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Summary

Transgenic (knock-out/-in) rodent models more precisely mirror human phenotypes and pathologies, providing a model to explore mechanisms and translational potential of targets. Such models are especially useful in assessment of fertility and effects on the embryo/fetus development.

SAFETY ASSESSMENT

Transgenic Animal Models in Reproductive Toxicology

Over the past few years, there has been a steady increase in the development of animal models that are considered more closely related to human disease. Typically, these include both induced and spontaneous models of disease, and transgenic animals - gene knock-out/-in models. Such models are useful to evaluate pharmacological activity, pharmacokinetics and dosimetry, as well as safety. In certain cases, they may be used as an acceptable alternative to toxicity studies in normal animals if the scientific justification can be provided. With the use of transgenic animal models gaining momentum in the area of drug development, the practice has also continued to garner acceptance in mechanistic research.

Alongside this, there has also been a rise in biotechnology-derived pharmaceuticals and, as a result, a greater need for flexibility in assessing reproductive hazards, including modification of traditional developmental and reproductive toxicology (DART) study designs, use of alternative animal models or use of surrogate molecules.

Regulatory guidelines for assessing the reproductive hazards of a biotechnology-derived pharmaceutical call for “relevant” animal models (based on the pharmacological activity of the test material). As noted in the ICH S6 (R1) guidance describing “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”, relevant animal models for testing of biotechnology-derived pharmaceuticals are those that express the desired epitope and demonstrate a tissue cross-reactivity profile similar to that of human tissues.

If there is no activity in the traditional toxicology animal models, it is acceptable to consider the use of transgenic (genetically modified) animals that express the human target (Figure 1). Transgenic animal models have been successfully used in DART studies to assess the hazards associated with functional gains or losses in a given target during conception and development. For the purpose of DART assessment, most of the transgenic mouse models have been derived from the C57BL/6J, BALB/c or CD-1 mouse strains.

Figure 1. Uses and Limitations of Transgenic Mice.

Type	Knock-In	Knock-Out	Humanized
Definition	May have gain of function to mimic agonists (worst case of overexpression)	May have reduced or loss of function for a particular target (worst case of maximum inhibition)	May express the human protein or receptor
Known Uses[1,2,3]	Chronic drug exposures, investigate potential developmen effects of drug candidates	Used to access drug specificity, investigate mechanisms of toxicity, screen for mutagenic/carcinogenic activity	Chronic drug exposures, investigate potential development effects of drug candidates
Dose Administration			Clinical drug candidate may be directly assessed
Comments		Unaffected by target deficiencies, with the exception of during reproduction and development of the animals	
Concerns	Limited to no historical control data; availability and life span; immunogenicity; signal transduction pathways; compensatory mechanisms; over- or underpredicting observed effects.		

In general, the natural delivery phase of the combined fertility, embryo-fetal development and peri- and postnatal development study is similar to that recommended by the ICH S5 (R2) guidance. F0 generation wild-type controls and knock-out females are evaluated for mortality, clinical signs, body weights and maternal observations through lactation day 21. F1 generation wild-type and knock-out litters are evaluated for mortality, clinical signs and body weights, and assessments for developmental landmarks may be incorporated into the study designs, where appropriate (Figure 2).

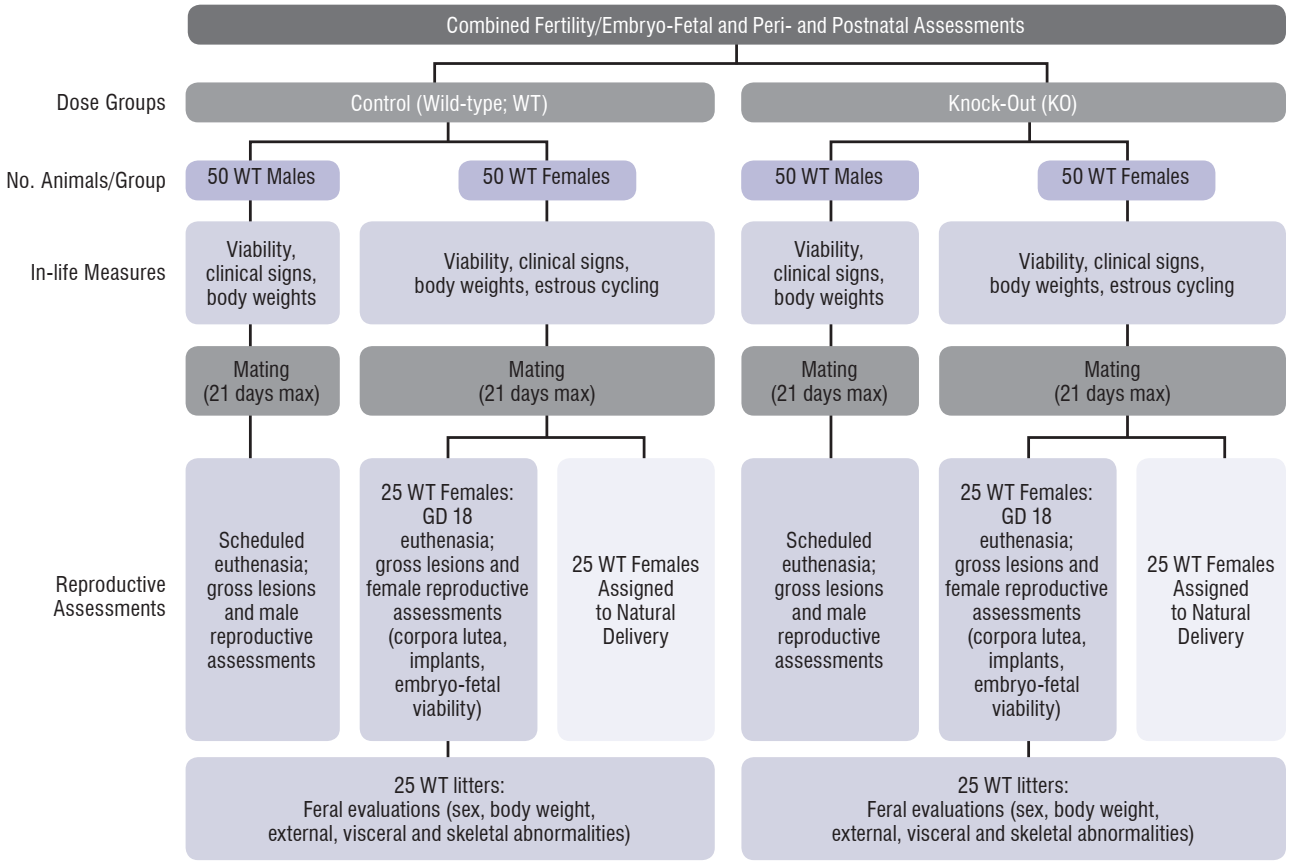
During the postweaning period, the F1 generation mice are evaluated for sexual maturation, behavioral assessments (e.g., passive avoidance, motor activity, learning and memory via water maze testing) and reproductive capacity. Additional endpoints that may be included in the combined fertility, embryo-fetal development and peri- and postnatal development study include placental transfer, milk collections and immunological assessments.

Summary

The principles for evaluating the effects of biotechnology-derived pharmaceuticals on reproduction and development are similar to those for small molecules. Models other than the standard toxicology animal models can be used to evaluate the effects of biotechnology-derived pharmaceuticals in DART studies. The use of traditional species should be considered first, even if the study designs and/or the dosing regimens require modification.

If alternative models are the only viable option, scientific justification must be provided and all aspects of the animal model should be understood prior to use. It is advisable to obtain regulatory approval of the experimental design prior to initiating DART studies in alternative animal models. For studies intended to evaluate the hazards associated with functional gains or losses in a given target during conception and development, combined study designs are acceptable and have been published in the literature below.[4,5]

Figure 2. Example study designs for combined fertility, embryo-fetal development and peri- and postnatal development studies using transgenic knock-out models. In some cases, it may be necessary to mate heterozygote (WT/KO) mice. Phenotyping of offspring would then be added to the study design.



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