MINIPIGS AS ALTERNATIVE FOR NON-HUMAN PRIMATES AND DOGS IN SAFETY TESTING OF (BIO)PHARMACEUTICALS

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In general, the pre-clinical safety evaluation of new (bio)pharmaceuticals for human use should be conducted in a rodent and a non-rodent species. The guidelines, however, do not specifically prescribe which non-rodents tend to be used.

For several years the minipig has been considered a useful alternative non-rodent species for safety testing of (bio)pharmaceuticals. Human parallels in many features of its anatomy, physiology, biochemistry and behavioural patterns along with its suitability for different types of study make the minipig a good model for man. This is particularly true for the cardiovascular system, the skin, the digestive tract, the urogenital system and drug metabolism. Given this, the minipig can replace dogs and non-human primates in several applications in pre-clinical safety testing, such as general toxicity (including immunotoxicity/immunogenicity), reproductive toxicity, juvenile developmental and safety pharmacology studies. Furthermore, this close similarity to man means that studies using minipigs will result in better human safety prediction.

STANDARD TOXICITY STUDIES (STS) IN MINIPIGS

At TNO Triskelion standard toxicity studies can be performed in minipigs (e.g. Ellegaard Göttingen minipigs) according to international guidelines and in compliance with GLP.

- Different exposure routes can be used (oral, i.m., s.c., i.d.) as well as dermal application by patch testing or semi-occlusive treatment.
- Adverse effects can be monitored by clinical signs, dermal reactions or injection site reactions, ophthalmoscopy, body weight, feed intake, body temperature, hematology and clinical chemistry, urinalysis, examination at necropsy for gross macroscopic changes, organ weights, and histopathology of dermal application or injection sites and major organs.
- Kinetics and metabolism can be included.

IMMUNOTOXICITY TESTING IN MINIPIGS

In evaluating potential immunotoxicity in standard toxicity studies, an immune pathology review is first undertaken and if a cause for concern is identified, additional functional studies should be performed. TNO Triskelion offers the following assays for immunotoxicity studies in minipigs:

Immune pathology signs of potential immunotoxicity

- Hematology/clinical chemistry
- Lymphoid organ weights and histology
- Lymphocyte subset analysis by flow cytometry

Functional assays to assess potential immunotoxicity

- Acquired immunity:
  - T cell Dependent Antibody Response (TDAR)
  - Delayed type hypersensitivity (DTH) reaction
  - Ex vivo lymphocyte proliferation assay including e.g. cytokine production
- Non-specific immunity:
  - Natural Killer cell (NK cell) activity

IMMUNOGENICITY TESTING OF BIOPHARMACEUTICALS IN MINIPIGS

Immunogenicity – the ability of a substance to elicit an immune response – is a primary matter of concern for the safety and efficacy of the increasing number of therapeutic biopharmaceuticals in development. Immunogenicity testing focuses on detecting and characterising anti-drug antibodies (ADAs), if these antibodies are neutralising (NABs), and if they affect the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug. Although animal studies tend to have a low predictive value and may overestimate immunogenicity in man, immunogenicity testing is important in helping to interpret data from standard toxicity studies and PK analysis.

As minipigs can replace dogs and non human primates in several applications in pre-clinical safety testing, the minipig can also be of relevance for immunogenicity assessment in connection with the safety and pharmacokinetics/dynamics evaluation of biopharmaceuticals.

At TNO Triskelion we offer:

- analysis of the formation of anti-drug antibodies (ADAs)
- assays to determine the neutralising capacity of the anti-drug antibodies (depending on the drug target: bridging ELISA, cell based assay)
- Pharmacokinetic (PK) analysis

JUVENILE (IMMUNO)DEVELOPMENT IN MINIPIGS

The minipig is considered a good alternative for non-human primates or dogs for those situations (e.g. logistic and/or scientific reasons) where the rat, as first species of choice, will not be the appropriate species. TNO Triskelion offers experience with the following assays for juvenile (immuno)developmental studies in minipigs from birth to 6 month of age:

General development parameters over time:

- Bodyweight growth
- Heamatology and clinical chemistry
- Weight and microscopy of main organs (25)

Immune pathology signs of immunodevelopment over time

- Lymphoid organ weights and histology
- Lymphocyte subset analysis by flow cytometry

Functional signs of immunodevelopment over time

- Acquired immunity:
  - T cell Dependent Antibody Response (TDAR)
  - Delayed type hypersensitivity (DTH) reaction
  - Ex vivo lymphocyte proliferation assay including e.g. cytokine production
- Non-specific immunity:
  - Natural Killer cell (NK cell) activity

FOR MORE INFORMATION

Minipigs as models for toxicity testing of new medicines and chemicals: an impact assessment. Special issue: the RETHINK project, in the Journal of Pharmacological and Toxicological Methods, Volume 62, number 3, 2010.

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