Collaborative cross attracting diverse genetics experiments

August 29 2007

Mice that are part of the Collaborative Cross project at Oak Ridge National Laboratory are helping scientists around the world learn more about possible causes of drug abuse, diabetes, sleep disorders, stress and pain, kidney disease and a number of other conditions that affect millions of people.

The Collaborative Cross, begun in 2005 with a grant from the Ellison Medical Foundation, represents a fundamentally new way of conducting genetics research and aims to create 1,000 strains of mice that feature the genetic diversity of the world population. When completed in about five years, the research community will have access to an extremely versatile resource plus data that is the click of a mouse away. There will be other benefits as well.

“With our new facility at ORNL, we offer economies of scale for the production of populations of mice,” said Elissa Chesler, leader of the systems genetics group in the Biosciences Division. “Without having to maintain their own mouse colonies, researchers will have access to mice that will enable them to do experiments that cannot be done anywhere else.”

While conventional genetics studies have primarily involved stand-alone experiments aimed at discovering single gene variants, the Collaborative Cross represents the new approach that researchers say is necessary to develop a community resource for understanding the genetic and environmental complexity of human diseases. With this approach, using

a reference population that allows for high genetic diversity and large sample size, researchers can more effectively examine combinations of genes responsible for diseases. This combination is what makes the Collaborative Cross special.

“We can stop blaming single genes for causing diseases,” Chesler said. “We now know that bad combinations of normal genes are at fault, and this mouse population will make it possible to determine complex causes and to develop drugs to treat those diseases.”

In one experiment at ORNL, William Lariviere of the University of Pittsburgh School of Medicine hopes to find genes that cause some people to be more sensitive to pain than others and to identify new drugs for treatment of different types of pain. The study involves collecting a standard set of thermal, chemical, inflammatory and mechanical sensitivity measures in groups of mice from 80 different lines in a genetic reference population called the BXD lines.

Data from Lariviere’s study will form an important foundation for integrative genomic analysis of pain. The results will be placed in the public domain through Web resource www.genenetwork.org.

“The BXD lines are a powerful tool for integration, but they do not have maximum precision and genetic diversity,” Lariviere said. “For that, we will collect additional trait data in the Collaborative Cross mouse population being created at ORNL.”

One area of specific interest to Lariviere is variations in the amount of messenger RNA (mRNA) produced by different individuals. This often determines how much of a particular protein is made, and that in turn might be related to biological pathways that are involved in processes such as pain perception.

“Because we will measure both the mRNA levels and the sensitivity levels in the same strains of mice, we will be able to efficiently not only study the genes that cause individual differences in pain sensitivity, but also identify the pathway of genes that make ideal targets for new pain drugs,” Lariviere said.

In another study, Michael Miles of Virginia Commonwealth University leads a team that hopes to learn more about the connection between anxiety and alcoholism. Working with Alex Putman and Chesler, the researchers have identified a region of a mouse chromosome that appears to significantly alter the effects of alcohol on anxiety.

“Understanding the basic mechanisms connecting brain events in anxiety and alcoholism could lead to better treatments for both disorders,” Miles said.

In this study, researchers used special strains of mice being raised and maintained at ORNL. Miles noted that the strains of mice used for his study are not available through any commercial source and offer a “great advantage to genetic studies of complex diseases.”

In upcoming months the researchers hope to identify the actual genes in this chromosome region that alter the response to alcohol.

In another study, Bruce O’Hara of the University of Kentucky is working to identify sleep- and wake-related genes. In addition to gaining a more thorough understanding of the sleep process, this research could lead to better drugs to help people with sleep disorders.

O’Hara’s study takes advantage of noninvasive piezoelectric sensors instead of conventional techniques that use electroencephalogram and eletromyogram recordings, which require surgical implants and cables that tether the mouse to a recording device. This limitation has made it

impractical to study large numbers of animals, which is necessary in genetic screening, according to O'Hara.

Source: Oak Ridge National Laboratory