Translational Accuracy Begins with Species Selection: Matching Models to Human Biology

Selecting the appropriate nonclinical species is a critical decision in drug development. The choice directly affects the predictive value, safety assessment, and clinical translation of new therapeutics. Because no animal species fully replicates human biology, the optimal model depends on a combination of organ-specific physiological similarity, molecular target homology, target expression profile, and pharmacodynamic/pharmacokinetic (PD/PK) behavior.

For small molecules, species selection is often driven by ADME characteristics, metabolic pathways, and similarity in the primary organ system targeted by the therapy. For biologics, the decision becomes even more constrained: molecular target homology to humans, receptor sequence identity, ligand-binding affinity, and FcRn biology are frequently decisive, as they determine both pharmacological activity and systemic exposure.

Many investigational drugs fail in translation because preclinical findings reflect species-specific biology rather than true human pharmacology. Therefore, the alignment between drug mechanisms, human target biology, and species physiology must be carefully evaluated prior to selection of the correct species for any drug development program.

This includes:

- **Organ-system homology:** Structural and functional similarity of major systems, including cardiovascular, pulmonary, hepatic, renal, CNS, GI tract, immune, endocrine, skin, bone, reproductive, and ocular systems. In particular, the system(s) that would be the target for the drug under development.
- **Molecular target homology:** Degree of amino acid sequence identity and receptor–ligand compatibility between human targets and their orthologs in each species.
- **Target expression profile:** Comparable distribution and density of the therapeutic target across tissues.
- **Pharmacology:** Similar receptor binding/internalization, activity, and biological response.

The following table quantifies these cross-species differences using a numerical homology scoring system across 11 major organ systems, along with total and average scores that summarize the overall translational relevance of each species. The table is based on an objective AI generated evaluation based on the following input: “Compare NHP, Göttingen Minipigs and dog with human in relation to different organ systems and rate the homology for each organ from 1-10 and provide a rational for the rating – make one table.”

ORGAN SYSTEM	NHP	MINIPIG	DOG	RATIONALE (SHORT SUMMARY)
Cardiovascular	9	8	7	NHP closest electrophysiology; pigs similar coronary anatomy; dogs differ in vascular perfusion, cellular repolarization and Purkinje network.
Respiratory	9	7	6	NHP airway structure and immune cells highly human-like; pigs moderately similar; dogs more divergent.
GI System	9	8	6	NHP gut anatomy closest; although the anatomy of the pig GI tract is different from humans, the physiology is remarkably similar; dogs have faster transit and carnivore-type physiology.
Liver/Metabolism	9	8	6	NHP CYP and UGT patterns closest to humans; pigs similar for many enzymes; dogs show notable CYP differences.
Kidney	9	8	7	NHP renal transporters and GFR match human; pigs similar nephron structure; dogs differ in concentrating ability.
Immune System	9	8	6	NHP T/B cells, cytokines, Fc receptors nearly identical to humans; pigs moderately similar; dogs less predictive for biologics. Humanized IgG1/IgG4 model in minipigs enables the dosing of human IgG1 and IgG4 antibodies and results in a better estimate of clinical ADA risk.
Skin	7	9	6	Minipig epidermal/dermal structure close to human; dogs have thinner epidermis and denser hair. NHP have thinner epidermis and dermis with denser hair.
Endocrine	9	8	6	NHP HPA/thyroid/islet biology match humans; pigs show similar insulin physiology; dogs differ in thyroid and cortisol kinetics.
Reproductive	9	7	6	NHP menstrual cycle & placentation very human-like; pigs have different placental type; dogs have species-specific endocrine cycles.
Nervous System	9	8	7	NHPs are the best approximation of the human brain for research, especially regarding brain architecture and BBB; pigs are highlighted for their gyrencephalic brains and structural similarity; dogs are less similar in cortical structure and function compared to NHPs and pigs.
Eye (Ocular System)	9	8	7	NHP ocular anatomy (retina, macula-like region, vasculature, accommodation) is closest to human. Minipig eye similar in size, retinal layering, and aqueous dynamics, widely used in ocular tox, but lacks a macula. Dog eye moderately predictive but differs in retinal vascular pattern and lens biomechanics, lacks a macula and possesses a tapetum lucidum which humans lack.

Across all evaluated organ systems, Non-Human Primates (NHP) show the highest overall homology to humans, particularly in immune biology, reproductive physiology, CNS structure, cardiovascular electrophysiology, and drug metabolism. This makes NHPs the most translationally predictive species, especially for biologics, CNS drugs, immunotherapies, reproductive toxicity, and complex human-like physiological responses. Their limitations lie mainly in ethical constraints, cost, and logistics, rather than biological relevance, although in some cases, e.g. skin, the minipig is superior to the NHP.

Göttingen Minipigs emerge as the strongest non-primate alternative, offering high similarity in skin, cardiovascular, GI, renal, and metabolic systems with anatomy and physiology often closer to humans than dogs. Their gyrencephalic brain, human-like dermal structure, cardiovascular perfusion, and predictive PK/PD and toxicology properties make them particularly valuable in dermal, cardiovascular, metabolic, and general toxicology studies. However, their immune system, FcRn biology, and reproductive physiology diverge more from humans than NHPs. The newly derived Humanized IgG1/IgG4 Göttingen Minipigs enable safety and efficacy testing of human recombinant antibodies and reduce the need for studies in NHPs, providing a new tool to mitigate clinical development risk. The sensitivity with which Humanized IgG1/IgG4 Göttingen Minipigs respond to immunogenic human mAbs while tolerating non-immunogenic human mAbs makes them an ideal model for safety assessments of therapeutic human mAbs and prediction of possible side effects.

Dogs show moderate but consistently lower homology than NHPs and minipigs compared to humans across most organ systems. Strengths include cardiovascular hemodynamics, renal function, but notable divergences in GI physiology, metabolism (CYPs), skin structure, immune responses, and reproductive biology reduce their human predictive power in several domains. As a result, dogs remain useful in some safety pharmacology and historical regulatory settings, but scientific homology increasingly favours minipigs in many areas.

In conclusion, with the push away from using NHPs in biomedical research unless absolutely necessary, the minipig, with its close similarity to humans in several areas, is an ideal non-human model with superiority to dogs in many ways.

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Ellegaard Göttingen Minipigs A/S
Sorø Landevej 302
DK-4261 Dalmose,
Denmark

Tel.: +45 5818 5818
ellegaard@minipigs.dk
www.minipigs.dk