Developing LK 514, a MC1R-Selective Tripeptide Analog of α-Melanocyte Stimulating Hormone, in a Topical Application for Increasing Pigmentation of Human Skin

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Introduction: Skin pigmentation and DNA repair are major photoprotective mechanisms against sun-induced melanoma. The melanocortin 1 receptor gene (*MC1R*) is a principal regulator of skin pigmentation and the diversity of human pigmentation. This gene codes for a G_s protein-coupled receptor expressed on the cell surface of melanocytes. In human melanocytes, activation of MC1R by its agonist α-melanocyte stimulating hormone (α-MSH) stimulates the synthesis of eumelanin, the photoprotective form of the pigment melanin, and enhances repair of UV-induced DNA damage. For melanoma chemoprevention, the Abdel-Malek laboratory is targeting the MC1R with small highly selective analogs of α-MSH. Some tetra- and tripeptide analogs were highly effective in mimicking the effects of the physiological α-MSH on primary cultures of human melanocytes and cultured human skin substitutes. About 60% of all whites are heterozygous for a *MC1R* allele, which reduces pigmentation and DNA repair capacity, and increases melanoma risk. This high-risk population should benefit from these α-MSH analogs.

Hypothesis: Topical application of the tripeptide LK 514 to human skin will stimulate pigmentation, in the absence of any exposure to ultraviolet radiation (i.e. “sunless tanning”).

Methods: Fresh human skin from surgical discards was maintained in culture at the air-liquid interphase, with daily change of culture medium. Ten-mm punch biopsies were obtained from the skin, tape-stripped, and 4 were included in each untreated, vehicle treated, and analog treated groups. LK 514 at a concentration of 20 mM in a vehicle consisting of 70% propylene glycol, 10% transcutol, and 10% ethanol, was applied daily to the appropriate group. After 8 days of treatment, change in pigmentation was measured using a Mexameter, and the skin samples were fixed in formalin, embedded in paraffin. Thin sections were stained with hematoxylin-eosin, and with Fontana-Masson for melanin. Light microscopic photographs were obtained, and Fontana-Masson stain was quantified using Image J.

Results: Preliminary data suggest that topical treatment of human skin with LK 514 increases pigmentation, evident as increase in Fontana-Masson staining and Mexameter readings.

Conclusions: Further modifications of vehicle should lead to efficacy of topical application of LK 514 in increasing skin pigmentation.

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