REGENERON

REGENERON RESEARCH AND DEVELOPMENT CAPABILITIES

THE VELOCISUITE OF TECHNOLOGIES

Keeping with its history of developing new and powerfully transforming technologies, Regeneron has created the *VelociSuite* of Technologies, comprising *VelociGene*®, *VelociMouse*™, *VelocImmune*® and *VelociMab*™. Together, these technologies increase the efficiency and decrease the time involved in the discovery and generation of drug candidates.

These technologies allow Regeneron scientists to determine which genes in the genome are the best targets for therapeutic intervention and then rapidly generate high-quality fully human antibodies as drug candidates addressing these targets.

KNOCKING OUT THE GENOME

Following the sequencing of the genome, the next challenge for the pharmaceutical industry became understanding the function of each gene and its product and determining the best candidates for therapeutic intervention. As there are now 20,000 to 30,000 genes that need to be characterized, the challenge cannot be met with pre-existing low-throughput approaches.

Perhaps the most powerful pre-existing approach for understanding a gene's function involves generating mice that are missing a specific gene (a "knockout") or that contain extra copies of a specific gene (a "transgenic"). To enhance this traditionally laborious and time-consuming process, Regeneron scientists developed *VelociGene* and *VelociMouse*, powerful new high throughput approaches for generating knockout and transgenic mouse models, allowing for the generation of thousands of such models, which can be used to evaluate each gene of interest.

The National Institute of Health (NIH) recently recognized that these approaches are critical for understanding gene function by initiating a $50 million effort called the "Knockout Mouse Project (KOMP)", and selecting Regeneron's *VelociGene* and *VelociMouse* technologies to play a major role in this effort.

PRODUCING A NEW GENERATION OF HUMAN ANTIBODIES

Mouse models for each gene of interest are evaluated in one or more of Regeneron's nine Therapeutic Focus Areas (TFA), such as oncology and angiogenesis, ophthalmology, metabolic and related diseases, muscle diseases and disorders, inflammation and immune diseases, bone and cartilage, pain, and cardiovascular disease, to determine the role the gene may play in a variety of disease.

Once a gene has been validated as a target for therapeutic intervention amenable to an antibody approach, Regeneron scientists can then utilize the *VelocImmune* and *VelociMab*

technologies to rapidly generate high-quality, fully human antibodies as drug candidates addressing these targets.

Although a variety of approaches for generating fully human antibodies already exist, these platforms have certain limitations. For example, the immune systems of these mouse lines into whose genomes human immune genes were incorporated, do not function normally and therefore antibody production is not optimally efficient.

To solve this problem, Regeneron scientists have successfully undertaken one of the largest genomic engineering challenges ever contemplated: they successfully genetically "humanized" over 6 megabases of the mouse immune genome (almost one hundred-times the size of any previous genetic humanization reported). The resulting mice, termed *VelocImmune* mice, which are a part of the *VelociGene* platform, represent a new standard for generating human antibodies, as their precisely humanized immune systems appear to work as efficiently as those of a normal mouse, except that they allow for the generation of human antibodies.

In the final step of the process, Regeneron scientists use the company's high-throughput *VelociMab* technology to extract the antibodies from the mice, quickly screen for antibodies with the best and most desirable characteristics, and then generate manufacturing lines that can produce high levels of the desired antibodies, suitable for clinical development and commercial use.

The capabilities of the *VelociSuite* of Technologies allow Regeneron scientists to efficiently evaluate hundreds of new gene targets every year, and generate therapeutic antibody candidates to validated targets, resulting in a robust antibody pipeline, with two-to-three new fully human antibodies expected to enter clinical trials each year.

Fully human antibodies are emerging as perhaps the most important new class of therapeutics in the pharmaceutical industry, with current combined sales over $30 billion and over 150 such antibodies in clinical trials.