POCMiB019 BB/L013711/1
01 October 2015 – 31 July 2016
Funded by Metals in Biology BBSRC NIBB Proof of Concept funding
metals.bbsrcnibb@durham.ac.uk @METALSBBSRCNIBB https://mib-nibb.webspace.durham.ac.uk

Light-activated caged-iron chelator for skin photoprotection based on the natural product pulcherrimic acid

"Our project provides a robust basis for the use of molecules inspired by pulcherrimic acid as ligands for the development of novel light-activated photoprotective compounds that could be used in sunscreen."
Charareh Pourzand, University of Bath

Charareh Pourzand, Ian M. Eggleston, Daniel Henk and Chris Chuck, University of Bath; Timothy Miller, Croda Europe

OUTCOMES: First, we produced pulcherrimin and purified pulcherrimic acid (PA) from non-sterile culture. Around 150 mg/L of pulcherrimin was produced on a 10L-scale culture of an over-producing strain of *M. pulcherrima*. In addition, synthetic authentic samples of PA were successfully prepared in the chemistry laboratory. The synthetic approach was robust and scalable, and should be suitable for the preparation of a range of amino-acid derived PA analogues and caged compounds. Although the natural PA extracted from the *Mp* yeast was indistinguishable from the authentic synthetic material, biological studies used the highly pure synthetic PA, due to lack of optimum purity of PA isolated from yeast. Our results showed that PA is not cytotoxic *per se* when exposed to cultured primary skin fibroblasts overnight up to a concentration of 50 uM. PA (20-30 uM) conferred significant photoprotection against UVA-induced damage and cell death, and was was superior to the clinically used bidentate iron chelator deferiprone at an equimolar concentration. Further chemical development work is required to build on the promising results obtained so far in order to obtain light-activatable caged compounds. Nevertheless, these promising results provide proof of concept for the potential development of photolabile caged PA as topical sunscreen ingredients.

INITIAL AIMS: There is a significant need to counteract the cellular mechanisms that cause skin damage upon prolonged exposure to the UV component of sunlight. Exposure of skin cells to UVA promotes the generation of harmful reactive oxygen species and leads to an immediate release of labile iron and susceptibility to oxidative membrane damage and necrotic cell death. We have previously synthesised and validated light-activated protective compounds (i.e. light-activated caged-iron chelators, CICs) that release an active iron chelator upon sunlight exposure, which could protect against iron-catalysed oxidative damage and cell death. A critical requirement for CIC technology is readily available, chemically tractable iron chelators, in which the iron-binding motif can be reversibly modified (caged). In this context, we plan to isolate and modify (cage) pulcherrimic acid, a natural product from the yeast *M. pulcherrima* with iron chelating activity, and subsequently evaluate its photoprotective activity against UVA-induced iron damage in cultured skin cells.

- Our chemical synthesis and biological validation of these compounds was essential to maximise impact for near future collaboration with Croda Europe
- We are considering medium-term collaborations with Croda Europe via BBSRC responsive mode or a BBSRC stand-alone LINK application