly prevalent in DEB, we hypothesized that topical VD3 application at sites of injury and chronic non-healing wounds could impart a clinical benefit to this patient cohort. *Materials & methods:* We initiated a placebo-controlled, randomized, double-blind, cross-over phase II clinical trial to evaluate the efficacy of a low-dose calcipotriol ointment (0.05 µg/g, ≈ 121 nM) in promoting wound healing in DEB patients (EudraCt.: 2016-001967-35). As secondary objectives, we evaluated safety and impact of therapy on bacterial wound colonization, pruritus and pain. Patients were randomized into two treatment arms and applied 1 g of ointment per day (containing either verum or placebo) topically onto two designated wounds (≥6 cm^2 each) over a period of 4 weeks. After a two-month washout phase, patients crossed-over to the other treatment arm. Patients were assessed at days 0, 14 and 28, when wounds were photographed and swabbed for microbiome profiling. In addition, pruritus and pain scores were determined using a visual analog scale. Six out of nine enrolled patients completed both intervention phases and were included for analysis. *Results:* Calcipotriol treatment accelerated wound healing, resulting in a significant mean reduction in wound size of 88.4% compared to 65.6% in the placebo arm at day 14. At day 28, effects on wound closure equalized with no differences longer observed between treatment arms. Notably, application of calcipotriol resulted in a significant and steady reduction in itch scores over the course of treatment, whereas no change was reported in the placebo arm. Both verum and placebo significantly reduced pain by day 28. Importantly, no adverse effects were observed at any time during the trial. The effect of each treatment arm on wound microbiota is still under investigation. *Conclusions:* Preliminary data from this study indicate that topical low-dose calcipotriol ointment may accelerate wound healing and reduce the burden of itch in DEB.

P36

SILICONE-BASED DRESSINGS AND FIXATION DEVICES IN THE MANAGEMENT OF EPIDERMOLYSIS BULLOSA: EVIDENCE REVIEW OF THIRTY YEARS OF CLINICAL EXPERIENCE

Ulana Pawlak[1] and Mark F. Rosenberg[2]
[1]MD, Global Medical Affairs and Safety Manager, Mölnlycke® Health Care, Gothenburg, Sweden,[2]Medical Writer, Medical and Economic Affairs, Mölnlycke® Health Care, Gothenburg, Sweden

Introduction & objectives: Whilst pharmaceutical and medical technology industries strive to improve health and well-being of patients with epidermolysis bullosa (EB) and provide innovative

solutions, pain-free daily wound care remains to be a cornerstone in the management of EB. Secondary infections and malignancies, scar formation with subsequent deformities due to repeated trauma and chronic inflammation are common complications which can be often avoided via the appropriate management of blisters. Atraumatic silicone-based dressings and fixation devices have been demonstrated to be suitable for EB for both protection from trauma and coverage of existing blisters. *Materials & methods:* This is a literature review summarising the published evidence on the use of silicone-based dressings and fixation devices which had been endorsed in the recent consensus documents on wound care in EB. *Results:* Due to the rarity of the condition, the majority of authors relied on their clinical experience and patient preferences in their wound management. Generally, it was suggested that the silicone-based foam dressings could be used for superficial erosions, protection from friction and shear forces. Soft silicone contact layers were suitable for ulcers, pruritus and hypergranulation, whereas a thin silicone foam dressing with or without exudate transfer layer was preferred for the prevention of digital webbing. Non-adherence to the wound bed was recognized as a critical feature determining the choice of the dressings. The soft silicone contact layer was reported to significantly alleviate pain and anxiety during dressing changes in several case studies in children. For instance, in a five-year old boy with severe EB complete epithelialization was achieved within 4 weeks with a restored previous hand function. Apart from the management of bullae, the soft silicone contact layer could be used to secure intravenous cannulae without blistering around the insertion site. Schumann et al 2005 reported on 22 patients aged between 1 and 91 years with bullous skin diseases (13 with EB and 9 patients with acquired bullous conditions) treated with a soft silicone foam dressing. Good wound healing was reported in the majority of patients. Minimal pain was experienced during dressing changes and no allergic reactions occurred. *Conclusions:* There were dozens of published case studies which demonstrated that the silicone-based dressings and fixation devices performed well, alleviated pain and improved clinical outcomes in patients with EB and related conditions.

P37
A CROSS-SECTIONAL OBSERVATIONAL STUDY OF PATIENTS WITH EPIDERMOLYSIS BULLOSA TO UNDERSTAND USAGE PATTERNS OF SILICONE-BASED DRESSINGS AND FIXATION DEVICES

Kristina Blom[1], Jane Clapham[2] ,Viktoria Körner[3], and Ulana Pawlak[4]

[1]Ph.D., Clinical Development Manager and Evidence Strategist, Molnlycke® Health Care, Gothenburg, Sweden, [2]Lead EB Nurse Specialist at Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [3]Clinical Development Manager and Evidence Strategist, Mölnlycke® Health Care, Gothenburg, Sweden, [4]MD, Global Medical Affairs and Safety Manager, Mölnlycke® Health Care, Gothenburg, Sweden

Introduction & objectives: Gaining insight into the experiences of patients can help shape best practice and optimise clinical outcomes. This is particularly relevant to the management of patients with epidermolysis bullosa (EB) who should always be involved in the selection of dressings as they are expert regarding their skin. A cross-sectional observational study of patients with various forms of EB was conducted to collect their experiences of silicone-based dressings and fixation devices. *Materials & methods:* Patients were asked to complete a series of 22 questions to capture demographic data, EB diagnosis, product usage patterns, and perception of the products' performance and safety. *Results:* Nineteen patients completed the survey. Six (32%) patients were 50 years old. Six (32%) respondents were male and 13 (68%) were female. Six (32%) respondents were diagnosed with EB simplex, 3 (16%) with Junctional EB, and 10 (53%) with Dystrophic EB. None was diagnosed with Kindler's syndrome. All products included in the survey had been used by the respondents. Only 2 (11%) patients had used a soft silicone wound contact layer, whereas a thin silicone-based foam dressing had been used by 17 (89%) patients. Just over half (53%) of the respondents had used an elasticated tubular bandage. Reported dressing change frequency ranged from 4 times per day up to once a week (average 1-2 per day). Length of time taken to undertake a dressing change ranged from 5 minutes to 4 hours (average 1 to 2 hours). In general, the products were reported to be easy to use and compatible with other topical treatments. With respect to absorbent dressings, their absorptive capabilities were perceived by all users to be very good. All dressings were well tolerated, however, there were 2 reports of a silicone foam dressing for moderately exuding wounds having caused pain in patients with Junctional EB. *Conclusions:* The survey indicates that the silicone-based dressings and fixation devices used by the respondents perform well and are well tolerated. The findings also highlight the importance of understanding the design features of different dressings in order to ensure that dressing choice is aligned with the needs and wishes of users.

P38
RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA DUE TO ALMOST COMPLETE HEMIZYGOUS DELETION OF COL7A1 AND A MUTATION C.425A>G MIMICKING HOMOZYGOUS STATUS

Alfred Klausegger[1], Niklas Jeschko[1], Jan Cemper-Kiesslich[2], Anja Diem[1], Gabriele Sander[3], Dieter Kotzot[3], Johann W. Bauer[1]

[1]EB House Austria and Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, [5]0[2]0 Salzburg, Austria, [2]Interfaculty Department of Legal Medicine, University of Salzburg, Ignaz Harrer-strasse [79], [5]0[2]0 Salzburg, Austria, [3]Division of Clinical Genetics, Department of Pediatrics, Paracelsus Medical University Salzburg, Salzburg, Austria

Results: Recessive dystrophic epidermolysis bullosa (RDEB) is a rare heritable blistering skin condition caused by loss-of-function mutations in the COL7A1 gene. Mutation analysis of a meanwhile 3-year old patient of an Austrian family diagnosed with RDEB resulted in a discrepancy of COL7A1 genotyping and raised the question of being uniparental isodisomy (UPD) or a hemizygous deletion. Gene transmission from only one parental part leading to homozygosity is usually regarded as UPD. NGS eb panel sequencing confirmed by Sanger sequencing identified two homozygous gene variants, the well-known hotspot mutation c.425A>G in exon 3 and a SNP c.6654C>G in exon 84, which were heterozygous in her mother and wildtype in the father. The implementation of a paternity test confirmed the affiliation of the child to the father. Analysis of microsatellite markers encompassing COL7A1 by RFLP using the Gene Mapper software showed heterozygosity, narrowing the region in between to be a short part of UPD or deletion. Finally, multiplex ligation-dependent probe amplification (MLPA) copy number analysis from the patient´s and parent´s DNA revealed a paternally derived hemizygous deletion spanning from exon 3 to exon 118. Herewith we report the 3rd microdeletion covering COL7A1 in the literature of epidermolysis bullosa. A detailed study to define the breaking points is currently ongoing.

P39
TREATMENT OF MULTIFACTORIAL ANAEMIA IN ADULTS WITH SEVERE EPIDERMOLYSIS BULLOSA USING INTRAVENOUS FERRIC

CARBOXYMALTOSE: A SINGLE INSTITUTION, OBSERVATIONAL, RETROSPECTIVE STUDY

A. Alheggi[1], J.A. McGrath[1], L. Hubbard[2], D.T. Greenblatt[1] and J.E. Mellerio[1]

[1]St John's Institute of Dermatology, [2]Dietetic Department, Guy's and St Thomas' NHS Foundation Trust, London, UK

Introduction & objectives: Anaemia in epidermolysis bullosa (EB) is multifactorial and is a common complication in severe subtypes. Iron deficiency is a significant contributing factor. Anaemia impacts on quality of life and may impair wound healing. Oral iron supplementation may cause gastrointestinal side effects and has variable absorption. There is limited evidence steering best practice on management of anaemia, or evidence on the use of intravenous (IV) iron in EB patients without concurrent erythropoietin (EPO). *Materials & methods:* We conducted an observational, retrospective, single institution study to investigate the efficacy and safety of periodic IV ferric carboxymaltose (FCM) in maintaining haemoglobin (Hb) levels ≥ 100 g/l in patients with severe EB seen between January 2009 and January 2019. Data collection and statistical analysis were conducted using SPSS-V.25 and Microsoft Excel. *Results:* Forty-three adults (60.5% female; mean age 35.2 (17 -71) years) with severe EB complicated by multifactorial anaemia were treated with IV FCM. EB subtypes included recessive dystrophic EB (RDEB) (n=38), dominant DEB (DDEB) (n=3) and generalized intermediate junctional EB (JEB-I) (n=2). All patients received IV FCM (Ferinject ®, Vifor Pharma UK Limited) infusion according to Hb level and body weight at baseline and received repeat infusions after a 12-16 week interval if indicated. All patients received at least one infusion of FCM and 25 (58%) received up to 6 infusions. Fourteen patients (32.5%) had previously received IV iron sucrose (Venofer®, Vifor Pharma UK Limited). Additionally, 5 of these 14 patients (35.7%) required blood transfusion at some stage. At each time point after FCM infusion, mean Hb levels improved. After initiation of FCM, Hb levels were maintained ≥ 100 g/l in all patients. The improvement in Hb level achieved statistical significance, apart from week 12 post 3rd infusion when the mean Hb pre-infusion was above 120 g/l. In contrast, treatment with IV iron sucrose resulted in an initial improvement of mean Hb but levels remained persistently below 100 g/l. Parenteral iron sucrose was discontinued in 3 of 14 patients (21.4%) due to side effects or poor efficacy, unlike FCM which was well tolerated. *Conclusions:* Despite the limitations of retrospective review, our results suggest that IV FCM as maintenance therapy resulted in an overall improvement in Hb levels in patients with EB-associated anaemia. We recommend IV FCM as first-line treatment for anaemia with Hb levels below 100-110 g/l in this patient group, repeated 3-4 monthly according to laboratory and clinical response.

P40
THE ITALIAN REGISTRY FOR PATIENTS AFFECTED BY EPIDERMOLYSIS BULLOSA

Michela Brena[1], Gianluca Tadini[1], Paola Marchisio[1], Cinzia Pilo[2], Sophie Guez[1]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Paediatric Highly Intensive Care Unit, Milan, Italy, [2]REB Foundation, Milan, Italy

Introduction & objectives: The reduced patient number, their geographic dislocation, and the difficulty to identify subpopulations for targeted studies hinder therapy development for epidermolysis bullosa (EB). In the field of rare diseases, registries can be a major determinant for successful translational research. Therefore, several EB patient registries have been established in other countries by initiative of researchers as well as patient organizations. However, in Italy, there has not been a systematic collaborative effort of this kind so far. To fill this gap, the Italian EB registry Foundation (REB) was established in 2017 by Debra Italy and since then has been working with major clinical centres to set up and managing the first multicentre and multi-stakeholder EB registry in the country. *Materials & methods:* The REB developed a longitudinal, multicentre clinical study that relies upon a comprehensive data collection from EB patients in Italy. So far, two Italian EB centres were involved. However, REB is seeking collaboration from other national clinical centres in order to eroll the highest possible number of patients and to increase collaboration among participating sites. The registry complies with the GDPR regulation and ensures the highest standards for data protection. It is equipped with a Patient Portal where patients access and fill in ad hoc Quality of Life questionnaires. Aggregated data analysed by means of queries, will inform about the epidemiological and clinical features of the patient population. This knowledge will be paramount to plan new researches. *Results:* Enrolment started in 2019 and, to date, approximately 1/3 of the patients already treated in the involved EB centres have been enrolled. *Conclusions:* Through systematic collection of patient data, registries allow a better understanding of diseases, facilitate clinical, epidemiological and basic research and improve post marketing surveillance of drugs and off-label therapies. A functional EB Registry will enable genotype-phenotype correlation and improve diagnosis, disease course prediction and counselling. It will also be instrumental to foster translational research as well as the recruitment of the patients in future trials. Furthermore, the Italian EB Registry aims to become a platform for collaboration among physicians, researchers and patients both nationally and internationally, where it can foster exchanges with the European Reference Networks (ERN), and specifically with ERN-Skin. Finally, this resource will be a means for sharing and disseminating data and new knowledge.

P41
CORD BLOOD PLATELET GEL IN DERMOLYTIC EPIDERMOLYSIS BULLOSA

Michela Brena, Gianluca Tadini, Paola Marchisio, Paolo Rebulla, Sophie Guez

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Paediatric Highly Intensive Care Unit, Milan, Italy

Introduction & objectives: The most common form of epidermolysis bullosa (EB) is dermolytic epidermolysis bullosa (DEB), caused by mutation in collagen VII gene, inherited as an autosomal dominant or recessive trait. Both type of inheritance and specific mutation determine the severity of clinical lesions, which are typically located on friction-exposed areas. Lesions can be acute, with spontaneous resolution within few days or weeks, or chronic among months or years. We used allogeneic cord blood platelet gel (CBPG), a novel blood component obtained from umbilical cord blood of healthy, term neonates, for the treatment of skin ulcers in patients with DEB. *Materials & methods:* During 2014-2018 our department treated 15 patients and a newborn baby affected by DEB. Patients were treated with several CBPG application (ranging from 3 to 8), weekly or every 3 days. The newborn had deep skin ulcers localized on both shins, a site frequently observed in DEB patients since it is a position prone to friction in uterus, often forcing the newborn's foot into a bent pose. *Results:* Clinical results were different, depending on the age of the lesions: acute wounds had a significant benefit from the CBPG application with complete recovery and skin re-epithelisation, with faster healing comparing to standard medications and a maintenance during follow-up. On the other side, CBPG was not equally effective on chronic, granulating lesions, but its use was helpful in reducing bleeding and exudate, with a significant improvement of the wounds. The newborn has been treated weekly with CBPG for 4 weeks, leading to a complete resolution of the lesions at the end of treatment, with a maintenance during follow-up, without requi-

ring any additional reconstructive surgery for aesthetic/functional reasons. *Conclusions:* The clinical results support the evidence on safety and clinically efficacy of CBPG for the topical treatment of skin lesions in DEB patients. Even if the best results have been obtained on acute lesions rather than in chronic lesions, it is important to point out that even a partial reduction of the ulcers can significantly reduce the risk of neoplastic transformation and have a positive impact on patients' quality of life. In conclusion, CBPG is a promising and safe option for treating skin lesions in DEB patients, even in the newborn, in order to prevent fluid loss, superinfections, retracting permanent scar development or evolution into neoplastic transformation.

P42
HAND CONTRACTURE DEVELOPMENT IN CHILDREN WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Nicky Jessop and Catherine Miller, Occupational Therapists, Anna Martinez and Gabriela Petrof
Paediatric Dermatology Consultants and Gill Smith, Plastic Surgery Consultant

Introduction & objectives: Children with recessive dystrophic epidermolysis bullosa (RDEB) develop hand contractures which impact on function and quality of life. Systematically recorded data on the progression of hand contractures is limited. We use the Assessment of Hand Contractures in Epidermolysis Bullosa (ACE) routinely in clinical practice. We report our findings regarding age of onset and sequence of hand contracture development in children with RDEB. *Materials & methods:* We carried out a retrospective case note review of patients who attended our specialist paediatric EB centre. We included children with diagnosis of severe generalised RDEB, without a history of hand surgery and regardless of conservative hand therapy routines. All patients had the ACE administered by an Occupational Therapist. The three typical component contractures, web spaces (pseudosyndactyly), finger flexion and thumb adduction were scored as mild, moderate or severe. They were also combined to provide a Hand Deformity Grade which gives an easily understood impression of the overall hand deformity. Descriptive data analysis was used to present the results. *Results:* We completed 186 assessments on 25 children aged 0-16 years (12 males, 13 females) between 2010 and 2019. We analysed the Hand Deformity Grades (HDG) and identified four significant time points regarding hand contracture development: At birth, none of the children had hand contractures; At age 2 years, half of the children had a mild HDG, involving web space contractures in the majority of cases; At age 6 years, all of the children had a HDG varying between mild, moderate and severe; At age 12 years, all of the children had a moderate or severe HDG, involving all three components in the majority of cases. Furthermore, we identified a trend in the sequence of contracture development: Web space contractures develop first, are subtle and progress slowly over time; Thumbs adduction contractures develop next and also progress slowly over time; Finger flexion contractures emerge later and progress more rapidly. *Conclusions:* We have systematically gathered data on hand contracture progression in children using the Assessment of Hand Contractures in Epidermolysis Bullosa (ACE). Despite the limitations of a small sample size and using a tool that is not yet validated, our results provide more detailed information about the age of onset and the sequence of hand contracture development. These findings show a predictable course of progression that may be used to guide treatment.

P43
THE ASSESSMENT OF HAND CONTRACTURES IN EPIDERMOLYSIS BULLOSA: A CLINICAL TOOL FOR THE SYSTEMATIC ASSESSMENT OF HAND CONTRACTURES

Nicky Jessop and Catherine Miller, Occupational Therapists, Anna Martinez and Gabriela Petrof,
Paediatric Dermatology Consultants and Gill Smith, Plastic Surgery Consultant

Introduction & objectives: There is wide agreement that patients with recessive dystrophic epidermolysis bullosa (RDEB) develop hand deformities in childhood, which impact on function and quality of life. The literature describes various methods to assess web space (pseudosyndactyly), finger flexion and thumb adduction contractures. Many of these methods lack the sensitivity to detect emerging contractures or recurrent contractures following surgery. There is no widely accepted clinical tool for the systematic assessment of the whole hand. We introduce the Assessment of Hand Contractures in Epidermolysis Bullosa (ACE) as a clinical tool. *Materials & methods:* We developed the ACE through clinical practice to enable sensitive measurement of hand contractures in children with RDEB. It scores three typical component contractures: web spaces, finger flexion and thumb adduction. Each component is graded as mild, moderate or severe. Additionally, these component scores are combined to provide a Hand Deformity Grade to give an impression of the overall hand deformity. The ACE also records wrist and forearm motion, splint and glove wear and patient satisfaction with hand function and appearance. We surveyed the expert opinion of Hand Surgeons, Dermatologists and Occupational Therapists regarding the content, sensitivity and clinical usefulness of this tool. We completed an inter-rater reliability study for the web space component. *Results:* We use the ACE routinely to monitor the hands of patients with RDEB with and without a history of hand surgery. We consider it to be a systematic tool with a structured method of administration. It is more sensitive than existing assessments, particularly for the web space contracture. We use the Hand Deformity Grade to communicate an impression of overall hand deformity to the clinical team. From our survey of experts, we received constructive feedback and subsequently made minor improvements. Our inter-rater reliability study found good agreement. Validation is the next step in the development of the ACE. *Conclusions:* The ACE is a clinical tool that can be used for the systematic assessment of hand contractures in children with RDEB. It can be used as an outcome measure following hand surgery. It helps clinicians and families make informed decisions about treatments. It can also be used together with functional measures to report on how contractures impact on hand function and quality of life. If validated it has the potential to be used to report on the natural progression of hand contractures.

P44
MODELING FIBROSIS IN EPIDERMOLYSIS BULLOSA PATIENT FIBROBLASTS

G. Tartaglia[1], I. Fuentes[1,2], T. Webster[1], A. South[1]
[1]Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA, USA, [2]Fundación DEBRA Chile, Santiago, Chile

Introduction & objectives: Recessive Dystrophic Epidermolysis Bullosa (RDEB), otherwise known as butterfly disease, can be classified as a fibrotic disorder due to its excessive extracellular matrix (ECM) turnover, accumulation of fibrillar collagen, elevated TGF-beta signaling, and tissue scarring. Fibrosis is also a major concern in RDEB patients because it contributes to cutaneous squamous cell carcinoma development and metastasis. Previous work in the lab has developed a 3D tissue-engineering model of fibrotic ECM deposition by primary RDEB fibroblasts. We have used this model to screen 1,443 FDA approved compounds and identified a number with potential therapeutic application. In

addition to identifying compounds that delayed fibrosis, we also observed three compounds that accelerated fibrosis compared with the TGF-beta positive control. The three compounds are a nicotinic receptor inhibitor, an antineoplastic agent, and an integrin inhibitor. *Materials & methods:* In order to investigate the mechanisms of action of these compounds we first performed dose-response time courses, measured TGF-beta activation and collagen content, and quantified protein expression profiles of fibrotic markers after treatment of RDEB fibroblasts and normal fibroblasts. In addition, we assessed proliferation and viability of each compound at varying doses. *Results:* We noted an unexpected downregulation of downstream targets of the canonical and non-canonical TGF-beta signaling pathways, using phospho-SMAD3 and phospho-AKT, in cells treated with the antineoplastic agent. Collagen levels also differed due to compound treatment; however, we also noted that RDEB fibroblasts secrete more collagen than normal fibroblasts do, which offers another insight into the complexities behind collagen's role in fibrosis. *Conclusions:* With these data, we aim to further elucidate the intricacies behind the mechanism of action of fibrosis in RDEB fibroblasts.

P45
PROOF OF CONCEPT AND CLINICAL FOLLOW UP OF A DISPOSABLE DRESSING GLOVE AND REINFORCED WEB SPACER GLOVE FOR EPIDERMOLYSIS BULLOSA

T. Graham[1], S. Sooriah[1], R. Box[2], T. Meydan[3], P. Williams[3], S. Hashimdeen[3] and P. Grocott
[1]King's College London, [2]Guy's and St. Thomas' NHS Foundation Trust, [3]Cardiff University

Introduction & objectives: Current hand devices to delay webbing and contractures are often not tolerated. Dressings are bulky, baggy and impede hand function. To overcome these problems a disposable dressing glove and reinforced web-spacer glove, were co-designed with people with Recessive Dystrophic Epidermolysis Bullosa (RDEB). The objective of this study was to evaluate the performance of the novel gloves and analyse the costs. *Materials & methods:* An N-of-1 proof of concept study was conducted to account for differences in clinical characteristics, skills and preferences regarding dressing use. Participants with RDEB (adults and children) who wore dressings on their hands or were advised to were recruited from two tertiary centres. Participants were invited to replace their conventional dressings with bespoke dressing gloves, manufactured to fit in an iterative process of measurement and adjustment. Self-reported outcome measures, co-designed and validated with patients and clinicians and uploaded to a Hand Therapy-Online (HTO) system included: experiences of wearing and changing dressings and hand skin condition (primary outcomes); and extent of finger webbing, wrist function, hand pain and hand function (secondary outcomes). Time taken for hand dressing changes, frequency and use of conventional products were also self-reported. Participants recorded contemporaneous notes. Visual inspection of plotted outcome measures, unpaired t-tests and telephone interviews were used to assess performance. Routine clinical follow-up is being conducted in one centre within a Service Evaluation using the HTO system. *Results:* Twelve participants were recruited, nine were fitted with the dressing glove and four completed the study. Eleven carers also provided data. Participants reported an improvement in their experience of wearing and changing dressings; reduced skin maceration; and improved skin appearance. Web spaces and wrist function were also mostly maintained. Participants reported a thicker viscose material could improve absorption and provide more protection. Achieving the correct fit took several iterations due to the difficulty of translating hand measurements into knitted gloves. Use of the dressing glove was cost neutral for two participants and increased for the other two because of more frequent dressing changes. All participants completing the study wanted to remain in the dressing gloves. Five additional patients adopting the gloves are self-reporting outcome measures within the Service Evaluation. *Conclusions:* This study provides early proof-of-concept for the novel dressing glove for patients who could wear the gloves. Both gloves are available through the bespoke supply chain. Continual data collection supports a shared patient-clinician record, long-term evaluation and cost analysis.

P46
AN ENHANCED MODEL OF CARE FOR EPIDERMOLYSIS BULLOSA (EB)

K Snelson, A Downe, JE Mellerio, JA McGrath, DT Greenblatt, J Clapham, C Mackenzie, S Wharton, C Bloor
Guy's and St Thomas' NHS Foundation Trust

Introduction & objectives: The first purpose built UK rare diseases centre (RDC) for adults and children opened in November 2017 and houses an extensive multi-disciplinary team (MDT) for specialist holistic care for adults with EB. The RDC, designed with patient engagement and needs in mind, has improved access to care and is supported by domiciliary visits and collaboration with wider hospital services. *Materials & methods:* Currently, 480 adults with EB are registered with the service, predominantly from England and Wales, although the cohort also includes some international patients The MDT includes consultant and trainee dermatologists, clinical nurse specialists (CNS), dietitian, plastic surgeon, psychotherapist, hand therapist, physiotherapist, podiatrist, dentist, ophthalmologist, palliative pain consultant, radiologists, anaesthetists, EB co-ordinator, Debra UK community support managers and dedicated RDC staff. Data has been collected since opening of the centre to record clinical activity and patient contact. *Results:* The RDC houses a variety of different clinics types where patients are triaged according to their MDT needs and complexity. These include: • monthly standard outpatient clinic (30-40 patients); • monthly MDT clinic for 6 complex patients to see the whole team; • once to twice monthly mini-MDT clinic for 8 complex patients to see select members of the wider MDT; • weekly CNS-led EB clinic; twice monthly all day EB podiatry clinic; • twice monthly CNS-led Skype clinic. In addition, the service supports elective and urgent admissions (e.g. for hand surgery, cancer surgery, oesophageal dilatations), hand therapy, psychotherapy, dietetic reviews, dental and ophthalmology appointments as well as ad hoc review e.g. of unwell patients or for review of possible skin cancers. An essential component of this holistic model are regular CNS home visits to complex patients for skin assessment and symptom management, enabling effective therapeutic relationships and partnership working with the patient and carers. Number of patients seen (Nov 2017- Sept 2019).

- Complex MDT (monthly) 86
- Mini-MDT (1-2 per month) 106
- CNS led (weekly) 85
- Skype (1-2 per month) 39
- Standard outpatients (monthly) 319
- Ad Hoc reviews 116
- Podiatry (twice monthly) 312
- CNS Home visits 212

17 patients have transitioned from the paediatric to adult EB service (Sept 2018 – Sept 2019) *Conclusions:* Since the opening of the RDC activity has increased and the unique model of care is provided in a purpose built environment. Patient benefits include access to a wide range of specialists in one place in a time efficient manner. Disease management is optimised by collaboration with appropriate services within the MDT and beyond. Hospital activity is underpinned by domiciliary visits by the CNS team.

P47
LOSARTAN FOR EB, OR 'IT TAKES A VILLAGE TO RAISE A CHILD'

Dimitra Kiritsi[1], Tobias Zahn[2], Frank Hoffmann[3], Sigrid Saaler-Reinhardt[3], Leena Bruckner-Tuderman[1]
[1]Medical Center – University of Freiburg, [2]3R Pharma Consulting GmbH (tobias.zahn@3rpc.com), [3]Midas Pharma GmbH

Introduction & objectives: Losartan, a well-established medication to treat hypertension, has shown promise for the treatment of dystrophic epidermolysis bullosa (EB), a skin blistering disease with secondary scarring and fibrosis. In a mouse disease model of dystrophic EB, losartan reduced fibrotic scarring and prevented fusion of digits. Our objective is to develop a pediatric formulation of losartan and to create medical evidence whether losartan is safe and efficacious for the treatment of EB, in particular the prevention of fibrotic scarring in DEB children. *Materials & methods:* A multidisciplinary team has come together to work towards this objective. Approvals by regulatory agencies (in particular the US FDA and the European Medicines Agency, EMA) are sought: Such approval will confirm a high standard of medical evidence, a positive benefit vs risk assessment, and the quality of the new medicine (manufacturing and controls). *Results:* Losartan faces fewer technical hurdles compared to other, novel treatments as it is an established medicine (available as tablets for the treatment of hypertension) – however, this fact poses new economic hurdles: With patents expired, companies cannot expect to recoup an investment into clinical studies and alternative funding sources are needed. A first clinical trial of losartan in EB, funded by DEBRA, is currently ongoing at the EB centers in Freiburg, Germany and Salzburg, Austria. The results will provide important safety data and aid in planning of a larger confirmatory, pivotal clinical trial. A clinical trial protocol and a study budget have been developed – now funding is needed for this decisive clinical trial. A pediatric formulation of losartan is no longer available in the market, posing an unexpected new hurdle: a new, easy-to-swallow formulation is needed. User requirements have been defined and funding is sought for the required technical development. Orphan drug designation has been obtained from FDA and EMA. This provides fee reductions and support by the agencies along the regulatory development and approval process. *Conclusions:* Promising drug candidates need to convince on a medical/technical level as well as on economic terms in order to attract funding by the pharmaceutical industry. For losartan for EB, only the former is fulfilled. Now it takes a concerted multidisciplinary effort by many parties to provide the technical expertise and the funding to turn this promising drug candidate into a new medicine for EB. The first steps have been made. The project is advancing and growing up. But to reach maturity much more funding is needed.

P48
IMMUNE CELL PROFILING OF WOUNDS FROM EPIDERMOLYSIS BULLOSA PATIENTS

Ignacia Fuentes[1,2], Christina Guttmann-Gruber[3], Birgit Tockner[3], Anja Diem[4], Alfred Klausegger[3], Glenda Cofré-Araneda[1], Olga Figuera[1], Yessia Hidalgo[5,6], Pilar Morandé[1], Francis Palisson[1,7], Boris Rebolledo-Jaramillo[2], María Joao Yubero[1,7], Raymond J Cho[8], Heather I Rishel[9], M. Peter Marinkovich[9,10], Joyce Teng[9], Timothy G Webster[11], Marco Prisco[11], Luis H. Eraso[12], Josefina Piñon Hofbauer[3],, Andrew P. South[11,13,14]**
*[1]DEBRA Chile, Santiago, Chile, [2]Centro de Genética y Genómica, Facultad de Medicina Clínica Alemana, Universidad de Desarrollo, Santiago, Chile, [3]EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, [4]B House Austria, Outpatient Unit, Department of Dermatology and Allergology, Paracelsus Medical University, Salzburg, Austria, [5]Consorcio Regenero, Chilean Consortium for Regenerative Medicine, Santiago [762]0[157], Chile, [6]Cells for Cells, Santiago, Chile, [7]Facultad de Medicina Clínica Alemana, Universidad de Desarrollo, Santiago, Chile, [8]UCSF Dermatology, San Francisco, CA, United States, [9]Dermatology Department, Stanford University School of Medicine, Stanford, CA, [10]Dermatology Service, VA Medical Center, Palo Alto CA, [11]Dermatology and Cutaneous Biology, Thomas Jefferson University, Philadelphia, PA, United States, [12]Vascular Medicine, Thomas Jefferson University, Philadelphia, PA, United States, [13]Joel and Joan Center for Fibrotic Diseases Research, Thomas Jefferson University, Philadelphia, PA, United States, [14]Sydney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, United States. Correspondence: Ignacia.fuentesbustos@gmail.com or andrew.south@jefferson.edu. *These authors contributed equally*

Introduction & objectives: Epidermolysis bullosa or EB, is a group of genetic diseases characterized by excessive skin fragility causing blisters with minimum trauma. In severe EB patients, blisters can develop into nonhealing wounds, which besides being extremely painful, are the starting point to other more severe –and deadly– clinical manifestations, such as systemic infections and cancer. The current state of research points towards EB being a combination of a heritable skin and inflammatory disease. However, the impact of host immune dysregulation has not been explored in the context of wound resolution. *Materials & methods:* In this study, we investigated the use of wound dressings from EB patients as a noninvasive sampling method to 1) profile the host cellular role in wound healing and 2) disease diagnosing. *Results:* We were able to isolate significant numbers of viable cells from wound dressings (ranging from 0.08 – 620x106 cells), consisting of a heterogeneous mixture of skin and immune cells. Also, after special culturing conditions, highly proliferative adherent fibrocyte-like populations were obtained and NGS quality genomic DNA could be isolated, resulting in accurate molecular diagnosis for patients. Immune Phenotyping of the isolated cells by flow Cytometry suggests our technique is able to distinguish CD45+ and CD45- populations, some minor representation of CD3+ T-cell (ranging from 0 to 78% of CD45+ cells) and others, indicating differential immune cell infiltrate in wounds. Currently we are actively correlating these population subtypes and healing status of a given wound to better understand wound resolution in EB patients. *Conclusions:* Together our data show that discarded wound bandages can be used for noninvasive molecular diagnostics and provide a platform to profile the cellular content of skin wounds. Understanding the relationship between immune cell infiltrate, bacterial infection and wound healing may lead to a better clinical management of patients with chronic wounds such as individuals with Epidermolysis bullosa.

P49
DIACEREIN 1% OINTMENT FOR THE TREATMENT OF EPIDERMOLYSIS BULLOSA SIMPLEX: RESULTS OF A PHASE 2 STUDY

Joyce Teng[1], Amy S. Paller[2], Anna L. Bruckner[3], Dedee F. Murrell[4], Jemima E. Mellerio[5], Christine Bodemer[6], Anna E. Martinez[7], Aida Lugo-Somolinos[8], Eli Sprecher[9], Johann W. Bauer[10], Mary C. Spellman[11]
[1]Stanford University, School of Medicine, Palo Alto, CA, USA, [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA, [3]University of Colorado School of Medicine, Aurora, CO, USA, [4]St. George Hospital, UNSW Sydney, Sydney, Australia, [5]St. John's Institute of Dermatology, Guy's and St. Thomas' NHS Foundation Trust, London, England, [6]Hôpital Necker-Enfants Malades, Paris, France, [7]Great Ormond Street NHS Foundation Trust, London, England, [8]University of North Carolina-Chapel Hill, Chapel Hill, NC, USA, [9]Tel Aviv Sourasky Medical Center, Tel Aviv-Yafo,

Israel, [10]University Hospital of the Paracelsus Medical University Salzburg, Salzburg, Austria, [11]Castle Creek Pharmaceuticals, Parsippany, NJ, USA

Introduction & objectives: Epidermolysis bullosa simplex (EBS) is a rare genetic disorder characterized by structural fragility of the skin and other tissues, resulting in recurrent blisters and erosions. Current treatment of EBS includes conventional wound care, and pain and itch management. The expression of interleukin-1β (IL-1β), a pro-inflammatory cytokine, is implicated in the pathogenesis of EBS. Diacerein 1% ointment, an inhibitor of IL-1β, has previously been shown to reduce blistering in patients with EBS. The objective of this study was to compare the efficacy of diacerein 1% ointment vs vehicle in EBS. *Materials & methods:* A randomized, double-blind, vehicle-controlled, Phase 2 study randomized 54 patients with genetically confirmed moderate to severe EBS to diacerein 1% ($n=28$) or vehicle ointment ($n=26$) once daily. The primary endpoint, a ≥60% reduction in body surface area (BSA) of EBS lesions, and the key secondary endpoint, at least a 2-point reduction in the Investigator's Global Assessment (IGA) score for the assessed area, were evaluated over 8 weeks. *Results:* The proportion of patients who achieved the primary endpoint (≥60% reduction in EBS BSA) was numerically greater in the diacerein 1% group (57.12%) than in the control group (53.8%), but not significantly ($p=0.9666$). The proportion of patients who achieved success on the IGA key secondary endpoint was higher in the diacerein 1% group (42.9%) compared with the control group (26.9%), but not significantly ($p=0.2861$). An IGA score of 0 or 1 was reported for 39.3% of the diacerein 1% group and 23.1% of the control group. Diacerein 1% ointment was generally safe and well tolerated; all study drug−related adverse effects were mild in severity. *Conclusions:* Although statistical significance was not achieved, a larger proportion of patients receiving diacerein 1% ointment achieved a ≥2-point reduction in IGA score for EBS lesions, compared to vehicle, supporting further study of diacerein at higher concentrations to optimize its efficacy.

P50
A NOVEL BLISTER-BURSTING TEACHING AID IN EPIDERMOLYSIS BULLOSA FOR PATIENTS AND PROFESSIONALS

Dharshini Sathishkumar[1], Ananda Ruby Jacob[2], Angel Gnanamuthu[2], Jamuna Panner selvam[2]
Departments of Dermatology[1] and Nursing[2], Christian Medical College, Vellore, Tamil Nadu India.

Introduction & objectives: Blisters occur in epidermolysis bullosa (EB) because the genetic weakness impairs skin adhesion, creating a space which fills with interstitial fluid. Once a blister has formed it readily enlarges as the fluid seeps along the plane of cleavage. To prevent this, blisters must be drained using a sterile needle, scalpel or scissors. The instrument should be kept parallel to the skin to avoid painful contact with the blister base and should neatly puncture the blister allowing fluid to drain freely, assisted by gravity if possible. Sterile gauze or clean tissue can be used to wick out and absorb the fluid. The blister roof should be left in place. Learning how to burst blisters safely, painlessly and without introducing infection is essential but can be a major challenge for patients and caregivers. Bubble wrap is sometimes used to simulate blisters for training but is not sufficiently realistic. To avoid demonstrating the technique on patients we have devised a simple teaching aid simulating a patient's forearm with multiple blisters which can be created with readily available materials. *Materials & methods:* A length of cardboard, such as the back of an A4 writing pad (approximately 21 x 30cm), is rolled lengthwise and elastic bands placed around the tube. A surgical glove is stuffed with gauze and fitted to one end of the cardboard to simulate an arm and hand. Then the fingers of 2 or 3 more gloves are snipped off, filled with water and the open ends tied with thread to create small water-filled balloons. The remaining wrist parts of these gloves can be used to cover the cardboard tube. Slits are made in the cardboard through which the threads hand tied ends of the balloons are inserted. The threads are pulled to the open end of the tube and taped in place. Thus, a model simulating a hand and forearm with multiple blisters is created (photograph attached) and can be used to practice bursting blisters. *Conclusions:* We have found this blister model to be extremely useful in teaching individuals, families and professional groups how to burst EB blisters. It provides an effective, low-cost substitute for real-life blisters, and empowers individuals in self-care. Furthermore, creating and using the model can be entertaining as well as instructive for children and young people, removing the anxiety associated with surgical interventions. We hope this model will help fellow EB professionals.

P51
AUTOSOMAL RECESSIVE EPIDERMOLYSIS BULLOSA SIMPLEX WITH NAIL DYSTROPHY DUE TO PLECTIN MUTATION - CASE REPORT FROM INDIA

Dharshini Sathishkumar[1], Naina Emmanuel[2], Renu George[1]
Departments of Dermatology[1] and Otorhinolaryngology[2], Christian Medical College, Vellore, India Results: Introduction: In the last 20 years plectin has emerged as a gene responsible for complex subtypes of basal epidermolysis bullosa simplex (EBS). We present a case illustrating the broad phenotype of plectin-related EBS.

Case report: A 3-month-old girl, first born of second-degree consanguineous parents, presented with easy blistering of the skin from birth. She also had progressive hoarseness, with cough and reflux. At presentation, she had a few erosions involving the face, hands and feet with thickening and separation of the nail plate on many digits. The oral and genital mucosae and eyes were unaffected. There was no relevant family history and she appeared underweight but otherwise well and developing normally. The clinical picture was initially suggestive of junctional epidermolysis bullosa (JEB). In view of the hoarse cry otorhinolaryngology consultation was sought. Cautious nasopharyngolaryngoscopy showed erosions confined to the ary-epiglottic folds and vocal cords with signs of reflux. Subsequent treatment with a proton pump inhibitor improved her reflux and airway symptoms significantly and she began to thrive. This made JEB less likely and therefore next generation sequencing was undertaken. This revealed c.4879C>T(p.Arg1627TER) homozygous mutations in exon 31 of the plectin gene (PLEC). *Discussion*: The OMIM database https://www.omim.org lists 4 EBS phenotypes caused by plectin mutations: EBS with nail dystrophy #616487, EBS with muscular dystrophy #226670, EBS with pyloric atresia #612138 and EBS Ogna type #131950. On review at 9 months, there was no clinical evidence of pyloric atresia or muscular dystrophy (normal muscle enzymes). Homozygosity excluded the dominant Ogna subtype. Thus, the final diagnosis is autosomal recessive EBS with nail dystrophy due to plectin mutations. The somewhat variable occurrence of systemic manifestations due to plectin mutations makes it difficult to counsel these parents about future risk. The single case of EBS with nail dystrophy described in literature(1) had a mutation in exon 1 affecting the plectin 1A isoform which is not expressed in striated muscle. However, the tissue distribution of the mutation in our patient is unknown and the child will be kept under regular follow up to assess if she will develop signs of muscular dystrophy in future. *Conclusions:* To the best of our knowledge, this is only the second case reported of EBS with nail dystrophy due to plectin mutations, and emphasises the complexity of the plectin phenotype.

Reference
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P52 RESULTS FROM A PHASE I/II STUDY OF A TOPICAL GENE THERAPY (BERCOLAGENE TELSERPAVEC, B-VEC) IN PATIENTS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB)

M.P. Marinkovich[1], Schuyler Vinzant[2], Pooja Agarwal[2], Suma Krishna
[1]Dermatology, Stanford University, Stanford, CA, United States, [2]Krystal Biotech, Inc, Pittsburgh, PA, United States

Introduction & objectives: Bercolagene Telserpavec (B-VEC) is a topically administered, replication-deficient HSV-1 vector containing two functional COL7A1 genes applied directly to RDEB patient wounds in an outpatient setting. *Materials & methods:* Two RDEB patients were enrolled in Phase 1 and four patients were enrolled in Phase II, and a total of ten wounds were administered B-VEC. Eight (8) of the ten wounds were analyzed against placebo as one patient in the Phase II trial dropped out of the study due to inability to travel to the clinical site. Subjects were monitored for safety, wound closure, and molecular correction. *Results:* In this update of the ongoing Phase I/II placebo controlled clinical trial, we report continued successful demonstration of a novel *in vivo* approach to RDEB gene correction. B-VEC has been well-tolerated and no B-VEC-related safety events have been reported in all six B-VEC administered patients. In the combined Phase 1/2, 7 out of 8 wounds treated with KB103 closed completely (100%). The average time to 100% wound closure on all KB103 treated wounds (7 out of 8) was 20.14 days (median 20 days). In Phase 1, the duration of wound closure on two patients following 100% wound closure as of the last follow up was 184 days (6.6 months) and 174 days (6.2 months). In the Phase 2 study, 5 out of 6, wounds remained closed 100% at the 90-day evaluation, and the wounds continue to be monitored. The one chronic wound that did not close completely was re-administered with B-VEC at the 90-day timepoint - 100% wound closure was achieved following re-administration. This wound continues to be closed at the ninety days (3 months) evaluation following complete closure, demonstrating the ability of B-VEC to treat difficult chronic wounds. In addition to wound closure, robust linear COLVII expression and presence of anchoring fibrils at the basement membrane zone in biopsies of the B-VEC treated sites demonstrate molecular correction. Two additional patients were enrolled onto the Phase 2 study and were administered B-VEC to wounds up to 70 cm^2 to study chronic wounds in further detail. The Phase 2 study is on-going in these two additional patients. *Conclusions:* Overall, results from the Phase I/II clinical studies demonstrate a novel, safe and effective approach to RDEB molecular correction which can be easily administered in basic clinic facilities worldwide. A multicenter Phase 3 trial is planned for late 2019.

P53
DIAGNOSTIC TESTING PATTERNS, CHRONOLOGY, AND CONCORDANCE IN A LARGE EPIDERMOLYSIS BULLOSA COHORT

Gregory S. Phillips, BS, Bret D. Augsburger, BA, Kathleen Peoples, BA, Anna L. Bruckner, MD, MSCS, Phuong Khuu, MD, Jean Y. Tang, MD, PhD, Irene Lara-Corrales, MD, Elena Pope, MD, MSc, Karen Wiss, MD, Kristen P. Hook, MD, Laura E. Levin, MD, Kimberly D. Morel, MD, Amy S. Paller, MD, Catherine C. McCuaig, MD, Julie Powell, MD, Lawrence F. Eichenfield, MD, Harper Price, MD, Moise L. Levy, MD, Lawrence A. Schachner, MD, John D. Browning, MD, Susan Bayliss, MD, Marla Jahnke, MD, Tor Shwayder, MD, Anne W. Lucky, MD, Sharon A. Glick, MD
SUNY Downstate Health Sciences University, Cincinnati Children's

Introduction & objectives: Accurate diagnosis and subtype specification of epidermolysis bullosa (EB) have significant implications for prognosis, management, and counseling. We set out to define the diagnostic testing patterns in a large cohort of EB patients and assess the diagnostic concordance of these tests in order to inform cost-effective management recommendations. *Materials & methods:* Participants enrolled in a longitudinal database of EB patients evaluated at 18 tertiary medical centers between January 1, 2004 and December 31, 2018 were analyzed. Patient data were retrospectively abstracted from the database including EB type and diagnostic testing results for electron microscopy (EM), immunofluorescence mapping (IFM), and genetic analysis. Diagnostic concordance was assessed by comparing EM and/or IFM conclusions regarding EB type (e.g. RDEB, JEB, DDEB, EBS) against genetic analysis conclusions: tests concluding the same EB type were concordant, tests concluding different types were discordant, and ambiguous diagnostic tests (e.g. EB type could not be definitively concluded) were equivocal. *Results:* Overall 854 patients were identified in the database, consisting of 338 (40%) RDEB, 127 (15%) DDEB, 230 (27%) EBS, 80 (9%) JEB, and 79 (9%) unknown/unspecified or other. A total of 970 diagnostic tests were conducted from 1984 to 2018 in the 760 patients with data available. Genetic analysis was more frequently performed on patients with JEB and RDEB versus EBS (76%, 72% vs 44% respectively, $p<0.001$). By Cox regression analysis, the likelihood of undergoing genetic analysis as a function of patient age was greater for JEB and RDEB, and the same for DDEB as compared to EBS (JEB HR 2.25, 95% CI 1.56-3.25; RDEB HR 1.43, 95% CI 1.09-1.88; DDEB HR 1.10, 95% CI 0.78-1.56). Genetic analyses were performed chronologically later than IFM or EM: median (IQR) test date 4/2014 (5/2010-3/2016) vs 4/2011 (10/2006-2/2014) and 12/2009 (3/2004-9/2013), respectively ($p<0.001$). The rate of genetic testing per eligible patient per year surpassed EM and IFM in 2008 (Figure). Diagnostic concordance between EM and genetic analysis among 163 patients showed EM to be largely equivocal (36%) and concordant (28%), but rarely frankly discordant (2%). Similarly, IFM results were equivocal, concordant, or discordant in comparison to genetic analysis in 40%, 31%, and 3%, respectively. *Conclusions:* Diagnostic testing has shifted in favor of genetic analysis over EM and IFM, particularly in the workup of RDEB and JEB. While EM and IFM can corroborate a diagnosis, they frequently offer equivocal findings when compared to the specificity afforded by genetic analysis.

P54
SERVICE EVALUATION OF A HAND THERAPY ONLINE SYSTEM - INITIAL FINDINGS

R .Box[1], S. Sooriah[2], T. Graham[2], P. Grocott[2]
[1]Guy's and St. Thomas' NHS Foundation Trust, [2]King's College London

Introduction & objectives: Hand data collection in Epidermolysis Bullosa (EB) is intermittent, particularly after surgery, and accurate measurement of range of movement is compromised by use of dressings and contractures. Current hand therapy outcome measures are also not specific enough for those with EB. As a result, we are unable to chart disease progression, responses to treatment care and costs and evidence best practice. A Hand Therapy-online (HTO) system was developed and validated. It comprises an electronic hand therapy patient record with patient-recorded outcome measures and automated data analysis, including a total hand score. To register a service evaluation of the HTO system within an Information Technology (IT) governance framework in our Hand Therapy Department. To set up the HTO system and

train participants in data collection and analysis. To collect routine hand therapy data with patients, in parallel with current Electronic Patient Records (EPR), over 12 months. To evaluate the acceptability of the HTO system with clinicians, patients and carers. To determine the consistency and quality of data recording on the HTO system compared with EPR data *Materials & methods:* The National Institute of Health Research Telehealth Implementation Toolkit framed the evaluation. Twenty English speaking patients with EB, undergoing hand therapy intervention, and their carers were invited to participate (February to November 2019). Minimum data capture to the HTO system was clinically determined by hand therapists and patients, with reciprocal monitoring by the therapists. Participants assessed, monitored and recorded their own outcomes on the HTO system over 10 months. The system was refined to meet service requirements. *Results:* Sixteen participants were recruited with two exclusions (English not first language). Fifteen baseline assessments were conducted with one IT failure preventing completion. Four participants were unable to complete their assessments remotely, and their data were collected in clinic. Of the remaining 12 participants, seven used the HTO system remotely, including two receiving post-surgical hand release. *Conclusions:* The HTO system facilitates shared patient and clinician records, with remote capture of objective hand data and contemporaneous qualitative accounts that have previously not been collected. It is quick and easy to complete and allows monitoring of patients' hand condition between clinic appointments. All the data are captured in one place, charting disease progression, response to treatment care and costs. The system relies on patient and clinician participation in data capture. The rewards include improved communication and understanding of how individual's situations impact upon hand therapy.

P55
FACILITATING FACTORS FOR THE QUALITY OF LIFE OF PEOPLE LIVING WITH EPIDERMOLYSIS BULLOSA AND THEIR FAMILIES, IDENTIFIED BY HEALTH CARE PROFESSIONALS AND EXPERTS

Gudrun Salamon and Vinzenz Hübl
Sigmund Freud University Vienna, Faculty of Psychology

Introduction & objectives: Epidermolysis bullosa (EB) is a group of rare genetic diseases characterized by skin fragility. As, at least for now, there is no cure for EB yet, quality of life is an extremely important issue. The WHO (World Health Organisation) defines quality of life as "the individual's perception of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns''. Health-related quality of life can be divided into physical, social, emotional, and functional dimensions. Our research aims to identify facilitating factors to the quality of life of people with EB and their families. *Materials & methods:* We chose a grounded theory approach, where experts' as well as patients' and their families' views will be taken into consideration. As a first step, we interviewed ten experts on EB, eight of them actively involved in EB care (doctors, nurses, psychologists, social workers, occupational therapists), two of them experts in rare diseases and community support, one of them furthermore a parent of a young adult with EB. *Results:* Facilitating factors to the quality of life and psychosocial wellbeing are: the highest possible degree of autonomy, built upon information, knowledge, and training, and with the help of medical, psychological, social and financial support as well as every-day support by home care or personal assistance; an easy-to-reach support for all needs, using a multidisciplinary approach, ideally interconnected and exchanging information amongst each other; being included in a supportive social network, consisting of a personal network of family and friends, a social surrounding such as kindergarten, school, or work, and the exchange with other patients and their families. Chances that support offers are actually accepted and used by EB patients and their families are higher with a stable and trustful relation between the health care professionals, the EB patients and their families. Building up such a relation needs honesty, the validation of the patients' and families' expertise and experience, and enough time. For a supportive and clear communication, it is important to differentiate between hopes and expectations; their alignment is recommended in order to avoid disappointment. *Conclusions:* Quality of life is a central issue for people living with EB. Our research explores facilitating factors to the quality of life and psychosocial wellbeing and thus adds a novel point of view to quality of life research.

P56
IMPROVING SURVIVAL IN EPIDERMOLYSIS BULLOSA PATIENTS WITH SQUAMOUS CELL CARCINOMA: LONG-TERM RESULTS FROM A NATIONAL REFERENCE CENTRE

Carlos Delgado-Miguel, Miriam Miguel-Ferrero, Antonio J. Muñoz-Serrano,Mercedes Díaz, Rocío Maseda, Raúl de Lucas, Juan Carlos López-Gutiérre

Introduction & objectives: An intensive protocol for early diagnosis of squamous cell carcinoma in patients with epidermolysis bullosa (EB) was started in our Centre 10 years ago; our aim was to analyze the results of this new protocol. *Materials & methods:* In 2008, we started a new protocol for early diagnosis of epidermoid carcinoma in EB which included: exhaustive exam of the entire body surface, performance of biopsies of all skin lesions suspected of malignancy and early excision of malignant lesions, PET-scan control of distance dissemination and frequent follow-up visits. We performed a retrospective study in patients with EB treated by the Department of Paediatric Surgery at our institution in the last 20 years (1998-2018) who developed squamous cell carcinoma. Two time periods 1998-2007 (pre-new protocol) and 2008-2018 (post-new protocol) were analyzed comparatively. Demographic data (sex and age) and tumor location were collected. The amputation rate and mortality rate of patients treated before and after the new protocol was introduced were compared. *Results:* Fifty-seven patients (28male; 29female) were analyzed. Fourteen patients developed squamous cell carcinoma (11male; 3female), with a mean age at diagnosis of 22.4 ± 5.5years. The lower limb was the most frequent location (7 on the feet and 4 on the knees), followed by the cervical region (2 patients) and hand (1 patient). During the first period of time (1998-2007), 7 squamous cell carcinomas were diagnosed (5 male; 2 female), with a mean age at diagnosis of 30.4 ± 6.5years. Five patients required limb amputation (amputation rate: 71%) and 6 of them died due to the spread of the cancerous disease (mortality rate: 85.7%). During the second period of time (2008-2018), 7 epidermoid carcinomas were diagnosed (6male, 1female), with a mean age at diagnosis of 18.6 ± 3.2years. The difference in the age at diagnosis between both groups was statistically significant. The amputation rate in this group was 42.8% (OR 0,42 CI95% [0,1-4,9]; $p = 0{,}577$) and the mortality rate was 57.1% (OR 0,53 CI95% [0,1-6,1]; $p = 0{,}512$). Although both rates were lower than those of the first period, no statistical significance was observed due to the small sample size. *Conclusions:* The introduction of this new intensive protocol, which relies on the protocolized study and treatment of skin lesions by a trained multidisciplinary team, promotes an earlier diagnosis and treatment of epidermoid carcinoma, increasing the quality of life and lengthening the survival of patients with EB.

P57
RIBOPOLYPLEX: THE GENE EDITING NANOPARTICLE TO TREAT RDEB

Irene Lara-Sáez[1], Jonathan O'Keeffe-Ahern[1], Sigen A[1], Qian Xu[1], Marta García[2], Rodolfo Murillas[3], Fernando Larcher[3], Wenxin Wang[1]
[1]Charles Institute of Dermatology, University College Dublin, Ireland, [2]Universidad Carlos III de Madrid, Spain, [3]Centro Investigaciones Energéticas, Medioambientales y Tecnológicas, CIEMAT Institute, Madrid, Spain

Introduction & objectives: Recently we have developed new hydrophobic cationic polymers (Cat-Polymers) specifically designed to be complexed with CRISPR ribonucleoprotein complex (RNP), forming a medical unit to treat RDEB editing the mutated COL7A1 gene by excision of the mutated exon 80, one of the most common mutation sites, this medical unit (ribopolyplex) has been developed to be a topical treatment for RDEB. Therefore, the main objective of this work was to test the efficiency of our ribopolyplexes as a therapeutic molecule to restore COL7A1 expression *in vivo* for RDEB. *Materials & methods:* The biocompatibility and efficiency of the ribopolyplexes was evaluated after 72 hours post-transfection in an immortalized recessive dystrophic epidermolysis bullosa (RDEB) keratinocyte line and primary RDEB keratinocytes, by alamarBlue test, PCR and immunofluorescence. *Results:* Intracellular localisation was observed 72 hours after transfection by fluorescence of the tracrRNA (red) added to the complex. After 72 hours post-transfection all the ribopolyplexes, formed by different Cat-Polymers, induced a cell viability over 70%, confirming their biocompatibility. The PCR from the genomic DNA extracted after 72 hours of transfection confirmed that the gene edition occurred, excising the exon 80 and obtaining a smaller band corresponding to the shorter COL7A1 once excised the exon, achieving 30% correction when using ribopolyplexes composed by Y4 Cat-polymer with 8ug of RNP. Collagen VII restoration was confirmed by immunofluorescence when transfections were done of primary patient RDEB keratinocyte cells from a biopsy. *Conclusion*: Given that currently there is no clinical therapy beyond palliative care for patients suffering with RDEB, the development of treatment strategies with significant clinical translational potential is paramount. Our proposal seeks to develop a non-invasive strategy to restore integrity of the skin by conferring type VII collagen expression to the patients' own cells. The results obtained indicate a very high potential of the ribopolyplexes as a treatment for RDEB. A full preclinical assessment is needed at this stage to confirm the *in vivo* efficiency in a murine RDEB model and explore the minimum effective dose, the biodistribution, the percentage of stem cells corrected and a formulation for a homogeneous topical application of the ribopolyplexes.

P58
CRISPR/CAS9-MEDIATED CORRECTION OF TWO RECURRENT COL7A1 MUTATIONS IN PRIMARY AND INDUCED PLURIPOTENT STEM CELLS FROM PATIENTS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Araksya Izmiryan[1,2], Camille Berthault[1,2], Alain Hovnanian[1,2,3]
[1]Imagine Institute, Laboratory of genetic skin diseases, INSERM UMR 1163, Paris, France ;[2]University of Paris, Paris, France, [3]Department of Genetics, Necker Hospital for Sick Children, APHP, Paris, France

Introduction & objectives: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a rare and severe genetic skin disease responsible for blistering of the skin and mucosa after minor trauma. RDEB is caused by a wide variety of mutations in COL7A1 encoding type VII collagen, the major component of anchoring fibrils which form key attachment structures for dermal-epidermal adhesion. Our study aims at investigating the therapeutic potential of *ex vivo* CRISPR/Cas9-mediated Homology Directed Repair (HDR) to correct two recurrent COL7A1 mutations in RDEB patient's primary and iPSCs-derived cells. These cells are homozygous for the c.425A>G (p.Lys142Arg) or the c.6508C>T (p.Gln2170*) mutations in exon 3 and in exon 80, respectively. *Materials & methods:* To achieve this goal, two strategies are developed in parallel. The first approach is based on the correction of RDEB primary keratinocytes and fibroblasts, while the second approach is based on the correction of RDEB iPSCs derived from RDEB fibroblasts. *Results:* Here, we achieved efficient COL7A1 correction through non-viral delivery of the CRISPR/Cas9 system in primary RBEB cells and in iPSCs. First, we designed different guide RNAs (gRNAs) targeting the specific mutation or sequences in close distance to the mutation to be corrected in exon 3 and in exon 80. Two of these gRNAs showed up to 70% cleavage activity in RDEB keratinocytes, fibroblasts and iPSCs, when delivered together with Cas9 as a ribonucleoprotein complex (RNP). We have also evaluated their off-target activity in primary RDEB keratinocytes and fibroblasts, and found no evidence for non-specific cleavage activity at the in-silico predicted sites. For gene correction purpose, we treated primary RDEB cells and iPSCs with site-specific RNPs together with the corresponding Donor delivered as ssODN by nucleofection. Genetic correction of COL7A1 was estimated to be 10% in bulk-nucleofected primary RDEB cells, as assessed by RT-qPCR. Type VII collagen re-expression was confirmed by western blot analysis. Up to 20% correction was observed in RDEB iPSCs, which were re-differentiated into keratinocytes and fibroblasts and confirmed type VII collagen re-expression at the protein level, as assessed by Western blot analysis. Currently, we are enriching gene-corrected primary RDEB keratinocytes and iPSCs by clonal dilutions and propagation to bypass cellular heterogeneity in bulk populations. *Conclusions:* In our study, we provide evidence for COL7A1 repair of two frequent mutations through CRISPR/Cas9-mediated HDR in patients' primary cells and iPSCs. Therefore, precise genome editing is a new and promising strategy to correct recurrent RDEB mutations for the development of transplantable skin models suitable for clinical application.

P59
NOVEL MUTATION IN DST GENE CAUSING AUTOSOMAL RECESSIVE EBSB2

M. Ogboli[1], D. Walsh[2], G. Ryan[2], C. Moss[1]
[1]Deparment of Dermatology, Birmingham Children's Hospital, [2]Genetics department, Birmingham Women's Hospital

Results: Epidermolysis Bullosa Simplex (EBS) is genetically the most heterogeneous subtype of EB, often with a relatively mild and non-specific phenotype. These factors and the emergence of new variants make accurate diagnosis challenging. We describe the findings in a patient with a rare autosomal recessive type of EBS caused by DST mutations. Our patient suffered recurrent itchy blistering, confined to the feet, from about 8 years of age, associated with gradual thickening of toe nails. The blistering occurred only in hot weather and was worse with friction, although she was able to tolerate sandals and flip flops and to participate in physical education activities most of the time. She was otherwise well. Her parents, who were consanguineous, and her 3 siblings were unaffected, with no relevant family history. Examination at age 11 years revealed thickened fifth toenails, maceration of the toe-web spaces, damp feet and hyper-pigmentation at sites of recent blisters but no active blistering. The differential diagnoses of tinea, pompholyx , juvenile plantar dermatosis and autoimmune blistering skin disease were excluded by appropriate investigations. Skin immunofluorescence revealed significant differences between patient and control in keratin 14 staining but no mutations were found in the panel of EBS genes available at that

time namely keratin 5, keratin 14 and TGM5. She was therefore recruited into the UK 100,000 genome project. Whole genome sequencing showed a novel homozygous frameshift variant in exon 23 of DST, c.5469_5470del, p.(Asn1823LysfsTer9) predicting a truncated protein. DST encodes dystonin, also known as BPAG1, a member of the plakin family of proteins which bridge cytoskeletal filament networks. DST is expressed in skin, central nervous system and muscle. Two previous families have been reported with a similar localized EBS phenotype and biallelic DST mutations in exon 23, but mutations elsewhere can cause more widespread disease including neuropathy. Pruritis, as seen in our patient, was a prominent feature of a patient with exon 24 mutations and more widespread, somewhat pemphigoid-like blistering (Turcan I et al. J Invest Derm 2017;137:2227-2230). We conclude that the homozygous DST variant found in our patient is pathogenic, and that the EB phenotype seen here is characteristic of exon 23 mutations.

P60
ESTABLISHING THE IMPACT OF GASTROSTOMY PLACEMENT ON WEIGHT-FOR-AGE Z SCORES IN PAEDIATRIC PATIENTS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA-GENERALISED SEVERE

Natalie Yerlett, Dr G Petrof, Mr J Curry and Dr A E Martinez.
Great Ormond Street Hospital, London.

Introduction & objectives: Patients with recessive dystrophic epidermolysis bullosa generalised severe (RDEB-GS) encounter elevated nutritional requirements due to a combination of factors such as wound healing, infection and malabsorption. The nutritional demands of RDEB-GS commonly outweigh achieving these high requirements through oral diet alone which leads to growth-faltering. In anticipation of growth-faltering, gastrostomy placement is considered early on. Families often find this decision challenging due to concerns of possible complications. Minimal evidence exists demonstrating the impact that gastrostomy placement has on growth in RDEB-GS patients. This retrospective study will analyse the impact of gastrostomy placement on weight gain in a cohort of paediatric patients with RDEB-GS at a national centre, by comparing weight-for-age z scores of patients with and without a gastrostomy. *Materials & methods:* All patients had RDEB-GS and were patients of the paediatric EB service. Data was collected at each patient consultation between 2013-2019; weight, height, age, date of gastrostomy insertion and weight-for-age z score was recorded. *Results:* 19 patients met the inclusion criteria and their data was analysed. 10/19 (52%) were male. 8/19 (42%) had gastrostomies placed. 4/19 (21%) patients already had a gastrostomy placed prior to the data collection period. 4/4 (100%) of these patients had an overall increase in weight-for-age z score with an average gain of +0.66 SD (range 0.34-1.09). 4/19 (21%) patients had a gastrostomy placed during the data collection period. Age of insertion ranged from 76-146 months (mean 107months). 4/4 (100%) had an overall increase in weight-for-age z score with an average increase of +0.62 SD (range 0.23-1.09SD). 11/19 (58%) patients did not have a gastrostomy placed and had an average overall weight-for-age z score loss of -0.32 SD (range -1.72 – -2.2 SD). Only 4 of these 11 (36%) patients had an individual gain of weight-for-age z score. 3 of these 4 patients were the youngest of the total cohort (40,62,83 months at completion), therefore, had received intensive dietetic input and had not yet displayed potential significant faltering growth. *Conclusions:* RDEB-GS patients showed a substantial improvement in weight-for-age z score once a gastrostomy was placed, or if a gastrostomy was already in situ, regardless of their age or the age of gastrostomy insertion. RDEB-GS patients showed an overall loss of weight-for-age z score over time if they did not have a gastrostomy placed. Further longitudinal and co-centre studies will provide further insight into the impact of gastrostomy placement for RDEB-GS patients.

P61
A RETROSPECTIVE REVIEW OF GROWTH FOLLOWING GASTROSTOMY TUBE FEEDING IN CHILDREN WITH EPIDERMOLYSIS BULLOSA

A.Z. Mughal[1], S. Unter[2], R. Jones[3], M-L. Lovgren[2], J. Heaton[2], D. James[2], G. Soccorso[4], M. Ogboli[2]
[1]University of Birmingham, [2]Deparment of Dermatology, Birmingham Children's Hospital, [3]Department of Dietetics, Birmingham Children's Hospital, [4]Department of Paediatric Surgery, Birmingham Children's Hospital

Introduction & objectives: Nutritional management of children with epidermolysis bullosa (EB) addresses multiple challenges including reduced oral intake and mucosal fragility. Nasogastric tube feeding is not a long-term option for nutritional support for EB children due to mucosal trauma. Gastrostomy feeding has been shown to be effective in improving EB patients' nutritional status1. The laparoscopically-assisted technique is increasingly favoured. We reviewed the early effects of gastrostomy placement in our cohort. *Materials & methods:* We conducted a retrospective observational study of 32 children with EB, who underwent gastrostomy insertion between 2003-2019. Demographics, EB subtype, reason for gastrostomy, age at insertion and operative procedure were collected from electronic and paper health records. Weight and height measurements at insertion and 12 months post insertion were analysed. Z-scores were calculated to compare height changes. Children aged 0-10 years' weight changes were compared using z-scores, children aged 10-15 years were compared using BMI z-scores (preferred due to variable weight gain during puberty). *Results:* 35 patients had a gastrostomy. Only 32 patients (12 female, 20 male) with complete data were included: 27 severe recessive dystrophic EB, 1 generalised severe EB simplex, 1 EB simplex with muscular dystrophy, 2 generalised severe junctional EB and 1 Kindler syndrome. Median age at insertion was 7.05 years (range 1.0-15.2). 27/32 (84.4%) patients underwent laparoscopic gastrostomy. The majority of gastrostomy tubes were inserted due to faltering growth; other indications included unsafe swallow (2/32, 6.3%), dysphagia (3/32, 9.4%) and recurrent oesophageal strictures (3/32, 9.4%). Weight data 12 months post-insertion was available for 25/32 patients, and height data for 24/32 (four patients excluded due to insertion within last 12 months, one device removal, one relocation, one unrelated death and one unable to stand). An improvement in mean height z-scores was observed 12 months after gastrostomy: -2.04 (range -5.26 to 0.45) to -1.77 (range -4.26 to 0.34). In patients aged 0-10 years, mean weight z-scores improved from -2.59 (range -4.36 to 0.54) to -1.80 (range -3.99 to 1.42); in patients over 10 years of age mean BMI z-scores increased from: -2.83 (range -4.51 to -0.13) to -1.78 (range -4.04 to -0.01). *Conclusions:* Gastrostomy tube feeding can assist in the nutritional management of children with EB and this has been confirmed in our cohort of patients. This review has shown improvements in height and weight with no related mortality in the first 12 months post-gastrostomy. Follow-up as the children grow older will show long-term implications of gastrostomy tube feeding in children with EB.

Reference

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P62
TRANSITION CARE FOR ADOLESCENTS WITH EPIDERMOLYSIS BULLOSA

Judith O'Haver PhD, RN, CPNP-PC, Kellie Badger BS, RN, Harper N. Price MD
Phoenix Children's Hospital, USA

Introduction & objectives: Transition of care for pediatric pa-

tients with chronic diseases is a current "hot topic" in developed countries. As medical therapies advance, patients with previously life-limiting diagnoses are living longer. Identifying physicians caring for adults to be a part of the transition team is often challenging for patients with rare diseases. Many adult patients with rare diseases often remain in the care of their pediatric team; patients with epidermolysis bullosa (EB) are no different. These patients may be cared for locally by a pediatric dermatologist, a dermatologist that sees both adults and children and/or a multidisciplinary team/center. The purpose of this presentation is to describe a pilot program for the transition of adolescent to adult centered care in patients diagnosed with EB. *Materials & methods:* A review of the current literature regarding transitional care for adolescents diagnosed with EB was performed. The Got Transition program was selected for this EB transitional care as the institution has selected this process to guide transitioning care from a pediatric to adult model for children diagnosed with chronic conditions. This program is a cooperative agreement between the Maternal and Child Health Bureau and The National Alliance to Advance Adolescent Health. *Results:* A comprehensive review of the English language literature yielded a single article by Foster and Holmes (2007) that described the transition program for children with severe EB at Great Ormond Street Hospital. Our multidisciplinary team adapted these recommendations using the Got Transition model to formulate an innovative pilot program for this population. A policy statement was developed and a section for documentation was incorporated in the electronic health record. Eligible patients were identified and a protocol was developed to use with a pilot group to ensure consistency in delivery. Barriers to care are being identified as well as a process to address this. Results will be used to model this care plan for other applicable populations in the organization. *Conclusions:* There is no standard of care program published on a method to transition the adolescent patient diagnosed with EB to an adult centered model. The literature for transition of adolescent dermatology patients with chronic disease is sparse. A pilot program was developed using the guidelines from the Got Transition program and currently is being tested in this population. Results from this ongoing pilot will be presented, highlighting key aspects of the program, barriers, and lessons learned.

P63
ASSESSING THE OUTCOME OF SURGERY FOR PAEDIATRIC EPIDERMOLYSIS BULLOSA HAND CONTRACTURE

Gill Smith[1], Nicky Jessop[2] and Catherine Miller[2]
Plastic Surgery[1] and Occupational Therapy[2], Great Ormond Street Hospital, London.

Introduction & objectives: Assessing the outcome of surgical intervention in RDEB with ongoing and progressive hand contracture is troublesome. Patients have the ability to maintain some function, despite limited anatomy, and to have improved appearance, despite loss of function. There are many measures of paediatric hand function but limited assessments that assess abnormal anatomy of the whole hand to establish change. Our purpose was to assess the impact on the hand of surgical intervention for contractures including survivorship of surgery. *Materials & methods:* Surgery was performed after MDT discussions and several meetings with the patient and family. The 1st web was released and covered with Matriderm and a push graft, the fingers were released without breaching the full thickness of the dermis where possible, but usually required fishmouth release at PIP +/- DIP joint levels. No formal joint release was performed. We used our Assessment of hand Contractures in Epidermolysis Bullosa (AChE), to score web spaces (pseudosyndactyly), finger flexion and thumb adduction preoperatively and to observe their recurrence post-hand surgery. We report the results for 7 patients, 10 hands and 14 surgical procedures, operated on by the same surgeon, at a mean age of 7 years. One had had previous surgery to one elsewhere. Three patients had repeat surgery on 4 hands – for one patient and 2 hands it was the third episode of surgery. The AChE was performed within the month prior to surgery and repeated on routine therapy review. Individual hands were followed up for a maximum of 53 months (median 24 months). *Results:* Patients were initially happy with both appearance and function after surgery but this gradually decreased with time as, with recurrence, they lost function and their scores increased. Finger flexion deformity recurred more quickly than 1st web space adduction contracture. Most had returned to their original total score by 2 years post surgery – sometimes this represented a worsening of a different component of the contracture with function preserved. *Conclusions:* We were able to assess recurrence and progression of contractures after surgery using AChE. There was a short survivorship. This should be combined with a functional measure. It allows an assessment of survivorship of the individual components of the release after surgery. We hope to help clinicians and families make informed decisions about hand surgery.

P64
TREATMENT OF AGGRESSIVE SQUAMOUS CELL CARCINOMA IN PATIENTS WITH EPIDERMOLYSIS BULLOSA: MITOCHONDRIA AS A POSSIBLE TARGET

Tobias Welponer[1,2], Lisa Trattner[1], Birgit Tockner[1], Victoria Reichl[1], Anna Kaufmann[1], Melanie Kienzl[1], Thomas Felder[3], Sepideh Aminzadeh-Gohari[4], Réné Feichtinger[4], Roland Lang[2], Johann W. Bauer[1,2], Julia Reichelt[1], Barbara Kofler[4], Christina Guttmann-Gruber[1], Josefina Piñón Hofbauer[1]**
*[1]EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University Salzburg, Austria, [2]Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University Salzburg, Austria, [3]Department of Laboratory Medicine, Paracelsus Medical University Salzburg, Austria, [4]Research Program for Receptor Biochemistry and Tumor Metabolism, Department of Pediatrics, University Hospital of the Paracelsus Medical University Salzburg, Austria, *equal contributors*

Introduction & objectives: Recessive dystrophic epidermolysis bullosa (RDEB) patients are at high risk for developing aggressive squamous cell carcinomas (RDEB-SCC), which constitutes the primary cause of premature mortality. Surgery, radiotherapy and chemotherapy constitute the only treatment options for metastatic RDEB-SCC. Cetuximab was successfully applied for metastatic RDEB-SCC, however, its dose-dependent skin toxicities can be limiting in this patient group. Therefore, combinatorial and alternative treatment options are needed. As many tumor stem cells depend on mitochondrial biogenesis, this appears to be a promising target. Metformin and doxycycline both compromise mitochondrial activity and exert anti-neoplastic effects *in vitro* and *in vivo*. Additionally, the ketogenic diet (KD), which has a high-fat, low-carbohydrate ratio, appears to sensitize most cancer types to standard treatment by utilizing the reprogramed metabolism of cancer cells. Combining metabolically active compounds with a KD can be a promising strategy for adjuvant cancer therapy. Our purpose is to reduce skin toxicities of established treatments and to identify novel treatment options for RDEB-SCC by targeting tumor metabolism. *Materials & methods:* Here we investigate the use of metformin, cetuximab, doxycycline and KD against the growth of human and murine SCC both *in vitro* and *in vivo*. In vitro studies included clonogenicity - and MTT-assays to investigate the individual and combined effects of the substances. In

our *in vivo* model we injected murine SCC VII cells in C3H mice and treated them with KD and/or metformin ad libitum. *Results:* Metformin, cetuximab, and doxycycline, alone or in combination demonstrated significant anti-proliferative effects against several human RDEB-SCC lines *in vitro*. In our *in vivo* model KD formulations administered ad libitum and also combined with metformin could not reduce tumor burden. However, metformin alone resulted in a small but statistically significant increase in overall survival with no adverse effects on the mice. At sacrifice, serum concentrations of metformin in the mice were below therapeutic serum levels in type-2-diabetes patients. *Conclusions:* As both metformin and doxycycline impede mitochondrial biogenesis in tumor cells, the combination of both drugs could induce additive effects. Doxycycline may pose additional benefits in controlling pathogenic skin infections linked to tumor development. By combining metformin or doxycycline with cetuximab, dosage and consecutively skin toxicities of cetuximab could potentially be reduced. Further investigations into pathways impacted by metformin and doxycycline are warranted in order to evaluate the efficacy of this strategy against RDEB-SCC.

P65
CORRELATION AMONG CLINICAL DIAGNOSTIC MATRIX, IMMUNOFLOURESCENCE ANTIGEN MAPPING, TRANSMISSION ELECTRON MICROSCOPY AND NEXT GENERATION SEQUENCING IN DIAGNOSING EPIDERMOLYSIS BULLOSA

Rahul Mahajan, MD[1], Seema Manjunath MD,[1], Manoj Gopal Madakshira, MD[2], Debajyoti Chatterjee, MD, DM[2], Anuradha Bishnoi, MD, DNB[1], Dipankar De, MD[1], Sanjeev Handa, MD, FRCP[1], Bishan Dass Radotra, MD[2]

[1]Department of Dermatology, Venereology, and Leprology, and [2]Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Introduction & objectives: Recently, a clinical diagnostic matrix (CDM) was developed and validated for the diagnosis of epidermolysis bullosa (EB) which showed a high concordance rate with the molecular diagnosis. The primary aim of our study was to correlate the performance of CDM versus immunofluorescence antigen mapping (IFM), and transmission electron microscopy (TEM) in the diagnosis of EB, and with mutational screening in a limited number of patients. *Materials & methods:* This prospective observational study included all patients (aged > 6 months) with the clinical diagnosis of EB. After a complete physical examination, a skin biopsy was taken for TEM and IFM. The primary antibodies used for the IFM were against cytokeratin 14, laminin 5, collagen VII, collagen XVII, and collagen IV. For TEM, the samples were immediately immersed in the TEM fixative containing glutaraldehyde. The samples were divided to allow adequate fixation and provision of informative semithin (0.5–1.0 mm thick) sections for light microscopy. This was followed by the trimming of resin blocks and ultramicrotomy. Semithin sections enabled the level of blistering or tissue splitting to be ascertained as per the features described in the literature. Where-ever possible, mutational analysis was done using targeted next-generation sequencing(NGS). *Results:* Sixty patients with EB, diagnosed clinically were screened and included in the study after satisfying the inclusion and exclusion criteria. Of the 60 patients, based on CDM, 7 patients had EBS- localized type, 2 patients had generalized intermediate type EBS, 2 had generalized severe type EBS. Five patients had JEB generalized intermediate, and 9 patients had a generalized severe type of JEB. Fifteen patients had RDEB generalized severe type and 10 had RDEB generalized intermediate type. Eight patients had DDEB, and 2 patients had Kindler syndrome. Of 60 patients, 49 patients/parents gave consent for biopsy, which was evaluated using transmission electron microscopy and/ or immunofluorescence microscopy (30 TEM and 49 IFM). Only 9 patients could be evaluated for mutational analysis using targeted NGS. Out of 30 samples evaluated with TEM, a diagnosis of EBS was offered in 7 (23.3%), JEB in 6 (20%), DEB in 16 (53.3%) and Kindler syndrome in 1(3.3%). There was a significant difference in all electron microscopy findings studied among the major EB subtypes (Tonofilaments clumping, characteristics of hemidesmosomes/ sub-basal dense plates, basal cell vacuolations, preservation of anchoring fibrils; $p < 0.0001$). Of 49 biopsies evaluated with IFM findings, a diagnosis of EBS was offered in 6 (12.2%), JEB in 20 (40.8%), DEB in 18(36.7%) and kindler syndrome in 2 (4.1%). In 3 patients, IFM findings were not confirmatory. There was a significant difference in all IFM findings studied among the major EB subtypes ($p < 0.0001$). There was statistically significant agreement between CDM and TEM ($k = 0.931$, $p = 0.0001$), CDM and IFM ($k = 0.8$, $p = 0.0001$), and TEM and IFM ($k = 0.883$, $p = 0.0001$). Although done for a small number of patients ($n = 9$), taking NGS as the gold standard for diagnosing EB, the sensitivity of CDM, TEM and IFM were estimated at 100% (9/9), 77.8% (7/9), and 88.9% (8/9), respectively. *Conclusions:* The highest concordance was seen between CDM and TEM followed by TEM and IFM, and the least between CDM and IFM.

P66
SEVERE EPIDERMOLYSIS BULLOSA: FOLLOW-UP BY A PEDIATRIC COMPLEX CHRONIC PATIENT UNIT AND FAMILIES' PERCEIVED SATISFACTION

Inés Cases[1], Silvia Ricart[1], Eduard Pellicer[1], Silvia Ciprés[1], Lucía Peñarrubia[1], Marta Viñals[1], Isabel Torrús[1], Asunción Vicente[2]

[1]Pediatric Complex Chronic Patient Unit, [2]Dermatology Service, Hospital Sant Joan de Déu (Barcelona)

Introduction and objectives: A complex chronic disease is one with a limiting and/or life-threatening condition that implies high fragility, with multiple bio-psycho-socio-spirituals related needs. Within this definition we found patients with severe epidermolysis bullosa (EB). In 2012, a specialized unit for complex chronic patient care (UCCP) was started to respond to this kind of patients, as a multidisciplinary team that offers patient & family centered care. The care is offered 24-h telematically and in-person in hospital, home and community. The main objectives are: to describe the type of interventions performed in one year with these patients and to know the families' perception regarding their main concerns and satisfaction with the follow-up offered. *Material & methods*: Descriptive observational study carried out to patients with an EB diagnosis registered in the UCCP on September 2019, aged 0-18 ($n = 15$). The data was collected from the information recorded in the medical history and the unit's computerized database. The tool for collecting data on families was a corporative mailing of an ad-hoc questionnaire with open questions and scoring on a Likert scale 1-5 on the degree of perceived satisfaction and the degree of concern about each EB-related problem. The study population included both parents. *Results:* From January to September 2019, with a total of 15 patients registered in the unit with some type of EB, a total of 159 calls have been made, 39 by email and 140 face-to-face services, of which: 40 were at home or in the community and 100 in the hospital. There were 2 first visits, 319 follow-ups and 51 interdisciplinary case discussions. The questionnaires were answered by a total of 4 parents. The overall satisfaction with the unit was 5 in 75% of cases. In descending order of concern, the parents indicated the following EB-related problems: pain, itching, dysphagia, infections, psychological problems, economic impact, social rejection, constipation, sleep problems and school integration, among others. Families highlight nurses' care, 24-hour care and support in the initial stages of the disease as positive points of

the follow-up; they also indicate that they would positively value greater home care. *Discussion*: The patient & family centered care model has shown to be well appreciated by families. It is important to know what aspects concern the caregivers of children with EB to continue improving the daily practice of professionals and to improve the patients and families' quality of life.

P67
SINCERELY SPEAKING ABOUT A RARE DISEASE IN SCHOOL: EPIDERMOLYSIS BULLOSA

Inés Cases[1], Silvia Ricart[1], Eduard Pellicer[1], Silvia Ciprés[1], Lucía Peñarrubia[1], Marta Viñals[1], Isabel Torrús[1], Asunción Vicente[2]
[1]Pediatric Complex Chronic Patient Unit, [2]Dermatology Service, Sant Joan de Déu Hospital (Barcelona)

Introduction and objectives: Schooling is a key phase in emotional and physical development, essential for the social development of the person. It must adapt and respond to individual needs to maximize schoolchildren's capacities. Providing proper support for children with epidermolysis bullosa (EB) and providing knowledge to educators is essential to ensure safe schooling, promote their inclusion and avoid referral to specific center when it is not indicated.
From the Chronic-Complex-Patient Unit of a third-level pediatric hospital there is a need to standardize the intervention performed with schools. It is proposed the implementation of a health and psychosocial intervention in schools of children living with EB, whose main objectives are; 1) Improve child's quality of life and integration in their usual environment, 2) Empower teachers for the safe handling of these children, and 3) Raise awareness in educational community about the disease and deny false beliefs that contribute to isolation. *Matherials & methods*: A pilot test is designed to carry out educational intervention in the classroom of an 11-year-old boy with recessive dystrophic EB, with marked emotional involvement; The intervention is aimed at teachers and their students, carried out in June 2019 by a nurse, psychologist and social worker. It consists in 1. Teachers' activity: training session, delivery of documentation and contact of the Unit. 2. Students' activity: interactive session, workshop and debate – which will generate questions that will be answered by the nurse later-. 3. Evaluation: ad-hoc pre-test for students, ad-hoc satisfaction survey for teachers. *Results:* Assistance of 43 students and 10 teachers. 100% answers to the student's pre-test. After the session, they sent a total of 10 questions that were answered by the nurse. There was no response from teachers to the satisfaction survey. Subjective response was received by the center's head. Subjectively, the patient and his family reported subsequent well-being and good relationship with his partners at the beginning of the next course (September 2019). *Conclusions:* An educational intervention has been designed for schools of children living with EB and the experience has been beneficial for the patient and has empowered the educational community. Given the student's participation, we consider that this type of intervention raise awareness and arouse interest in the topic. During the 2019/2020 course, at least 4 interventions more are planned in patient's school and it is planned to quantify its effectiveness through optimal tools.

P68
EXTRACELLULAR MATRIX DISTINCT SIGNATURE AMONG DYSTROPHIC EPIDERMOLYSIS BULLOSA VARIANTS

M. D. Malta[1,2,3], H. Osório[4,5,6], C. Guttmann-Gruber[7], T. Kocher[7], A. F. Carvalho[1,2], M. T. Cerqueira[1,2], A. P. Marques[1,2,3]
[1]3B's Research Group, I3Bs – Research Institute on Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine AvePark, Zona Industrial da Gandra, Barco, Guimarães, Portugal, [2]ICVS/3B's–PT Government Associate Laboratory, Braga/Guimarães, Portugal, [3]The Discoveries Centre for Regenerative and Precision Medicine, Headquarters at University of Minho, Avepark, Barco, Guimarães, Portugal, 4i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal, [5]Ipatimup - Instituto de Patologia e Imunologia Molecular da Universidade do Porto, Porto, Portugal, [6]FMUP – Faculdade de Medicina da Universidade do Porto, Porto, Portugal, [7]EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria

Introduction & objectives: Mutations in the COL7A1 gene, which encodes collagen VII protein, the major component of the anchoring fibrils in the dermal-epidermal junction, cause all forms of dystrophic epidermolysis bullosa (DEB). Different clinical variants have been described with both dominant and recessive inheritance. However, information regarding the consequences of different COL7A1 mutations in the cell microenvironment, particularly on extracellular matrix (ECM), is still scarce. Moreover, several studies found the spectrum of biologic and clinical phenotypes of DEB to be wider than initially anticipated. Hence, this work aims to unravel the main differences in ECM composition between DEB patients and healthy individuals, as well as between representative variants of the disease. *Materials & methods:* Healthy primary fibroblasts and immortalized cell lines of three DEB variants (generalized DDEB, generalized intermediate RDEB and generalized severe RDEB). The cells were seeded at a density of 50x103 cells per cm^2 for 14 days with 50µg/mL ascorbic acid, in order to promote maximum ECM deposition. Mass spectrometry-based label-free quantification was used to assess changes in the ECM deposited by the different cell populations. Then a combination of western blot, quantitative real-time PCR and histological methods were used to confirm the proteomic results and investigate the biological pathways linked to the obtained results. *Results:* Analysis of the extracellular proteome revealed that fibroblasts from each DEB variant have their own proteomic signature. Independently of the DEB variant – and its associated clinical aggressiveness – the different COL7A1 mutations studied impacted dermal ECM organization through the down-regulation of major ECM players such as collagen XII, decorin, biglycan and lysyl oxidase homolog 2. Furthermore, ECM organization-associated proteins were found to be differently expressed between DEB variants. For the phenotypes associated to increased severity of disease, a down-regulation of proteins linked to ECM structure and remodelling, namely collagens I, III and V and matrix metalloproteinases 1 and 2, was observed. *Conclusions:* Our results corroborate previous studies showing that total loss of collagen VII has an enormous impact on dermal ECM dynamics. Additionally, our results also demonstrated that a partial loss of type VII collagen impacts cell microenvironment, affecting mostly the ECM structural proteins. Overall, our work contributes to the generation of further knowledge on DEB variants molecular features. *Acknowledgements*: The authors would like to acknowledge FCT for grant SFRH/BD/137766/2018 (MDM) and contract CEECIND/00695/2017 (MTC), the ERC Consolidator Grant – ECM_INK (ERC-2016-COG-726061) the European Union for The Discoveries Centre for Regenerative and Precision Medicine (H2020-WIDESPREAD-2014-1-739572).

P69
EPIDERMOLYSIS BULLOSA PRURIGINOSA ASSOCIATED WITH RECESSIVE HOMOZYGOUS MUTATIONS IN COL7A1: CASE REPORT OF A RARE EPIDERMOLYSIS BULLOSA GENOTYPE-PHENOTYPE

C. O'Connor[1,2], S. O'Shea[2], J. McGrath[3], J. Bourke[1,2]

[1]University College Cork, Ireland, [2]Department of Dermatology, South Infirmary Victoria University Hospital, Cork, Ireland, [3] National Diagnostic Epidermolysis Bullosa Laboratory, Guy's Hospital, London

History: A 44 year old man was referred with multiple intensely pruritic lesions on his shins. He had been clinically diagnosed with dystrophic epidermolysis bullosa (EB) in infancy. This had manifested in the neonatal period as blistering, reducing in severity with age, and resolving in adolescence. The pruritic lesions on his shins had developed over the ten years prior to referral. He had a history of multiple sclerosis and immune thrombocytopaenic purpura. There was no family history of skin fragility or toe nail dystrophy. *Examination*: Multiple violaceous hypertrophic nodules and plaques were present on the anterior and lateral lower legs, with extensive milia formation. There was scarring at the elbows, knees, and knuckles. Several finger and toe nails were dystrophic. *Investigations:* Skin biopsy showed a cell-poor subepidermal bulla consistent with dystrophic EB. Direct immunofluorescence was negative. Genetic testing for mutations in the COL7A1 gene showed two heterozygous single nucleotide mutations: c.4341-1G>T (IVS39-aG>T) and c.7521+1G>A (IVS99+1G>A). These mutations are sited within the consensus region of an acceptor splice site and a donor splice site, respectively, and are therefore predicted to compromise intron/exon splicing. *Treatment*: Daily application of clobetasol 17-propionate 0.05375% ointment resulted in complete resolution of pruritus within four weeks. Therapy was switched to tacrolimus monohydrate (0.1%) ointment as maintenance therapy. *Conclusion*: EB pruriginosa is a rare subtype of dystrophic EB characterised by violaceous prurigo-like or lichenified nodules and plaques, typically confined to the pretibial area and/or forearms. The onset is usually in the second or third decade of life, following a history of skin fragility and blistering in childhood. Treatment is aimed at controlling pruritus and halting the progression of cutaneous lesions. It is caused by mutations in the type VII collagen gene (COL7A1), with variable modes of inheritance, and poor genotype-phenotype correlation. The majority of cases are autosomal dominant. Only 15% of cases of EB pruriginosa are autosomal recessive. This patient has two COL7A1 mutations, assigning a diagnosis of recessive dystrophic EB. In this patient both mutations are splice site mutations within the type VII collagen triple helix, and both could conceivably cause in-frame exon skipping. Such exon skipping could lead to dominant-negative interference. Thus each mutation could cause dominant dystrophic EB by itself. However, the lack of clinical features of skin fragility or toenail dystrophy in the patient's parents and four siblings is more consistent with a recessive mechanism of pathogenicity.

P70
HIGH PREVALENCE OF AN INFREQUENT PATHOGENIC VARIANT ASSOCIATED WITH EPIDERMOLYSIS BULLOSA SIMPLEX WITH MOTTLED PIGMENTATION

M. Natale[1,2], L. Valinotto[1,2,3], R. Andrada[4], S. De Freijo[5], G.B. Manzur[1,2]

[1]CEDIGEA - Centro de investigaciones en Genodermatosis y Epidermólisis Ampollar- Facultad de Medicina, Universidad de Buenos Aires, Argentina, [2]Hospital de Niños Dr. Ricardo Gutiérrez, Buenos Aires, Argentina, [3]CONICET, [4]Hospital Pediátrico Dr. Castelán, Resistencia, Chaco, Argentina, [5]Hospital Público Materno Infantil de la Provincia de Salta, Argentina

Introduction & objectives: Epidermolysis bullosa simplex with mottled pigmentation (EBS-MP OMIM 131960) is a rare form epidermolysis bullosa. Blisters and erosions are present at birth, and it is clinically indistinguishable from EBS severe generalized. Hyper- and hypopigmentation of the skin begins in childhood in the extremities and the trunk and is often accompanied by focal palmoplantar keratoderma. Most of the worldwide reported cases are associated to a KRT5 pathogenic variant in domain V1 (c.74C>T, p.Pro25Leu), and less frequently in KRT5 domain V2 (c.1649delG/ p.Gly550AlafsX77), two variants in KRT14 (c.356C>T, p.Met119Thr) and (c.1117_1158dup42/ p.Ile373Glu386dup) and one variant in EXPH5 gene (c.3917C>G, p.Ser1306*). *Objective:* Perform molecular diagnosis of EBS-MP patients and find phenotype-genotype correlations. *Materials & methods:* Thirty patients belonging to 12 unrelated families showing clinical features of EBS-MP where molecularly diagnosed. Detailed clinical information was gathered through screening into patients' medical records. *Results:* We found that 11 families had an unusual KRT5 pathogenic variant (c.1649delG/ p.Gly550AlafsX77), and only one family presented the most frequent KRT5 variant (c.74C>T,p.Pro25Leu). Some of the patients presented typical clinical features of EBS-MP, and others had EBS with circinate migratory erythema. *Conclusions:* In most of the patients an infrequent variant was found. According to the pedigrees, the families are not related, although they are from a specific region in our country. Some of the patients presented typical clinical features of EBS-MP, and others had EBS with circinate migratory erythema. Considering that c.1649delG has been associated with both phenotypes, this cases may be a different presentation of same EBS subtype or this patients may have additional molecular modifiers. Remarkably, some of our patients presented EBS with circinate migratory erythema phenotype during their first years of life, and afterwards turned into a typical EBS-PM.

P71
CLINICAL SUBTYPES AND MOLECULAR PATHOLOGY OF EB IN TAIWAN

Wei-Ting Tu[1], Ping-Chen Hou[2], Hsin-Yu Huang[2], Yi-Ting Huang[2], Jing-Yu Wang[2], Yi-Huei Wu[7], Yu-Hsiu Kuo[1], Chun-Lin Su[2], Wan-Rung Chen[1], Sheau-Chiou Chao[1], Julia Yu-Yun Lee[1], John McGrath[3], Peng-Chieh Chen[4,5], Chao-Kai Hsu[1,6]

[1]Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2]School of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [3]St. John's Institute of Dermatology, King's College London (Guy's Campus), London, UK, [4]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [5]Center of Clinical Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [6]International Research Center of Wound Repair and Regeneration (iWRR), National Cheng Kung University, Tainan, Taiwan

Introduction & objectives: Inherited epidermolysis bullosa (EB) is a group of heterogeneous diseases characterized by mechanical fragility of the skin, blister formation, and abnormality wound healing. It is now known that EB has over 30 clinical subtypes, caused by mutations in least 20 genes. Despite tremendous progress in research for EB therapy in the last several decades, the understanding of molecular pathology of Taiwanese EB patients is limited to case reports and small case series. We aimed to identify the genetic mutations and clinical subtypes of Taiwanese EB patients. *Materials & methods:* With informed consent, we collected clinical information including previous diagnostic test results of Taiwanese EB patients in National Cheng Kung University hospital. Skin biopsy was performed for routine histopathology, electron microscopy (EM), immunofluorescence (IF) study and RNA extraction, if not done before. DNA was extracted from peripheral blood obtained from EB patients and sent for whole exome sequencing to identify disease-associated allele variants. Sanger sequencing and segregation analysis were carried out for variants with a sufficiently low frequency in the general population. Novel disease-associated allelic variants were studied with laboratory tests including reverse transcription PCT (RT-PCR),

gene transfection, and Western blotting as appropriate. Clinical subtypes and genetic mutations were determined by both clinical presentation and results of diagnostic tests. *Results:* A total of 47 patients in 31 families were included in this study, including 14 (29.8%) cases of EB simplex, 4 (8.5%) cases of junctional EB, and 29 (61.7%) cases of dystrophic EB. 44 mutations, including 24 novel mutations, were found in KRT5, KRT14, PLEC, LAMA3, LAMB3, COL17A1, ITGB4, and COL7A1 genes. *Conclusions:* Our study expanded the understanding of clinical subtypes and molecular pathology of EB in Taiwan. It is the first large scale attempt at mutational analysis for Taiwanese EB patients.

P72
RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA INVERSA ASSOCIATED TO AN INFREQUENT VARIANT

L. Valinotto[1,2,3], M. Natale[1,3], E. Cella[4], M. Giovo[5], J. Goitia[6], G. B. Manzur[1,3]
[1]CEDIGEA - Centro de investigaciones en Genodermatosis y Epidermólisis Ampollar-Facultad de Medicina, Universidad de Buenos Aires, Argentina, [2]CONICET, [3]Hospital de Niños Dr. Ricardo Gutiérrez, Buenos Aires, Argentina, [4]Hospital de Pediatría Dr. Juan P. Garrahan, Buenos Aires, Argentina, [5]Hospital de Niños la Santísima Trinidad, Córdoba, Argentina, [6]Hospital de Pediatría Sor María Ludovica, La Plata, Argentina

Introduction & objectives: Recessive dystrophic epidermolysis bullosa inversa (RDEB-I) is a rare subtype of DEB that usually presents with blisters and erosions at or shortly after birth that heal leaving atrophic scars and milia. During early childhood, blisters form in intertriginous skin sites, predominantly at axillary, sub-mammary, perineal and inguinal folds. Different degrees of severity of nail dystrophy are observed among patients. Although skin manifestations are mild, the oral cavity, esophagus and the lowermost portion of the genitourinary tract are severely affected. Additional extracutaneous manifestations include external ear canal stenosis, corneal erosions and anemia. The objective of this work is to molecularly diagnose RDEB-I patients that were clinically diagnosed as EBS, and analyze genotype-phenotype correlations. *Materials & methods:* We performed molecular diagnosis of eight unrelated families presenting inconclusive clinical diagnosis of epidermolysis bullosa and detailed clinical information was gathered through screening into patients' medical records. *Results:* All the families studied had one of variant that resulted in a premature stop in COL7A1 gene. In seven of the families the second variant was found in exon 107 (c.7957G>A/ p.Gly2653Arg). Only one patient had the (c.6205C>T/ p.Arg2069Cys) variant. *Conclusions:* All our patients presented mild cutaneous involvement, and therefore they were clinically misdiagnosed as EBS. Preventive measures to reduce oral, pharyngeal and esophageal mucosa damage were not considered leading to dysphagia and esophageal stenosis. Interestingly, to the best of our knowledge, p.Gly2653Arg variant was never associated to RDEB-I, suggesting a new genotype-phenotype association in RDEB patients.

P73
MORPHOLOGICAL AND MORPHOMETRICAL ANALYSIS OF CUTANEOUS SQUAMOUS CELL CARCINOMA IN PATIENTS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA: A PROSPECTIVE STUDY

Angela Filoni[1], Lucia Lospalluti[1], Gerolamo Cicco[1], Antonella Maglietta[2], Giuseppina Annichiarico[3], Leonardo Resta MD[2], Domenico Bonamonte[1]
[1]Section of Dermatology, Department of Biomedical Science and Human Oncology, University of Bari, Bari, Italy, [2]Section of Pathology, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy, [3]Regional coordination for Rare Diseases, AReS Puglia, Bari, Italy

Introduction & objectives: Recessive dystrophic epidermolysis bullosa (RDEB) is a highly disabling genodermatosis characterized by skin and mucosal fragility and blistering. Cutaneous squamous cell carcinoma (cSCC) is one of the most devastating complications of recessive dystrophic epidermolysis bullosa (RDEB) with a high morbidity and mortality rate. Patients with RDEB were reported to have up to a 70-fold higher risk of developing SCC than unaffected individuals. Immune cells play a role in cancer evolution. *Materials & methods:* The aim of our study is to evaluate immunohistological difference between cSCC in RDEB with primary cSCC and secondary cSCC (developed by burn and radiotherapy scars). The immuno-histological evaluation was performed also in skin biopsies in RDEB non-neoplastic skin. Consecutives biopsies of cSCC taken by 5 RDEB patients were analysed. As controls we analysed 5 primary cSCC, 5 secondary cSCC and 5 cutaneous pseudoepithliomatous hyperplasia in RDEB patients. *Results:* We found a significant reduction in immune infiltration in RDEB compared to controls. In particular we found a reduction in CD3+, CD4+, CD8+, CD20+, CD68+. No significant difference was found in size, histology, grading, number of mitoses and EGFR expression between the different groups. *Conclusions:* Our data shows a reduction in immune cell peritumoral infiltration. Considering the well-known evolution of cSCC in RDEB as well as the youngest age at diagnosis, we could assume that immune dysfunction can lead the cSCC aggressivity in these patients.

P74
ITCH AND PAIN REPORTED BY INDIVIDUALS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB): FINDINGS OF THE PEBLES STUDY

Eunice Jeffs[1], Elizabeth I Pillay[1], Alessandra Bisquera[2], Susan Robertson[3], John McGrath[1], Anna E Martinez[4], Jemima E Mellerio[1]
[1]Guy's & St Thomas' NHS Foundation Trust, London, UK, [2]King's College London, UK, [3]Royal Children's Hospital, The Royal Melbourne Hospital, Monash Health and Murdoch Children's Research Institute, Melbourne, Australia, [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Introduction & objectives: Introduction: Itch and pain are acknowledged problems for individuals with RDEB. PEBLES is a prospective register study to record detailed information about what happens to an individual with RDEB and how it affects them over time, including itch and pain. To report preliminary findings regarding itch and pain reported by individuals with RDEB. *Materials & methods:* Methods: Individuals recruited to PEBLES were reviewed annually for those 10 years and older and 6-monthly for those under 10 years. All participants reported background and procedural pain (dressing changes) on a 10cm visual analogue scale (VAS) and indicated the number of nights their sleep was disturbed by pain. Participants aged 8 years and above also completed the Leuven Itch Scale (version 1.0). The study was ethically approved by the UK Research Ethics Committee and Health Research Authority. *Results:* Data regarding itch and pain at initial review were available for 38 adults (79%) and 10 children (21%). Of these, 31 (65%) completed four reviews spanning 2-4 years. Participants with RDEB generalised severe (RDEB-GS) reported the greatest number of nights sleep disturbed by pain: only 19% had undisturbed sleep compared to 39% of individuals with RDEB generalised intermediate (RDEB-GI) and 29% with RDEB-other. Participants in all subtypes reported significant background pain (median 4.3, IQR 2.9,6.0) with greater procedural pain (median 6.0, IQR 4.0,7.6); background and procedural pain levels were greatest for participants with RDEB-GS. Individuals with RDEB-GS ($n=36$) experienced more frequent itch, greater

severity and distress, but shortest duration. More than half of all individuals reported consequences of itching such as skin damage, disturbed routine, difficulty falling asleep, being woken up by itch, bad mood and loss of concentration. Reduced quality of life was a common consequence of itch in RDEB-GS not other subtypes. Nearly half (44%) were not using treatment for itch. Others used antihistamines (28%), emollients (22%) or a combination of both (6%), although they were generally ambivalent or slightly dissatisfied with treatment effect. Participants were frustrated by the lack of effective treatment for itch. *Conclusions:* These findings from a substantial cohort of individuals with RDEB confirm the morbidity and impact on quality of life caused by pain and itch. They highlight the current lack of effective treatments for these common symptoms and provide a baseline against which to test the benefit of future therapies.

P75
QUALITY OF LIFE REPORTED BY INDIVIDUALS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB): FINDINGS OF THE PEBLES STUDY

Eunice Jeffs[1], Elizabeth I Pillay[1], Alessandra Bisquera[2], Susan Robertson[3], John McGrath[1], Anna E Martinez[4], Jemima E Mellerio[1]
[1]Guy's & St Thomas' NHS Foundation Trust, London, UK, [2]King's College London, UK, [3]Royal Children's Hospital, The Royal Melbourne Hospital, Monash Health and Murdoch Children's Research Institute, Melbourne, Australia, [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Introduction & objectives: Introduction: RDEB has a significant impact on the quality of life of affected individuals and their families. (1,2) PEBLES is an prospective register study designed to record detailed information about what happens to an individual with RDEB and how this affects them over time. This includes both the physical aspects and impact on quality of life. *Objective*: To report preliminary findings from the PEBLES study regarding quality of life for adults and children with RDEB. *Materials & methods:* Methods: Individuals recruited to PEBLES were reviewed annually for those 10 years and older and 6-monthly for those under 10 years. At each review, participants completed an age-appropriate quality of life questionnaire. Children aged 5-18 years and parents of children aged 2-18 years completed the Pediatric Quality of Life Inventory version 4 (PedsQL). Adults aged 19 years and above completed the Quality of Life in EB questionnaire (QOLEB). The study was ethically approved by the UK Research Ethics Committee and Health Research Authority. *Results:* Thirty-seven adults completed QOLEB at their initial review, and 25 (68%) completed two subsequent reviews spanning a period of three years. Adults with RDEB generalised severe (RDEB-GS) reported severe impact on overall quality of life scores (24/51) and physical functioning (19/36), but only mild impact on emotions (5/15). Other subtypes reported less overall impact on quality of life, with very mild impact on emotions (≤4/15). Individuals with RDEB-GS reported greater impact of EB on all aspects of daily life than other subtypes except for being worried/anxious and being made to feel uncomfortable because of their EB. Four children and 11 parents completed PedsQL at their initial review; of these, 7 children and their parents (64%) completed PedsQL at a further 4 reviews spanning a period of three years. Children and their parents reported impact on quality of life was greater for physical health, with less impact for psychosocial health. Parents reported greater impact on their child's quality of life than did the child *Conclusions:* RDEB, especially RDEB-SG, has a negative impact of quality of life, particularly as relates to physical functioning. Interestingly, the impact on emotional or psychosocial wellbeing appears less marked, perhaps reflecting psychological adjustment in individuals with RDEB suggesting further study is warranted.

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P76
PRELIMINARY SAFETY AND EFFICACY OUTCOMES OF A PHASE I TRIAL OF SYSTEMIC MESENCHYMAL STROMAL CELLS FOR RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

L. Martínez-Santamaría[1], R, Maseda[2]*, R. Sacedón[3], M.C. de Arriba[1], E. Jimenez[3], M. García[1], E. Chacón[1], S. Suárez-Sancho[4], I. Fernandez-Bello[5], M. Carretero[1], R. Yañez[6], S.M. Lwin[7], M. Martinez-Queipo[7,8], L. Liu[7], J. Mee[7], R. De Paz[5], A. Borobia[9], M.E. Fernández-Santos[4], N. Butta[5], V. Yuste[5], J.A. McGrath[7], M. del Río[1], A. Vicente[3], R. de Lucas[2], M.J. Escámez[1]*
*[1]U[714]-CIBERER, UC[3]M-CIEMAT, IISFJD, Madrid, Spain, [2]Dermatology Department, La Paz University Hospital, Madrid, Spain, [3]Cell Biology Department, UCM, Madrid, Spain, [4]Cell Therapy Unit, IISGM, TERCEL, Hospital General Universitario Gregorio Marañón, Madrid, Spain, [5]Hematology Unit, La Paz University Hospital-IdiPAZ, Madrid, Spain, [6]U[715]-CIBERER, CIEMAT, IISFJD, Madrid, Spain, [7]St John's Institute of Dermatology, King's College London, London, UK, [8]NIHR Biomedical Research Centre, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK, [9]Clinical Pharmacology Department, IdiPAZ, La Paz University Hospital, UAM, Madrid, Spain. *The first two authors contributed equally to this work*

Introduction: Recessive dystrophic epidermolysis bullosa (RDEB), due to partial or complete absence of type VII collagen (C7), is an incurable inherited mucocutaneous fragility disorder with systemic complications secondary to chronic inflammation. One promising therapy is the allogeneic mesenchymal stromal cells (MSCs), which have remarkable anti-inflammatory properties. Furthermore, MSCs modulate the cellular behaviour in wound healing, tissue remodeling and fibrosis, and improve epithelial-mesenchymal adhesion. MSCs are usually well tolerated and transient clinical benefits have been reported in RDEB and other inflammatory diseases. However, the therapeutic mechanism and the variability in clinical benefits are poorly understood. Our study aims to further elucidate the safety and efficacy of systemic MSCs and stratify the patients' responses. *Methods*: A single-centre, phase I, open-label, exploratory clinical trial in which 9 children with RDEB (aged 1 to 17 years) were enrolled. In order to minimize the potential risk of autoimmune response, patients with a minimal C7 expression and a negative anti-C7 antibodies on their skin were included. A total of three intravenous infusions of MSCs (2–3 million cells/kg/infusion) derived from haplo-identical bone marrow donors were administered every 21 days. Clinical, histological and molecular characterisation of patients was performed at baseline and 2, 3, 6, 9 and 12 months after the first infusion. *Results:* Five of the 7 patients enrolled (aged 4 to 14 years; 1 male/4 females) were treated without severe adverse reactions. No deposition of anti-C7 antibodies was found in the skin. Regarding efficacy, there was an improvement in wound healing of both, skin and mucous membranes, as well as alleviation of itch and pain, an increase in skin resistance, and a modest increase in C7 expression. All patients had variable but significant alterations in the percentages of peripheral blood leukocyte population at baseline, particularly the T cell subpopulations. Those alterations were more modest in the responding patient. *Conclusions:* MSCs were well tolerated without any serious adverse reactions. Improvement in wound healing, itch and pain with a modest increase in C7 expression promise MSCs as a potential effective therapy for RDEB. Anomalies associated with T cells could be key to determining the progress of the disease and the regenerative capacity of the skin.

The variability in the efficacy may reflect the differences in the patient's inflammatory/immunological status at baseline. Further correlation of the patients' immunological status at baseline and their responsiveness to MSCs may help stratify responders, intermediate responders and non-responders.

P77
TREATMENT COSTS FOR INDIVIDUALS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB): FINDINGS OF THE PEBLES STUDY

Elizabeth I Pillay[1], Eunice Jeffs[1], Alessandra Bisquera[2], Susan Robertson[3], John McGrath[1], Anna E Martinez[4], Jemima E Mellerio[1]
[1]Guy's & St Thomas' NHS Foundation Trust, London, UK, [2]King's College London, UK, [3]Royal Children's Hospital, The Royal Melbourne Hospital, Monash Health and Murdoch Children's Research Institute, Melbourne, Australia, [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Introduction & objectives: Introduction: Little information exists about the cost of treating individuals with RDEB. PEBLES is a prospective register study designed to record detailed information about what happens to an individual with RDEB and how it affects them over time, including costs of dressings and associated treatment. *Objective*: To report preliminary findings regarding the cost of dressings and associated treatment of individuals with RDEB. *Materials & methods:* Individuals recruited to PEBLES were reviewed annually for those 10 years and older and 6-monthly for those under 10 years. At each review, participants reported their weekly use of dressings and fixings, and details regarding care provision and funding. Costs are reported per annum (pa) as GBP (£) and were calculated as at August 2017; cost of paid care was calculated at £12.50 per hour regardless of location or carer's actual pay scale. The study was ethically approved by the UK Research Ethics Committee and Health Research Authority *Results:* A total of 53 patients with RDEB had an initial review at which the total annual cost of wound dressings, tubular bandages and retention garments was £2,431,844; as some participants provided incomplete data, these findings are a conservative estimate. The average wound care cost ranged from £2,709 pa for RDEB inversa (RDEB-INV, $n=5$), increasing to £81,858 pa for RDEB generalised severe (RDEB-GS, $n=18$); participants with RDEB-GS accounted for 61% of total annual dressings costs. Only four participants did not require any dressings: 2 with RDEB-generalised intermediate (RDEB-GI) and 2 with RDEB-INV. The average time taken to change dressings ranged from 105 minutes daily for RDEB-GS to 39 minutes daily for RDEB-GI. Most participants (71%) changed their dressings all at once, with patch-ups as required. Ten (56%) participants with RDEB-GS received paid care at an average cost of £31,980 pa. Thirteen (72%) participants with RDEB-GS received unpaid care from a family member who was unable to seek employment due to providing daily EB care, whereas only 4 carers (25%) of those with RDEB-GI and 1 (14%) for RDEB-other were financially impacted. *Conclusions:* Individuals with RDEB-GS and their families have the greatest financial impact; the cost of wound and paid care is up to 30 times higher than in other RDEB types. These data highlight the economic burden of wound care to families living with EB as well as the wider healthcare system.

P78
EPIDERMOLYSIS BULLOSA SIMPLEX WITH MOTTLED PIGMENTATION - A CASE REPORT

Charmaine E Lim, Kong YL.
National Skin Centre, Singapore

Results: We describe a rare case of epidermolysis bullosa simplex with mottled pigmentation (EBS-MP). The patient presented with non scarring vesicles since infancy, arising on the soles of her feet after minor trauma and subsequently spreading from the extremities to the trunk. Reticulate brown pigmentation on her trunk and limbs was observed after the erosions healed. Genetic analysis revealed a mutation in the V2 domain of keratin 5: c.1649_1649delG, p.Gly550AlafsX77. We examine the possible pathophysiologic processes which contribute to the EBS-MP phenotype.

P79
PLECTIN MISSENSE MUTATION P.LEU319PRO IN THE PATHOGENESIS OF AUTOSOMAL RECESSIVE EPIDERMOLYSIS BULLOSA SIMPLEX

Wei-Ting Tu[1], Peng-Chieh Chen[3,4], Ping-Chen Ho[2], Hsin-Yu Huang[2], Jing-Yu Wang[2], Sheau-Chiou Chao[1], Julia Yu-Yun Lee[1], John McGrath[5], Ken Natsuga[6], Chao-Kai Hsu[1,3,7]
[1]Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, [2]School of Medicine, College of Medicine, National Cheng Kung University, [3]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, [4]Center of Clinical Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [5]St. John's Institute of Dermatology, King's College London (Guy's Campus), London, UK, [6]Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [7]International Center for Wound Repair and Regeneration (iWRR), National Cheng Kung University, Tainan, Taiwan

Results: Plectin is a linker-protein that interacts with intermediate filaments and hemidesmosomal proteins, including the beta4 integrin subunit. Mutations in the plectin gene (PLEC) can underlie both autosomal dominant and autosomal recessive (AR) subtypes of the inherited blistering disease, epidermolysis bullosa simplex (EBS). Typically, the mutations in PLEC which cause AR-EBS are nonsense mutations or out-of-frame indels. In contrast, pathogenic AR missense mutations in PLEC are rarely observed. Here, we describe two Taiwanese AR-EBS patients with compound heterozygous nonsense/missense PLEC mutations: in both cases the missense mutation is a previously unreported variant, p.Leu319Pro. Both patients had generalized erythematous blistering and erosions, dystrophy of all toe and fingernails, and palmoplantar keratoderma. They did not have obvious muscles weakness, hoarseness, ptosis, or pyloric atresia. Immunofluorescence microscopy of patient skin showed an almost complete absence of plectin labeling. Whole exome sequencing (WES) revealed two heterozygous PLEC mutations, c.6955C>T (p.Arg2319Ter) and c.956T>C (p.Leu319Pro) in case 1, and c.2807G>A (p.Trp936Ter) and c.956T>C (p.Leu319Pro) in case 2. In vitro studies on overexpression of plectin and beta4 integrin revealed significantly reduced plectin in HEK293 transfected with mutant PLEC complementary DNA (cDNA) harboring p.Leu319Pro, than those transfected with wild-type PLEC cDNA. The findings for p.Leu319Pro were similar to those observed for a different reported pathogenic duplication mutation affecting this residue, p.Leu319dup. Our studies highlight the detrimental effect of a missense PLEC mutation on protein stability and extend genotype-phenotype correlation in EBS.

P80
ORAL GLUTAMINE ALLEVIATE EPIDERMOLYSIS BULLOSA RELATED ORAL EROSIONS AND ULCERS

Chung-Ching Chang[1] Claudia Yun-Tzu Chang[2] Hao-Hueng Chang[3]
[1]Taipei Municipal Chenggong High School, [2]Department of Public Health, National Taiwan University [3]School of Dentistry, National Taiwan University, Department of Dentistry, National Taiwan University Hospital

Introduction & objectives: Epidermolysis bullosa (EB) represents a group of inherited dermatological diseases that are characterized by blistering and mechanical fragility of the skin and mucosa. Oral bullae, ulcers, and erosions may be the most common oral feature of EB. Oral mucosa ulcer and erosion usually lead to pain and dysphagia, which may exacerbate the nutrition status of patients. Oral glutamine has been shown to alleviate mucositis in patients who received radiotherapy and shown promote healing. The purpose of this study is to evaluate the influence of oral glutamine on erosion and ulcer of oral mucosa in EB patients. *Materials & methods:* From Jan 2016 through Dec 2017, 5 patients with recessive epidermolysis bullosa were enrolled. The patients were allocated blindly and randomly to either use glutamine suspension (10 g in 240 ml normal saline) or placebo (normal saline) at different intervention period for 6-weeks. We evaluated and documented the response and the number of oral ulcers periodically at each intervention period. Furthermore, patient record their subjective improvement in printed format on the duration and severity of oral erosions and ulcers around the intervention period. After completing the survey, the influence on the severity of oral ulcer and were compared between the period with glutamine suspension and period with placebo. *Results:* Partial Response and total response rate of EB patients in glutamine administrated period (70%) as compared with placebo administrated period (30%). The number of oral ulcers EB patients in glutamine administrated period (3.6 ± 2.6) as compared with placebo administrated period (6.0 ± 3.2). The objective parameter such as response rate, number and number of oral ulcers were better in the glutamine period than the placebo period($p < 0.05$). Subjective improvement (60%) of EB patients in glutamine administrated period on severity of oral erosions and ulcers as compared with placebo administrated period (20%). The duration of oral erosions and ulcers of EB patients in glutamine administrated period (9 ± 4 days) as compared with placebo administrated period (12 ± 6 days).The subjective improvement, including duration and severity of oral erosion and pain score reported, were significantly improved with glutamine compared with placebo($p < 0.05$). *Conclusions:* Oral glutamine may significantly reduce the duration and severity of both objective and subjective in oral ulcers and erosion. It may shorten the duration of healing of oral ulcers and erosion in EB patients.

P81
CRISPR/CAS9-BASED GENE EDITING STRATEGIES FOR CLINICALLY-RELEVANT *EX VIVO* CORRECTION OF RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Bonafont[1,2], A. Mencía[2,3], W. Srifa[4], S. Vaidyanathan[4], R. Romano[4], M. Garcia[1,2,3], MJ. Escamez[1,2,3,4], B. Duarte[2,3,5], MH. Porteus[4], M. Del Rio[1,2,3,5], R. Murillas[2,3,5] and F. Larcher[1,2,3,5]

[1]Department of Biomedical Engineering, Carlos III University (UC3M), Madrid, Spain, [2]Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz, Madrid, Spain, [3]Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER) U714, Madrid, Spain, [4]Department of Pediatrics, Stanford University, Stanford, California, USA, [5]Epithelial Biomedicine Division, Centro de Investigaciones Energéticas Medioambientales y Tecnológicas (CIEMAT), Madrid, Spain

Introduction & objectives: Mutations in COL7A1, the gene encoding type VII collagen (C7), are the cause of RDEB, one of the most severe subtypes of Epidermolysis Bullosa. The main goal of this research is to achieve highly efficient and precise correction of multiple pathogenic mutations in COL7A1 gene using different genome editing tools in primary patient cells. *Materials & methods:* We have recently shown that a one-step NHEJ-based correction protocol consisting of dual gRNA/Cas9 complexes delivered by electroporation, achieved highly efficient removal of a mutation-containing COL7A1 exon in primary patient keratinocytes. In this *ex vivo* correction strategy, gene-corrected patient keratinocytes could be used to generate skin equivalents that can be grafted onto affected skin of RDEB patients. Exon 80 was chosen as a target because a frame-shift mutation in this exon is highly prevalent in the Spanish RDEB population (46% of Spanish RDEB patients). This exon removal strategy has been adapted to other exons of the COL7A1 collagenous domain by changing the pair of gRNAs, spreading the benefits for a large number of patients. On the other hand, we have designed a marker free HDR-based strategy for RDEB correction, using Cas9 as RNP to create double stand breaks in the DNA and a donor template-carrying AAV, aiming to precisely correct the gene. This donor template design covers 10 exons of COL7A1 gene, potentially enabling HDR-based correction for a wider spectrum of mutations. *Results:* With the NHEJ approach, we achieved efficiencies of exon removal close to 90% in primary RDEB keratinocytes, with practically every cell in the bulk population expressing functional C7. On the other hand, HDR-based gene correction strategy showed efficiencies over 40% in primary keratinocytes, releasing a corrected full lenght C7 protein. C7 expression in bulk populations of gene edited keratinocytes is comparable to that detected in normal keratinocytes, showing that these are feasible strategies to restore dermal-epidermal adhesion in regenerated skin tissue with a clinically-relevant application. *Conclusions:* Both genome editing tools offer remarkable gene correction efficiency able to support normal healthy skin regeneration when transplanted onto nude mice. NHEJ-based approach offers a therapeutic option that could be applied to other mutation-containing exons suitable for exon removal. Otherwise, HDR-based strategy offers a precise gene correction covering a wider number of mutations. The use of gene corrected bulk keratinocytes, thanks to high gene editing frequencies achieved, enables the translation of both approaches into clinics.

P82
CUTANEOUS SQUAMOUS CELL CARCINOMA IN EPIDERMOLYSIS BULLOSA: A 28 YEAR RETROSPECTIVE STUDY

Susan J. Robertson,[1] Elizabeth Orrin[2], Manpreet K Lakhan[2], Gavin O'Sullivan[2], Jessie Felton[3], Alistair Robson, Danielle T. Greenblatt[2], Catina Bernardis[2], John A. McGrath[2], Anna E. Martinez[4], Jemima E. Mellerio[2]

[1]The Royal Children's Hospital, The Royal Melbourne Hospital, Monash Health, Murdoch Childrens Research Institute, Melbourne Australia, [2]Guy's and St Thomas' NHS Foundation Trust, London, UK, [3]Brighton General Hospital, E Sussex, UK, [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Introduction & objectives: Some forms of epidermolysis bullosa (EB), notably severe generalized recessive dystrophic EB (RDEB-SG), are associated with an increased risk of developing mucocutaneous squamous cell carcinomas (SCCs) which behave aggressively and are the major cause of mortality in early to mid-adulthood. We report our centres' experience of EB-associated SCCs over the last 28 years. *Materials & methods:* An observational, retrospective, double institution case record review of EB patients diagnosed with SCC between July 1991- June 2019. *Results:* Forty-four EB patients with SCC were identified with a total of 221 primary SCCs. They comprised: 31 (70%) with RDEB-SG, 1 (2.3%) with RDEB-pruriginosa, 1 with RDEB-inversa (2.3%), 2 (4.5%) with RDEB-generalised intermediate, 3 (6.8%) with junctional EB generalised intermediate (JEB-GI), 5 (11.4%) with dominant dystrophic EB, and 1 (2.3%) with Kindler syndrome. Diagnosis of first SCC was earlier in the RDEB-SG group (median 29.5 years (range 13-52 years)) compared to other groups collectively (median 47.1 years (range 30-89 years)). Most SCCs occurred in the RDEB-SG group, and the majority had multiple tumours (mean 5.8 (range 1-44)). SCC-associated

mortality was high in this group (64.5%), with a median survival after diagnosis of first SCC of 2.4 years (range 0.5-12.6 years). Most SCCs were well-differentiated (53.4%) and located on the extremities. Wide local excision was undertaken for the majority of tumours (86.4%). Metastatic disease occurred in 16 of 31 (51.6%) RDEB-SG patients and 1 with JEB-GI. Treatments for metastatic disease included lymph node dissection ($n=6$), radiotherapy ($n=5$), chemotherapy ($n=3$), electrochemotherapy ($n=2$), and targeted cancer therapies erlotinib ($n=1$), cetuximab ($n=2$) and cemiplimab ($n=1$). Treatments were generally well-tolerated, however were limited in response with the exception of cemiplimab. *Conclusions:* EB-associated SCCs differ from those in the general population: they affect a younger age group and there are often multiple primaries. They behave aggressively and metastasise early despite well-differentiated histopathology. The median survival after diagnosis of first SCC in RDEB-SG patients of just 2.4 years underscores the poor prognosis in this group. As the largest cohort of EB SCC patients with comprehensive data regarding clinical course and management to date, our data reinforce the need for regular clinical surveillance for SCCs in EB patients, starting from adolescence in RDEB-SG and from the 3rd or 4th decade for other at-risk groups. It also highlights the pressing need for more effective treatments for this devastating condition.

P83

IMPROVING PATIENT VERSIONS OF CLINICAL PRACTICE GUIDELINES FOR PEOPLE LIVING WITH EPIDERMOLYSIS BULLOSA

Kattya M. Mayre-Chilton[1,2], Olivia Mullins[1], Lie A. Taguchi[1,3]
[1]DEBRA International, Vienna, Austria, [2]Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK, [3]DEBRA Brasil, Santa Catarina, Brazil

Introduction & objectives: Epidermolysis bullosa (EB) is a complex condition that affects the skin and many parts of the body. Although an unusual undertaking for a patient organisation, it is unlikely that patient versions (PVs) of the clinical practice guidelines (CPGs) would have been developed without the drive of patients. International guideline developers are producing patient information or PVs as they acknowledge that there is an increasing demand for them. The objective was to review two different PV development methods to determine what met the EB Community's requirements. *Materials & methods:* Two CPG panels were invited to develop PVs for their published guidelines: one panel consisted of only clinical staff focussing on one PV and the other was a mixed panel of experts, people living with EB (PPI), and a design team that produced four user-targeted PVs. In August-September 2019 external experts in EB, experts in PV development, and PPI from the CPG network were invited by email to review one PV from each group. A survey was modified using the honeycomb model and key themes from the Developing and Evaluating Communication Strategies to support Informed Decision and practice based on Evidence (DECIDE) project1. Their feedback was collected using a PVs feedback SurveyHero link. *Results:* Eight participants were PPI, six were clinical experts, and one was both. They represented Belgium, Australia, UK, Ireland, Norway, Singapore, Netherlands, and Brazil. Overall PV "A" scored highly on the measures of 'Useful' and 'Valuable' whereas PV "B" scored highly in 'Desirable', 'Usable', 'Useful', and 'Valuable'. PV "A" scored poorly on the information coming from 'Credible Sources'. Both scored poorly in 'Findable' and 'Accessible' but were given 4-5 star rating. The summary of results can be seen in Table 1. *Conclusions:* There is generally a low level of access and awareness of PVs linked to EB-focussed CPGs. We are starting to understand what people living with EB know about CPGs or PVs and what they want from them. As a "one size fits all" approach is not possible, we need to reach the right balance between keeping the EB PVs simple while providing sufficient information to facilitate shared decision-making and support the international EB Community.

Table 1. Summary of key survey results

Patient version (PV)	A	B
Participants complete survey	6	9
Types of EB representation	Dystrophic EB	EB Simplex, Junctional EB, and Dystrophic EB
Did the PV cover all topics they wanted information on	100% Yes	56% Yes
Positive feedback	All parts are very useful and thoroughly described	Patient quotes, photos, tips and 'Recommendation' boxes
Could the layout and/or language be improved	67% Yes	33% Yes
Require content in another language	83% Yes	56% Yes

1. Fearns et al. Improving the user experience of patient versions of clinical guidelines: user testing of a Scottish Intercollegiate Guideline Network (SIGN) patient version BMC Health Services Research (2016) 16:37

P84

MIR-10B AS A MARKER FOR DISSEMINATED DISEASE IN RDEB-LINKED SCCS

Moksha Manish Shah[1,2], Hannelore Bodocian[1,3], Roland Zauner[3], Mila Sajinovic[1], Paul De Souza[1,2], Verena Wally[3], Albert S. Mellick[1,2]
[1]Ingham Institute for Applied Medical Research, Medicine, University of New South Wales, Liverpool NSW, Australia, [2]Medicine, University of Wollongong, Wollongong NSW, Australia, [3]EB House Austria, University Hospital of the Paracelsus Medical University, Salzburg, Austria

Introduction & objectives: Squamous cell carcinoma (SCC) is the second most common form of skin cancer, and the most common form of nonmelanoma skin cancer (NMSC). When caught early, most SCCs are curable. However, for patients with recessive dystrophic epidermolysis (RDEB), the diagnosis of an SCC can be a death sentence. SCCs from RDEB patients tend to be significantly more aggressive than SCCs appearing in an otherwise healthy population. Consequently, there is a great need to shorten the time between diagnosis and treatment. However, current methods, which involve traumatic skin biopsies, do not encourage regular screening. In EB patients such screening is especially problematic given that patients already have significant problems with wound healing. *Materials & methods:* In the last couple of years, we have begun work investigating the use of small RNAs (micro/miRNAs) as markers of malignancy in cancer. miRNAs are key regulators of cell differentiation and development. Changes in miRNA expression can be indicative of significant changes in disease pathology. Importantly for diagnostic purposes, as they are the end products of enzyme (RNase) degradation they are also remarkably stable. In previous work, we developed methods in fluorescent in situ hybridization that have allowed for the cell specific localisation of small RNAs in disseminated cancer cells isolated from the blood of cancer patients (liquid biopsy) [Gasch et al. (2015) Scientific Reports]. *Results:* In collaboration with the Wally Laboratory, EB House , Salzburg, Austria, we have identified miR-10b as up regulated in primary cell lines isolated from SCCs and RDEB-linked SCCs, compared to normal control keratinocytes. We have also found that miR-10b is up-regulated in primary tumors and lymph node metastases from RDEB-linked SCCs; and begun optimizing methods for analysis of blood of RDEB patients for disseminated tumor cells that express miR-10b. *Conclusions:* The use of the liquid biopsy (blood draw) for diagnosing disseminated disease in RDEB-linked SCCs is particularly attractive because it has the potential to avoid traumatic skin biopsies. In our laboratory by combining methods in cell specific localisation of mRNAs with filtration-based (Creatv Microtech, CellSieve System) methods of detecting circulating tumor cells (CTCs) in the blood of patients

we hope that we will be able to provide an objective and effective tool that can aid in diagnosis of malignant of SCCS in EB patients.

P85
GENETIC PROFILE OF EPIDERMOLYSIS BULLS CASES IN KING ABDULAZIZ MEDICAL CITY, RIYADH, SAUDI ARABIA

Raghad Alharthi[1], Muhannad Alnahdi[1], Ahad Alharthi[1], Seba Almutiri[1], Sultan Alkhenaizan[2], Mohemmed Al Balwi[3]
[1]College of Medicine, King Saud bin Abdulaziz University, Riyadh, Saudi Arabia, [2]Dermatology Division, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3]Department of Molecular Pathology and Genetics, King Abdulaziz Medical City, Riyadh, Saudi Arabia.

Introduction & objectives: Epidermolysis bullosa (EB) is a rare genetic mechano-bullous skin disorders characterized by increased skin fragility leading to blister formation after minor injuries. EB may be inherited as an autosomal dominant or an autosomal recessive and can be classified into dystrophic EB (DEB), junctional EB (JEB) and EB simplex (EBS). To explore the genetic profile of Saudi EB patients at a tertiary healthcare center. *Materials & methods:* This was an observational, retrospective chart-review study targeting patients with EB registered in our tertiary care center, Riyadh, Saudi Arabia. Consecutive non-probability sampling technique was used to approach all affected patients. Molecular analysis was done by testing patients' genomic DNA using a custom design AmpliSeq panel of genes. All disease-causing variants were checked against HGMD, ClinVar, Genome Aggregation Database (gnomAD) and Exome Aggregation Consortium (ExAC) databases. *Results:* A cohort of 28 EB cases were collected and thirteen (46.4%) of which were with DEB followed by 6 (21.4%) EBS, and 6 (21.4%) JEB. The molecular genetic result revealed 24 various genetic variations detected among EB associated genes and of which 14 were novel mutations. Most frequent variations were detected in 12 (42.9%) of COL7A1 followed by LAMB3 in 5 (17.9%), and TGM5 in 4 (14.3%). Furthermore, majority (87.5%) of EB cases were documented positive consanguinity history and confirmed by presence of homozygous mutations. Only three cases were found to be autosomal dominant displaying heterozygous mutations. *Conclusions:* To our knowledge this is the first report of EB genetic profile in Saudi Arabia. DEB was the most frequent type associated with COL7A1 gene mutations and we identified 14 novel mutations previously not detected. Due to the common consanguinity level among Saudi population, we propose a nationwide EB program that would help to extend the spectrum of the genetic profile and to prevent future of such rare genetic disorder.

P86
POSSIBLE APPLICATION OF BROAD AND UNIDIRECTIONAL GENOME EDITING USING THE NOVEL CRISPR-CAS3 SYSTEM FOR AUTOSOMAL DOMINANT EPIDERMOLYSIS BULLOSA

Hiroyuki Morisaka[1], Kazuto Yoshimi[2], Yuya Okuzaki[3], Akitsu Hotta[3], Junji Takeda[4], Tomoji Mashimo[2] and Shigetoshi Sano[1]
[1]Department of Dermatology, Kochi Medical School, Kochi University, Kochi, Japan, [2]Division of Animal Genetics, Laboratory Animal Research Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan, [3]Center for iPS Cell Research and Application (CiRA), Department of Life Science Frontiers, Kyoto University, Kyoto, Japan, [4]Research Institute for Microbial Diseases, Osaka University, Osaka, Japan.

Introduction & objectives: Clustered regularly interspaced short palindromic repeats (CRISPR)-CRISPR associated (Cas) is an adaptive immune system in prokaryotes. The CRISPR-Cas systems are taxonomically grouped as Class 1 and Class 2. Although single-component Class 2 CRISPR systems, such as Cas9, are widely used for genome editing in eukaryotic cells, the application of multi-component Class 1 CRISPR has yet to be realized. The Class 1/Type I CRISPR system functions as a CRISPR RNA (crRNA)-bound multiprotein complex, termed CRISPR-associated complex for antiviral defence (Cascade), and a Cas3 endonuclease, which is recruited upon target binding by Cascade to cleave foreign DNA. Here, we demonstrate that type I-E CRISPR, composed of Escherichia coli Cascade, Cas3, and programmable crRNA, mediates distinct DNA cleavage activity in human cells. *Materials & methods:* To assess the DNA cleavage activity of the type I CRISPR-Cas system in human cells, we used a luciferase-based single-strand annealing (SSA) recombination assay. Human codon-optimized Cas3, Cas5, Cas6, Cas7, Cas8, and Cas11 from E. coli were individually cloned downstream of the CAG promoter. The luciferase activity were measured 24 hours after the lipofection of Cascade, Cas3, crRNA, and reporter plasmids into 293T cells. To characterize Cas3 deletion patterns, we targeted endogenous EMX1 gene in human cells. We conducted custom array-based capture sequencing with 2,000–2,300× coverage of a 1-Mb region of the EMX1 gene. To assess whether the CRISPR-Cas3 syastem applied to therapy for epideromolysis bullosa, we targeted COL7A1 gene in primary fibroblast with CRISPR-Cas3. *Results:* CRISPR-Cas3 system showed higher SSA activity than negative control. The absence of any Cas effector resulted in a complete loss of activity. Multiple Cas effectors without crRNA or with crRNA targeting different spacer sequences also showed no activity. In Custom array-based capture sequencing, we identified a wide variety of Cas3-mediated large deletions through a long stretch of the targeted region upstream of the PAM. After CRISPR-Cas3 treatment of primary fibroblasts, several genome edited clones were detected PCR genotyping and sanger sequencing. *Conclusions:* Large deletions of mutated allele would be introduced by CRISPR-Cas3, so that it induces exon skipping of dominant negative mutations to attenuate skin diseases with autosomal dominant inheritance, such as autosomal dominant epidermolysis bullosa. These findings broaden our understanding of the Class 1 CRISPR system, which may serve as a novel and unique genome editing tool in eukaryotic cells in a manner distinct from the Class 2 CRISPR system.

P87
ORAL CARE PROGRAM IMPROVES THE LIFE QUALITY OF PATIENTS WITH EPIDERMOLYSIS BULLOSA: A TAIWANESE PERSPECTIVE

Chung-Ching Chang[1], Claudia Yun-Tzu Chang[2], Hao-Hueng Chang[3]
[1]Taipei Municipal Chenggong High School, [2]Department of Public Health, National Taiwan University, [3]School of Dentistry, National Taiwan University, Department of Dentistry, National Taiwan University Hospital

Introduction & objectives: Epidermolysis bullosa (EB) represents a group of inherited dermatological diseases that are characterized by blistering and mechanical fragility of the skin due to a defect in anchoring between the epidermis and dermis. Blisters can form anywhere on the surface of the skin, within the oral cavity and in more severe forms may also involve the respiratory, and gastrointestinal tracts. Oral manifestation such as rampant dental caries, advanced gingivitis, and mucosa erosion following rupture of blister lead to pain and dysphagia, which may exacerbate nutrition status. An oral care program was developed to assist EB patients in oral health care since 2015 in Taiwan to reduce these complications and improve quality of life. The purpose of this study is to investigate the effectiveness of the oral care program for patients with Epidermolysis bullosa. *Materials & methods:* Epidermolysis bullosa patients received dental treatment between 2010 to 2019 in a medical centre were recruited for analysis. Since 2015 an oral care program, including the adequate supplements of fluoride,

execution of the Bass brushing technique, and frequent periodic dental review based on DEBRA clinical practice guidelines on oral health care were employed. For each patient whose dental caries experience was assessed by DMFT (Decayed, Missing, Filled Teeth) index, oral hygiene status was evaluated by oral hygiene index, and periodontal condition was assessed using community periodontal index (CPI). These indexes were compared between the preintervention and intervention periods. One-way ANOVA and t-test were used to with p-value fixed at 0.05. *Results:* Ten patients with age between 6 and 35 years old (7 females and 3 males) were surveyed. Eight patients suffered from EB dystrophy type, one suffered from EB simplex type and one suffered from junctional EB. The incidence of oral manifestation among these patients, including enamel hypoplasia (50%), trismus (40%), leukoplakia (20%) was noted. The increments of the DMFT index slow down during the intervention periods while comparison between the preintervention and intervention periods. The significant difference ($p=0.01$ and $p=0.05$ respectively) was noted in the oral hygiene index, and community periodontal index (CPI) while comparison between the preintervention and intervention periods. Patient also show less pain and frequency of dysphagia following intervention. *Conclusions:* Oral care program, including adequate supplements of fluoride, well-executed brushing technique, and frequent periodic surveillance had positive effects on the reduction of dental caries and improvement of the oral hygiene maintenance and periodontal status condition, therefore, improve the situation of food intake and satisfy the patients.

P88
SYSTEMICALLY ADMINISTERED FLIGHTLESS I NEUTRALISING ANTIBODIES IMPROVE SURVIVAL OF RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA MICE AND PROMOTE HEALING OF MULTIPLE INCISIONAL MURINE WOUNDS

Natalie E. Stevens, Zlatko Kopecki, Allison J Cowin
Regenerative Medicine Laboratory, Future Industries Institute, University of South Australia, Adelaide

Introduction & objectives: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a chronic inheritable disease linked to severe blistering and fibrosis. Previous studies have demonstrated that Flightless I (Flii) is increased in blistered skin of all sub-types of EB patients and impairs healing of wounds. Topical application of Flii-neutralising antibodies (FnAb) to murine blistered skin improves healing outcomes. This study aimed to explore if systemically-administered FnAbs could improve healing in EB. *Materials & methods:* Using an incisional wound model in wild-type mice we investigated the effect of intraperitoneal injections (IP) of FnAb, saline or IgG control, at the time of injury, on healing. Using fluorescently-labelled FnAb we further investigated FnAb biodistribution in this in-vivo wound model. Finally, we determined the effect of systemic FnAb administration on the survival of Col7a1-/- RDEB mice. *Results:* Systemic administration of FnAbs resulted in significantly improved healing responses compared to saline or IgG controls as evidenced by reduced macroscopic and microscopic wound area and wound length as well as improved wound re-epithelialisation. Biodistribution analysis of systemically administered FnAbs showed localisation of the antibody to the wound areas which was maintained up to 7 days post-injury. Using Col7a1-/- null RDEB mice we found that daily IP injections of FnAb from birth significantly improved the lifespan of these mice increasing the mean survival rate from 8 to 17 days. *Conclusions:* Systemically administered FnAbs localise to the site of injury and improve healing of multiple wounds simultaneously. The antibodies remain at the site of injury for at least 7 days. Systemic treatment of Col7a1-/- RDEB mice with FnAbs increases their lifespan suggesting that FnAbs reduce the symptoms of RDEB and may be a potential new and effective treatment strategy for the management of EB-related wounds and blisters.

P89
ON THE TOPIC OF SEX: IT'S REAL, LET'S TALK

Alex King, CCLS, CTRS, OTR/L
Phoenix Children's Hospital, USA

Introduction & objectives: The growing understanding of the vitality, variability, and complexity of sexual participation demands that the medical community develop greater understanding and intervention skills to address sex when it is affected by a functional or health-related impairment. As a rare condition, Epidermolysis Bullosa is a condition for which there is a paucity of sexual participation-related data. This presentation seeks open conversation related to sexual participation and EB by sharing preliminary data and perspectives from individuals living with EB and clinicians supporting people with EB. *Materials & methods:* This presentation reports data collected from a needs assessment survey developed and distributed in the process of clinical practice guideline development. The survey was developed by a team of thirteen researchers (8 clinical, 5 living with EB) with consensus achieved on all questions and format prior to distribution. Ethical and logistical oversight was provided by Debra International. Funding for this, as well as the larger CPG project, was received from Debra Norge. The survey was distributed through Debra International and through the professional and social networks of all involved to reach the greatest number of participations. *Results:* The clinician survey received 63 responses, 23 with omissions. The survey for individuals living with EB received 112 responses, 37 omitting some responses. Results from both survey's were evaluated for themes and significant findings to direct the emphasis of this presentation. *Conclusions:* Key themes from clinician surveys revealed a wide range of comfort in address sexual participation in practice with 36% not addressing the topic at all, while 58% reported not addressing puberty with the EB population in practice. Very few clinicians reported have specific training or evidence based models to direct assessment or intervention for sexual participation. Key themes in the survey for people living with EB included specific methods of improving sexual participation including lubrication, educating sexual partners, physical adaptations, and timing/planning were endorsed by many respondents. Most common barriers to participation related to fear of pain/injury, fear of others' reactions/thoughts, feelings about self, physical restrictions, and lack of confidence. Themes of desire for increased support to manage psychosocial, physical, and pain-related complications and increased information/education around puberty and sexual participation arose as well. Finally, numerous respondents highlighted their achievement of successful sexual experiences and relationships and greatly attributed that success to self-confidence/comfort and communication with their partner. Further investigation of specific needs and intervention options is required to progress toward clinician competency and comfort in addressing sexual participation for people living with EB.

P90
PROGNOSIS OF PATIENTS WITH EPIDERMOLYSIS BULLOSA INFECTED WITH PSEUDOMONA AERUGINOSA

María Joao Yubero G, MD[1,2], Ignacia Fuentes, PhD[3], Susanne Krämer[4], Constanza Fuentes, MD[1], Francis Palisson, MD[1,2].
[1]Fundación DEBRA Chile, Santiago, Chile, [2]Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile, [3]Centro de Genética y Genómica, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago, Chile, [4]Facultad de Odontología, Universidad de Chile

Introduction & objectives: The objective of this review was to know if our microorganisms were the same isolates and described in the literature. Find out if infectious screening tests were a diagnostic aid. And to know the microbiology of the wound isolates of our population. *Materials & methods:* All the results of skin cultures, registered in the electronic file of our institution, were reviewed. Registration goes from 05/09/2005 to 12/23/2015. 502 samples were collected from 70 patients. 314 samples were from women and 188 samples were from men. Average age 10.75 (from newborn to 60.95 years). 181 samples are from deceased patients. *Results:* 83% of the samples were positive. 32 different types of microorganisms were isolated. The most frequent Staphilococcus aureus, with a prevalence of 54.98. We mostly obtained 1 microorganism per culture, but we got to have up to 6 in some samples. Our most frequent isolated microorganisms were: Methicillin-susceptible strain of Staphylococcus aureus, Pseudomona aeruginosa, Methicilin-resistant Staphilococcus aureus, Candida albicans, Klebsiella pneumoniae, Acinetobacter baumannii and Proteus mirabilis. There is no significant statistical difference between the different sedimentation rates of the samples, with a $p=0.1739$. There is no statistically significant difference between the different C-protein samples, with a $p=0.8023$, (T test). *Conclusions:* Requesting sedimentation rate, C-reactive protein or even white blood cell count does not correlate with infection. Being colonized with Acinetobacter baumannii and Pseudomona aeruginosa of poor prognosis. But Pseudomona aeruginosa infection generates a 40% greater chance of death. Perhaps the first treatment when isolating Pseudomona aeruginosa, should be as in patients with cystic fibrosis with a minimum of 21 days. Find other markers that help us in the determination of infection.

P91
CHARACTERIZATION OF WOUND MICROBES IN EPIDERMOLYSIS BULLOSA: RESULTS FROM A MULTICENTER DATABASE

Laura E. Levin, MD, Leila H. Shayegan, BA, Anne W. Lucky, MD, Kristen P. Hook, MD, Anna L. Bruckner, MD, James Feinstein, MD, MPH/MSPH, Susan Whittier, PhD, Christine T. Lauren, MD, MHA, Elena Pope, MD, MSc, Irene Lara-Corrales, MD, MSc, Karen Wiss, MD, Catherine C. McCuaig, MD, Julie Powell, MD, Lawrence F. Eichenfield, MD, Moise L. Levy, MD, Lucia Diaz, MD, Sharon A. Glick, MD, Amy S. Paller, MD, Harper N. Price, MD, John C. Browning, MD, MBA, Kimberly D. Morel, MD.
NewYork-Presbyterian/Columbia University Medical Centre (Morgan Stanley Children's Hospital of New York), Columbia University Irving Medical Centre

Introduction & objectives: Given the potential role of bacteria-induced inflammation in the development of wound-associated squamous cell carcinoma (SCC) in a subset of patients, we sought to improve our understanding of what microbes colonize and infect the wounds of patients with Epidermolysis bullosa (EB) by analyzing wound culture results from EB patients from multiple centers, including methicillin and mupirocin susceptibilities, when available. *Materials & methods:* The EB Clinical Characterization and Outcomes Database (EBCCOD) serves as a repository of information from EB patients at multiple centers in the United States and Canada. Access to this resource enabled broad scale analysis of wound cultures. A retrospective analysis of 739 wound culture results from 158 patients captured in the database between 2001 and 2017 was performed. *Results:* 158 patients had at least one wound culture recorded in the database. A total of 739 wound culture results were recorded for these patients. 152 out of 158 patients had at least one positive culture result. The remaining 6 patients had cultures with no growth only. Staphylococcus aureus (SA) grew in 131 (83%), Pseudomonas aeruginosa (PA) in 56 (35%) and Streptococcus pyogenes (GAS) in 34 (22%) patients. Of 117 patients with SA positive cultures with recorded beta-lactam susceptibilities, 68% were methicillin-sensitive SA (MSSA) and 47% methicillin-resistant SA (MRSA). Of 15 cultures positive for SA with mupirocin susceptibility testing, 11 were mupirocin susceptible and 6 were mupirocin resistant. SCC was reported in 22 patients, of which 10 had documented wound culture results positive for SA, PA and Proteus species in 90%, 50% and 20% of cases, respectively. *Conclusions:* SA and PA were the most commonly isolated bacteria from wound cultures in EB patients. Methicillin and mupirocin resistance were reported in 47% and 40% of the patients tested, respectively. Resistance to many systemic and topical antibiotic agents in individuals with EB, supports surveillance cultures with routine testing for mupirocin resistance as a means to guide antibiotic stewardship and patient counseling. Given the important role of bacteria-induced inflammation in the development of wound-associated SCC, improved understanding of what microbes are colonizing the wounds of our patients may help to isolate those bacteria that confer additional risk for carcinogenesis and therefore may require earlier, more aggressive treatment.

P92
OTOLOGICAL COMPLICATIONS IN INVERSA TYPE RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

C. Prodinger[1], S.J. Robertson[2], S. Chottianchaiwat[3], M. Laimer[1], G. Petroff[3], A.E. Martinez[3], D. Greenblatt[4], J.E. Mellerio[4]
[1]Department of Dermatology and Allergology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, [2]The Royal Children's Hospital, The Royal Melbourne Hospital, Monash Health, Murdoch Childrens Research Institute, Melbourne Australia, [3]Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [4]St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

Introduction & objectives: The rare inversa form of recessive dystrophic epidermolysis bullosa (RDEB-I) is characterized by predominant blistering in body flexures and marked mucosal involvement. It has been postulated that specific recessive missense mutations in the collagen VII triple helix may give rise to this clinical entity. Literature data on ear complications is highly limited in this patient group. Herein we characterize an adult cohort of RDEB-I patients, revealing a high prevalence of otologic morbidity. *Materials & methods:* We conducted an observational, retrospective, single institution case record review of adult patients with RDEB-I presenting with otological complications between January 2000 and June 2019. Diagnosis was established on the basis of clinical features, family history and mutation analysis of COL7A1. *Results:* Twenty patients with RDEB-I were identified from our database. Nine adult patients (45% of cohort; 89% female; mean age 47.3, range 31-72 years) had otological complications, all having suffered from recurrent episodes of otitis externa. Seven (78%) had meatal stenosis and 5 (56%) had recurrent blistering of the external auditory canals. All 9 patients complained of hearing loss, with conductive hearing loss confirmed by audiology testing in 5 (56%) patients. Three (33%) patients received bone anchored hearing aids (BAHA) with favourable outcomes. *Conclusions:* We observed a high prevalence of ear problems in RDEB-I. Of the 20 patients with this form of EB identified in our database, 9 (45%) displayed relevant otological complications. This prevalence is higher than previously published studies. Considering the therapeutic challenges and impact on patients' quality of life, clinicians should be vigilant in monitoring for ear disease in this patient group with early referral to an ENT specialist.

P93

THE EFFECT OF ROCKER BOTTOM FOOTWEAR ON FOOT BIOMECHANICS AND THE DEVELOPMENT OF PLANTAR BLISTERS IN PATIENTS WITH EPIDERMOLYSIS BULLOSA SIMPLEX; A PILOT STUDY

Mark O'Sullivan, Lisa James, Adrian Heagerty, Natasha Harper
National EB Adult Service – UBH Solihull

Introduction & objectives: Patients with Epidermolysis Bullosa (EB) simplex tend to present with plantar blistering in typical areas due to natural foot biomechanics and their resultant forces. These areas are typically the heels, metatarsal heads (balls of the feet) and the big toes. These areas are known as the three natural rockers of the foot which as act as pivots to aid propulsion during the gait cycle. However, these areas are exposed to peaks in plantar pressure which, in combination with EB, results in regular blistering. Rocker bottom footwear is believed to reduce the peak pressures through these areas and spread force more evenly across the sole of foot. They have been used as a treatment modality for a variety of lower limb musculoskeletal pathologies. However, as far as we are aware, the effect of the altered foot biomechanics has not been considered as part of any treatment plan in reducing the development of plantar blistering in patients with EB. *Materials & methods:* The authors selected 9 suitable patients with EB simplex (6 males and 3 females, ages ranging from 18-75yrs old) that reported regular plantar blistering formation as part of their clinical presentation. Each recruit's plantar pressure measurements during dynamic gait were taken in their current footwear using an in-shoe plantar pressure measurement system. The measurements were repeated in their newly issued and fitted rocker bottom footwear. Along with the pressure analyses, at the time the new footwear was issued, subjects filled in a tailored questionnaire about the development of blisters on their feet, activity levels and pain scores. These questionnaires continue to be completed monthly, and we are collating subjective data on alterations in size, frequency and location of blisters along with the affect that this is having on quality of life, alongside our objective measurements. As controls, questionnaires have been completed by subjects with EB receiving more standardised insoles and footwear. *Results:* The comparison of before and after pressures showed a significant alteration in biomechanical progression including peak plantar pressures and centre of mass displacement. Early questionnaire feedback has shown a reduction in pain scores, reduction in overall blistering, altered blistering sites and increased activity as a result. *Conclusions:* The study so far indicates that rocker bottom footwear could become a newly considered treatment option as part of a tailored program for patients with EB simplex.

P94

MISDIAGNOSIS IN EB: YET ANOTHER BURDEN ON PATIENTS AND THEIR FAMILIES

Carlos Delgado-Miguel, Miriam Miguel-Ferrero, Antonio J. Muñoz-Serrano, Mercedes Díaz, Rocío Maseda, Raúl de Lucas, Juan Carlos López-Gutiérrez

Results: Epidermolysis bullosa is a devastating disease relatively unknown by most healthcare professionals; our aim is to raise awareness about this condition through the presentation of a fatal case which was misdiagnosed. We present the case of a male infant who developed within the first hours of life a few bullae on both thumbs, which were diagnosed at his local hospital as "suction blisters". In the following days, the patient rapidly developed extensive blistering of the skin. He was then diagnosed as Staphylococcal scalded skin syndrome and subsequently as neonatal bullous pemphigoid. Due to the lack of response to treatment and to worsening of the lesions, he was referred to our centre at 44 days of life, where he was diagnosed of Herlitz junctional EB (HJEB), after antigen mapping of a skin biopsy showed a complete lack of laminin 332. The baby presented extensive hemorraghic lesions which involved 60% total body surface area, painful erosions of the pharyngeal mucosa (which required the performance of a gastrostomy due to diminished ingestion), severe hydroelectrolytic and haematological disorders, and recurrent infections. The child died at the age of 3 months because of cardiac and respiratory failure due to severe sepsis caused by Pseudomonas aeruginosa. Patient's parents required psychological support all through the course of the disease and have received genetic counselling. HJEB is ultimately fatal, even with the best of care. In the case we present here, the wrong initial diagnosis probably did not alter the final outcome. However, an earlier diagnosis would have expedited the referral of the patient to a specialized EB centre, allowing for earlier and better supportive care. EB parents usually complain of the feeling of uncertainty when dealing with this disease. A prompt and correct diagnosis is paramount to inform them as honestly as possible about the disease and its lethal prognosis, and to help both the patients and their parents to deal with such a desolating condition. Cases such as the one we present here should result in education and training of health personnel at all levels. As health- care providers, we have a responsibility to provide the best possible medical care, both to our patients and their families.

P95

EPIDERMOLYSIS BULLOSA: CASE REPORT

Mendes, Luciana[1], Santos, Paloma[2], Araújo José[3]
[1]WOCN Nurse, Sales Manager, Mölnlycke® Health Care Brazil, [2]Dermatology Nurse, Clinical Manager, Mölnlycke® Health Care Brazil

Introduction & objectives: Epidermolysis Bullosa (EB) is a rare and congenital disease characterized by fragility of the skin and mucosa. It is a group of hereditary diseases whose common manifestation is the formation of epithelial blisters. The skin consists of several layers linked together by collagen protein fibers. In EB, these bonding fibers do not work effectively, so the various layers of skin separate easily[3]. Thus, the space formed between the layers is filled with whey or protein-rich fluid, giving rise to the bubble[2]. They fall into three main groups: Simple, junctional and dystrophic bullous epidermolysis. Injuries have considerable repercussions and impacts on patients' quality of life; the need for special atraumatic and easy-to-remove pain-free covers is extremely important as it avoids further stress for EB patients. *Objective:* Report the care of the health team and family members in one child, one newborn (RN) and two adults, both patients with Epidermolysis Bullosa for 6 months. *Materials & methods:* This is an observational and descriptive case report, conducted between February and August 2018, through home visits, medical records analysis, use of care manual, reports of mothers and family. *Results:* The management with the lesions caused by the disease proved to be the main challenge faced by all, the lack of adequate care, such as dressings and diets. The conduct with the NB presents a major problem to maternity professionals, as the disease is not diagnosed by ultrasound. Depending on the type of delivery: surgical or natural, the baby already suffers severe birth injuries. The routine procedures that are performed after delivery can leads to newborns worsening their injuries and long hospital stay. In adults, the difficulty is similar, they suffer more from prejudice and non-insertion in socialization, they are called "wounded". They also present the severe evolution of the disease, which is due to the development of carcinoma. *Conclusions:* EB is a very rare dermatological disorder and it has a great impact on the lives of patients and their families. The disease may affect eyes, nose, oral mucosa, dentition, gastrointestinal and genitourinary tract, musculoskeletal system, as well as metabolic disorders such as malnutrition and anemia. EB patients are more likely to develop sepsis due to the loss of the stratum corneum barrier,

facilitating microbial penetration. The development of squamous cell carcinoma can also occur in these patients in sites with chronic lesions, and there may be multiple primary sites, leading the patient to amputation and life-threatening.

P96
SYMPTOMATIC BENEFIT OF FLUOROSCOPICALLY-GUIDED OESOPHAGEAL DILATATION IN EPIDERMOLYSIS BULLOSA

C.A. Drislane, N. Thulasidasan, J. Clapham, D.T Greenblatt, J.A. McGrath, J.E. Mellerio, A. Diamantopoulos
Guy's and St Thomas' NHS Foundation Trust

Introduction & objectives: Epidermolysis bullosa (EB) is a group of rare genetic skin conditions characterised by fragility of the skin and mucous membranes. Dystrophic Epidermolysis Bullosa (DEB), in particular, is associated with oesophageal complications. In brief there is blistering of the oesophageal tract and subsequent scarring, stenosis and associated dysphagia. This has a profound effect on a patient's quality of life affecting not only their swallow but exacerbating nutritional deficits, wound healing and growth as well as limiting social activities. The aim of this study was to assess the clinical benefit and immediate and long-term outcomes of fluoroscopically-guided oesophageal dilatation (OD) of an Epidermolysis Bullosa (EB) patient cohort by improvement in the dysphagia score (DS). *Materials & methods:* We undertook a retrospective review of the medical records of 35 EB patients undergoing fluoroscopically-guided OD at a single reference centre for adults with EB. All dilatations between 2005 and 2019 were included. Dysphagia scores pre- and post-procedure were also recorded. Dysphagia scores were available from 2017 onwards and were measured on a scale from 0 (normal swallow) to 4 (unable to swallow liquids or solids). The primary endpoints of the study were improvement in the clinical dysphagia score and major complications. We also recorded the interval between dilatations. Statistical analysis was done using excel. *Results:* Twenty-five recessive dystrophic epidermolysis bullosa (RDEB) patients, 6 dominant dystrophic epidermolysis bullosa (DDEB) patients and finally 4 patients with Kindler syndrome were included in this study. In total, 325 ODs were performed during the study period. The median interval between ODs for all patients collectively was 10 months. Patients with RDEB had a total of 276 ODs within the study period with a mean number of ODs of 9.3 per patient (median 5). Collectively, the mean pre-procedure dysphagia score was 1.96. The mean post procedure dysphagia score was 0.44 with a mean improvement of 1.52. There were no major complications over the study period. *Conclusions:* Repeat fluoroscopically-guided oesophageal dilatation is a safe and very effective way of treating dysphagia caused by oesophageal strictures in individuals with EB.

P97
BUTTERFLY KIT - CLINICAL AND LOGISTIC SUPPORT TO THE NEWBORN WITH EPIDERMOLYSIS BULLOSA

J. A. Magno[1], A. Mehl[2], K.A. Osti[3]
[1]Pediatric Dermatologist, Teacher at the FURB - Regional University Foundation of Blumenau and Medical Director of DEBRA Brazil, [2]Medical Consultant, Teacher and Researcher on New Technologies for the Prevention and Treatment of Acute and Chronic Wounds, [3]Nurse at the FURB - Regional University Foundation of Blumenau and Nursing Coordinator of Debra Brazil

Introduction & objectives: The birth of a child with Epidermolysis Bullosa (EB) is a dramatic moment for the family and the team of professionals in charge. Adequate initial care in the neonatal period is crucial for a good evolution of the disease. To provide a kit containing information about the disease, non-adherent dressings, and medical support to health teams, as well as family support. *Materials & methods:* Based on the 2017 International Wound Consensus, we have organized a 3-month non-adherent dressing kit which is being sponsored by the major wound care companies. Along with the supplies, it is also included infographics, information in a simplified language and a butterfly doll that symbolizes the affection and concern of the team with the newborn. *Results:* Epidermolysis bullosa is a rare incurable disease that causes intense suffering to the patient and their families, having also high costs, which makes it impossible for an average family to bear the costs alone. Professional's lack of knowledge about the disease, complications and the use of conventional products for other diseases in the treatment of EB leads to worsening of the condition. In a continental country, with an incidence of 19 cases/million live births, where EB is unknown to most neonatal professionals, coupled with the difficulty of quick access to primary care of babies, such as special dressings, a team of volunteers bring information, proper wound care products and support at the time of the neonatal period. This project was launched on January 2018, and it was named "little butterfly KIT". Once the birth is notified, we provide healthcare teams with technical support for proper management of the newborn and special dressings needed for in-hospital care. An important initiative that minimizes the occurrence of new injuries, reducing pain and preventing complications and future sequelae and increasing the baby's quality of life. The little butterfly KIT has since became the symbol of the institution and the battle for the quality of life of babies with EB. *Conclusions:* With the Little Butterfly KIT project, there was greater dissemination of EB and increased notification of newborns with Epidermolysis bullosa, as well as increased confidence in the volunteer team and with this we were able to give newborns a higher quality of life and lower mortality.

P98
COMPLEX DENTAL REHABILITATION IN CHILDREN WITH DYSTROPHIC EPIDERMOLYSIS BULLOSA

M. Korolenkova, A. Poberezhnaya, N. Starikova, N. Udalova, N. Dmitrieva
Central Research Institue of Dentistry and Maxillofacial Surgery, Moscow, Russia

Introduction & objectives: The aim of the study was to evaluate the feasibility of dental diseases prevention program, dental care, prosthodontic and orthodontic treatment in children with dystrophic epidermolysis bullosa (DEB). *Materials & methods:* The study comprised 86 children with DEB aged 2-18 years who received oral rehabilitation in 2013-2018. Soft tissues complication rate was assessed immediately after the procedures, 1 week and 6 months after. Oral wound and mucosa microbiota were also inoculated in DEB patients as well as in 22 healthy aged-matched controls in two 6-months intervals to reveal the efficacy of oral diseases preventive programs. *Results:* Oral rehabilitation under general anesthesia, 8 adolescents received prosthodontic treatment with separate crowns, 10 children with extreme tooth crowding were successfully treated by consecutive sequences of orthodontic splints. CAD/CAM system was used for intraoral scanning (replacing challenging impression taking) and splints manufacturing in 5 severe microstomia cases. Bullas and erosions were seen in all children immediately after local anesthesia, teeth extractions and pediatric crowns placemen on molars. The lesions resolved completely one week after the procedures. No long-term complications were seen after all types of dental care, teeth extractions and use of teeth-retained prosthodontic and orthodontic appliances. Oral diseases prevention program proved to be efficient in children with DEB but only under the condition of strict adhesion to prevention protocol (among 21 of these patients 9 were caries free at the age of 12). Oral microbiota analysis at initial examination showed high prevalence of Candida albicans (69.8% vs. 9,1% in controls), Stap-

hylococcus aureus (60.5% vs. 9,1 in controls), Rhotia dentocariosa (84.1% vs. 22,7%) and Streptococcus mutans (97.5% vs 59.1%) colonization in DEB patients. In 42,2% of DEB cases receiving oral diseases prevention program elimination of the germs was seen at the second 6-month interval examination. *Conclusions:* All routine dental care, prosthodontic and orthodontic treatment options were feasible in DEB children due to soft tissues sparring techniques and use of CAD/CAM system. Higher prevalence of pathogenic microbiota in DEB patients is probably a result of the compromised local immunity in the oral cavity.

P99

C3 GLOMERULONEPHRITIS IN DYSTROPHIC EPIDERMOLYSIS BULLOSA: A REPORT OF FIVE CASES

Erica Hughley, MD[1]; Anne W Lucky, MD[2]; Bret Augsburger[2] and Edward Nehus, MD[1]

[1]Division of Nephrology and Hypertension, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH [2]Cincinnati Children's Epidermolysis Bullosa Center, Division of Dermatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

Introduction and Objectives: Patients with severe forms of epidermolysis bullosa (EB) may have renal glomerular disease causing morbidity, such as the need for dialysis. Currently there is no known unifying etiology or optimal treatment for EB-associated renal dysfunction. This case series describes the renal histopathology, treatment and clinical outcomes of five patients followed at our institution for dystrophic EB (DEB) who underwent renal biopsy for glomerulonephritis (GN). *Materials and Methods*: Retrospective chart review of EB patients followed at our institution who underwent renal biopsy. *Results:* Between years 2015 - 2019, five patients (3 male, 2 female) with DEB currently followed at our institution underwent renal biopsies for indications of hematuria, proteinuria and acute kidney injury (AKI, defined per Kidney Disease Improving Global Outcomes guidelines to be an increase in serum creatinine by at least 0.3 mg/dL or 1.5 times baseline). Patient ages at time of biopsy ranged from 10 to 18 years. One patient underwent repeat biopsy. Renal histopathology for all patients showed increase mesangial proliferation with intense mesangial staining for C3. Electron microscopy revealed deposits located in the sub-endothelial, sub-epithelial and/or mesangial or para-mesangial regions. In addition, tubulointerstitial inflammation was found in four patients and interstitial fibrosis in 2 patients. Four of the patients had previously documented cutaneous Streptococcal infections and one had pyelonephritis. Three patients were treated empirically with antibiotics, one patient was treated with steroids and an angiotensin-converting enzyme inhibitor (ACEI), and one patient was treated with steroids and mycophenolate. The 3 patients treated with antibiotics had mild to significant improvement in renal dysfunction, including complete resolution of proteinuria and AKI in two patients. *Conclusions:* This case series is unique in that it describes five patients with dystrophic EB and renal dysfunction who were all found to have glomerulonephritis (GN) with mesangial C3 deposition. C3 GN may be a potentially unrecognized cause of glomerulonephritis in EB patients with renal dysfunction. The role of prior Streptococcal infections as causative of GN is unclear. Such patients may have improved renal outcomes with antibiotic therapy, as did three in this case series. Future larger cohort studies are needed to determine if our results are generalizable to the larger EB population.

Table 1. Overview of DEB Patients Biopsied for Renal Dysfunction

Patient n#	1	2	3	4	5
Sex	Male	Male	Male	Female	Female
EB Type	DDEB*	RDEB-GS	RDEB-GS	RDEB-GS	RDEB-GS
Indication for Renal Biopsy	- Microscopic hematuria - Proteinuria - AKI	- Gross hematuria - Proteinuria - AKI	- Proteinuria - AKI	- Gross hematuria - Proteinuria - AKI	- Gross hematuria - Proteinuria - AKI
Age at Biopsy (years)	18	17	10	14	14 /15
Histopathology	Mesangial staining for C3 & IgA; sub-endothelial deposits	Mesangial staining for C3	Mesangial staining for C3; mesangial and para-mesangial deposits	Mesangial staining for C3; mesangial deposits	Mesangial staining for C3; mesangial and sub-epithelial para-mesangial deposits
Renal Diagnosis	IgA nephropathy	C3 GN	C3 GN	C3 GN	Mesangial proliferative GN
Treatment	Steroids, ACEI	Antibiotics	Steroids, Mycophenolate	Antibiotics	ACEI/Antibiotics
Clinical Outcome	No long term change	Improved proteinuria, resolved AKI	Unknown	Resolved AKI, hematuria and proteinuria	Improved AKI

*genetic work-up for COL7A1 mutations pending.

DDEB, dominant dystrophic EB; RDEB-GS, recessive dystrophic EB-generalized severe

P100

THE EFFICACY AND SAFETY OF COLD ATMOSPHERIC PRESSURE PLASMA VERSUS LOW LEVEL LASER FOR THE TREATMENT OF WOUNDS IN EPIDERMOLYSIS BULLOSA PATIENTS

Reza Shakouri[1], Fahimeh Abdollahimajd[2], Shirin Samsavar[1], Leila Youssefian[3], Hassan Vahidnezhad[3], Jouni Uitto[3], Babak Shokri[1,4]*

[1]Physics Department of Shahid Beheshti University, G.C., Tehran, Iran, [2]Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA, [4]Laser - Plasma Research Institute, Shahid Beheshti University, G.C.,Tehran, Iran

Introduction & objectives: Epidermolysis bullosa (EB) is a genetic inherited disease characterized by skin fragility and chronic mucocutaneous bullae and erosions. In the absence of a definitive treatment, there are a number of modalities which can help wound healing including cell therapy and specific dressings. Low level laser and recently cold atmospheric pressure plasma have been used for the treatment of difficult to heal ulcers. Plasma is the fourth state of the matter, composed of ionized atoms and emits several kinds of ultraviolet radiation and electric fields and can produce heat and reactive oxygen and nitrogen species. One of the important contributing factors to the anti-inflammatory, antimicrobial, tissue stimulation, and other therapeutic effects of plasma in medicine and dermatology may be a special tissue-reactive species interaction. Recently, studies have focused on the potential effects of cold atmospheric pressure plasma on the wound healing. In this study, we aimed to compare the efficacy and safety of cold atmospheric pressure plasma versus low level laser or standard wound care with Vaseline gauze for the treatment of EB wounds. *Materials & methods:* Six EB patients who had failed to respond to previous therapies (wound that persists more than 3 months with no response to standard treatments) were recruited and in each patient, 2 wounds were randomly treated with plasma, 2 wounds with laser and one was dressed with Vaseline gauze as the control, twice a week until complete improvement (or average 8 weeks) and the wounds were evaluated in each session of treatment, 4 and 12 weeks after the last session of treatment. *Results:* One out of 6 (16.66%) wounds in the control group, 10 out of 11 (90.90%) wounds in plasma and all wounds (12/12; 100%) in the laser group completely healed in the 8th session of treatment. Although both laser and plasma methods reduced significantly the size of the wounds compared to the Vaseline gauze ($p < 0.001$), the plasma was more successful to reduce the pain more rapidly and also the time to heal was less compared with that of laser or Vaseline gauze. *Conclusions:* The study results suggested that cold atmospheric pressure plasma is as effective as low level laser and can be considered a valuable modality for the wound healing in this very challenging disease. Further studies with more sample sizes are needed to clarify the mechanism of plasma effects in wound healing in these patients.

P101
NATIONAL REGISTER - A CHALLENGE TO BE OVERCOME

J.A. Magno[1], M.M. Frant[2], V.O. Carvalho[3]
[1]Pediatric Dermatologist, Teacher at the Regional University Foundation of Blumenau and Medical Director of DEBRA Brazil, [2]Student of Medicine in Positivo University, [3]Carvalho V.O. Coordinator of the Specialization Course in Pediatric Dermatology at UFPR and Teacher at the Federal University of Paraná (UFPR)

Introduction & objectives: Hereditary Epidermolysis Bullosa is a rare disease affecting 11 people per million inhabitants. Treatment involves a multidisciplinary team and it is expensive. For everyone to have access to the right treatment, development and public policies are needed, along with knowing the number of patients. Only few countries have adequate epidemiological data. This data is collected in support groups and dermatology care centers. Countries such as the USA and Scotland have official EB records, from which the incidence is calculated. In Brazil we haven't found publications containing the number of patients. The Dystrophic Epidermolysis Bullosa Research Association (DEBRA) is unifying the treatment. With an approximate number of cases in the country and a single database, we will be able to discuss public care policies and give patients access to new treatments. The aim of this study is to determine the epidemiological data and compare it with the global literature. *Materials & methods:* The data from the national EB registry, from DEBRA website, was analysed January 2014 to April 2019. We searched for patients in regional associations, on social networks, support groups and dermatological medical services. We used descriptive statistics for data analysis. The variables were described according to the average and standard deviations or absolute frequencies and percentages. Patients were separated by gender and age and tested for normality by the Shapiro-Wilk test. Using chi-square test, we tested the difference between genders. Fisher's exact test assessed the proportion of patients between men or women. Statistical analyzes were performed with GRAPHPAD PRISM® statistical package and a significance level of 5% ($\alpha = 0.05$) was considered. *Results:* The number of registered cases was 883, with 113 deaths. There was no significant difference between genders. Recessive dystrophic epidermolysis bullosa was the predominant form and the main cause of death. The prevalence in 2018 was 3.26/1,000,000 population and is lower than the world literature, although it has increased in recent years after new data release. The incidence in the last 2 years has remained stable, 1.77 cases/10.000.000, which is lower than the cases in the world literature. *Conclusions:* The notifications are below the worldwide statistics and there is a need to create methods to increase their. We intend to disclose the national register of Epidermolysis Bullosa and publish the statistics to use as a source for planning for the public polices and stimulating research on EB in our country.

P102
EB PATIENTS NEED EB SPECIALIZED SURGEONS: THE ROLE OF PAEDIATRIC SURGEONS IN EPIDERMOLYSIS BULLOSA

Carlos Delgado-Miguel, Miriam Miguel-Ferrero, Antonio J. Muñoz-Serrano, Nuria Leal, Paloma Triana, Juan Carlos López-Gutiérrez

Introduction & objectives: Epidermolysis bullosa (EB) is a complex disease which requires a multidisciplinary approach; our aim was to describe and analyze the relevance of specialized paediatric surgeons in the integral management of patients with EB treated in our multidisciplinary unit. *Materials & methods:* We performed a retrospective study in patients with EB who were treated by the Department of Paediatric Surgery at our institution in the last 15 years (2004-2018). We analyzed the surgical procedures performed and the age at which they were performed. *Results:* Fifty-seven patients (28 male; 29 female) underwent 263 surgical procedures. Fifty-five of them presented recessive dystrophic EB, 2 simplex EB and 2 junctional EB. Sixty-one interventions to release pseudosyndactyly were performed: 34 on the right hand, 22 on the left hand, 4 on both hands simultaneously and only one on the lower limb. Most patients (87.7%) referred the procedure improved their quality of life. Gastrostomies (placed percutaneously, guided by endoscopy) were performed in 37 patients, with a mean age of 7.9 ± 4.7 years. All patients presented a major improvement in their nutritional status, allowing for subsequent gastrostomy closure in 5 of them, after a median time of 16years. Twenty-two patients presented esophageal stenosis during the course of EB, which impeded normal oral feeding. Endoscopic esophageal dilatation was performed on 68 occasions, with a mean of 3.1 ± 2.1 dilations per patient, allowing for recovery of regular oral intake. Fourteen patients developed squamous cell carcinoma (11 male; 3 female), with a mean age at diagnosis of 22.4 ± 5.5 years. Twelve patients required pre-excisional biopsy. In all 14 patients, tumors were excised with free margins. In 11 of them, the carcinoma relapsed, with a median of 10.5 months, requiring 43 subsequent excisions in total (mean of 3.9 ± 3.1 surgeries per patient), which involved limb amputation in 9 patients. Other less frequent procedures were: partial skin grafting on benign chronic wounds (5 patients), circumcision (3 patients), release of skin retractions (2 patients), colostomy (2 patients), port-a-cath placement (1 patient) and appendectomy (1 patient). *Conclusions:* Paediatric surgeons play a very relevant role in the management of patients with EB: syndactyly release, gastrostomies and esophageal dilations improve the quality of life of these patients; early biopsy and excision of malignant tumors decrease morbidity and mortality. EB patients benefit from the existence of multidisciplinary units which include specialized paediatric surgeons in their staff.

P103
A MULTICENTER COHORT STUDY EVALUATING PATIENT-REPORTED OUTCOMES IN EPIDERMOLYSIS BULLOSA

Anna L. Bruckner; James A. Feinstein; Kathleen Peoples; Irene Lara-Corrales; Elena Pope; and the EB Clinical Research Consortium
Children's Hospital Colorado, Aurora, CO USA and Sick Kids, Toronto, ON, Canada

Introduction & objectives: Although the symptoms and impact of epidermolysis bullosa (EB) on patients' quality of life are understood, larger scale studies that systematically assess patient-reported outcomes across EB types/subtypes and over time, particularly in a real-world setting, are lacking. The Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa (iscorEB) includes both clinician-assessed and patient-reported sections; the patient-reported section (iscorEB-p) measures pain, itch, functional limitations, sleep, mood and effect on daily and leisurely activities. The goals of this study are to 1) describe the range of iscorEB-p scores and sub-scores in patients with different types/subtypes of EB; 2) evaluate the relationship of age to iscorEB-p score; and 3) discern trends in iscorEB-p scores in patients with repeated assessments over time. *Materials & methods:* Longitudinal, repeated measures cohort study conducted at EB centers in the United States and Canada contributing data to the EB Clinical Characterization and Outcomes Database (EBCCOD). Patients completed iscorEB-p when presenting for routine care. The primary outcomes are iscorEB-p composite and sub-scores stratified by EB type/subtype (EBS, JEB, DDEB, RDEB). Within patients with RDEB, the relationship of decade of age to iscorEB-p score was determined by ANOVA, and in patients with 2 or more assessments, change in iscorEB-p score over time was analyzed. *Results:* 253 patients from the EBCCOD had 1 or more iscorEB-

p assessments. 29.6% had EBS, 7.6% JEB, 14.6% DDEB, and 48.2% RDEB. Most patients were <10yo (53%), white (78%), and female (50%). 45% of patients had 2 measurements with interval spacing of 0.7-1.2 years depending on EB subtype. Mean baseline total scores were highest in RDEB patients (34.0; 95%CI 31.0-36.9), followed by JEB (29.7; 95%CI 21.3-38.1), EBS (21.5; 95%CI 18.5-24.5), and DDEB (15.6; 95%CI 11.0-20.1). Domain sub-scores differed at baseline. Baseline total scores differed by age category for RDEB patients (1-9yo: 29.9, 10-19yo: 34.6, 20-29yo: 38.4; $p=0.02$), but not significantly for other subtypes. Among RDEB patients who had 2 or more iscorEB-p assessments, increases in scores were observed across some symptoms (overall pain, bone pain, hand issues, problems with eating and drinking, problems with bowel movement), but not others (itching, eye pain, and urinary problems). *Conclusions:* Patients with RDEB and JEB are more impacted than patients with EBS or DDEB, and in patients with RDEB, disease impact correlates with age. Although iscorEB was designed to be used in clinical trials, iscorEB-p can be used to assess patient-reported outcomes in the clinical setting and detects changes in those outcomes over time.

P104
EPIDEMIOLOGY OF EPIDERMOLYSIS BULLOSA IN THE NETHERLANDS

R. Baardman[1], V.K. Yenamandra[1], J.C. Duipmans[1], A.M.G. Pasmooij[1], M.F. Jonkman[1], P.C. van den Akker[1,2], M.C. Bolling[1]*
University of Groningen, University Medical Centre Groningen, Department of Dermatology[1] and Genetics[2],Centre for Blistering Diseases, Groningen, the Netherlands

Introduction & objectives: Significant scientific advances are made towards finding a cure for EB, which are currently being translated into therapeutic trials. To ensure valid and representative trial outcomes, recognition of well-characterized EB-cohorts is essential. Here, we present valuable epidemiological data for each subtype of EB, extracted from the well-characterized EB-cohort of the Dutch Expertise Center for Blistering Diseases in Groningen, the Netherlands, established over the past 31 years. *Materials & methods:* In this cross-sectional study, all patients with EB registered in the Dutch EB register from 1988 to 2018, and based in the Netherlands, were included. Patients with EB referred by specialists from foreign countries were excluded to calculate accurate incidence and prevalence rates for EB in the Netherlands. Epidemiological figures were calculated based on accurate diagnostics and follow-up. Incidence rates were calculated per million live births and prevalence rates calculated per million population. *Results:* Overall, 490 patients (311 families) with EB were identified in the Netherlands between 1988 and 2018. The average annual number of newborn patients with EB was 9, with an incidence rate of 45.1 per million live births. The prevalence rate for EB in the Netherlands was calculated to be 23.9 per million population. EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler syndrome (KS) were diagnosed in 48.6% [238 patients (132 families)], 17.8% [87 patients (72 families)], 32.9% [161 patients (103 families)] and 0.8% [4 patients or families] respectively, with mutations in 17 different genes. The incidence and prevalence rates for each major subtype of EB were 21.1 and 13.3 [EBS], 9.3 and 2.1 [JEB], 14.2 and 8.3 [DEB] and 0.5 and 0.2 [KS], respectively. During the investigated time-period, 77 of the patients with EB in our Dutch EB-cohort had died, of which 70 patients having a recessive subtype of EB (47 JEB, 16 DEB and 7 EBS). The median age of death for patients who died of EB-related complications was 5.5 days for JEB-pyloric atresia, 2.9 months for JEB-generalized severe and 43.8 years for JEB-generalized intermediate, 14.6 years for RDEB [17.6 years for RDEB-generalized severe and 7.1 years for RDEB-generalized intermediate] and 8.1 years for recessive EBS. *Conclusions:* Our clinically and molecularly well-characterized EB-cohort provides accurate epidemiological data for EB that is invaluable for the design of upcoming trials. Additionally, this data demonstrates the need for care and disease burden for patients with EB in the Netherlands.

P105
SAFETY AND CLINICAL EFFECTS OF SYSTEMIC ALLOGENEIC UCB-MSCS THERAPY FOR PATIENTS WITH RDEB

Seung Ju Lee[1], Kinam Kim[2], Boyoung Cho[2], Kyounghwan Roh[3], Soo-Chan Kim[1], Sang Eun Lee[1]
[1]Department of Dermatology, Yonsei University College of Medicine, Seoul, Korea, [2]Cellular Therapeutics Team, Daewoong Pharmaceutical, Co., Ltd, [3]Department of Clinical Development, Kangstem Biotech Co., Ltd

Introduction & objectives: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is a severe genodermatosis caused by mutations in COL7A1 and characterized by mucocutaneous blistering after minor trauma. Bone marrow–mesenchymal stromal cells (MSCs) have shown therapeutic potential for RDEB patients. Recent preclinical study demonstrated that a systemic infusion of human umbilical cord blood (UCB)-derived nonhematopoietic stem cells correct RDEB murine model. The objective of this study is to determine the safety and possible clinical efficacy of systemic allogeneic UCB-MSCs therapy for RDEB patients. *Materials & methods:* Six Korean RDEB patients (4 adults and 2 children) were included in this clinical trial. Each participant received three intravenous infusions of allogeneic UCB-MSCs (1–3 × 10^6 cells kg–1) with no HLA matching. *Results:* Change in mean disease severity measured by Birmingham Epidermolysis Bullosa Severity Score (BEBSS) was -16 point at 60 days. Mean BEBSS total body surface area (%) was significantly reduced (-15 point) from baseline to day 60. Blister count and blister area/body surface area (%) were reduced by 50% at day 60 compared to baseline. Pain and pruritus score (VAS) were also reduced by 43% and 13% at day 60 compared to baseline. We also found the increased number of c-kit+ mast cells and CD68+ macrophages in the patient's skin at baseline, but the number of both cells were markedly reduced at day 60. No significant increase in C7 deposition was observed at day 60. There were no severe adverse events during day 180. *Conclusions:* The results suggest that administration of allogeneic UCB-MSCs in patients with RDEB is safe and provide indications of possible clinical benefits, to be confirmed in further clinical trials.

P106
THE EPIDEMIOLOGY OF EB IN THE UK: DATA FROM THE NATIONAL DATABASE

Gabriela Petrof[1], Malobi Ogboli[2], Anna E. Martinez[1], Jemima E. Mellerio[3], Maria Papanikolaou[3], Adrian Heagerty[4] , Celia Moss[2]
[1]Department of Dermatology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [2]Department of Dermatology, Birmingham Women's and Children's Hospital, Birmingham, United Kingdom, [3]Department of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [4]Department of Dermatology , University Hospitals Birmingham, Solihull, United Kingdom

Introduction & objectives: In 2002 a national Epidermolysis Bullosa (EB) service was set up in the UK. To date 2345 individuals born since 1922 have been registered, providing a unique opportunity for epidemiological study. *Results:* Regarding prevalence, on 23/09/2019 there were 2141 living patients, with diagnosis recorded in 96%: There were 1056 with EB simplex (EBS): localised (EBS-LOC)=690, generalised severe and intermediate (EBS-GS/GI)=153, with mottled pigmentation (EBS-MP)=35, with muscular dystrophy (EBS-MD)=13, not otherwise specified

(EBS-NOS)=131. There were 675 with dystrophic EB (DEB): recessive (RDEB)=216, dominant (DDEB)=419, DEB-NOS=40. Seventy-two had junctional EB (JEB): generalised severe (JEB-GS)=4, generalised intermediate (JEB-GI)=25, with pyloric atresia (JEB-PA)=7, JEB-LOC=10, JEB NOS=4. There were 21 with Kindler syndrome and 36 with EB-NOS. Prevalences /million population are EBS=15.6, DEB=10, JEB 1.0, and all EB=27.7. Regarding incidence, during the 20 year period to 23/09/2019 we registered 1209 newborns with EB. There were 515 with EBS: EBS-GS=62, EBS-GI=34, EBS-LOC=288, autosomal recessive EBS=22, EBS-MP=22, EBS-MD=11, EBS-NOS=67. There were 129 with JEB: JEB-GS=82, JEB-GI=13, JEB-PA=14, JEB-LOC=8. There were 376 with DEB: RDEB=121, DDEB=238, DEB-NOS=10, 15 with Kindler syndrome and 27 with EB-NOS. Forty-seven had EB-related conditions including epidermolytic ichthyosis (50) and acral peeling skin syndrome (51). This gives the following incidence rates/million live births/year: all EB=76.7, EBS=39.8, DEB=27.6, JEB=9.5, EB-NOS=1.2. Comparing earlier (2002-2010) and later (2011-2019) birth cohorts, we observed reductions in birth rates for JEB-GS from 9 to 3.8/million live births and RDEB-GS from 6.8 to 2.9/million live births. In this 20-year birth-cohort 117 died before age 16y, 76 with JEB-GS, 8 with JEB-PA, 11 with RDEB, 4 with EBS-GS, 1 with EB-NOS and 1 with JEB-GI. Regarding JEB-GS, excluding 1 surviving outlier aged 19 years, the UK median age of death was 150 days (IQR 60-300) with mean of 8 months, higher than reported in Austria (5 months - Laimer et al, Dermatol Clin, 2010), the Netherlands (5.8 months - Yuen et al, Br J Dermatol, 2011) and Australia (6.8 months - Kho et al, Arch Dermatol, 2010). Survival rates at 3, 6, 12 and 18 months in JEB-GS were 70%, 47%, 28% and 15% respectively. There is a suggestion of increased survival for UK babies with JEB-GS ($p=0.11$). *Conclusions:* Our figures exceed those reported from the USA and Australia, possibly reflecting ethnographic factors and more complete ascertainment. The modest increase in survival time of babies with JEB-GS, and possible reduction in birth incidence for severe types may reflect better care and genetic counselling over the last 20 years.

P107
UNDERSTANDING OCULAR DISEASE IN THE DEB MOUSE MODEL: CHALLENGES OF ASYMMETRY AND SURVIVAL

Vicki M. Chen, MD[1], Lauren Richey, DVM, PhD[2], Michael Esmail, DVM[2], Rajani Shelke, MS[2], Zhiyi Cao, PhD[2] Noorjahan Panjwani, PhD[2], M. Peter Marinkovich, MD[3]

[1]Tufts Medical Center, Floating Hospital for Children, [2]Tufts University School of Medicine, Boston, MA, USA, [3]Stanford University, Palo Alto, CA

Introduction & objectives: Ophthalmic study of the DEB hypomorphic mouse model has unique challenges, including asymmetry of ocular involvement, and survival to an age that ocular disease can be seen. Herein, we report the natural course of ophthalmic disease, and lessons learned from 36 months of breeding and examination of these animals. *Materials & methods:* Survival rates of collagen VII deficient hypomorphic mice were recorded over 36 months. Special precautions were taken to promote survival including cellulose fiber bedding, diet-gel 76A, and hydrogel. Genotyping was performed on all mice to confirm homozygous status. Twenty mice were examined and photographed weekly using a Topcon camera enabled slit-lamp, from 8 until 20 weeks (ethical endpoint). Corneal opacities were graded on a scale of 0-4 (previously published). Histology with H&E staining of 16 eyes (8 mice) was performed by an ocular pathologist. Grading of 10 corneal features known to be potentially abnormal in this model was made using a standardized scoring scale of 0-3. Five sections were examined per eye, scores were averaged and compared between eyes (t-test). Electron microscopy of two hypomorphic mice ages 4 and 14 weeks was compared with WT mice. *Results:* A total of 268 hypomorphic mice were produced, 146 (54%) survived to weaning age of 5 weeks. Declines in survival rate to less than 40% were noted at 9,13,16,19,22, and 27 weeks. Refreshing the colony every 10-12 months doubled survival of the next round (see Figure 1). Of the 20 mice photographed, 75% survived to the 20-week endpoint. The most common reason for early sacrifice was penile prolapse. The prevalence of corneal opacity in mice increased with age, peaking at 41% of mice (24% of eyes) at 18 weeks. Mean histology scores were similar between eyes (2.14 ± 1.49 in the right eye and 2.83 ± 1.56 in the left eye, $p=0.243$). One mouse (17%) showed statistically significant asymmetry between the two eyes ($p=0.000$). Electron microscopy showed no lamina densa, absent anchoring fibrils, and hemidesmisomes present. *Conclusions:* More than half of the hypomorphic mice survived to weaning, and 75% reached the 20-week endpoint. Our overall survival rate is nearly double the typical rate, which we attribute to special husbandry considerations. The asymmetry of ocular involvement was lower than expected. Our novel grading system captures severity of disease in mice and can be directly translated to scoring of ocular scan data in patients for use in clinical trials.

P108
NUTRITIONAL PROFILE OF CHILDREN AND ADOLESCENTS WITH EB: IS THERE AN INFLUENCE OF ETHNICITY?

Silvia Ricart[1], Inés Cases[1], Eduard Pellicer[1], Silvia Ciprés[1], Lucía Peñarrubia[1], Isabel Torrús[1], Asunción Vicente[2]

[1]Pediatric Complex Chronic Patient Unit, [2]Dermatology Service, Sant Joan de Déu Hospital (Barcelona)

Introduction & objectives: With the development of technology applied to health, natural history of infants with EB has changed. Nutritional management and early gastrostomy placement have delayed the development of malnutrition and other derived comorbidities. However, eating habits have deep cultural roots that can influence the results of dietetic and nutritional interventions in severe EB patients. The aim of the study is to describe the nutritional status of children and adolescents with severe forms of EB and to compare it according their ethnic origin. *Materials & methods:* Descriptive study conducted in children and adolescents attended in a reference pediatric hospital for severe EB patients: recessive dystrophic (RDEB) and junctional (JEB). Weight, height, body mass index (expressed as percentiles related to age), nutritional parameters (albumin, prealbumin), oligoelements (iron, zinc, selenium) deficits and vitamin status were recorded. The use of nutritional supplements, aage of G-button placement and ethnic origin of the families were also collected. *Results:* Fifteen severe EB patients, aged between 3 months and 17 years, were included: 7 RDEB generalized severe, 2 RDEB generalized intermediate, 1 JEB generalized and 4 JEB intermediate. Family origin: 33.3% Moroccan, 6.7% Pakistani, 33.3% Gypsy and 26.7% Caucasian. Eleven children had nutritional supplements prescribed. Four children (all RDEB) had a weight below percentile 3 for age (3 Morocco, 1 Pakistani). Two of them have refractory iron deficiency anemia that need intravenous iron or blood transfusion. Both patients had a G-tube placed at 8 years of age, but the medical indication of G-tube placement was done 1,5 years before. One patient was obese (BMI >p95) and 2 were overweighted (BMI >p90); all of them had JEB intermediate and were of Gypsy origin. All the overweighted children have vitamin deficiencies (D, B12 and A). *Conclusions:* Even all the patients underwent the same EB care protocol and nutritional approach (close follow-up and early dietetic interventions), 46.7% had reached malnutrition. All the malnourished children had parents of foreign origins and there was some degree of language or cultural barrier. This fact

could explain some difficulties in reaching therapeutic compliance and more concerns of the parents about G-tube placement, which caused a delay in the surgery. Of the overweight children (20%), all were Gypsy without esophageal involvement. The dietetic habits of this ethnic group in Spain and the less severe phenotype would explain this finding. Although larger samples are needed to confirm these findings, it is important to recognize the influence of cultural aspects in the evolution of the disease.

P109
RECOMBINANT HUMAN COLLAGEN VII DECREASES MARKERS OF FIBROSIS AFTER CORNEAL ABRASION IN MICE WITH EPIDERMOLYSIS BULLOSA

Vicki M. Chen, MD[1], Rajani Shelke, MS[2], Ilene Gipson, PhD[3], Rajendra Kumar-Singh, PhD[2], Noorjahan Panjwani, PhD[2], Zhiyi Cao, PhD[2], Abdulraouf Ramadan, PhD[2] ,M. Peter Marinkovich, MD[4]

[1]Tufts Medical Center, Floating Hospital for Children, [2]Tufts University School of Medicine, Boston, MA, USA, [3]Schepens Eye Research Institute, Boston,MA, [4]Stanford University, Palo Alto, CA

Introduction & objectives: Absent collagen VII within the corneal basement membrane results in abrasions, scarring and vision loss in patients with dystrophic EB. Recombinant human collagen VII (rhC7) has been developed to potentially treat DEB in skin but has not been tested in the eyes for efficacy or toxicity. Herein, we describe the impact of *in vivo* topical application of rhC7 to the eyes of mice with DEB. *Materials & methods:* Topical drops were first tested and rhC7 did not penetrate through intact epithelium. Therefore, the central corneal epithelium was necessarily removed from both eyes of 24 mice. The right eye was then injected with 0.8 mg/ml rhC7 in BSS subconjunctivally every 48 hours (up to 5 doses). The contralateral eye received BSS and served as internal control. Slit-lamp examinations (SLE) were performed weekly. After 4 weeks, animals were sacrificed and corneas were examined with immunohistochemistry (IHC) for presence of collagen VII, alpha smooth muscle antigen (α-SMA), transforming growth factor beta 1 (TGF-β1), and connective tissue growth factor (CTGF). Intensity of staining was compared using imageJ. Quantitative real-time single cell polymerase chain reaction (Rt-PCR) was performed to compare mRNA expression of the same markers. Enzyme linked immunosorbent assay (ELISA) was then performed to quantify markers. Eyes were examined with electron microscopy (EM), histology and external slit lamp photography before and after treatment. *Results:* All markers were consistently reduced in eyes that received rhC7. Lower doses were also effective. Semiquantitative analysis of IHC samples demonstrated a reduction in α-SMA, TGF-β1, and CTGF after treatment. Rt-PCR results were inconclusive. ELISA for α-SMA and TGF-β1 confirmed the reduction of biomarker levels in response to rhC7 in WT mice but not in hypomorphic mice (repeat of ELISA is in progress). More "anchoring fibril candidates" were seen on EM, but there was no clear evidence of basement membrane normalization. Histology and SLE showed no difference in opacification score between rhC7 and control eyes. Conjunctival overgrowth of the corneal surface was seen in 50% (5/10 eyes). Steroid was added to the regimen, but again 50% (4/8 eyes) showed conjunctivalization. *Conclusions:* Subconjunctival injection of rhC7 reduces fibrotic markers after corneal abrasion in hypomorphic mice. However, opacity scores were confounded by conjunctival overgrowth of the cornea. Anchoring fibrils (AF) were not clearly seen on EM. Proof-of-concept that rhC7 leads to AF formation after epithelial injury is challenging in this animal model. Paths forward include therapies that do not require removal of epithelium such as gene therapy.

P110
THE QUALITY OF LIFE IN PATIENTS WITH EPIDERMOLYSIS BULLOSA IN IRAN: A CROSS SECTIONAL STUDY

Mohammad Mahdi Parvizi[1], Farhad Handjani[1], Soulmaz Ghahramani[2], Zahra Parvizi[2]*

[1]Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran, [2]Health Policy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Introduction & objectives: Epidermolysis bullosa (EB) is a rare hereditary skin disease caused by mutations in the collagen-forming genes in the skin. It affects several aspects of the patient's life and the patients' families. The aim of this study was to evaluate the quality of life of EB patients in Iran. *Materials & methods:* This cross-sectional study was conducted in 2016 among patients with EB aged over 15 years. The patients were selected by convenient sampling method. The researchers used the specific epidermolysis bullosa quality of life questionnaire (EBQOL), which consists of functional and emotional domains. SPSS software version 18 was used for statistical analysis. *Results:* Overall, 33 patients of which 19 were men and 14 women were enrolled in the study. The mean ± standard deviation (SD) age of patients was 26 ± 7.24 years. The mean ± SD score of quality of life in the functional domain was 18.57 ± 8.15 (maximum score = 36) and in the emotional domain 7.18 ± 3.70 (maximum score = 15). There was no statistically significant difference between the mean ± SD scores of these domains in men and women ($p > 0.05$). Overall, 48.5% of patients had low quality of life and 21.2% had very low quality of life. *Conclusions:* According to the results of this study, EB can disturb the functional and emotional aspects of life in these patients, mostly having a poor quality of life.

P111
COMING OF AGE: AUDIT OF THE TRANSITION PROCESS IN OUR EB SERVICE

D. James, K. Begum, K. Dewsbery, H. Light, C. Knowles, A. Heagerty, M. Ogboli

EB Department, Birmingham Children's Hospital, EB Department, Solihull Hospital

Introduction & objectives: Epidermolysis Bullosa (EB) is a lifelong condition and transition to adult services is an important part of the management of young people with EB. In 2019 our adult and paediatric centres audited their current transition practices. *Materials & methods:* The respective teams used a jointly-developed retrospective transition audit tool to review the records of all those who had transitioned into the adult service within a 2-year period and the records of young person's currently in transition in their service. The Adult tool had 15 review questions, whilst the Paediatric tool had 22 questions. We present some of the results. *Results:* In total 55 young people's transition pathways were audited, 50 (30 female, 20 male) in the paediatric service aged between 14 – 19 years and 5 (1 female, 4 male) young people in the adult service. 64% (27) of the paediatric cohort had started transition at 12 years of age. The range was 11 – 16 years. In 96% of cases there was documentation of the transition process in the notes. 90% of young persons and 84% of their carers were given an opportunity to discuss queries and concerns. Only in 50% were adult team leaflets and contact details given. In 44% of cases a choice of adult centre had been offered and 68% of the paediatric cohort had seen a member of the adult team. The mean age at transfer was 17.6 years. All 5 young adults were involved in the choice of adult centre, 4 of them met an adult EB specialist prior to transfer at the hospital and 3 of them also had an joint outreach visit from both services and in 3 patients a member of the paediatric team attended their first adult appointment with them. *Conclusions:*

The Paediatric and Adult services had a well-established collaborative provision for transition, this audit provided information that showed areas of good practice but highlighted areas for further improvement. In particular it identified a need for more detailed record keeping during the period of transition. Our teams need to increase the use of patient information. We have very limited patient feedback information in our processes at present and this needs to be addressed.

P112
NOVEL PLAYERS IN THE ESTABLISHMENT AND PROGRESSION OF FIBROSIS IN RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Esteban Chacón-Solano[1,2], Francisco Quero[1], Carlos León[1,2], Marta García[1,2], Marta Carretero[1,2], María José Escámez[1,2], Alexander Nyström[3], Fernando Larcher[1,2] & Marcela del Río[1,2]
[1]Epithelial Biomedicine Division (UC3M-CIEMAT-CIBERER) Madrid-Spain, [2]Regenerative Medicine and Tissue Engineering Group, Fundación Jiménez Díaz (IIS-FJD) Madrid-Spain, [3]Department of Dermatology, Medical Center, Freiburg University, Germany

Introduction & objectives: Recessive dystrophic epidermolysis bullosa (RDEB) is an inherited skin fragility disorder associated with chronic blisters, altered wound healing, mitten deformities in hands and feet, and aggressive squamous cell carcinomas. Previous studies revealed a contributing role play by the dermal component in the pathophysiology of this disease. In order to find new disease-severity modulators, we have compared the gene expression profile of RDEB fibroblasts against healthy donors, which allowed us to identify several altered signaling pathways. Here we explored in detail the actual relevance of some of these pathways. *Materials & methods:* We performed a gene expression analysis (RNA-Seq) of primary fibroblasts from 3 healthy donors and 9 isogenic patients with RDEB (including two siblings with the same null mutation and different clinical manifestations). Functional enrichment analysis of Gene Ontology terms and KEGG pathways were carried out. Transcriptomic data were validated by q-PCR and Western Blot. Phenotypic *in vitro* characterization such as expression of pro-fibrotic markers, cellular contraction, response to TGF-β and oxidative stress was performed. In addition, a lentiviral vector was used to overexpress PRELP as a candidate gene potentially implicated in the progression of the disease. *Results:* Enriched GO-terms suggested that major differences between healthy donor and RDEB fibroblasts were concentrated in the extracellular space and the extracellular matrix (ECM) component. Furthermore, over-represented terms were associated with cytokine production, oxidoreductase activity, response to mechanical stimulus, cellular contraction, and response to TGF-β. Since RDEB fibroblasts differentially expressed genes related to redox imbalance (SOD3, ALDH1A1, HIF1A), fibrosis (COMP, MMP3, PLOD2), inflammation (IL1RL1) and basement membrane adhesion (PRELP), we analyzed the consequences of that and found higher levels of reactive oxygen species (ROS), greater expression of pro-fibrotic markers and increased response to TGF-β. Remarkably, fibroblasts from a RDEB patient with a very mild phenotype (despite absence of collagen type VII), showed a compensation in the gene expression of some of these genes (e.g. PRELP, COMP, ALDH1A1, MMP3) and showed a less contractile and synthetic phenotype in comparison to other patients. In particular, downregulation of PRELP in RDEB received our attention. Overexpression of this gene in RDEB fibroblasts decreased the expression of pro-fibrotic markers and counteracted the response to TGF-β. *Conclusions:* This study identified novel players involved in the pathophysiology of RDEB, which would be useful to develop new symptom relief therapies to treat RDEB patients.

P113
EATING DISORDERS AND DISORDERED EATING AND BODY IMAGE IN CHRONIC ILLNESS: A FIRST DESCRIPTION IN PATIENTS WITH EPIDERMOLYSIS BULLOSA

Harper N. Price, MD[1], Judith O'Have, PhD[1], Liz Langreck, RD[1], Mark P. Popenhagen, PsyD[1], Jenna Rudo-Stern, PhD[1], Israel Andrews, MD[1], Daniela Russi, MD[1], Kellie Badger, BS, RN[1], Milie M. Fang, BS[2], Moise L. Levy, MD[3], Anne Lucky, MD[4], Amy Paller, MD[2]
[1]Phoenix Children's Hospital, Phoenix, AZ, [2]Ann & Robert H, Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Dell Children's Medical Center, Dell Medical School/University of Texas, Austin, TX, [4]Cincinnati Children's Hospital, Cincinnati, OH

Introduction & objectives: Patients with severe forms of epidermolysis bullosa (EB) suffer from nutritional complications related to several complex and interrelated factors. Gastrostomy tubes (GT) may help improve nutritional status, facilitate medication administration and prevent complications 1. Chronic illnesses (CI) that require a therapeutic diet or nutritional intervention can increase patient risk for disordered eating (DE) and specific eating disorders (ED). A systematic review of literature on diet-treated chronic illnesses showed increased associated ED and DE in children/adolescents with CI 2. Involvement of caregivers with children requiring nutritional interventions may also have inherent risks, resulting in patient lack of control over eating and risk for disordered eating. Coping with a CI during adolescence can lead to body image disturbance that can have detrimental consequences. There are no published reports regarding DE/EDs and distorted body image in EB patients with chronic malnutrition. *Materials & methods:* We describe two related young adults with RDEB with signs of disordered eating and family dysfunction around eating, despite continued severe malnutrition and declining health. The Body Dissatisfaction Assessment Scale; Beck Depression/Anxiety Inventory; Functional Disability Inventory; EDI-3 SC; EDI-3; EDI-RF were administered. Other examples of patients exhibiting DE/EDs, and dysfunctional eating and functional delays around eating exemplify these issues in this population. *Results:* 29 year-old woman with RDEB, chronic non-healing wounds, anemia, multiple SCCs, nutritional deficiency and poor oral intake with low drive for oral supplementation, esophageal strictures, poor dentition and depression and refusal of GT; 28 year-old woman with RDEB, anemia, nutritional deficiency, esophageal/oral blistering with GT, poor dentition, chronic-non-healing wounds and depression. Standardized assessment negative for an ED. However, since adolescence, there has been familial and patient concern regarding becoming "fat" via nutritional supplements, use of NGT or GT. Patients wear slimming clothing and voiced concern that placement of a GT would be visible to peers and cause weight gain, despite chronic malnutrition and overall poor health. Additional cases described include food aversion, anorexia nervosa, and dysfunctional eating. *Conclusions:* Providers caring for chronically ill EB patients should be aware of potential DE/ED and related psychological conditions. Routine screening for DE/ED and related conditions and intervening with early treatment is ideal. However, available screening tools have not been validated in this population. Not to be underestimated is the role of the family unit and social peers/influences to encourage a positive body image, coping skills, and prevention of disordered eating behaviors to improve overall health outcomes in this population.

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P114

CORNEAL ABRASIONS, SCARRING AND VISION LOSS IN EPIDERMOLYSIS BULLOSA: RESULTS OF AN INTERNATIONAL PATIENT SURVEY

Adam C. Tanaka, MPH[1], MS, Calvin C. Robbins, BA[1], Karen Wiss, MD[2], Vicki M. Chen, MD[1]

[1]Tufts Medical Center, Floating Hospital for Children, Boston, MA, USA, [2]University of Massachusetts Memorial Medical Center, Worcester, MA

Introduction & objectives: Ocular surface disease is seen in all types of EB, but it is most severe in recessive dystrophic EB (RDEB) and JEB. In RDEB patients, the cumulative risk for corneal abrasions reaches 63.53% by age 10, and 83.18% by age 5 years in those with JEB (Fine 2004). Clinically pertinent information regarding history of abrasion, such as age of onset, frequency, duration, severity, or cumulative number prior to scarring and vision loss, has not been published. In June of 2019, the United States Food and Drug Administration (US-FDA) released guidelines for EB drug development, in which the "natural history", "patient reported outcomes (PRO)" and "observer-reported outcome (ObsRO)" instruments are specifically marked as a key elements in interventional study design to "provide evidence of how patients feel or function in daily life". The objective of this study is to characterize and report the patient experience of EB-related corneal abrasions, and to examine the relationship of these factors with visually significant complications. *Materials & methods:* This international cross-sectional survey included 62 questions, was internally validated, and distributed to 171 EB families through 3 major EB research foundations and posted on-line. *Results:* Ninety-five respondents completed the survey (60 caregivers of children and 35 adults), 37% with EB simplex, 51% with dystrophic EB and 15% with junctional EB. Mean age of onset for abrasions was 4.6 ± 4.9 years, 72% experienced their first abrasion before age 5. For 70% of respondents, pain lasted 3 days or more, and for 43%, abrasions occurred every 1-4 months. Mean pain score with a typical abrasion was 7.8/10, with 88% reporting pain severity at 6/10 (narcotic level of pain), and 41% reporting pain of 8/10 or higher. Family distress was high, with 73% of caregivers reporting moderate to extreme emotional impact from abrasions. Onset of scarring and vision loss was mean age of 10.8 ± 11.3 and 8.3 ± 5.3 years, respectively. Corneal scarring occurred in 52% of respondents, and vision loss in 33%. Those with frequent abrasions were 5.18 times more likely to have corneal scarring (odds ratio, $p = 0.001$). *Conclusions:* Pain from corneal abrasions is severe and prolonged in most patients. Frequent abrasions confer higher risk of corneal scarring and vision loss. Detailed inquiry regarding ophthalmic symptoms is recommended during comprehensive EB examinations to identify patients whose daily lives are significantly affected, and those at higher risk of vision loss.

P115

EFFICIENT GENOME EDITING FOR CORRECTION OF RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA IN IPS CELLS USING CRISPR/CAS9 RIBONUCLEOPROTEIN COMPLEXES

Joanna Jacków[1], Zongyou Guo[1], Hasan E. Abaci[1], Yanne S. Doucet[1], Jung U Shin[1], Corey Hansen[1], Ryota Hayashi[1], Yudai Kabata[2], Satoru Shinkuma[2], Julio C. Salas-Alanis[3] and Angela M. Christiano[1]

[1]Department of Dermatology, Columbia University, New York, USA, [2]Division of Dermatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, [3]School of Medicine and Health Sciences TecSalud ITESM, N.L, Mexico

Introduction & objectives: Recessive dystrophic epidermolysis bullosa (RDEB) is a severe inherited skin disorder caused by mutations in the COL7A1 gene encoding type VII collagen (C7), the major constituent of anchoring fibrils (AFs) at the basement membrane zone (BMZ). Patients with RDEB lack functional C7 and have severely impaired dermal-epidermal stability. This results in extensive blistering and open wounds on the skin which negatively impact patients' quality of life. There are currently no therapies approved for the treatment of RDEB. *Materials & methods:* Here, we demonstrated the correction of mutations in exons 19 (c.2470insG) and exon 32 (c.3948insT) in the COL7A1 gene through homology-directed repair (HDR). We used the clustered regulatory interspaced short palindromic repeats (CRISPR) Cas9-gRNAs system using RiboNucleoProtein-(RNP) (CRISPR-Cas9-gRNA complex) in induced pluripotent stem cells (iPSCs) derived from RDEB patients to target both heterozygous and homozygous mutations. *Results:* 3D skin constructs (SCs) were generated from gene-corrected iPSCs that were differentiated into both keratinocytes (KC) and fibroblasts (FB) and grafted on to immunocompetent mice. These skin constructs showed normal expression of C7 at the BMZ, and restored AFs at 2 months post-grafting. In order to translate this approach into the clinical setting, both efficiency and safety experimental aspects must be improved and optimized. Here, we used xeno-free reprogramming and differentiation methods for iPSCs. We also utilized a GMP-certified Cas9 protein with a chemically modified synthetic guide RNA (sgRNA) and single-stranded DNA as our repair donor template for efficient gene editing via HDR *Conclusions:* This novel method represents a significant advance towards the development of therapeutic applications of gene correction for treatment of RDEB.

P116

DEVELOPMENT OF A TOOL TO ASSIST DISCUSSIONS FOR INSERTION OF GASTROSTOMY TUBE IN CHILDREN WITH EPIDERMOLYSIS BULLOSA (EB)

R. Jones[1], D. James[2], M. Ogboli[2]

[1]Department of Dietetics, Birmingham Children's Hospital, [2]Deparment of Dermatology, Birmingham Children's Hospital

Introduction & objectives: Gastrostomy tube feeding is frequently used for children with Epidermolysis Bullosa (EB) requiring long term nutritional support. Limited outcome data, reported complications and surgery placement make the decision challenging for patients, parents and health professionals. Tools are available to assess severity of disease and nutritional compromise for children with EB, but additional factors such as stressful mealtimes may also be considerations for gastrostomy placement. We present a scoring tool designed to assist these discussions as part of a service pathway *Materials & methods:* Discussions amongst Health professionals provided a list of reasons for gastrostomy placement and benefits reported after insertion. These were developed into a scoring tool to assess occurrence including: faltering growth, refusal or tears completing meals/medication, anaemia, oesophageal strictures, reduced school attendance, nutritional supplement use, dysphagia, hospital management of constipation and anaemia, as well as percentage body surface area of wounds and recent IV antibiotic use for skin infections. This was piloted on 35 children: at clinic reviews and retrospectively for time of insertion for those with gastrostomies insitu. Consideration was given to scores for children felt not needing gastrostomy and children currently being prepared for the procedure. Review of these scores by health professionals caring for these children and experienced with EB and its subtypes, enabled production of suggested scores at which further information should be provided and referral considered. It was felt the tool was not reliable for children under 2 years of age. The tool was reviewed informally by one external centre cohort of EB children with gastrostomies and one centre where gastrostomy not offered for ease of use. *Results:* For 35 children

(age range1.5-7.0 years median 7) a score was calculated range 0 -70 median 35. EB subtypes included: 2 junctional EB, 3 EBS-generalised severe and 27 EB recessive dystrophic- generalised severe. A Score of ≥15 for growth section only and/or total score ≥40 were suggested to prompt further education and referral to surgeon *Conclusions:* The decision for gastrostomy placement can be a difficult one for health professionals to guide on and families to make. Few resources are available to assist with this. We believe annual assessment with this tool can contribute to discussions and potentially guide optimal time of insertion at EB centres where this procedure if supported. Further validation is planned to assess use as predictor of optimal time for gastrostomy referral, considering regional factors such as waiting-list times.

P117
RDEB-CSCC DERIVED INDUCED PLURIPOTENT CANCER CELLS FOR STUDYING CANCER INITIATION AND PROGRESSION

Joanna Jacków, Ryota Hayashi, Avina Rami, Zongyou Guo and Angela M. Christiano
Department of Dermatology, Columbia University, New York, NY

Introduction & objectives: The early onset of aggressive cutaneous squamous cell carcinoma (cSCC) and its rapid progression in recessive dystrophic epidermolysis bullosa (RDEB) leads to high mortality rates in these patients. Reprogramming differentiated cancer cells into induced pluripotent cancer cells (iPCCs) is a novel tool used to investigate cancer progression and understand the epigenetic transformation process during tumorigenesis. We hypothesized that if cSCC cells were converted to pluripotency and then allowed to differentiate back into cSCCs, they wound undergo changes reminiscent with the stages of early-onset cancer. Due to the genetic and epigenetic barriers in cancer cells, the reprogramming efficiency is very low. *Materials & methods:* In this study, we used a humanized version of the single polycistronic lentiviral (LV) vector to reduce the number of viral integrations in cSCCs derived from RDEB patients to generate iPCCs from cSCCs. *Results:* Successful generation of iPCCs from RDEB-cSCC after infection with a single LV vector was demonstrated by epithelial-like morphology, colony-forming efficiency, the expression of pluripotency markers such as Sox2, Oct-4, SSEA-3 and TRA-1-60, and the ability of the cells to differentiate *in vitro*. Moreover, TaqMan assays of human stem cell pluripotency gene signatures of RDEB-cSCC-iPCCs were similar to WT-iPCCs generated from normal human fibroblasts demonstrating that the RDEB-cSCC-iPCCs correlated with the stem cell state. The RDEB-cSCC-iPCC undergo differentiation into RDEB-cSCC - cancer stem cells (CSC) and will be used to generated 3D skin constructs (SCs) and grafted onto immunocompetent mice. After tumors develop, they will be characterized and used as a model to test ruxolitinib for its *in vivo* activity to reverse the growth of a tumors formed by RDEB-cSCC-iPCCs. *Conclusions:* Taken together, the RDEB-cSCC-iPCC tumor model offers a valuable tool to study early RDEB-cSCC development and progression, as well as the development of novel therapeutic approaches

P119
PSYCHOSOCIAL ASPECTS OF EPIDERMOLYSIS BULLOSA AND QUALITY OF LIFE. A SYSTEMATIC REVIEW

Gudrun Salamon, Alexander Ruberl and Laura Maar
Sigmund Freud University, Vienna, Faculty of Psychology

Introduction & objectives: Epidermolysis bullosa (EB) is a group of rare diseases characterized by skin fragility. As indicated in previous research, EB has an enormous impact on all aspects of psychosocial life. Hence, quality of life is an important measure in psychological as well as in clinical research. However, quality of life is highly influenced by individual perception. The same applies to the concept of wellbeing, which describes the individual balance between personal resources and challenges faced. Coping strategies are an individual's mental or behavioural response options to stress and to challenging situations. In EB, stress is caused by chronic pain, the need of intensive wound management and restrictions in everyday life. Additionally, these restrictions lead to social and emotional challenges. *Materials & methods:* In order to address all psychosocial aspects of EB and corresponding coping strategies thoroughly, we conducted a systematic review of literature. A set of exclusion and inclusion criteria led to a final selection of 38 papers presenting original work, comprising quantitative, qualitative, mixed methods and single case studies with the focus on EB patients or their families. *Results:* The following psychological aspects were described as helpful on an individual coping level: Control of life is associated with autonomy, which can be increased by active EB management and by the help of external support (like care assistance) when necessary; Containing the impact of EB relies on strategies for dealing with pain and for emotion regulation and is positively correlated with self-esteem and self-efficacy. The validation of the expertise for the own or a family member's EB case based on specific knowledge and personal experience in, e.g., helpful routines for wound care, is highly appreciated; Interaction with others is a great resource and easier when taking an active role in the exchange with health care professionals, with healthy people, with people in a similar/comparable condition, and with people with EB. Strategies for communicating the personal health situation are helpful in order to enhance knowledge and understanding of others; The attitude to live a close-to-normal life or at least close-to-normal moments is linked to decisions in favour of physical or social activities in spite of pain. It needs situational impact assessment and flexible decision-making. *Conclusions:* Quality of life and wellbeing are highly individual and vary widely within people living with EB. Our systematic review identifies and explores psychosocial aspects of EB and their corresponding coping strategies.

P120
ANTERIOR SEGMENT SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN EPIDERMOLYSIS BULLOSA

Nihaal Mehta, BA, Calvin Robbins, BA, Elizabeth Noh, BS, Nadia K. Waheed, MD, MPH, Vicki M. Chen, MD
Sigillum Universitatis Tuftensis Pax Etlux 1852, Children's Glaucoma foundation, Massachusetts Lions Eye Research Fund Inc, Research to Prevent Blindness, Floating Hospital for Children at Tufts Medical Centre

Introduction & objectives: As therapies for DEB make progress in skin, there remains a great distance between skin application and readiness for ophthalmic use. Unlike skin, the cornea is not easily biopsied, which limits objective assessment of disease modification in response to therapy. Anterior segment optical coherence tomography (AS-OCT) provides high-resolution, depth-resolved, cross-sectional and three-dimensional imaging of the cornea. We developed a non-invasive tool to assess EB-associated corneal pathology. *Materials & methods:* Patients were recruited during the 3-day long DEBRA care conference in Phoenix Arizona, USA in 2018. A 10-item "vision and abrasion symptoms" questionnaire was given to all subjects. Visual acuity (VA) was tested monocularly. AS-OCT images were acquired by a trained ophthalmic photographer on the Optovue RTVue-XR Avanti SD-OCT system (Optovue, Inc., Fremont, CA, USA). We examined the ability of corneal AS-OCT imaging to visualize EB-associated corneal lesions, as well as associations between OCT findings and clinical metrics including visual acuity, abrasion frequency,

duration and pain. *Results:* In total, 62 EB patients and 60 controls were included for final analysis. Distribution of EB subtypes was Simplex 21%, RDEB 59.7%, DDEB 8.1%, JEB 11.3%. Highly statistically and clinically significant differences between patients and controls were seen for: time since last abrasion, frequency of abrasions, duration of abrasions, and severity of ocular pain ($p=0.0000$). Amblyopia was substantially higher in patients than controls (9.7% vs. 0%, $p=0.0132$). The median age for onset of abrasions was significantly lower in patients than controls (1.80 vs. 15.00 years, $p=0.0004$). Discrete fibrotic lesions were significantly more prevalent and numerous in EB patients compared with controls ($p=0.0000$). Six of the nine sectors showed statistically significant thickening (stromal fibrosis) in the central 5-, 7- and 9-mm zones of the cornea. Stromal fibrosis spared the superior quadrant. Epithelial hypertrophy was significant in the inferior quadrant, atrophy was not seen in any patients. Vision loss was associated with increased stromal, not epithelial, thickness. *Conclusions:* This study demonstrates that eyes of patients with EB are significantly different than those of age-matched controls. Novel findings include epithelial hypertrophy (not atrophy) over areas of stromal fibrosis, sparing of the superior quadrant, quantification of depth, length and number of discrete lesions per eye. Scarring can span the entirety of the corneal stroma. These findings may be used in the design of clinical trials of ophthalmic therapeutics to offer objective assessment of corneal surface disease in response to interventions. Larger longitudinal studies are needed for prognostic guidance.

P121
RATIONAL FOR OTR4120-BASED MATRIX THERAPY IN A NEW WOUND MANAGEMENT PROCEDURE FOR EPIDERMOLYSIS BULLOSA

Barritault Denis
University Paris Est Creteil, OTR3

Introduction & objectives: The Extra Cellular Matrix (ECM) microenvironment maintains tissue homeostasis by local regulation of cellular regeneration. Heparan sulfates (HS) are key elements of the ECM scaffold which act both as linkers, bridging structural matrix proteins such as collagens, laminin etc.. and as storage and protector sites to most of the communication peptides, playing a pivotal role in the regulation of cell proliferation, migration and differentiation that are all required for tissue regeneration and repair. We have engineered biodegradable nano-polysaccharide mimicking HS, alpha 1-6 polyglucosecarboxymethylsulfate registered as OTR4120. Introduced at the site of injury, OTR4120 replaces the destroyed HS, bridges the matrix proteins of the damaged ECM, and provides storage and protection to the local newly produced growth factors and cytokines, thereby restoring the ECM microenvironment conditions necessary for tissue homeostasis and repair. Efficacy of OTR4120-based Matrix Therapy is supported in several animal tissue lesion models including surgical, ischemic and burn skin wounds, showing healing improvement in speed, quality and resistance to breakage. This efficacy was further observed over the last 5 years in tens of thousands of patients treated for chronic skin ulcers of various origins and reported in several publications (doi: 10.1007/s10719-016-9744-5). Interestingly, no adverse effects were reported and pain relief associated with this improved healing was also observed. A similar OTR4120 based product was also developed to treat corneal ulcers with similar healing and pain relief observation (doi:10.1001/jamaophthalmol.2016.3019). A 12 year old male with recessive Epidermolysis Bullosa, EB, was reported to respond to a twice a week matrix therapy treatment until complete and rapid healing was achieved without recurrence for 2 years. Furthermore, the treatment resulted in rapid pain relief (Eplasty. 2012;12:ic15). Similar successful closure, pain relief and stable closure were reported following years of unsuccessful treatments of ulcers in patients with sickle cells (doi:10.1111/iwj.12217) and Steward Bluefarb syndroms (doi:10.1111/iwj.12074)wounds. Despite these encouraging responses also observed in other EB cases, the use of the original OTR4120 based device consisting of an impregnated gauze was not adapted and it was decided to further delay the evaluation of the OTR4120-based Matrix Therapy technology in EB until a spray form became available on the market. We now present the rationale and future plans to adapt this technology to a specific wound management procedure for EB patients.

P122
CERAGENINS, MIMICS OF ENDOGENOUS ANTIMICROBIAL PEPTIDES, AS NOVEL THERAPEUTICS FOR EB

Michael Moore and Paul Savage
Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT, Calvary Pharma, Chandler, AZ

Introduction & objectives: Human cathelicidin LL-37 is a well-characterized antimicrobial peptide, primarily expressed in neutrophils and epithelial cells, endogenously generated as protection against infection and to facilitate wound-healing. In vitro models of EB have shown reduced expression of LL-37, leading to impaired wound-healing, which improves with activation of LL-37 expression. Ceragenins mimic the behavior of LL-37, displaying antimicrobial properties (including fungal, and ESKAPE pathogens), anti-inflammatory and wound-healing properties. The unmet clinical need for EB is a therapeutic with ability to alleviate pruritis and pain resulting from chronic blisters, while preventing infection and accelerating wound healing through cell migration. Given their demonstrable mimicry of LL-37 in wound-healing and infection control, Ceragenins have potential for development as this optimal therapeutic. Multiple studies support this hypothesis, two of which are described below. Study 1. Pre-clinical assessment of the antimicrobial capacity of CSA-44, a lead ceragenin, in porcine burn models. Study 2. A randomized, double-blind vehicle-controlled study to evaluate the safety and efficacy of ceragenin CSA-44 as an adjunct to standard care in treating chronic diabetic lower extremity ulcers *Materials & methods:* Study 1. 2nd degree burns were administered in a porcine model and subsequently inoculated with Pseudomonas aeruginosa. Treatment with various formulations of CSA-44, and silver sulfadiazine, were administered for 7 days. Study 2. Patients with type II diabetes received treatment twice daily with CSA-44 for related foot ulcers. Wound areas were measured weekly. *Results:* Study 1. The largest reduction in bacterial burden, and minimal erythema was seen in CSA-44 treated burns. Silver sulfadiazine-treated burns had larger bacterial counts and continued to display erythema. Study 2. Wounds treated with CSA-44 trended toward faster healing in terms of reduced wound area compared to vehicle-treated wounds, healing almost twice as quickly. Furthermore, a larger portion of the CSA-treated wounds reached full closure at the end of the 8-week time point compared to the control group. *Conclusions:* Reduced bacterial counts and erythema from study 1 are consistent with bactericidal and anti-inflammatory properties of ceragenins. Data acquired in study 2 indicate significant ability to promote wound-healing, especially evident in refractory wounds that are otherwise resistant to standard-of-care treatment. Additionally, Ceragenins (unlike standard topical creams) are formulated for delivery as an aqueous spray, avoiding friction that exacerbates blister formation. These experimental results, given the role of LL-37 in EB pathology, lend support to the hypothesis that Ceragenins have the potential to be a valuable therapeutic for EB lesions.

P123
A PHASE 1/2 STUDY OF GENETICALLY-CORRECTED, COLLAGEN VII EXPRESSING AUTOLOGOUS HUMAN DERMAL FIBROBLASTS INJECTED INTO THE SKIN OF PATIENTS WITH RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (RDEB)

M.P. Marinkovich[1,4], A. Lane[1,3], K. Sridhar[1], D. Keene[2], A. Malyala[3], M. Spellman[3], J. Maslowski[3]*

*[1]Stanford University School of Medicine, Stanford, CA, [2]Shriners Hospital for Children, Portland, OR, [3]Castle Creek Pharma, Exton, PA, [4]Veterans Affairs Medical Centre, Palo Alto, Stanford, CA, *mpm@stanford.edu*

Introduction & objectives: Recessive Dystrophic Epidermolysis Bullosa (RDEB) is an inherited genetic skin disorder caused by mutations in the COL7A1 gene encoding type VII collagen (C7). We report the results of the ongoing Phase 1/2 clinical trial of an *ex vivo* gene therapy for the treatment of RDEB. *Materials & methods:* Five adult and one pediatric subjects enrolled in this trial carried various null COL7A1 mutations resulting in undetectable C7 expression by immunofluorescence microscopy (IF) and a lack of intact anchoring fibrils (AF) by electron microscopy (EM). Autologous RDEB fibroblasts isolated from skin biopsies were transduced with a third-generation self-inactivating lentiviral vector encoding the wild type COL7A1 gene and expanded to obtain a sufficient quantity for study treatment. Wounds in study were shown to be open at each monitoring visit up to 8 months prior to dosing. These chronic wounds ranging in size from 4.3 cm^2 to 34.1 cm^2 as well as intact skin sites were intradermally injected with gene-corrected fibroblasts. All six subjects received a single intradermal treatment session at baseline. Four subjects received a second treatment session in the target wound at 52, 25, 12 and 4 weeks after initial treatment session. *Results:* The primary endpoint was to evaluate safety and treatment was well tolerated through 52 weeks post-administration. Linear C7 expression at the dermal-epidermal junction and restoration of AF and were seen in a subset of treated sites. No treatment emergent serious adverse events or replication competent virus detected and no significant antibody responses to C7 detected. At 4 and 12 weeks, 80% (8/10) of wounds showed significant wound healing as defined by ≥75% wound closure as compared with baseline. At 12 weeks, 50% (5/10) showed complete wound closure and two additional wounds showed almost complete wound closure (≥95% wound closure). This trend continued to later time points of 25 and 52 weeks. In contrast, none of the control wounds achieved complete wound closure at 4, 12 or 25 weeks. Genetically engineered fibroblast injections did not require general anesthesia or inpatient hospitalization. *Conclusions:* These data demonstrate that genetically engineered fibroblast therapy has a favorable safety profile and wound healing efficacy, thus leading to initiation of a Phase 3 trial.

P124
PHASE 1/2A CLINICAL TRIAL OF GENE-CORRECTED AUTOLOGOUS CELL THERAPY FOR RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

E. Gorell[1], S. Eichstadt[1], M. Barriga[1], A. Ponakala[1], C. Teng[1], N. Nguyen[2], Z. Siprashvili[1], J. Nazaroff[1], A. Chiou[1], L .Taylor[1], P. Khuu[1], D. Keene[3], K. Rieger[1], R. Khosla[1], H.P. Lorenz[1], L. Furukawa[1], M.P. Marinkovich[1,4], J.Y. Tang[1]

[1]Stanford University, Stanford, CA, [2]Abeona Therapeutics, Cleveland, OH, [3]Shriner's, Portland, OR, [4]Veterans Affairs Hospital, Palo Alto, CA

Introduction & objectives: Recessive dystrophic epidermolysis bullosa (RDEB) patients have mutations in the COL7A1 gene and thus lack functional type VII collagen (C7) protein; they have marked skin fragility and blistering. This single-center phase 1/2a open-label study evaluated the long-term efficacy, safety, and patient-reported outcomes in RDEB patients treated with gene-corrected autologous cell therapy. *Materials & methods:* Autologous keratinocytes were isolated from participant skin biopsies. Epidermal sheets were prepared from cells transduced with a retrovirus carrying the full-length human COL7A1 gene. These gene-corrected autologous epidermal sheets measured 5x7 cm (35 cm^2) and were transplanted onto 6 wound sites in each of 7 adult participants ($n=42$ sites total) from 2013 to 2017. Participants were followed for up to 5 years. *Results:* No participants experienced any serious related adverse events. Wound healing of 50% or greater by Investigator Global Assessment was present in 95% (36 of 38) of treated wounds versus 0% (0 of 6) of untreated control wounds at 6 months ($p<0.0001$). At year 1, 68% (26 of 38) of treated wounds had 50% or greater healing compared with 17% (1 of 6) of control wounds ($p=0.025$). At year 2, 71% (27 of 38) of treated wounds had 50% or greater healing compared with 17% (1 of 6) of control wounds ($p=0.019$). Evidence of C7 restoration was seen on skin biopsy at 2 years in 2 participants. Prior to treatment, participants reported pain in 53% (20/38) of wound sites. At treated sites with wound healing ≥50%, participants reported pain in 0% (0/26) of sites at 1 year, 4% (1/27) at 2 years, and 0% (0/16) at 3 years. Prior to treatment, itch was present in 61% (23/38) of wounds compared to 19% (5/26) of treated sites at year 1, 7% (2/27) at 2 years, and 0% (0/16) at 3 years. *Conclusions:* C7 expression persisted up to 2 years after treatment. Treated wounds with 50% or greater healing demonstrated improvement in patient-reported pain, itch, and wound durability. This study provides additional data to support the clinically meaningful benefit of treating chronic RDEB wounds with *ex vivo*, C7 gene–corrected autologous cell therapy. This approach was safe and promoted wound healing that was associated with improved patient-reported outcomes.

P125
OLEOGEL-S10 FOR THE TREATMENT OF EPIDERMOLYSIS BULLOSA (EB) – A 4-PATIENT CASE SERIES

Stella Gewert[1], Dimitra Kiritsi[1], Hauke Schumann[1], Agnes Schwieger-Briel[2], Franziska Schauer[1]

[1]Department of Dermatology, Faculty of Medicine, Medical Centre, University of Freiburg, Freiburg, Germany, [2]Deaprtment of Paediatric Dermatoloty, University Children's Hospital Zurich, Zurich, Switzerland

Introduction & objectives: Epidermolysis bullosa (EB) describes a heterogeneous group of chronic skin disorders characterized by fragility of epithelial tissues and repeated development of skin blisters, mucous membranes and nonhealing wounds. No effective pharmacological or genetic therapy exists. Treatment is primarily symptomatic with optimal wound care and protection of the fragile skin. *Materials & methods:* Oleogel-S10, is a preparation from birch bark containing 10% triterpene combined with sunflower oil. Both components have a low potential for allergic sensitization. Oleogel-S10 has activity of three of the classic stages of wound healing: inflammation, proliferation and remodelling. The following four cases with different types of EB were treated using Oleogel-S10 1mm thickness for chronic wounds (>21 day). *Results:* 1. 57 year-old male with dystrophic EB and type 2 diabetes with a chronic scrotal wound for 3 months. The wound was treated twice daily with Oleogel-S10 and foam dressing for 6 days. Wound size decreased from 9.48 cm^2 to 0.65 cm^2 and re-epithelialized within the treatment period. Pain and discomfort improved rapidly. 2. 4 year-old male with EB simplex with upper back and lower abdomen annular, herpetiform blisters, crusted wound, and extensive pruritus. Treatment consisted of antihista-

mine and Oleogel-S10. Blistering, erythema and pruritus improved over 3 months. Once Oleogel-S10 was discontinued (switched to polidocanol or urea ointments), pruritus increased immediately. 3. 3 year-old girl with chronic, junctional EB wounds on body, face, neck and arms. Various secondary complications were evident. Treatment consisted of Oleogel-S10 and foam dressing. After 48 hours, the wound developed epithelium bridges between wound edges, wound size reduced from 13.63 cm^2 to 9.58 cm^2. Wounds treated with dressing alone did not reduce in size. Post discharge (Oleogel-S10 stopped), wound healing deteriorated. 4. 12 year-old girl with permanent, spontaneous and trauma-induced blistering, on extremities and body associated with recessive dystrophic EB. A lateral left ankle wound was treated daily with Oleogel-S10, fatty gauze and foam dressing at home – an intra-individual control wound below the right knee was treated without Oleogel-S10. After 5 weeks, both wounds healed. The wound treated with Oleogel-S10 healed faster; itching and pain persisted at the control site. *Conclusions:* Oleogel-S10 was effective and well tolerated in the treatment of EB wounds in four selected individual EB patients. Dressing requirements were reduced and quality of life improved in these patients during treatment. The phase III EASE study will assess the safety and effectiveness of Oleogel-S10 in EB-related wounds in patients with different types of EB (www.clinicaltrials.gov NCT03068780).

P126
PRESSURE ULCER PREVENTION AWARENESS IN EPIDERMOLYSIS BULLOSA (EB)

Samantha Wharton
Guy's & St Thomas' NHS Foundation Trust

Introduction & objectives: Identifying pressure damage can be challenging especially with patients who have epidermolysis bullosa (EB). This encouraged the development of a patient information leaflet for pressure ulcer prevention for patients with EB to ensure patients and carers are informed and correct management/ treatment is in place in a timely manner. *Materials & methods:* Pressure ulcers are in large preventable harm and ensuring patients, carers and family are informed and known the ways to prevent pressure damage is key. In EB the patients experience wounds that often present as blistering and superficial skin loss. In pressure damage wounds are often presented as blistering and superficial skin loss this then make identifying pressure damage very challenging. The purpose of the patient leaflet is to give information to patients/ carers and family to explain what a pressure ulcer is, causes of pressure damage, help identify pressure damage, common locations and the differences between an EB related wound compared to a pressure related wound. With this information it is hoped that pressure damage will be prevented or if any pressure damage occurs early intervention and treatment can be provided. The leaflet also contains information regarding who to contact if concerned, it is hoped the introduction of the leaflet will start the conversation about pressure ulcers and allow an opportunity to discuss concerns, thus empowering the patients/ carers to take responsibility for their own care. *Results:* A pressure ulcer leaflet was created and shared within the EB multidisciplinary team, adaptations were made as required following the feedback. The leaflet was then given to some patients with EB for comment/ feedback. Following this the leaflet is presently awaiting final sign off before becoming readily available within the EB community. The leaflet will then be given to patients and carers and is hoped will raise awareness of pressure ulcers within this very unique population. *Conclusions:* This patient leaflet is hoped to be a good resource for patients and carers, it will start the conversation to raise awareness of pressure damage and is anticipated patients check their skin and be aware of skin changes over bony prominences.

P127
YASMIN ELSAMRA CHARITY FOUNDATION FOR EB IN EGYPT

Hanaa Elsadat
Yasmin ElSamra EB Foundation

Introduction & objectives: Establishing a charity foundation since 2014 under the name of my daughter Yasmin Elsamra (1997-2012) born with RDEB to help EB patients (120) in Egypt who are referred to me by dermatologists. *Results:* Epidermolysis Bullosa (EB) is a genetic condition that causes the skin to be fragile, blistering easily. Blisters and skin erosions form in response to minor injuries or frictions. Mutations in the COL7A1 gene cause all three major forms of dystrophic EB. It is a rare skin disease with no cure. EB is always painful, often pervasive, debilitating and in some cases lethal before the age of 30. My name is Hanaa ElSadat mother of Yasmin ElSamra, born with RDEB (1997-2012). Yasmin tried to lead a normal life, despite her disease. At the age of 5, we discovered her talent in drawing, and encouraged her first drawing exhibition at the age of 9. She spread awareness about EB through three exhibitions during her short lifetime and was known as the youngest Egyptian artist. She donated revenues from her paintings to governmental hospitals for research. When she passed away, I established a charity foundation under her name for EB patients in Egypt, to spread awareness, provide medications, pay for hand and teeth surgeries, blood transfusions and to recommend qualified doctors in different fields who are able to deal with EB cases. EB is not covered by any medical insurance. Starting with 10 cases in 2014, today I have 120 of all genders, ages 0-35, including some cases from different Arab Countries. EB patients are referred to me through dermatologists that trust that I can advise and teach mothers how to handle their children, as well as, offer them all medical needs. Based on my experience as a mother of EB Yasmin, I had the feeling that their pain was different from the pain we feel. It is their mind and the way people perceive them because of their appearance and disability when they integrate in Society. I addressed this in through good nutritional advice and psychologically, through drawing, crafting, story writing, dancing and participating in charity bazaars, drawing competitions and encouraging them to handle small businesses, to earn their own money and feel that they have the right to live happily. Conclusion, I see their wounds and blisters decreasing, as they spread awareness about their illness with pride, while their lifestyle changes for the better. Feeling happy when I relieve their pain and see the smiles on their faces, giving them hope that one day there will be a cure. Yasmin's mission and her foundation will always leave a lasting legacy. *Conclusions:* Advising them with good nutrition and psychological way,I see their wounds and blisters are healing better with care and love. They also feel proud making awareness about EB with pride and self confidence to people and media.

P128
HETEROGENEOUS ADDICTION TO TGFB SIGNALLING IN LIFE THREATENING CUTANEOUS SQUAMOUS CELL CARCINOMAS ARISING IN RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Jasbani H.S. Dayal[1,2], Susan Mason[1], Julio C. Salas-Alanis[3], John A McGrath[4], Richard Tylor[2], Karen Blyth[1,5], Andrew P South[6], Gareth J. Inman[1,2,5]
CRUK Beatson Institute[1],University of Dundee[2],Universidad de Monterrey[3] ,King's College London[4], University of Glasgow[5], Thomas Jefferson University[6]

Introduction & objectives: Recessive dystrophic epidermolysis bullosa (RDEB) is a debilitating skin blistering disorder characteri-

sed by the onset of aggressive cutaneous squamous cell carcinomas (cSCC) that frequently metastasise resulting in a high mortality rate (cumulative risk of ~90% by the age of 55). Transforming Growth Factor β (TGFβ) signalling is elevated in RDEB cSCC but it is not known whether TGFβ functions as a tumour suppressor or promoter in these patients. Here we investigate the use of TGFβ signalling for therapeutic intervention in RDEB cSCC. Investigate the potential application of inhibiting TGFβ signalling for therapeutic intervention in RDEB cSCC patients *Materials & methods:* Primary keratinocytes were isolated from RDEB cSCC patient tissue and used in a range of invitro assays following treatments with TGFβ1 and its type 1 receptor (TGFBR1) kinase inhibitors, SB-431542 and AZAO1 (AZ12601011, AstraZeneca). In vitro findings were confirmed using in-vivo subcutaneous xenografts. RNA sequencing was performed using the Illumina platform to understand the mechanism underlying the specific TGFBR1 kinase inhibitor responses in RDEB cSCC primary keratinocytes. *Results:* Proliferation, clonogenic potential, migration and invasion of 63% of RDEB cSCCKs ($n=7/11$) was inhibited upon inhibition of endogenous TGFβ signalling. However, inhibition of TGFBR1 kinase activity was also able to promote ($n=2/11$) or have no effect ($n=2/11$) on proliferation and clonogenicity of RDEB cSCCKs. In-vivo experiments confirmed our in-vitro findings where overall survival of SCID mice subcutaneously injected with cells, inhibited in in-vitro assays, was significantly enhanced ($p=0.01$, Kaplan Meir) following pre-treatment with SB-431542 compared to vehicle control. Tumour volume was also significantly lower 5 weeks post injection ($p=0.03$, Mann-Whitney) in the same mice. Cells promoted by SB-431542 in in-vitro assays did not respond to pre-treatment with SB-431542 *in vivo*. RNA sequencing analysis of a promoted (RDEB2 cSCCK) and two inhibited cell lines (RDEB62/70 cSCCK) showed significant differences in gene expression following treatment with SB-431542. Ongoing validation of candidate genes will help identify key downstream biomarkers and shed light on the potential role of TGFβ signalling in RDEB cSCC. *Conclusions:* Inhibiting TGFBR1 signalling has potential therapeutic benefits for only a subset of RDEB cSCC patients as they exhibit heterogeneity in their response to treatment with TGFBR1 kinase inhibitors. Clinical use of TGFBR1 inhibitors should proceed with caution due to the potential tumour suppressing benefits of TGFβ signalling in a subset of RDEB cSCC patients

P129
GENOMIC ALTERATIONS IN CUTANEOUS SQUAMOUS CELL CARCINOMA OF RDEB PATIENTS

Hélène Ragot[1], Matthias Titeux[1], Claire Barbieux[1], Sonia Gaucher[1,2], Sylvain Hanein[3], Rose Boudan[4], Emmanuelle Bourrat[4], Alain Hovnanian[1,2,5]

[1]Imagine Institute, Laboratory of genetic skin diseases, INSERM UMR [1163], F-[75]0[15], Paris, France , [2]Université de Paris, Paris, France , [3]Imagine Institute, Translational Genetics Platform , INSERM UMR [1163], F-[75]0[15], Paris, France [4]Reference Centre for Genodermatoses ("Maladies Génétiques à Expression Cutanée", MAGEC), Saint-Louis Hospital, Paris France, [5]Department of Genetics, Necker-Enfants Malades Hospital, Paris, France

Introduction & objectives: Recessive dystrophic epidermolysis bullosa (RDEB) is a severe hereditary skin disease caused by mutations in COL7A1 encoding type VII collagen. Patients with RDEB display skin and mucosa fragility leading to blister formation and erosions resulting in local and systemic complications. The most severe complication in RDEB patients is the development of aggressive cutaneous squamous cell carcinoma (cSCC) leading to premature mortality. The aim of our study is to characterize the genomic alterations in cSCC occurring in RDEB patients, and notably by distinguishing the clinical outcome of the patients. *Materials & methods:* To investigate the mechanisms involved in skin carcinogenesis in RDEB patients, we searched for pathogenic variants in 383 epithelial cancer-related genes using a next-generation sequencing (NGS) custom panel. Panel sequencing was applied to both tumoral and non-tumoral skin biopsies from each patient to exclude germline alterations or variant calling. Driver mutation search was performed with the in-house developed Polyquery software and mutational signatures were identified using the DeconstructSig R-package. *Results:* Genomic analyses were performed on 16 cSCC from 9 RDEB patients (4 men and 5 women). Patients' age ranged from 18 to 52 years old (average age 32 years). Two patients died from an aggressive and metastatic cSCC, whereas 7 patients developed one or several cSCC without metastasis and are still alive. We identified mutational signatures related to ultraviolet alterations (signature 7) and APOBEC (signature 2) as previously reported. We also identified 57 genes with recurrent deleterious mutations as well as copy number variants of cancer associated genes. Mutated genes were in particular involved in pathways related to cell cycle, immune system, gene expression transcription, and serine/threonine kinase. We also found 39 additional mutated genes specifically in the tumors of the two patients who died from metastatic sSCC. Some of these mutations may impact signaling pathways related to the epithelial-mesenchymal transition process. *Conclusions:* Taken together, the NGS approach based on 383 targeted cancer-related genes in cSCC of RDEB patients identified various molecular alterations, some of which appear to be associated with tumor aggressiveness, which can expand our understanding of the pathogenesis of SCC in RDEB.

P130
TREATMENT OF EPIDERMOLYSIS BULLOSA PRURIGINOSA-ASSOCIATED PRURITUS WITH DUPILUMAB

Waseem Shehadeh[1], Ofer Sarig[1], Jonathan Bar[1], Eli Sprecher[1,2], Liat Samuelov[1]

[1]Division of Dermatology, Tel-Aviv Sourasky Medical Center, [2]Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv, Israel

Introduction & objectives: Epidermolysis bullosa pruriginosa (EBP) is a rare subtype of autosomal dominant (or less commonly recessive) dystrophic epidermolysis bullosa (DEB) caused by heterozygous or biallelic mutations in the gene COL7A1 encoding collagen VII. In addition to usual manifestations of DEB (trauma-induced skin fragility, milia, nail dystrophy), EBP features severe pruritus, prurigo nodularis (PN) and lichen simplex chronicus-like lesions. The pathomechanisms underlying the clinical manifestations unique to EBP are not fully understood. Dupilumab is a fully humanized monoclonal antibody targeting the interleukin (IL)-4 receptor alpha (IL-4Rα), a receptor subunit shared by two type 2 cytokines: IL-4 and IL-13, which play an important role in the pathogenesis of atopic dermatitis (AD). Besides being an effective treatment for AD, dupilumab has been shown to be effective for the treatment of generalized pruritus and PN, suggesting that it may possibly benefit patients with EBP. *Materials & methods:* Here we report a case of EBP successfully treated with dupilumab. *Results:* An otherwise healthy 52-year-old female presented with a history of blisters and erosions since birth associated with extremely pruritic erythematous lichenified papules and plaques covered with scales, crusts and milia involving the scalp, ears and shins. Anonychia was present since early childhood. Laboratory workup revealed mild eosinophilia and mildly elevated IgE levels. Genetic testing identified two heterozygous mutations in the COL7A1 gene establishing the diagnosis of EBP. The patient complained about persistent itch interfering with all daily functions. No significant improvement was evident with many topical and systemic therapies. She was administered a 600 mg loading dose of dupilumab followed by 300 mg every two weeks. Patient

evaluation at 4 weeks and 12 weeks of treatment revealed significant improvement in pruritus and quality of life using a visual analogue scale (VAS) for pruritus and a standard DLQI scores. Her skin exam revealed marked improvement at 4-weeks follow up with progressive improvement noticed at 12 weeks with flattening of plaques and significant improvement in redness, scales, crusts and lichenification. The Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) also revealed a slight improvement at 12 weeks of treatment. *Conclusions:* The disabling pruritus associated with EBP (and DEB) has been attributed to immune dysregulation. The rapid and significant clinical improvement in the presented case suggests that EBP is driven by Th2-immune mechanisms. Larger and controlled studies are needed to confirm the therapeutic potential of dupilumab in EBP.

P131
KINDLER SYNDROME WITH ORAL, INTESTINAL DAN UROLOGY INVOLVEMENTS

Suci Widhiati[1], Willa Damayanti[1], Wibisono[2], Indah Julianto[1], Tri Wibawa[2,3] Dewajani Purnomosari[2,3], Hardyanto Soebono[2,3]
[1]Department Dermatology and Venereology Faculty of Medicine Universitas Sebelas Maret, Surakarta/Dr. Moewardi General Hospital, [2]Departement Urology Faculty of Medicine Universitas Sebelas Maret/Dr. Moewardi Hospital, Surakarta, [3]Faculty of Medicine Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta

Introduction & objectives: Kindler syndrome (KS) is an autosomal recessive disorder characterized by blisters, atrophy, photosensitivity, colon inflammation, and mucous involvement. Kindler syndrome is a part of epidermolysis bullosa, a spectrum of mechano-bullous disorder with a broad range of clinical variations. The multiple mucous involvements in KS have been reported in many case studies. However, in Indonesia, our case is the first one to be reported, a KS with oral ulcer inguinal hernia, meatal and urethral stenosis affecting a 10-year old boy. *Materials & methods:* A 10-years old boy came with urine retention and pain during urination; these conditions developed for about three days before hospital admission. There are blackish patches on his dry skin. He also suffered from recurrent sore mouth and pain in swallowing. He had been suffering from intermittent blisters since he was two years old but completely healed when he was seven years old. He also had an inguinal hernia and was removed last year. He was born aterm with normal delivery, somehow his skin was scaled, two days later, blister containing reddish fluid appeared on his left calf. Both parents are not consanguineous. *Results:* Dermatological examination revealed poikiloderma on his face, neck and legs, xeroderma, and "cigarette paper" skin atrophy on hands and feet. Oral examination showed calculus teeth and buccal ulcers. Uretrography demonstrated urethral external occlusion suspected for urethral and meatal stenosis. Biopsy with hematoxylin-eosin suggested for Kindler's syndrome, which was supported by clinical matrix diagnostic tool. Meatotomy and urethrotomy were performed, and his urinating problems improved two months later. After one year of surgery, there was no urinating problem. Oral and dental problems were managed with scalling and keeping good oral hygiene. His skin was treated with topical emollient and sunscreen SPF30. His skin was no longer dry. *Conclusions:* In our case, the definitive diagnosis of KS was established with clinical matrix diagnostic tool since we do not have immunofluorescence examination and genotyping as the standard diagnostic tool for KS. Therefore, in the limited resources setting, clinical matrix diagnostic tool can be considered as a reliable supporting diagnostic tool. KS can manifest in many organs, leading to comprehensive treatment involving various disciplines, in our case, we managed the patient together with surgery and oro-dental department.

P132
DYSTROPHIC DOMINANT EPIDERMOLYSIS BULLOSA WITH ALBOPAPULOID LESIONS - WITH RARE DE-NOVO G2064R MUTATION

Pankhuri Dudani, Neetu Bhari
All India institute of Medical Sciences, Delhi, India

Results: We are describing a case report of a 10 year old male Indian child with history of transient bullous lesions over extremities since 1 year of age which healed with hyperpigmentation and atrophy (no milia). At 4 years of age he started developing spontaneous hypopigmented atrophic scars which progressed proximally over bilateral legs, thighs and waistband area of trunk. There was no family history. On examination, we noted multiple irregular erosions in various phases of healing, ranging from 0.5 to 3 cm diameter, especially around the ankle joints. These healed with hyperpigmentation and atrophy, with conspicuous absence of milia. There were multiple atrophic hypopigmented scars over bilateral feet, legs, Thighs and lower abdomen, with few over mid upper back, consistent with the albopapuloid lesions described in the Pasini variant of the disease. There were two small vesicles over one leg, which had not been noticed by the patient. The oral cavity and other mucosae were uninvolved. Histopathological examination of the vesicle as well as the albopapuloid lesions revealed a subepidermal cleft with minimal infiltrate and papillary dermal sclerosis. Genetic analysis showed a mutation in the COL7A1 gene, G2064R, which has been reported only twice in the past- and once reported associated with the albopapuloid variant. There is an ongoing debate on whether this phenotypic variant is related to a particular genotype, and it has been reported with Gly-Arg substitutions in two different loci. This is the first report of this mutation in the indian context, and third overall. This mutation may be associated with a milder variant of the disease, as seen in the previous two reports.

P133
DRY EYE DISEASE IDENTIFIED IN A PROSPECTIVE STUDY OF OCULAR INVOLVEMENT IN EPIDERMOLYSIS BULLOSA AND AUTOIMMUNE BLISTERING DISEASES

Brendon W.H. Lee[1,2,3], Jeremy Tan[2], Melissa Radjenovic[3], Lien Tat[2], Minas T. Coroneo[1,2], Dedee F. Murrell[1,3]
[1]Faculty of Medicine, University of New South Wales, Sydney, Australia [2]Department of Ophthalmology, Prince of Wales Hospital, Sydney, Australia [3]Department of Dermatology, St George Hospital, Sydney, Australia

Introduction & objectives: Inherited Epidermolysis Bullosa (EB) and Autoimmune Blistering Diseases (AIBD) are a heterogeneous group of chronic blistering dermatoses that are associated with mucocutaneous lesions involving the ocular surface. This is the first study in EB and second in AIBD to prospectively examine the range and severity of ocular manifestations in an Australasian cohort. *Materials & methods:* Prospective, cross-sectional, observational study of 61 patients with diagnoses confirmed by histopathology were recruited from a Dermatology subspecialty centre and the Australasian registries of EB and AIBD. Participants underwent a comprehensive ophthalmic examination according to a standardised protocol, including an Ocular Surface Disease Index questionnaire, slit lamp, and tear-film examination. *Results:* 122 eyes of 61 patients (female = 54.1%), aged 2-88, were examined. Fifty-seven patients (93.4%) exhibited one or more symptoms of Dry Eye Disease. The mean Ocular Surface Disease Index score was 13.63 (range = 0-100) with 24.6% of patients graded moderate-severe (23+/100). Best-corrected visual acuity was 20/60 in 57.4%, with 42.6% achieving 20/20. Slit lamp examination demonstrated blepharitis (50.8%, $n = 62$), conjunctival/corneal scarring (20.5%,

$n=25$), limbal broadening (17.2%), symblepharon (8.2%, $n=10$), trichiasis (5.7%, $n=7$), and ectropion/entropion (3.3%, $n=4$). Tear film dysfunction was substantial; 95.1% of patients tested had a reduced tear break-up time and 92.4% had an abnormal Schirmer's test. Furthermore, 57.9% exhibited significant corneal staining and 59.4% had elevated tear osmolarity (>308mOsm/l). *Conclusions:* A novel finding of Dry Eye Disease was found in EB on patient-reported symptoms, Ocular Surface Disease Index score, and objective assessment. Given EB manifests at birth or early age, paediatric dermatologists should be aware of the potential of ocular manifestations and their negative effect on quality of life, risk of scarring, and subsequent visual impairment. Referral for ophthalmological evaluation should be an integral part of the multidisciplinary management of EB.

P134
IVF FOR PARENTS OF EB PATIENTS

J. Kotalevskaya, T. Volgunova, E. Pomerantseva, A. Isaev, S. Zhikrivetskaya, I. Kotov, Y. Kozlova, E. Musatove, Yu. Grigorieva, V. Kaimonov, V. Gnetetskaya
Genetico®, DEBRA Russia

Introduction & objectives: IVF for parents of EB patients - is a pilot project implemented with the organizational and financial support of DEBRA Russia with the participation of a Genetic Research Laboratory and a Mother and Child Clinic. The aim of the project is to give an opportunity to couples having children with dystrophic epidermolysis bullosa and a high risk of having a sick child again, to give birth to a healthy baby without a genetic mutation. We had two missions: Mission 1 - the birth of a healthy child without a genetic mutation in couples - carriers of the genetic mutation EB. Mission 2 - to give a woman who already has a child with DEB, hope and a chance for happiness - to know the world of another motherhood. IVF for parents of EB patients project was initiated and implemented by DEBRA Russia for those families who cannot receive such a service in standard state medical institutions. This is an experimental study for Russia in the field of epidermolysis bullosa and a unique opportunity for couples who have already children with EB to come their dream true. *Materials & methods:* In the case of a sick child in a family with DEB, the repeated risk of having a sick child is 25% for each pregnancy, which is a high risk. For such families, the question of using an IVF procedure with the selection of an embryo without a genetic mutation for the birth of a healthy child may be considered. Of course, he IVF procedure itself does not guarantee the birth of a healthy child in the event of a genetic disease in the family. In this case, IVF is a tool with which you can get a certain number of embryos available for genetic analysis and determination of their genotypes (preimplantation genetic diagnosis), which means that we can choose an embryo "free" from a pathogenic mutation before transferring to the body of a woman. Thus guaranteeing the birth of a child without DEB. For IVF with preimplantation genetic diagnosis (PGD), it is mandatory to conduct a comprehensive genetic screening of the family in order to determine the specific causative mutations in the family and determine their parenthood. The next important preparatory stage is the development of an often individual genetic test system for examining an embryo in a particular family. Next is the *in vitro* fertilization procedure. The next is the cultivation of an embryo, which usually lasts up to 5 days and the transfer of 1-2 embryos into the uterine cavity of a woman and pregnancy is expected. But if genetic diagnosis of embryos is necessary, embryo transfer is delayed until their genotype is clarified. Usually, on the 3rd day, a so-called "embryo biopsy" is performed to obtain and analyze its DNA. This procedure does not have any consequences for the embryo! Since the genetic diagnosis of DEB is not a quick procedure, the embryo is frozen (cryopreservation) until its genetic status is clarified. *Results:* The project was launched on April 20, 2018. However, it took 1.5 years before embarking on the project to resolve all legal and bureaucratic issues. 2 families from different cities were selected to participate in the project, taking into account the necessary criteria. Both women are mothers of children with severe recessive dystrophic form of EB. Then, the families underwent a preliminary comprehensive genetic examination to determine specific causative mutations in this family and determine their parenthood. The next important preparatory stage was the development of an individual genetic test system for examining an embryo in a particular family. Next is obtaining a quota and implementing a long stage of conducting comprehensive measures to prepare a woman's body for replanting and giving birth to a child. The first patient underwent long-term treatment before the IVF procedure, in connection with which the quota was received only in July 2019. On November the patient will undergo IVF with PGD, the results of which will be known at the end of November 2019. A second patient, having passed a series of examinations and all stages of the project, received a quota for IVF in early December 2018. On December 27, 2018, she underwent the IVF procedure, and on September 14, 2019, the patient gave birth to a healthy girl! *Conclusions:* This is the project about unlimited courage. The courage to take a step and take risks without confidence in the result. The courage to accept that a mistake may occur and a child with EB will be born. Courage to pay sufficient attention to both a newborn and a sick child with EB who needs a special approach and a lot of time. The courage to go forward, despite the misunderstanding from society. The courage to allow yourself to dream about another motherhood. The courage to just dream. This is a project about love ... about love for children. This is the project about life.

P135
DEVELOPING EVIDENCE-BASED INFOGRAPHICS FOR EPIDERMOLYSIS BULLOSA CARE IN LOW-RESOURCE SETTINGS

Kattya M. Mayre-Chilton[1,2], Lie A. Taguchi[1,3], Lea Prujean[4], Olivia Mullins[1]
[1]DEBRA International, Vienna, Austria, [2]Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK, [3]DEBRA Brasil, Santa Catarina, Brazil, [4]DEBRA New Zealand, Wellington, New Zealand

Introduction & objectives: Epidermolysis bullosa (EB) is a rare condition affecting the skin and various body parts with little clinical guidance for daily care in low-resource settings (LRS). The DEBRA International EB Without Borders (EBWB) team initiated a programme to develop EB infographics for LRS to help EB patients, their families, and doctors in countries without a DEBRA group. EBWB is not alone in striving to bring evidence into practice in LRS. The World Health Organisation recognises that the evidence/practice mismatch in developing countries burdens LRS health systems. The challenge of putting evidence into practice is exacerbated in rare conditions such as EB in LRS. The objectives were for infographics, linked to clinical practice guidelines (CPGs), to present evidence in a clear and simple way with considerations for LRS alternatives. *Materials & methods:* Using the "Plan, Do, Study, Act cycles1" approach, "The Health Body and Skin: EB Infographics" were developed in English and Portuguese with supporting evidence from 3 published CPGs and EB experts' experiences in LRS. Advice and reviews were obtained from a multidisciplinary team of 8 international EB experts (UK, India, New Zealand, Austria, Australia, Spain) including 2 nursing teams (Spain, UK). From June 2019, the English draft was piloted for 3 months in India, New Zealand, Brazil, Chile, and Columbia across a total of 7 clinical sites. From July 2019, the Portuguese EB infographics were piloted for 3 months in 1 clinical site in Brazil; out of 23 healthcare professionals approached, only 2 accepted. All pilot sites were given the same instructions and feedback was collected using surveys. *Results:* 3 sites found using infographics

in their mother-tongue appropriate (2 in English; 1 in Portuguese). Other languages requested included Spanish and Hindi. Only 1 (1%) EB patient from India, out of 93, reported blisters resulting from the saline bath, baths were summarily stopped. This was due to language misunderstanding. Feedback on baths ranged from confusing, inaccuracies, and fear of use to mainly liking them and very useful. *Conclusions:* LRS are challenged by numerous languages, cultures, and beliefs. The evidence suggests further translation of infographics be considered. Our next steps are to collate direct EB Community feedback in English, Portuguese, and Spanish over 1 month to finalise the EB infographics for implementation in 2020.

Table 1. Demographics of the EB subtypes accessing the pilot sites and those who were given the "The Health Body and Skin: EB Infographics" (*n* = 93/160; 58%)

Language	English		Portuguese	
	N°of EB patients seen	N° given the EB Infographics	N°of EB patients seen	N° given the EB Infographics
EBS	40	19	1	1
JEB	18	8		
KS	4	4		
DDEB	24	14		
RDEB	63	40	4	4
Other	6	3		
Total	**155**	**88**	**5**	**5**

P136
EFFICACY OF ATRAUMATIC SOFT SILICONE TRANSFER FOAM DRESSINGS IN EPIDERMOLYSIS BULLOSA: CASE SERIES

Mendes, Luciana[1], Pinheiro, Suyanne[2], Duque, Carla[3], Carmen, Mirelly[4]

[1]WOCN Nurse, Sales Manager, [2]WOCN Nurse, Sales Representative, [3]WOCN Nurse, Sales Representative, [4]WOCN Nurse, Sales Representative, Cobermed® Brazil, [1,2,3]Mölnlycke® Health Care Brazil

Introduction & objectives: Bullous epidermolysis (EB) is defined as a rare, hereditary dermatosis that includes a group of diseases characterized by the tendency to produce vesicles in the skin and sometimes in the mucous membranes. There are four main groups that are subdivided according to inheritance pattern, lesion morphology, involvement distribution, cleavage level, and involved mutation. Due to the complexity of treating these lesions and the need to prevent complications, patients were treated with atraumatic soft silicone dressings and outcomes recorded on follow up. Objective: Evaluate the effectiveness of soft silicone transfer foam dressings in treating patients with epidermolysis bullosa. *Materials & methods:* Case series, descriptive study. Reporting three Epidermolysis Bullosa cases treated in Brazil in 2019, in different periods of the year. All the patients used soft silicone transfer foam dressings to treat wounds and skin lesions. Home follow-up forms and photographs of the lesions were used to evaluate the efficacy of the dressing. *Results:* Case 01: IAS, Female, 2 years old, dystrophic bullous epidermolysis, presenting lesions in the right and left lower limbs. Foul smelling odour. She had used silicone gel absorbent foam and hydrofiber dressings without a positive response. During follow-up, the lesions were cleansed with 0.9% saline solution, followed by application of a soft silicone transfer foam cover and bidirectional tubular mesh. Dressings were changed every 2 days, resulting in an improvement of the healing process. Case 02: A.T.S.,2 Years, female, Aplasia Congenital Cutis and Epidermolysis Bullosa since birth. There was absence of skin on legs and blisters in other regions of the body: hands, neck, elbows and buttocks. Dressings were used every 48 hours after an immersion bath. The use of soft silicone transfer foam was started as primary cover of the areas without skin and blisters and an absorbent dressing as secondary cover, remaining occluded for 5 days. Cases 03: R.C.P, 39 years old, female, EBDR diagnosed with carcinoma, with right lower limb lesion. The lesion presented a bed with a large amount of serous exudate, adhered necrosis and a fetid odor. On 03-06-19, the lesion was debrided and subsequently treatment with silver sulfate and soft silicone exudate transfer foam was applied. Dressing change was performed every 2 days, for a period of 2 months. *Conclusions:* These cases suggest that soft silicone transfer foam use is effective and safe for the treatment of patients with epidermolysis bullosa, considerably improving the exposed area of the lesions and is effective in promoting healing without trauma or pain and maintains the integrity of the injury edge.

P137
BIALLELIC JUP MUTATION IN FAMILIES WITH ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY AND SKIN FRAGILITY IN THE FORM OF EPIDERMOLYSIS BULLOSA SIMPLEX: NAXOS DISEASE

Hannah Mumber, Bs[1,2,14,#]; Anjali Rajan[1,2,15,#]; Hasssan Vahidnezhad, PhD[1,2,3], Leila Youssefian, MSc[1,2,4,5], M. Faghankhani, MD[1,2], Nikoo Mozafari, MD[6], Amir Hossein Saeidian, MSc[1,2,4], Fatemeh Niaziorimi, MSc[1,2], Fahimeh. Abdollahimajd, MD[6], Soheila Sotoudeh, MD[7], F. Rajabi, MD[6], Z. Liaosadat Mirsafaei, MD[8], Alizadeh-Sani[9], Lu Liu, PhD[10], Alyson Guy, MSc[10], Sirous Zeinali, PhD[3,11], Ariana Kariminejad, MD[12], John A. McGrath, MD, FRCP, FMedSci[13], Jouni Uitto, MD, PhD[1,2]. [#]Both authors contributed equally to this work

[1]Jefferson Institute of Molecular Medicine, Thomas Jefferson University, USA, [2]Department of Dermatology and Cutaneous Biology, Thomas Jefferson University, USA, [3]Pasteur Institute of Iran, Iran, [5]Tehran University of Medical Sciences, Iran, [6]Shahid Beheshti University of Medical Sciences, Iran, [7]Children's Medical Center,Tehran University of Medical Sciences, Iran, [8]Mazandaran University of Medical Sciences, Iran [9]Rajaei Cardiovascular Medical and Research Center Iran, [10]Viapath, St Thomas' Hospital, UK, [11]Kawsar Human Genetics Research Center, Iran, [12]Kariminejad-Najmabadi Pathology & Genetics Center, Iran, [13]St John's Institute of Dermatology, King's College, UK, [14] Boston University School of Medicine, USA[15] New York University College of Global Public Health, USA

Introduction & objectives: Naxos disease (NXD) presents with arrhythmogenic right ventricular cardiomyopathy (ARVC) along with skin abnormalities including skin fragility in the form of epidermolysis bullosa simplex (EBS), palmoplantar keratoderma, and woolly hair. It has been previously associated with biallelic loss-of-function mutations in JUP. Genotype-phenotype correlations regarding disease penetrance, age of onset, and variable expression in NXD has not been completely established. *Materials & methods:* We examined a large cohort of 362 families with epidermolysis bullosa (EB) syndromes for underlying genetic mutations with a targeted next-generation sequencing panel as well as with whole-transcriptome and exome sequencing. The consequences of the mutation were determined by expression profiling at both tissue and ultrastructural levels. *Results:* In two unrelated families presenting with EBS, a previously unreported biallelic homozygous mutation in JUP:c.201delC;p.S68Afs*92 was disclosed within 10.7 Mb of a region of homozygosity. Whole-transcriptome sequencing by RNA-Seq revealed JUP as the highly down-regulated gene among the 21 EB-related genes in the patient versus controls. Immunofluorescence showed the lack of plakoglobin in the epidermis, and ultrastructure electron microscopy displayed hypoplastic desmosomes. Two probands, a 2.5 year old and a 22-year-old, with the same homozygous mutation allowed us to study the progression of cardiac involvements in relation to age. Neither of them showed any cardiac symptoms or significant family history. The younger patient showed reduced heart rate variability in Holter-monitoring, while the older patient

showed inverted T waves in V1, V2, and V3. Echocardiography displayed mild mitral and tricuspid regurgitation in both patients and pulmonary valve insufficiency in the younger patient. To explore structural changes in early stages of ARVC, cardiac magnetic resonance imaging with and without Gadolinium was conducted in the adult patient. It revealed normal size and function of chambers, including myocardial thickness and wall motion, and no evidence of myocardial fibrosis was seen. Based on 2010 revised task force criteria, the younger patient had one major criteria categorized as possible ARVC diagnosis, and the older patient showed two major criteria categorized as definite diagnosis. *Conclusions:* Thus, we associate a previously unreported biallelic homozygous mutation in JUP in two patients with concomitant cutaneous and cardiac valve involvement with progression towards ARVC.

P138
IMPROVING UNDERSTANDING AND TREATMENT OF EB-RELATED PAIN USING A NOVEL MOUSE MODEL OF DOMINANT DYSTROPHIC EPIDERMOLYSIS BULLOSA

B.R.C. Smith[1,2], P.A.Shenoy[3,4], J.S. Kern[5], N.A. Veldhuis[3,4], K.C. Pang[1,2,6]

[1]Genetics Theme, Murdoch Children's Research Institute, Parkville, VIC, Australia, [2]Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia, [3]Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences (MIPS), Monash University, Parkville, VIC, Australia, [4]ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, MIPS, Monash University, Parkville, VIC, Australia, [5]Royal Melbourne Hospital, Parkville, VIC, [6]Department of Adolescent Medicine, Royal Children's Hospital, Parkville, VIC, Australia

Introduction & objectives: Dystrophic Epidermolysis Bullosa (DEB) is characterized not only by blistering but often severe pain. Despite this pain being a significant clinical problem, its pathogenesis and optimal treatment are poorly understood. We recently used CRISPR technology to establish a novel mouse model of dominant DEB (DDEB). These mice carry a mutation in mouse Col7a1 (ΔG2037R) that directly corresponds to that most commonly responsible for DDEB in patients (ΔG2043R). Like DDEB patients, the mice display mild, dominantly-inherited blistering as well as nail and digit loss over time, reduced COL7A1 protein expression via immunostaining, abnormal anchoring fibrils via electron microscopy, and reduced COL7A1 thermal stability. To better understand and treat DEB-related pain, the aim of this project was to establish the baseline responses of our Col7a1ΔG2037R mice in standardised pain-related behavioural assays and to compare the effectiveness of drugs commonly used to treat EB-related pain. *Materials & methods:* Col7a1ΔG2037R mice and wild-type littermates were compared in the absence of any visible blistering using both the von Frey and Hargreaves assays, which are standardised behavioural pain tests that assess for hypersensitivity to mechanical and heat stimuli respectively. Subsequently, the effectiveness of different analgesics – including a non-steroidal anti-inflammatory drug (Meloxicam) and an opioid (Buprenorphine) – was tested by comparing their ability to normalize the responses of Col7a1ΔG2037R mice in the von Frey assay. *Results:* In the absence of any visible blistering, Col7a1ΔG2037R mice showed significantly increased pain sensitivity to both mechanical and heat stimuli. Importantly, this increased sensitivity directly mirrors what has been observed in recessive DEB patients previously (von Bischhoffshausen et al, Brain, 2017), and provides evidence that our mice are a clinically-relevant model for investigating DEB-related pain. Next, we compared the effectiveness of Meloxicam and Buprenorphine, and observed that at standard clinical doses both drugs were able to only partially normalize the mechanical hypersensitivity of the Col7a1ΔG2037R mice. *Conclusions:* Our novel Col7a1ΔG2037R mouse model, which recapitulates the clinical features of DDEB seen in patients, demonstrates an increased sensitivity to mechanical and thermal stimuli similar to that seen in DEB patients, and can be used to compare the effectiveness of different clinically-relevant analgesic agents. Moving forward, we plan to use this model to better understand the underlying pathophysiology of DEB-related pain and to help develop more effective treatments for EB-related pain.

AUTHORS INDEX (POSTERS – by first author)

P numbers relate to poster number

SPEAKERS - Abstracts of oral presentations

By page number