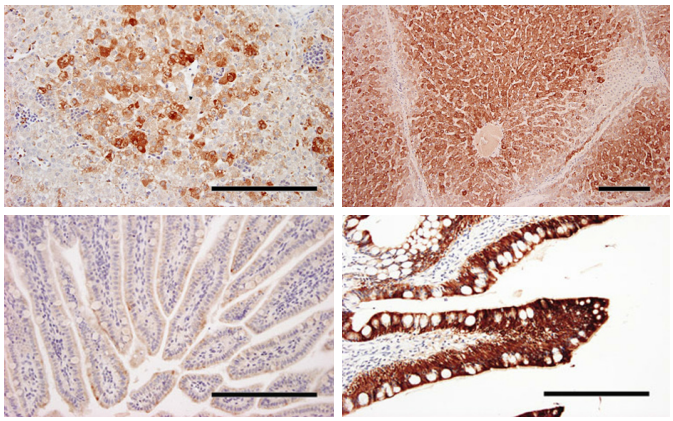
Göttingen Minipigs in ADME studies – specific advantages

For several routes of administration, Göttingen Minipigs have specific advantages over other preclinical species in terms of predicting the drug absorption in humans. For the oral route, these advantages were addressed in another recent whitepaper.

For dermally applied drugs, Göttingen Minipigs are typically the preferred species as the skin is very similar to the human skin.[1] The similar thickness and structure of the epidermis and stratum corneum is especially important in that regard. These upper layers are thinner in other (furred) preclinical species, and this can lead to falsely high absorption and to local toxicity findings of compounds that are well tolerated in humans.[2,3] In accordance with this, the permeation through human skin can be predicted from in vitro studies using Göttingen Minipigs skin.[4,5] The thickness of the epidermis does not change notably in animals above approx. 3 months of age, but still, the dermal permeability of certain compounds can change with age. In general, however, animals at the age of 4-5 months, which is the typical age used in regulatory toxicology studies, are representative of the absorption rates in humans.[4]

The subcutaneous tissue in Göttingen Minipigs is relatively firmly connected to the deep fascia in a similar manner as in humans, and it furthermore has a thickness and fat content like that in humans. In the other (furred) preclinical species the subcutaneous tissue is generally looser, sparser and more hydrophilic. These characteristics can be important for obtaining results that are translatable to humans for subcutaneously administered compounds. In terms of local toxicity, for instance, long-term subcutaneous toxicity studies have been used to evaluate the impact of factors such as drug concentration and dose volume.[6] In terms of PK, it was only possible to show the faster absorption profile of insulin aspart over human insulin in pigs – not in rats or dogs.[7] Also, it has been nicely shown that Göttingen Minipigs can be used to predict the PK properties of monoclonal antibodies in humans.[8] Specifically, the linear clearance can be nicely predicted and the minipigs even gives an estimate of the s.c. bioavailability[8] – something which is difficult to obtain in other species, including non-human primates.[8,9]

In terms of metabolism, an excellent and detailed review has compared minipig, dog, monkey and human metabolism and disposition.[10] From that, it can be seen that Göttingen Minipigs have a favorable profile with regard to factors such as CYP activities and different drug transporters.[10] Specifically, it is concluded that when a drug candidate is metabolized by aldehyde oxidase (AOX1), N-acetyltransferases (NAT1 and NAT2) or cytochrome (CYP2C9-like) enzymes (which are not expressed in dogs), the minipig may be a better choice than dogs. Also, dogs do not have the organic anion transporter OAT3. In general, it is recommended to perform in vitro drug metabolism studies prior to selecting the non-rodent species to ensure that the most optimal choice is made. Recently, the metabolism of several model compounds was studied in developing, juvenile Göttingen Minipigs, and it was concluded that the maturation of drug metabolizing capacities occurs in a similar way as described in man.[11]



"Göttingen Minipigs are generally accepted as a good model for human drug absorption and metabolism, which is why we are focussing on this species for translational research in our lab. The illustration[12] shows a markedly higher expression of CYP3A in the liver (top) and small intestine (bottom) from adult (right) as compared to juvenile (left) Göttingen Minipigs – illustrating the similarity, also in this aspect, to humans".

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