Histological differences in skin of minipigs related to age and sex

Gitte Jeppesen, Nanna Grand, Jeanet Løgsted and Andrew Makin

TOXICOLOGY SERVICES
• General toxicology:
  - Rodents
  - Non-rodents: dogs, NHPs and minipigs
• Inhalation
• Oral
• Dermal
• Ocular
• Reproductive toxicology: including minipigs and NHPs
• Carcinogenicity studies also in rasH2 and p53+/- mice
• Genetic toxicology: ICH compliant package
• In vitro toxicology: BCOOP, MUSST, OPRAH, Photo 3Ts, Episom™
• Agrochemical / Chemical / REACH
• QSAR
• Physical chemistry
• Ecotoxicology: wide range of test species

SAFETY PHARMACOLOGY
• Integrated Safety Pharmacology in Toxicology Studies
  - CV (JET), BF
  - Respiratory (JET), plethysmography
  - CNS (FOB) and JET-EEG
• Safety pharmacology core battery
• Early safety pharmacology screening
• Rodent and non-rodent LVP telemetry
• Anesthetized models: ECG, ABP, LVP and QA

DMPK AND BIOMARKERS
• Radiolabeled DMPK: in all species
• Bioanalysis LC-MS/MS, GC-MS/MS, LC-ICP/MS, ELISA, RIA
• Toxicogenomics, miRNA: Affymetrix™ Accredited service provider, Next Generation Sequencing (Illumina®)
• Immunology: 30-color flow cytometry, Luminex, Mesoscale

SPECIALIZED EXPERTISE
• Juvenile studies including minipigs
• Fertility studies in rodents and NHPs
• Radiation safety and efficacy studies
• Tissue Cross Reactivity: human and animal tissue banks
• Gene therapy vector biodistribution via qPCR
• ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
• Lead optimization and predictive toxicology services: Leadscreen™

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INTRODUCTION
Minipigs are routinely used in testing of drugs intended for dermal application. The skin of the minipig is widely regarded as being the closest in structure to that of humans. In the design of studies it is important to ensure that the site used for dosing is as uniform as possible in terms of thickness, density of hair follicles, etc., otherwise on the choice of site may introduce bias in terms of penetration and consequent systemic exposure. Typically, minipigs are dosed on 10% of their surface, normally the sides and back, where the skin is fairly uniform. We are sometimes requested to use other parts of the body or larger areas, also there is a question about skin in younger animals compared with adults; is it thinner and is there greater likelihood of absorption of xenobiotics? Therefore we have initiated a project to study the differences in the skin between various sites on minipigs of different ages, and some preliminary results are presented in this poster, looking at skin from animals of ages between 4 weeks and ca. 21 months old. In our database is background data on skin from hundreds of control minipigs within this span of ages; the examples in this poster are representative images.

BACKGROUND
The skin of animals is primarily to provide a physical barrier to external hazards whilst preventing water loss in contrast to the GI tract which is designed to take up substances into the body. The physiology of the skin varies both between and within animals; epidermal thickness, density of hair follicles, degree of pigmentation are variable. Penetration of the skin by drugs and chemicals involves various pathways, but is in principle by diffusion. The stratum corneum is a barrier through which, particularly small molecules, can diffuse, while passage through the epidermis itself is normally intercellular - that is to say that passage is between the cells rather than by active transport through the cells. Xenobiotics are first taken up by the systemic circulation once they reach the dermis because the epidermis is largely avascular. Skin structures like hair follicles and sweat glands provide further opportunities for absorption. In this case, molecules do not first need to pass through the stratum corneum before coming into contact with the epithelial cells. The density of follicles or sweat glands (number per unit of skin surface) can therefore influence absorption.

RESULTS AND DISCUSSION
Figures 1 to 8 show representative photomicrographs of skin from both male and female minipig skin of different ages from 4 weeks old to ca. 21 months of age. The skin is sampled from a similar area on the flank of the animals. It is seen that there are no obvious major differences related to age, although the epidermis of the older animals is a little thicker and the rete ridges are somewhat more well defined (the rete ridges are epidermal thickenings that extend downward into the dermis) compared to the younger animals. Otherwise the stratum corneum and epidermis are of similar thickness at all ages and therefore there would not be expected to be significant differences between the barrier function of the skin in the younger animals versus the older ones. Therefore, one would not expect to see an increased absorption and systemic exposure in younger animals; at least not based on the physiology of the skin.

CONCLUSION
Our histopathological evaluation of the skin of minipigs over an age range of up to 21 months old indicates that there are no significant differences related to age, and that therefore we would not expect to see age-related differences in systemic exposure to dermally administered xenobiotics in minipigs.