Of mice and men

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praguepost.com, by Daniel Bardsley The Academy of Sciences of the Czech Republic

Center in Prague uses rodents to understand human genetics

A century and a half ago at St. Thomas' Abbey in Brno, the monk Gregor Mendel carried out pioneering experiments on pea plants that are now studied in biology lessons in schools the world over.

Largely unappreciated during his lifetime, Mendel produced a body of work that helped demonstrate how characteristics are inherited, giving rise to the science of genetics.

It took another 100 years for researchers to work out the structure of DNA, the inherited genetic material, but since then the tools of molecular biology have allowed progress at a breathless pace.

There is now a vast and sophisticated understanding of how genes produce the proteins that control how organisms function at the cellular level. The effects of genes on illnesses are increasingly understood, and genetically engineered organisms produce everything from breakfast cereals to medicines.

Given the country's link to Mendel, it seems appropriate that the Czech Republic is strengthening its position as a center for genetic research, with mice taking center stage in the latest efforts.

In the south of Prague, the Institute of Molecular Genetics, part of the Academy of Sciences of the Czech Republic (AVČR), is building a vast resource of genetically engineered mice that enable scientists to analyze the function of individual genes.

These creatures can be used to uncover the reasons behind an array of diseases in mice and humans, potentially leading to improved medical treatments.

"The center that we're building should have all the necessary pillars to produce the mice and analyze them completely. It will be one of the largest mouse clinics in Europe," said Radislav Sedláček, head of the project.

Sedláček, a 47-year-old Czech professional who has spent most of his career in Germany, has worked at the Institute of Molecular Genetics for the past four years, increasing the center's stocks of mice, each of which has a mutation in a different single gene.

"They asked whether I was able to build this technology. In the Czech Republic there were many attempts to do this, but all of them were unsuccessful [until now]," he said.

Sedláček heads the functional genomics program of Biocev, a joint initiative of the AVČR and Charles University, to be constructed in Vestec just south of Prague over the next two years at a cost of 2.8 billion Kč, most from the European Union.

The research in the Czech Republic is part of an international effort to use mice, which have about 21,000 genes, as a model for understanding the genetics of disease.

Mice and humans are similar genetically, most of their genes being equivalent, so by analyzing mice that have one gene that no longer works, researchers can develop a greater understanding of the functions of individual human genes.

"If we modify something in the mouse, we try to use this information for humans," Sedláček said.

Internationally, the International Knockout Mouse Consortium hopes to create a resource of 21,000 different types of mice, and the creatures produced in Prague are sent for study across the world. Already, they have been supplied to around 20 institutions, mostly overseas.

Linked to this initiative is the International Mouse Phenotyping Consortium (IMPC), which looks at what characteristics are produced by each mouse gene. It goes beyond merely understanding the genetic code of genes, the sequence of DNA base pairs, by analyzing the actual function of these genes.

"When we know the human genome and the mouse genome, it doesn't say anything about what the purpose of the gene is, what the gene is doing in the organism," Sedláček said.

Indeed, Professor Steve Brown, director of the UK Medical Research Council's Mammalian Genetics Unit in Oxford, has described the IMPC as being about producing "an encyclopedia of mammalian gene function."

It is a complex process producing the "knockout mice," each of which has one gene that does not work.

First, that gene has to be sequenced before scientists can produce a manipulated version of the gene and link it to a marker gene.

The manipulated version of the gene is mixed in with the stem cells, the undifferentiated cells that go on to develop in different ways to form the tissues of each organism.

An electric current is applied to the stem cells, making them more likely to take up the foreign genetic material and incorporate it into their own chromosomes, the structures through which genes are inherited.

Stem cells that have incorporated this new genetic material are isolated and injected into mouse embryos, using an ultrafine syringe.

It can be expensive, with an objective for one of the microscopes used when this is carried out costing as much as 1 million Kč.

"We use it to drill a very fine hole into the embryo," Sedláček said.

The embryos are inserted into "foster mothers," and offspring that result are crossed with one another to produce a pure line of animals that have the manipulated gene in all their tissues. Scientists can study this line to help understand what the gene does.

Among the medical conditions being looked at are skin diseases, for which a special form of red shining mice has been developed.

Using animals for research is controversial, and Sedláček acknowledged campaigners may be justified in criticizing experiments to test cosmetics, for example. But, he said, despite there being many ways to study gene function that do not involve animals, there is no substitute for the creatures themselves.

"Our primary purpose is to … understand the development of disease. There's probably no way without the model organism," he said.

"They are coming up with more and more sophisticated things in vitro, but none of these things can match the things in vivo. You can use a specific culture of organs, but … this has very limited information. You need the whole complex organism."

The number of strains of mice held at the center increased this year by between 20 and 25, bringing the total to more than 300. Over the coming years, the facility is set to add between 50 and 100 new strains each year. It is no wonder researchers from across the globe are showing an ever-greater interest.

"Just last month, we got the request for eight mutants, not just [from] the Czech Republic, but [from the] United States," he said, adding plans were at hand for further growth.

"In the summer, we'll get many thousands of cages."