

# Translating Genomes | Personalizing Medicine



## X-MAN™ - Genetically defined, patient-relevant human disease models

- ▶ Library of more than 400 genetically defined, isogenic human cell line pairs
- ▶ Genetically identical except for knock-in or knock-out of mutation of interest

- ▶ Patient-relevant and disease-relevant DNA mutations introduced to endogenous genes
- ▶ Definitive tools for studying cancer vs. normal cell biology and drug responses
- ▶ Produced using a patented, virally-mediated precision genome editing technology - GENESIS™

## X-MAN™ - Applications in drug discovery

- ▶ Identify and validate patient-relevant drug targets
- ▶ *In vitro* & *in vivo* applications
- ▶ Identify selective compounds earlier
- ▶ Match drug to responsive patient populations
- ▶ Design shorter, stratified patient-relevant clinical trials
- ▶ Find diagnostic and predictive biomarkers
- ▶ Genomic reference materials for diagnostic controls

## What are the features of X-MAN™ cell lines that make them different from other cell lines?

The most important feature of X-MAN™ cell lines is that DNA modifications are always made within the endogenous gene, closely recapitulating the genetic events that lead to a specific disease. The second important feature is that a matched 'isogenic' normal cell line is also provided, containing a wild type version of that gene. This enables the definitive and controlled study of a chosen genetic alteration on a cell's function and the search for novel pharmaceutical agents that selectively target it.

## Can X-MAN™ cell lines model diseases other than cancer?

Any genetic variation can be introduced using the GENESIS™ precision genome editing technology, enabling any disease-causing variation to be modelled as an X-MAN™ cell line.



## GENESIS™ - Proprietary rAAV-mediated precision genome editing

GENESIS™ targets the gene of interest at its endogenous locus allowing for the first time the accurate modelling of disease-causing mutations (knock-ins or knock-outs) and single nucleotide polymorphisms (SNPs) in human somatic cell lines. GENESIS™ also permits the definitive study of gene function or protein activity via highly specific targeted knockouts of the whole protein or discrete protein domains, respectively.

## Why are rAAV-vectors better at gene targeting than other methods?

In somatic cells, the homologous recombination machinery is essentially shut off, however, rAAV-vectors uniquely deliver their targeting constructs in the form of a single-stranded DNA-species which induces a unique single stranded homologous recombination process. rAAV vectors are consistently more efficient than double-stranded plasmid-based vectors. Moreover, rAAV-vectors elicit precise alterations within their target genes, without introducing confounding 'side-modifications' that are inherent with nuclease-based gene targeting techniques.

## Will GENESIS™ knock-out or modify a gene in my cell line of interest?

Yes, GENESIS™ has been used to knock-out genes, including tumour suppressor genes p53, PTEN and BRCA2, as well as being able to perform knock-ins of activated mutant oncogenes such as K-Ras, PI3K and EGFR in a range of cell lines (both human and mouse). The tropism of rAAV is wide with respect to tissue type and species of cell. The only major requirement is that the cell line grows continuously in culture conditions. There is no limit to the number of rounds GENESIS™ can be used. Sequential gene targeting enables either both alleles of a target endogenous locus to be modified, or the building of multiple disease genotypes within one target cell.

## Gene knock-ins

Targeted insertions or modifications are created within endogenous genes and so are subject to:

1. The correct gene regulation mechanisms
2. Accurately reflect the disease events found in real patients

GENESIS™ can introduce subtle point mutations, SNPs as well as small insertions with high efficiency. Moreover, GENESIS™ does not introduce any confounding 'off-target' genomic events that occur when using other nuclease-based technologies.

## Gene knock-outs

Gene knock-outs are at the endogenous locus, and thus are definitive, stable and patient-relevant. No confounding off-target effects are elicited at other genomic loci. It requires a 2-step process:

1. Generate a heterozygous knock-out
2. Generate a bi-allelic knock-out by targeting the second allele

This process can therefore generate 3 genotypes (+/+), (+/-) and (-/-) enabling the analysis of haplo-insufficient gene function.