Retinoic Acid Metabolism Blocking Agents and the Skin: *In Vivo* and *In Vitro* Studies of the Effects on Normal and Diseased Human Epidermis

Elizabeth Pavez Loriè
Sigtuna, Sweden. E-mail: tallmilan@telia.com

Elizabeth Pavez Loriè from the Department of Medical Sciences/Dermatology, Uppsala University Hospital, Sweden defended her thesis on November 20, 2008 at Uppsala University hospital. The opponent was Professor Helena Håkansson from Karolinska Institute, Stockholm, Sweden and the supervisors were Professor Anders Vahlquist, Dr. Hans Törmä and Dr. MD. Marie Virtanen.

I completed my PhD, on the subject of retinoic acid metabolism blocking agents (RAMBAs, e.g. liarozole and talarozole) in normal and diseased skin (i.e. lamellar ichthyosis) and how these substances affect the metabolism of vitamin A in the skin, by defending my thesis on 20 November 2008. Prior to this research, clinical studies had shown that these substances (primarily liarozole) might be used in the treatment of keratinization disorders without causing the severe side-effects seen with the systemic use of retinoids. Very little was known about how these blocking agents affected the complex process of vitamin A regulation in the skin. Furthermore, knowledge of the metabolism of vitamin A, especially the catabolism of the active metabolite retinoic acid (RA) needed to be further explored in order to be able to draw any conclusion on the role of RAMBAs in the skin. For my thesis the effect of two RAMBAs, liarozole and talarozole, was studied *in vivo* (1, 2) and these drugs were compared with retinoids (i.e. RA) (3, 4) *in vitro*. Retinoid-regulated biomarkers and enzymes involved in the metabolism of vitamin A were studied at both gene and protein level, as well as the accumulation of [3H] RA in both organotypic epidermis and monolayer culture of keratinocytes.

In conclusion, this research showed that both liarozole and talarozole have the ability to increase the RA levels in keratinocytes and elicit similar, but not identical, effects to those seen with RA in retinoid-regulated biomarkers and in enzymes involved in vitamin A metabolism. This demonstrates that liarozole and talarozole are promising drugs that might complement retinoid therapy in different skin disorders. However, the results also show that they should be considered as drugs that have their own effects unrelated to RA, which may yield unpredicted clinical and biological effects.

The dissertation opponent was Professor Helen Håkansson from Karolinska Institute, and members of the thesis committee were Professor Håkan Melhus from Uppsala University, Associate Professor Toomas Talme from Karolinska Institute and Associate Professor Maria Norlin from Uppsala University.

Fig. 1. From the left: Hans Törmä *(supervisor)*, Helen Håkansson *(opponent)*, Anders Vahlquist *(supervisor)*, Elizabeth Pavez Loriè *(respondent)*, Toomas Talme and Håkan Melhus *(both members of the thesis committee)*.

List of original publications

1. Pavez Lorie E, Cools M, Borgers M, Wouters L, Shroot B, Hagforsen E, et al. Topical treatment with CYP26 inhibitor talarozole (R115866) dose dependently alters the expression of retinoid-regulated genes in normal human epidermis. Br J Dermatol 2009; 160: 26–36.
2. Pavez Lorie E, Ganemo A, Borgers M, Wouters L, Blockhuys S, van de Plassche L, et al. Expression of retinoid-regulated genes in lamellar ichthyosis vs. healthy control epidermis: changes after oral treatment with liarozole. Acta Derm Venereol 2009; 89: 12–20.
3. Pavez Loriè E, Chamcheu J C, Vahlquist A, Törmä H. Both all-trans retinoic acid and cytochrome P450 (CYP26) inhibitors affect the expression of vitamin A metabolizing enzymes and retinoid biomarkers in organotypic epidermis. Arch Dermatol Res (in press).
4. Pavez Lorie E, Li H, Vahlquist A, Torma H. The involvement of cytochrome p450 (CYP) 26 in the retinoic acid metabolism of human epidermal keratinocytes. Biochim Biophys Acta 2009; 1791: 220–228.