Mathematical Modelling Predicts the Spatial Distribution of Metabolism in Skin

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INTRODUCTION: The expression of RNA and protein for a multitude of different phase 1 & 2 xenobiotic metabolizing enzymes has been demonstrated both in *ex vivo* human skin and in *in vitro* tissue-engineered human skin equivalents by microarray and mass spectrometry techniques [1-2]. The presence of these enzymes in the skin is of considerable importance for the pharmaceutical/ cosmetic industry as xenobiotic compounds delivered topically or systemically to the skin may be metabolized to produce active metabolites that may either be beneficial (release of active drugs from pro-drugs) or may cause toxicity or hypersensitivity. Here we use mathematical models, parameterised against *in vitro* experimental data, to inform the spatial distribution of metabolism in tissue-engineered skin samples.

METHODS: A coupled system of partial differential equations was developed to describe the transport of parent compound and metabolites through a geometry representative of engineered skin equivalents (including corneum, granulosum, spinous, basal and dermal layers, with a fluid pool underneath, as used in the culture set-up). Diffusion and metabolism were defined based on literature values, and were specific to each layer [3-5]. The model was solved using COMSOL Multiphysics (a finite elements package), subject to boundary conditions that mimic the typical *in vitro* setup (for example, prescribed concentration of parent compound on the upper corneum surface, representative of topical delivery).

RESULTS: The model predicts spatial heterogeneity in the parent compound and metabolite concentrations within the skin (see Fig. 1). The parent compound concentration is highest at the upper corneum surface where it is delivered, and decays to a minimum within the basal cells at the bottom of the epithelium, as a consequence of cellular metabolism. The compound also diffuses through the extra-cellular spaces into the dermis, which consequently has a slightly higher concentration than the basal and lower spinous cell layers. This spatial distribution is mirrored by the metabolite, which is lowest in corneum/ granulosum/ dermal layers, and highest within the spinous cells. In both cases, intra- versus extra-cellular transport routes are easily identifiable, and the patterning of cells within the spinous layer is a strong determinant of the spatial distributions of parent compound and metabolite.

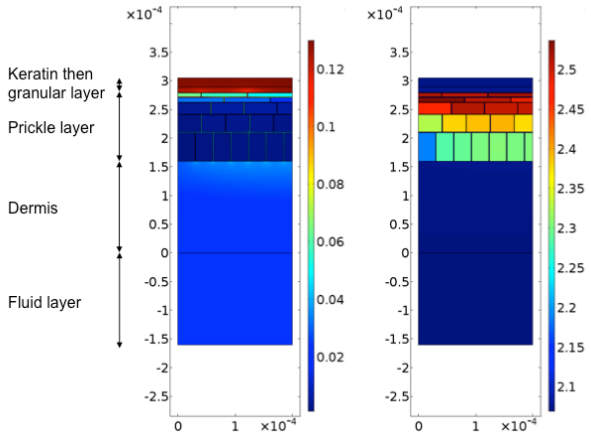

Fig. 1: Mathematical model predictions of the spatial distribution of parent compound (left) and metabolite (right) concentrations (both mol/m^3); parent compound delivered topically on the upper corneum surface with results shown after 10 hours. Physical dimensions measured in metres.

DISCUSSION & CONCLUSIONS: The mathematical model, parameterised by literature diffusion and metabolism parameters, was able to predict the spatial distribution of parent compound and metabolite within *in vitro* skin equivalents. This complete spatial information is particularly challenging to extract using a purely experimental approach. The model is generic, and next will be used to explore alternative delivery routes (e.g. systemic delivery of parent compound through the vasculature), and human skin geometries.

REFERENCES: [1]F Oesch et al. (2014) *Arch Toxicol* **88**:2135-63. [2]NJ Hewitt et al (2013) *Toxicol Sci* **133**:209-17. [3]Menochet et al (2012) *Drug Metabolism* **40**:1744-1756. [4]Dancik et al (2013) *Adv Drug Delivery Rev* **65**:221-236. [5]Mitragotri et al *Int J Pharmaceutics* **418**:115-129.

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