



Custom Humanized Mouse Models

HUMANIZED KNOCK IN OR HUMANIZATION WITH
OPTIONAL CONDITIONAL KO MOUSE MODELS

Custom Humanized Mouse Models

The study of human biology in an *in vivo* setting is limited by both technical and ethical considerations. As an alternative approach, the mouse is commonly used to study complex biological process related to humans. However, not all experimental data obtained from mice readily translate to human biology.



Humanized mouse models can bridge this data gap, enabling scientists to develop human disease models that are more predictive when testing therapeutics for a variety of diseases.

The most successful genetically humanized mouse models are generated by replacing a mouse gene with its human ortholog *in situ*. This process can be technically demanding. Failure to exchange large gene fragments, and lack of human gene expression of disease-relevant human splice variants not encoded by the mouse ortholog are commonly encountered risk factors. To generate your humanized model effectively, get the experts on your side. Taconic Biosciences' deep experience in producing humanized mouse models is unparalleled. In fact, our scientists have successfully completed more than 200 humanization projects to date.

This experience, combined with Taconic's strict adherence to quality control measures, ensures your humanized mouse model will provide the most reliable and meaningful data in the quickest possible time.

HOW TACONIC GENERATES A CUSTOM HUMANIZED MOUSE MODEL

To begin the process of generating your humanized mouse model, Taconic simply requires the client to provide a gene accession number. Our expert design team then carefully evaluates your project, and discusses with you the most viable strategy to successfully humanize your mouse target gene. A gene targeting vector is then constructed using cloning technology that will minimize the introduction of unwanted mutations. The vector is fully sequenced, and then electroporated into our highly germline competent C57BL/6NTac ES cells (other ES cell lines are also available for humanization).

After careful validation, positive ES cell clones are injected into mouse blastocysts followed by transfer into pseudopregnant female mice. The resulting chimeras are then bred to our highly efficient Flp-deleter mice to achieve removal of the selection marker and germline transmission in a single step. Alternatively, the selection marker can be removed *in vitro* which may enable testing of the humanized allele already at the ES cell stage.

TACONIC OFFERS A BROAD RANGE OF TECHNOLOGIES FOR HUMANIZATION

Taconic is continuously raising the bar in technology development, and is pleased to offer our customers multiple technologies for mouse humanization. These include:

- Humanizing mutation(s) of mouse gene.
- Insertion of a human minigene.
- Replacement of mouse with human genomic sequence of up to 120kb in a single step.
- Random insertion of human transgene/BAC by electroporation of ES cells or microinjection.

COMBINING HUMANIZED KNOCK IN WITH CONDITIONAL KNOCKOUT IN YOUR MODEL

Combining humanized knockin with optional conditional knockout allows you to remove the humanized gene through the use of an appropriate Cre-expressing mouse strain. This flexibility enables the *in vivo* testing of compounds and antibodies against human proteins in the mouse, and then comparing the effect against the null allele.

WHY CHOOSE TACONIC FOR YOUR CUSTOM HUMANIZED MOUSE MODEL?

When you choose Taconic to generate your humanized mouse model, know that you are working with the world leaders in generating custom mouse models. You can also be assured that all biological reagents employed for its generation have been subjected to regular health and genetic testing by Taconic scientists. For construction of the targeting vector, Taconic uses cloning technology that minimizes the introduction of mutations that commonly occur with PCR approaches. Complete sequencing of your targeting vector is standard practice at Taconic, allowing us to identify possible SNPs. In addition, periodic health/genome scan testing of ES cell lines and Flp-/Cre-deleter mice are also performed. When multiple gene targeting steps are employed, the karyotype of ES cell clones is verified at each step as well.

Timelines for the production of humanized mouse models at Taconic are short: Typically 40-42 weeks for gene replacements of up to 30 kb in length. More complex humanization projects may have longer timelines, depending on the complexity. Our deep commitment to quality control significantly reduces the likelihood of unwanted mutations,

CONJUGATED BILIRUBIN LEVELS IN MOUSE PLASMA



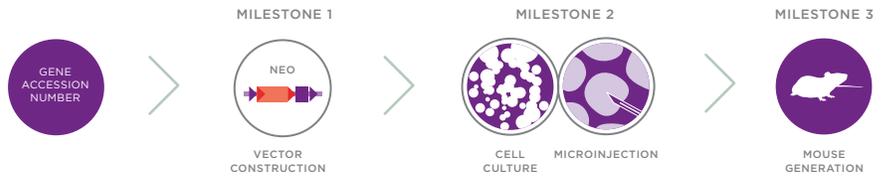
Conjugated bilirubin levels in mouse plasma significantly increase when the mMrp2 (multi drug resistant protein) gene is knocked out. Replacement of the mMrp2 gene with its human ortholog hMRP2 functionally compensates for the loss of mMrp2 in humanized mice.

TO ORDER

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TACONIC MILESTONES IN MOUSE MODEL GENERATION



aberrant gene expression, and other confounding variables that may necessitate additional mouse model production, delay data acquisition, and significantly increase your research costs.

KEY APPLICATIONS OF TACONIC'S HUMANIZED MOUSE MODELS

Taconic's humanized mouse models are ideal for a variety of research applications.

HUMANIZED DISEASE MODELS

Mouse models recapitulating a variety of human disease processes can be generated for target validation and *in vivo* compound testing.

IN VIVO COMPOUND TESTING

Humanized mice can provide a more predictive methodology to test the efficacy of compounds for the treatment of human diseases compared to wild-type animals.

In addition, Taconic has generated an array of humanized mice for our tADMET™ program. These strains are invaluable tools to more accurately predict the metabolism of therapeutic compounds in humans.

BENEFITS OF TACONIC'S HUMANIZED MOUSE MODELS

INCREASED PREDICTABILITY

Compound evaluations in mice may not always translate to humans. False positives and false negatives are a common occurrence. In contrast, humanized mouse models provide pharmaceutical scientists a more predictive model in which to test compounds for the treatment of human diseases.

REDUCED TIME FOR DRUG DEVELOPMENT

The increased predictability conferred by humanized mouse models will significantly speed up the drug discovery process.

EXPERT STRATEGY DESIGN

With more than 200 humanized models designed, our strategy design team has extensive experience and can devise the optimal approach for your humanization project.

LARGE GENE-SIZE CLONING

Exchange of up to 120 kb of genomic sequence can routinely be done at Taconic. We are continuously pushing the technological boundaries to increase the size limit for single-step gene replacements.

MULTIPLE HUMANIZATION TECHNOLOGIES

Taconic offers multiple ways to humanize a gene. This allows our scientists to provide you with most appropriate strategy for your humanization project.

STRICT QUALITY CONTROL

Multiple quality controls include complete vector sequencing and regular health/genetic testing of ES cells, Flp- and } Cre- deleter mice. Our strict adherence to quality control ensures you will get the most reliable and meaningful data from your humanized mouse with the shortest possible timeline.

FAST TIMELINES

On average, vector construction for humanized models at Taconic takes no longer than 8 weeks. Completion of a standard humanized mouse project takes

approximately 42 weeks from cloning to delivery of heterozygous mice.

SINGLE POINT OF CONTACT FOR COMMUNICATION

Regular updates by one of our dedicated experienced project managers ensure you are up-to-date on the current status of your humanized mouse model project.

DETAILED MILESTONE REPORTS

The progress of your humanized mouse model generation project will be documented in detailed reports at the end of each milestone. In general, the milestones include targeting vector construction, targeted and validated ES cells, and finally, mouse model completion.

END-TO-END SOLUTION

Once Taconic has generated your humanized mouse model, you have the option to have our experts design and implement a breeding program to generate the cohort you need for your research.

Please contact your customer service representative to discuss our breeding program options.

TACONIC MOLECULAR ANALYSIS SERVICES

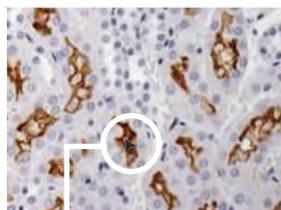
Taconic is pleased to offer its customers Molecular Analysis Services. Our scientists will perform qRT-PCR analysis on a wide panel of humanized and wild-type mouse tissues. Analysis includes relative quantification, and a detailed report.

FURTHER READING

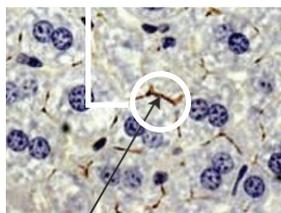
Scheer NI, Snaith M, Wolf CR, Seibler J. Generation and utility of genetically humanized mouse models. *Drug Discov Today*. 2013 Dec; 18 (23-24): 1200-11. Doi: 10.1016/j.drudis. 2013.07.007.

Scheer NI, Wolf CR. Genetically humanized mouse models of drug metabolizing enzymes and transporters and their applications. *Xenobiotica*. 2014 Jan; 44(2): 96-108;doi:10.3109/00498254.2013.815831

KIDNEY - HUMANIZED MRP2 MOUSE



ANTI-HUMAN MRP2 IMMUNOSTAINING



LIVER - HUMANIZED MRP2 MOUSE

Immunohistochemistry of kidney and liver from humanized mice expressing hMRP (human multi drug resistance gene). Results demonstrate correct tissue and intracellular expression of hMRP.

Visit taconic.com/resources/white-papers to download Taconic's humanization white papers.

DISCUSS YOUR NEEDS

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Take Your Research Further



ADDITIONAL SERVICES

GEMS DESIGN

Taconic Biosciences GEMS Design empowers our clients to develop research models specifically suited to the unique needs of their discovery and development studies or therapeutic programs.

- Gene Inactivation
- Gene Mutation or Replacement
- CRISPR Gene Editing
- Transgene Expression
- miRNA expression
- Cohort Production Packages

HUMANIZATION

Taconic offers both genetic and cell and tissue based humanization of mouse models. Humanized mouse models are increasingly being utilized for a variety of research applications.

- Genetically Humanized Mice
- Cell and Tissue Humanized Mice

GEMS MANAGEMENT

Taconic's fully integrated GEMS Management brings innovative models from design to study-ready cohorts with unprecedented speed and transparency.

- Embryology
- Rapid Colony Expansion
- Contract Breeding
- Surgical Services
- Tissue Collection
- Genotyping and Molecular Analysis
- Microbiome and Germ Free Research Models and Services

CHOOSE TACONIC

For more than 60 years, Taconic has anticipated the needs of the scientific community to deliver models and services that meet the diverse needs of biomedical and biopharmaceutical researchers.

Today that forward thinking and commitment to working collaboratively has resulted in a client-centric environment infused with a knowledge bank that allows you to draw on informed insight about next generation GEMS and humanized mouse models, enabling fast and reliable outcomes in your research.

YOUR COLLABORATIVE PARTNER

As a full-service biosciences company, Taconic can help you acquire, test, develop, breed, cryopreserve, prepare, and distribute highly relevant research lines worldwide. Whether you require custom genetically engineered, humanized or research-ready models, Taconic's scientists will partner with you to rapidly and efficiently deliver the highest quality models.

TALK TO A SCIENTIST

Our scientific teams are happy to meet and talk with you about the most efficient way to achieve your study goals. Working in partnership with clients the world over, our scientific teams offer expert advice that can help you speed up your research and reduce your overall costs.

TALK TO A REPRESENTATIVE

For general information, you can talk to a member of our customer service team. Our customer service team is here to help you make the right decisions and get the models you need fast. Contact us at info@taconic.com

VISIT TACONIC.COM

For more information on the entire Taconic portfolio of products and services designed to help further your research, visit taconic.com

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