The New York Times
nytimes.com

December 10, 2002

At Genetic Frontier, the House Mouse Serves Humanity

By NICHOLAS WADE

Now that the mouse's genome has been decoded, revealing just as many genes as its host, the 25 million mice that work in laboratories throughout the world may be demanding a lot more respect. It is the close cousinship that makes this vast labor force of furry little human surrogates so useful for exploring the human genome.

Many of the ills that humans inherit occur or can be generated in mice, making them models for studying how disease works in people. There are obese mice, mice with heart problems and even mice being developed as models for psychiatric diseases like autism and schizophrenia.

Because so much biomedical research is undertaken in mice, many laboratories now have to incur the large extra costs of operating mouse colonies. Nothing can so much incite a colleague's displeasure as sending a mouse with some pox that decimates the guest mouse colony. So mice, neatly stacked in wire baskets, are kept in germ-free high-containment rooms where they are fed and pampered and kept scrupulously free of mouse and human germs.

The disputes over human embryonic stem cells that perplexed the Clinton and Bush administrations emerged from a technique developed in mice, which are still the test bed for most basic work on stem cells. Last month, a group of scientists met at the New York Academy of Sciences to discuss whether human embryonic stem cells should be tested by seeing how well they performed in a mouse embryo.

While the researchers' idea was to let the embryos live only transiently, no one knows what kind of creature might result from a mixture of mouse and human embryonic stem cells. A mouse with all its brain cells of human origin is an interesting concept, though it might disappoint in practice. And though made by a different method, a mouse already exists that has a human immune system in place of its own.

In exchange for free board and lodging and excellent medical care, the mice have to submit to a number of genetic indignities. Some strains, called knockout mice, have had a specific gene removed, allowing researchers to figure out what the gene is meant to do by observing the knockout's flaws.

Some mice are so inbred, a result of many generations of brother-sister mating, that they carry the same versions of each gene from both parents. There are mutant mice descended from parents who were obliged to eat a chemical that interferes with their DNA, creating random mutations in the genes of the mouse's eggs or sperm.

The mecca of the mouse world is the Jackson Laboratory in Bar Harbor, Me. The laboratory maintains breeding colonies of many mutant mice strains and can generate rarer strains from a library of frozen embryos.

"We are about making sure the biomedical community has a broad assortment of mutant alleles," said the lab director, Dr. Richard Woychik, referring to the variant forms of a gene.

Besides mutant mice, the lab also maintains a computer database, Mouse Genome Informatics (www.informatics.jax.org), which assembles most known information about the mouse. It has lists of known mouse genes and reports of nomenclature committees on how to refer correctly to mouse strains. An anatomical dictionary browser tells the reader how to name each part in the developing mouse from egg to adult.

Just as biologists who study the Drosophila fruit fly call themselves fly people, researchers with a special interest in the mouse for its own sake are known as mouse people. A wider circle of biologists plunge from time to time into the mouse world in pursuit of their own projects.

The Mouse Genome Sequencing Consortium undertook the multimillion dollar task of decoding the 2,500 million units of DNA in the mouse genome. The Fantom Consortium, standing for Functional Annotation of the Mouse, has captured and decoded all the 61,000 transcripts of the mouse genome — essentially the products of activated genes — that are made by all the different kinds of cells in a mouse.

There is also a Complex Traits Consortium, whose aim is to find the genetic roots of the many important diseases that are caused by several genes acting in concert. That goal has long eluded human geneticists, and the consortium hopes to achieve the feat in the mouse.

A major ambition of mouse people is to twist up the mouse in every conceivable way by creating a comprehensive collection of mice strains, each one of which has a different gene mutated or disabled. That will provide the basis for a researcher to study any mouse gene of choice through its absence in the mutated strain. So far, only 5,000 genes have been mutated

study any mouse gene of choice through its absence in the mutated strain. So far, only 5,000 genes have been mutated, and the International Mouse Mutagenesis Consortium aims to generate strains with mutations in the remaining 25,000.

That is also the goal of a company, Lexicon Genetics of the Woodlands, Tex., just north of Houston. "We have coverage of 59 percent of the genes in stem cells," said the chief executive, Dr. Arthur Sands.

Lexicon Genetics has a technique to disrupt genes in embryonic stem cells, which can then be grown into full mice. The mice are given an "executive physical," Dr. Sands said, an exhaustive examination to see what defects are caused by whichever gene they are missing.

The mice can be used to test drugs before they are invented, Dr. Sands says. That is because most drugs aim at enzymes or receptors, which are products of genes, and a mouse in which that gene has been eliminated mimics the effects of any drug that singles out the gene's product.

Mice are not obviously people's equal in terms of intellect, but scientists have found ingenious ways to make mice serve as models for psychiatric diseases. Lexicon has a knockout mouse that lacks the brain cell receptor that Prozac focuses on and that has the predicted behavioral effects.

At the Jackson Laboratory, Dr. Wayne Frankel is looking for mice that do not become used to the same stimulus, an anomaly that may underlie schizophrenia. "The approach is not necessarily to find a mouse that's depressed or autistic, but to understand aspects of the disorder," Dr. Frankel said.

The laboratory mouse is something of an international creation, owing its heritage to mouse fanciers in China, Japan, Europe and the United States. There are four subspecies of wild house mouse, of which the two most prominent are Mus musculus, which evolved in Western Europe, and Mus domesticus, which came from Eastern Europe.

Mus domesticus colonized much of the world outside Europe, including the Americas, Africa and Australia. By the 1700's, mouse fanciers in Japan and China had domesticated many varieties of mice, mostly from musculus and domesticus, and Europeans later imported them, according to an article last week in Nature by the Mouse Genome Sequencing Consortium.

When Harvard biologists in the early 1900's needed mice to test Mendel's newly discovered laws, they bought mouse strains from Abbie Lathrop, a retired school teacher who bred fancy mice on her farm in Granby, Mass. Mice from her farm were developed into the common laboratory strains known as DBA and C57BL.

Harvard's Clarence Little, who bred C57BL, was given money by Edsel Ford and Roscoe Jackson, head of the Hudson Motor Car Company, to set up the Jackson Laboratory. It is C57BL whose genome is being decoded by the consortium.

House mice are often called commensals because they live in houses and barns almost as guests, albeit uninvited ones, at the same table. But some consider that description is too kind.

"Rather than being commensals," Dr. Dustin Penn of the University of Utah writes sternly in his "House Mouse Primer," "house mice are usually kleptoparasites, as they have been stealing our food stores since the agricultural revolution."

Maybe. But in sharing their genome and serving diligently as guinea pigs in genetic tests, mice are well into repayment of their long-term debt.