Humanizing the Mouse Genome: Generating New Tools for Preclinical Research

Adriano Flora, Jochen Welcker, Alexander Klimke, Steffen Guettler, Petric Kuballa, Taconic Biosciences GmbH, Cologne, Germany
Eleanor Kolosovski, John Couse, Taconic Biosciences, Inc., Rensselaer, NY

ABSTRACT
Animal models are a key tool for assessing toxicity and efficacy of molecules before they are tested in humans. In many cases, however, potential therapeutic molecules that are active on human targets do not efficiently modulate their counterparts in other species. Expression of human proteins in the mouse is therefore becoming one of the most common approaches to overcome these limitations. The most effective way to generate mouse models expressing human proteins is to insert genes in the mouse genome, a process defined as genetic humanization. In this poster, we will present examples of genetic humanization projects and discuss the pros and cons of the most common strategies: BAC transgenesis, minigene insertion, and full gene replacement. We will discuss which factors influence the success of these complex projects and which aspects should be taken into consideration while generating a humanized mouse model. Finally, we will present the success rate derived from the analysis and of over 100 independent genetic humanization projects using the two most common approaches, namely gene replacement and minigene insertion, and provide specific guidelines for generation of these preclinical models.

APPLICATIONS OF HUMANIZED MOUSE MODELS
• In vivo drug efficacy testing by expressing the human target in the mouse
• ADMET (absorption, distribution, metabolism, excretion, toxicity) by accurately modeling drug metabolism
• In vivo testing of complex therapeutic approaches (i.e. in vivo genome editing, enzymatic complementation, etc.) by mimicking human diseases
• Target discovery and validation by modeling human physiology and pathology
• Study of infectious disease by humanizing specific pathogen receptors

HUMANIZATION BY TRANSGENESIS

HUMANIZATION BY GENE REPLACEMENT

APPROACHES TO HUMANIZING THE MOUSE GENOME

HUMANIZATION STRATEGY BY TRANSGENESIS

Experimental Goal
To compare the efficacy of enzyme replacement and gene therapy in treating a monogenic disease (mucopolysaccharidosis V)

Experimental Tool
A mouse model lacking a functional Arsb gene and tolerating human ARSB protein

Approach
Generation of a targeted transgenic model expressing a non-functional human ARSB protein and crossed with an Arsb knockout mouse model

Results
Using the humanized model, the group of Alberto Auricchio at TIGEM showed that low-dose gene therapy can efficiently substitute enzyme replacement therapy

HUMANIZATION STRATEGY BY GENE REPLACEMENT

Experimental Goal
To test the activity of drug metabolism by cytochrome P450 2D6 (CYP2D6) in vivo

Experimental Tool
A mouse model where the Cyp2d cluster has been replaced by the human CYP2D6 gene

Approach
Knock-in of the human CYP2D6 gene and deletion of the entire mouse Cyp2d cluster

Results
Using the humanized mouse model, McLeod et al. proved that exposing the transgenic mouse to tamoxifen

TIMELINES

44 Weeks
44 weeks
8 months
12 months
12 months
12 months
Random Transgenesis

70 Weeks
70 weeks
8 months
12 months
12 months
12 months
Standard Gene Targeting

54 Weeks
54 weeks
8 months
12 months
12 months
12 months
ExpressMODEL®