ELLEGAARD
GÖTTINGEN MINIPIGS

Humanized IgG Göttingen Minipigs for pre-clinical safety assessment of therapeutic antibodies

Genetically altered Göttingen Minipigs carrying a mini repertoire of human Ig-γ1/γ4 heavy and the human κ light chain genes are available at Ellegaard Göttingen Minipigs A/S. The humanized Göttingen Minipigs show tolerance to a broad range of human antibodies, providing a novel model for safety testing and an important and viable alternative for toxicology studies of therapeutic antibodies in non-human primates.

Background

Therapeutic antibodies have recorded a huge increase in sales in the pharmaceutical market and have experienced an immense growth in recent years. The majority of FDA approved monoclonal antibodies (mAbs) are in the format of human or humanized IgG[1,2]. mAbs are increasingly used for a variety of targets in cancer, diabetes, autoimmune, inflammatory, respiratory, ophtalmological, and infectious diseases.

Toxicological testing of antibodies in vivo can be challenging as most human therapeutic antibodies trigger xeno responses in preclinical animal models, resulting in rapid clearance of the drug or toxicities. This can be circumvented by using genetically altered animals that express the human protein and therefore recognize it as self. Humanized murine models have been generated to evaluate the in vivo stability of human mAbs[3]. However, data obtained in mice are not always translatable into humans in terms of application routes and pharmacokinetics. Furthermore, mice differ significantly from humans in general physiology, anatomy, and immune mechanisms, and the murine models are not ideal for long-term toxicological evaluations.

Non-human primates (NHPs) are the closest species to humans in biological terms, and NHPs are historically the primary choice for testing of biologics[4]. However, NHPs are not humanized and and will, like other species, develop an anti-drug antibody after repeated dosing of human molecules.

In addition, the FDA strongly encourages the use of appropriate alternative models to NHPs when possible[5].

Göttingen Minipigs have for decades been accepted as a non-rodent large animal species by national authorities including FDA and EMA[6] and is the most commonly minipig breed in pharmaceutical research[7]. Göttingen Minipigs have many advantages for preclinical studies, including similarities in physiological and pathophysiological responses and high level of immunological similarity[8,9]. Genetically altered Göttingen Minipigs are thus a viable alternative to NHPs in many areas of preclinical research[10,11].

Ideal model for safety testing

As demonstrated by Flisikowska et al*, the humanized Göttingen Minipigs' sensitivity and immunogenic response to therapeutic antibodies make them an ideal model for safety assessments of human or humanized IgG based molecules as well as prediction of possible side effects.

The amount of human IgG protein expressed is sufficient to induce and preserve immunological tolerance to a range of human IgG antibodies tested including bevacizumab, daratumumab, atezolizumab, and cergutuzumab*. Furthermore, the model has shown to fully reflect the difference in immunogenicity between these antibodies.

Humanized Göttingen Minipigs are bred in a fully AAALAC accredited barrier facility at the premises of Ellegaard Göttingen Minipigs A/S, Denmark, with an equally high health status as that of the standard Göttingen Minipigs. Trait inheritance has been confirmed. The humanized Göttingen Minipigs are fully immunocompetent and are commercially available in large uniform groups, sexually mature, and ready to use.

*Flisikowska T., Egli J., Flisikowski K. et al. A humanized minipig model for the toxicological testing of therapeutic recombinant antibodies. Nat. Biomed. Eng (2022). https://doi.org/10.1038/s41551-022-00921-2

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