Northwestern Lab is a “Knock Out”

In the late 1980s, Mario R. Capecchi, Oliver Smithies, and Sir Martin Evans revolutionized biomedical research with a gene-targeting technique that allows for the creation of animal models, called “knockout mice,” for hundreds of human diseases. Their pioneering work earned them the 2007 Nobel Prize in Physiology and Medicine. Groundbreaking work of this type is performed daily in Northwestern University’s Transgenic and Targeted Mutagenesis Laboratory.

“When we make knockout mice, we’re replacing a very specific gene,” explains Lynn Doglio, director of the facility. “We could be disrupting a gene so that it no longer functions. Or we could actually replace a good gene with a mutated gene.”

Knocking out the activity of a gene helps researchers understand the gene’s normal function and how a single gene may contribute to disease. Because many types of cancer and genetic diseases are caused by a single-point mutation in the genome, this research could lead to potential therapeutics for treating serious illnesses.

“But a lot of it is also basic research,” Doglio says. “If you want to know how a gene is regulated or why it is only expressed in a certain tissue, then we can study these questions in a mouse. If we have a certain gene in all the cells in our entire bodies, then why is it only expressed in the pancreas, for example?”

The Transgenic and Targeted Mutagenesis Lab also creates transgenic mice for research purposes. Instead of having a particular gene knocked out, a transgenic mouse has a specific gene expressed. Once a gene is isolated, it can be injected into an embryo and integrated into the mouse genome. The lab of Teepu Siddique, neurology, uses this technique to study amyotrophic lateral sclerosis (ALS), more commonly known as Lou Gehrig’s disease. Mutations in superoxide dismutase (SOD) gene have been linked to ALS. By isolating mutated copies of this gene from individuals with ALS and creating mice that carry these specific mutations, Siddique is exploring if the mutated SOD genes cause ALS in mice similar to the disease in humans.

“Because certain strains of mice, unlike humans, are all genetically identical, you can change a single parameter for study,” Doglio says. “Then you can see how that change effects the onset or course of a disease, for example.”

When the facility was created by Philip M. Iannaccone, pediatrics, it was housed in the Tarry Building where staff only performed transgenic injections. From there, it moved to Children’s Memorial Research Center in 1995, and the scope of work expanded to include knockout mice. In 2004, the core relocated back to the Chicago campus and broadened its reach even further to include cryopreservation of mouse germplasm and rederivation.

Cryopreservation is a newer technique performed in which embryos or sperm are frozen for storage on a long-term basis. “In the future, if you want to study the same mouse that you made 10 years ago, then we can thaw out the embryo and revive the line,” Doglio says.

Rederivation is a practice that keeps the mouse population healthy, which is one of the major priorities of the core facility. Mice with known pathogens arriving from outside institutions can be rederived into healthy, disease-free lines. Embryos from unhealthy mice are collected and washed several times, then surgically transplanted into a healthy mother from the facility. By keeping safety levels high, the facility has never experienced an outbreak of disease.

Science aside, Doglio says one of the most satisfying parts of the job is when the pups are born. “Everyday, there’s something new to come in and see,” she says. “It’s instant gratification.”

For more information about the Transgenic and Targeted Mutagenesis Lab, follow this link.