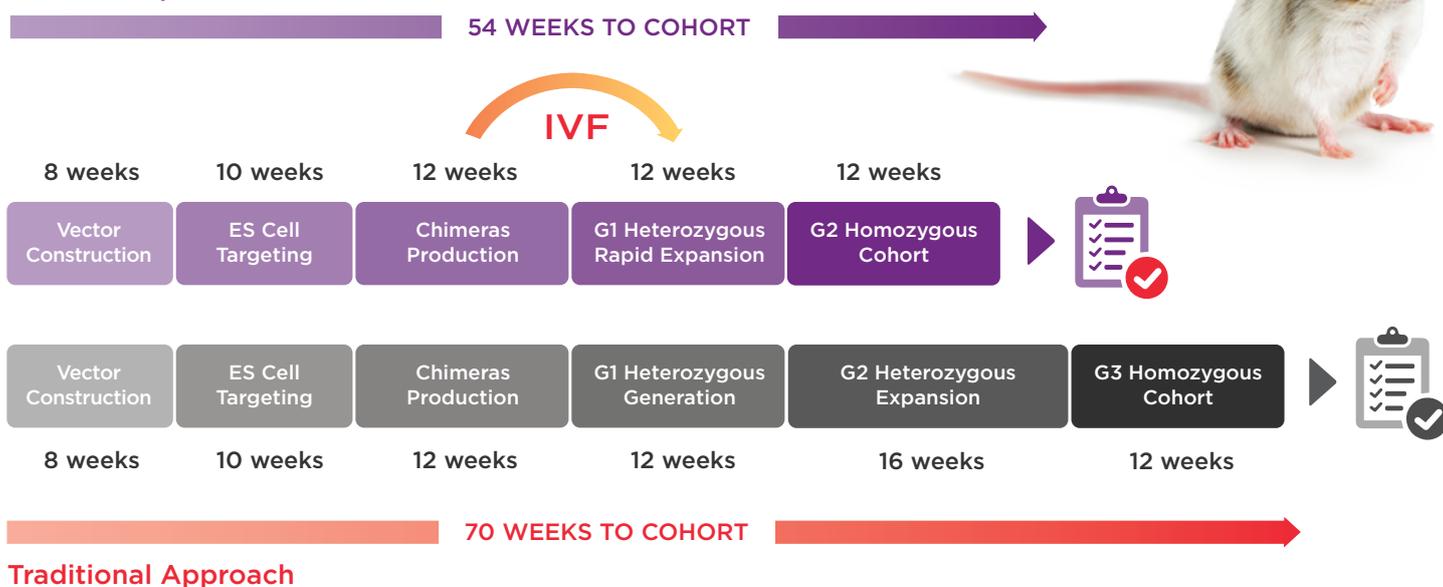


# ExpressMODEL<sup>®</sup> Generation

A NOVEL APPROACH TO  
ACCELERATE TIMELINE TO RESULTS

**OBTAIN RESULTS UP TO FOUR MONTHS FASTER  
THAN TRADITIONAL MODEL DEVELOPMENT**

Taconic ExpressMODEL<sup>®</sup>



## ExpressMODEL<sup>®</sup>: BENEFITS OF PERFORMING IVF FROM CHIMERAS

- Skip one downstream breeding generation
- More predictable timeline than natural mating
- Generation of the colony at the desired health status
- Possibility to scale up or down deliverables based on project needs

### DISCUSS YOUR PROJECT NEEDS

All projects will be assessed by Taconic Scientific Program Managers for eligibility. Most ES cell-based model generation projects will be eligible for the ExpressMODEL<sup>®</sup> program.

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## STANDARD MODEL GENERATION

Traditionally, the creation of a new genetically engineered mouse model has been split in two distinct steps: 1) introduction of the desired modification in the mouse genome, and 2) expansion of the transgenic colony. At the end of the first step, chimeras or founder mice are bred to wild-type congenic mice to generate a small number of animals (typically 3-4) carrying the desired mutation. In most cases, mouse models created using the embryonic stem (ES) cell gene targeting approach carry a deleter transgene<sup>1</sup> in addition to the desired genetic modification. The genetically modified mice are then bred to expand the colony in order to segregate the deleter transgene and generate enough cohort animals to perform experiments. The time required for the colony expansion step depends on how many animals are generated in the first phase and the desired size and genotype of the experimental cohort. Usually, expansion of the transgenic colony requires at least two to three mouse generations, spanning a period of five to eight months. Overall, the entire model generation process can last well over eighteen months before a researcher can perform any experiment.

## ExpressMODEL® APPROACH TO ACCELERATE TIMELINES

ExpressMODEL® is a novel approach developed by scientists at Taconic Biosciences to accelerate the timeline to the generation of experimental cohorts. Through extensive R&D efforts to optimize *in vitro* fertilization (IVF) procedures using chimeras, Taconic scientists have developed a cost effective method to rapidly expand the founder mice, thereby increasing the number of mice carrying the targeted alleles in the first generation from 3-4 to at least 20-30. In essence, sperm from chimaeric founder animals are collected and subsequently assessed for the potential germline transmission rate and viability of the spermatozoa.

Upon passing quality controls, IVF technology is used to generate the desired number of heterozygous animals carrying the mutated allele. Due to technical improvements in the genome modification step, the animals derived from then IVF procedure do not carry the resistance cassette and can be used directly for experiments or to generate experimental cohorts of genetically modified mice.

## TRADITIONAL APPROACHES TO REDUCE TIMELINE

New approaches, such as the genome editing technology CRISPR/Cas9, have recently become available to reduce the timeline of the model generation process. Despite their effectiveness, these technologies have inherent limitations in the manipulation of the mouse genome such as founder mosaicism<sup>2</sup> and off-target effects. Consequently, conditional knockout and knockin projects still rely on ES cell-based gene targeting methodologies. To accelerate the model generation process using ES cells, some laboratories have focused on expediting the genome modification step, reducing timelines by up to six weeks compared to the typical duration of this procedure. The disadvantage of hastening the genome manipulation phase is that such condensed timelines can be obtained only by reducing the level of controls applied to the different procedures, therefore increasing the risk of introducing unwanted genetic modifications in parallel to the desired allele. In the end, accelerating the genomic manipulation step might result in models carrying additional mutations leading to the generation of potentially confusing data and erroneous experimental conclusions.

## ADVANTAGES OF ExpressMODEL®

By providing a sizeable colony of heterozygous animals in the first generation, ExpressMODEL® allows researchers to skip at least one round of colony expansion, therefore saving 3-4 months on the overall project timeline. Elimination of natural breeding in the germline transmission step provides the additional advantage of resulting in predictable timelines and better planning of the experiments. Importantly, by not rushing procedures in the genome modification step, ExpressMODEL® does not compromise on the use of stringent controls during the genome modification process, therefore minimizing the risk of generating a mouse model carrying the wrong transgenic allele or additional unwanted mutations. Finally, by optimizing the size of the IVF rapid expansion procedure on the germline potential of the collected sperm, ExpressMODEL® can reduce the number of wild-type animals generated during germline transmission, in compliance with the 3 Rs of animal experimentation.

**Learn more about model generation:**

[taconic.com/CRISPR-advantages-limitations](https://taconic.com/CRISPR-advantages-limitations)

[taconic.com/why-transgenic-design-projects-fail](https://taconic.com/why-transgenic-design-projects-fail)

<sup>1</sup> The deleter transgene is required to eliminate the selection cassette used in the process of selecting the correct genomic targeting event in ES cells.

<sup>2</sup> Oliver, D.; Yuan, S.; McSwiggin, H.; Yan, W. Pervasive Genotypic Mosaicism in Founder Mice Derived from Genome Editing through Pronuclear Injection. *PLOS*. 2015, 1-12.