# Targeted Therapy Possibilities for Metastatic Melanoma

**Janne Kallio**
*Department of Dermatology, University of Turku and Turku University Hospital, MediCity Research Laboratory, University of Turku, Finland. E-mail: janne.kallio@utu.fi*

**Janne Kallio defended his PhD thesis in Turku (Åbo) on December 10th 2010. The thesis was supervised by Professor Veli-Matti Kähäri, Department of Dermatology, University of Turku, Finland. The opponent was Professor Jorma Keski-Oja, University of Helsinki, Finland. This thesis can be found at: http://www.doria.fi/handle/10024/66260.**

The incidence of malignant melanoma of the skin has been steadily rising worldwide during the past decades. Most early detected primary tumors can be removed surgically and the prognosis is good. However, at the same time there still is no permanent cure for metastatic melanoma and its prognosis is poor, although lately new effective drugs have emerged.

In this thesis, four different approaches of experimental therapy for metastatic melanoma were studied. Endogenous *cis*-urocanic acid (UCA) is found in every individual's skin, where exposure to UV light from the sun generates it from its inactive *trans*-conformation. *Cis*-UCA was found to destroy malignant melanoma cells in culture under an acidified pH and sufficient concentration through caspase-3 mediated apoptosis. Furthermore, *cis*-UCA is able to considerably diminish the growth rate of human melanoma tumors on living severe combined immunodeficiency (SCID) mice.

Using replication-competent Semliki Forest viruses, human melanoma tumors grown in SCID mice were dramatically shrunken as the fulminant production of viruses in melanoma cells leads them to apoptosis within 72 h. In another set of experiments, small oligopeptides attaching to melanoma cells were identified using *in vivo* phage display. The melanoma-specific peptides found were further tested *in vitro* on adenoviruses. Ultimately, the adenoviral retargeting using the peptides was tested *in vivo*. One peptide homed to human transferrin receptor, upregulated on melanoma cells.

In order to kill the malignant melanoma cells with the retargeted adenoviruses, the viruses should carry genetic material producing apoptotic proteins in the cancer tissue. TIMP-3 has been identified as a good candidate for such a protein, as it inhibits malignant cell adhesion as well as promotes apoptosis through the caspase-8 pathway. It is further shown that adenovirally delivered TIMP-3 is even more potent, as it could kill non-adherent cancer cells, lacking the fully functional death receptor signaling pathway. Adenovirally delivered TIMP-2 also showed marked antitumor effects in human malignant melanoma xenografts on SCID mice, both in *ex vivo* and systemic delivery.

*Fig. 1.* Janne Kallio (*middle*) defended his PhD thesis in Turku, Finland on December 2010. Opponent was Jorma Keski-Oja (*right*) and Veli-Matti Kähäri (*left*) acted as a custos.