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The Sinclair Nanopig™—The Other Non-rodent

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ABSTRACT

The minipig has been an underutilized non-rodent species for nonclinical safety assessment for years. Since minipig skin is the best model for humans, it has been used for wound healing and dermal programs for many years. It is an accepted species by all the regulatory agencies for safety assessment studies. There are growing concerns about using non-human primates (NHPs) and dogs in safety assessment studies. Hence, the minipig is an excellent option as a non-rodent species for drug development for both small molecules and biologics.

For small molecules, the focus is on metabolism. To address this, genomic and proteomic assessments were conducted to characterize the Sinclair Nanopig™ (Nanopig™) in relation to humans. There were 47 CYP450 genes identified in the Nanopig™, with 20 of these in the CYP 1/2/3 families, which compares nicely with humans, which have 57 CYP450 genes and 24 in the CYP 1/2/3 families. Looking at CYP450 activity, the Nanopig™ shows more similarity than canine for CYP2C and CYP3A, which are involved with the metabolism of more than half of the marketed clinical drugs.

For biologics, there is literature indicating that human IgG binds to the FcR in minipigs and that there are orthologs in the minipigs for chemokines, cytokines, and growth factors, common targets for biologics in development (Egli et al., 2019). A review of the literature revealed that many biologic programs submitted to the regulatory bodies included both rodents and non-rodent (Prior et al., 2020), indicating that the rodent (mostly rats) was found to be pharmacologically relevant for those programs. This means the target could likely be present in minipigs as well. Taken together, this supports the inclusion of the minipig in the early screening efforts that are geared toward selecting the species for safety assessment.

METHOD

The Nanopig™ was created over a 10-year effort. The process started with selective breeding designed to generate smaller animals. The next phase of the process involved carefully examining the diet, considering the animals' caloric needs through their growth phases. The combination of these efforts generated an animal that is smaller than the Gottingen® and slightly larger than the beagle through 12 months of age, the typical age of an animal at the end of a chronic toxicology study.

To evaluate the potential for the Nanopigs™ to be useful as a model for safety assessment of small molecules, genomic and enzymatic activity assays were conducted. These evaluations compared the Nanopigs™ to humans and dogs looking at CYP450 enzymes since they are central in the metabolism of small molecules.

There is data in the literature that supports the potential for the Nanopigs™ to be an option for use in the safety assessment for biologics, with more directed evaluations planned.

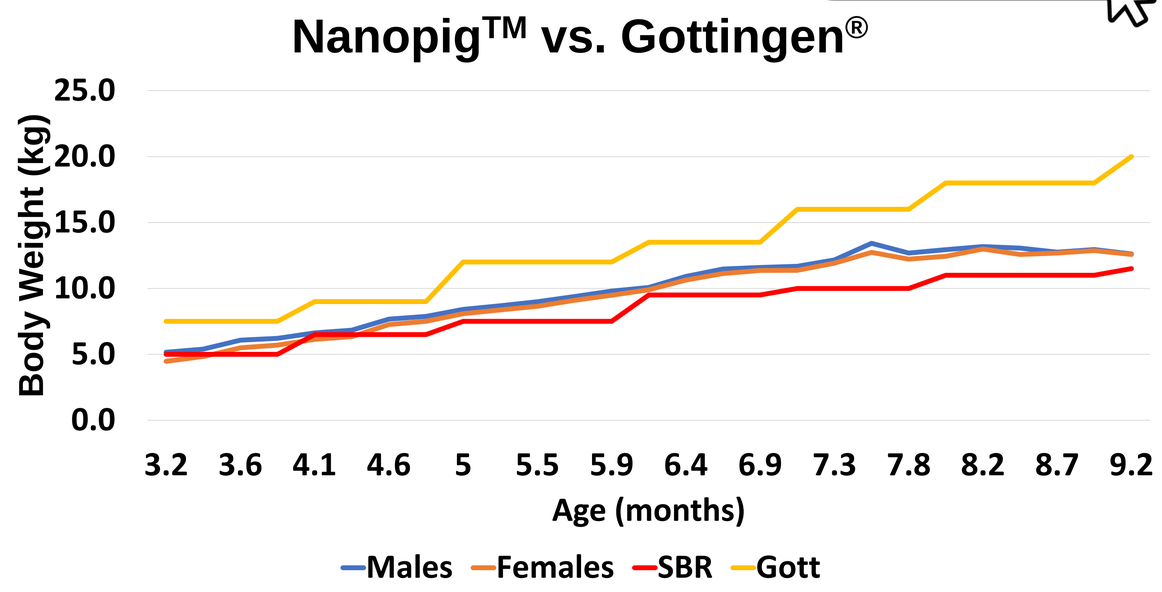

Figure 1. Body Weights for the Nanopig™ in a CRO Setting

Body weights for the Nanopig™ in a CRO setting tracked well when compared to body weights generated in production. At approximately 9 months of age, the Nanopig™ is almost 30% smaller than the Gottingen® minipig.

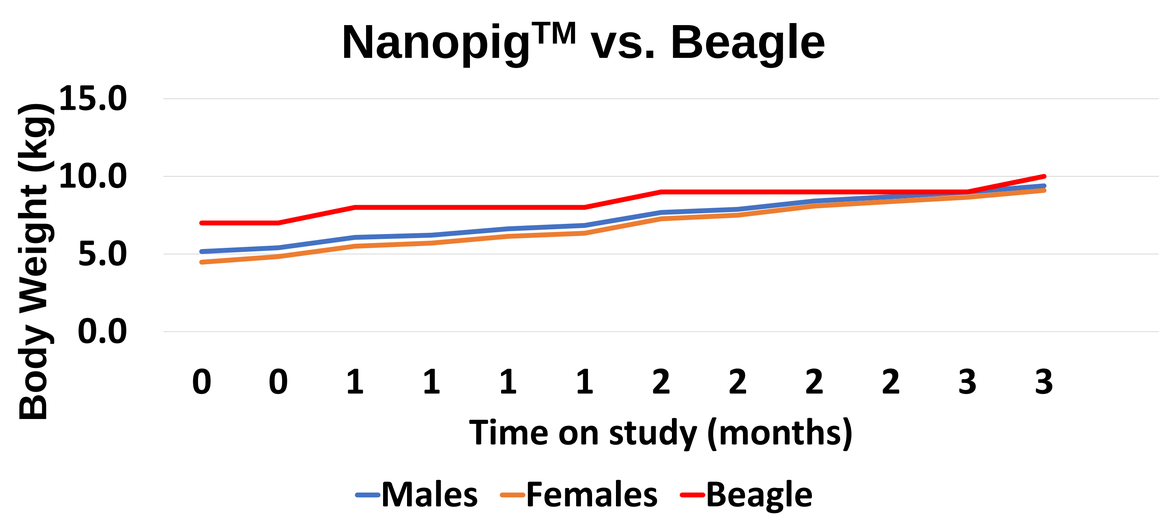

Figure 2. Body Weights for Nanopigs™ and Beagles for a Typical IND-Enabling Study

Evaluation of the body weights for Nanopigs™ and beagles for a typical IND-enabling study (4 weeks in duration). Assuming the starting age is 3 months for the Nanopigs™ and 6 months for the beagles, the Nanopigs™ weigh less than the beagle for the duration of the 4-week study, meaning reduced test article requirements.

Genomic Analysis of Nanopig™ vs. Human CYP450

Table 1. Number of Genes

	Nanopig™	Human
Total CYP450	47	57
CYP450 1/2/3 families	20	24

Enzymatic Activity for Nanopig™ vs. Human/Dog

- CYP2C and CYP3A: most similar between Nanopig™ and human
- CYP2D: most similar between Nanopig™ and dog
- CYP1A: most similar between human and dog

CONCLUSIONS

- Through selective breeding and diet management, the Nanopig™ is smaller than the Gottingen®, as well as smaller than the beagle for IND-enabling studies saving test article.
- Based on genomic evaluation, the Nanopig™ demonstrates a high degree of similarity to human; enzymatic activity assessments further support this.
- Literature indicates that porcine FcR interacts with human IgG1 and that orthologs for targets of biologic therapeutics exist in the minipig.
- The Nanopig™ is a cost-effective option as a non-rodent for safety assessment. It should be included in the early studies designed to select the non-rodent species for a drug development program for small molecules and biologics.

REFERENCES

Egli et al. The Binding of Human IgG to Minipig FcγRs – Implications for Preclinical Assessment of Therapeutic Antibodies, Pharm Res (2019) 36: 47
Prior et al., Justification for species selection for pharmaceutical toxicity studies. Toxicology Research. 2020, 9