Return of the rat

European investment could see knock-out rats catching up with mutant mice in medical research.

The European Commission has approved the world's first major systems-biology programme to study the rat.

Known as EURATRANS — for European large-scale functional genomics in the rat for translational research — the multimillion-euro project includes collaborators in the United States and Japan. The aim of the initiative is to expand databases of genes, proteins and other biomolecules, analysing the information and translating it into a form that is useful to clinical researchers.

The effort represents a comeback for the rat, which fell from scientific prominence during the mouse-dominated genomics era, despite the unprecedented amounts of physiological data that have been gathered from it over the centuries.

"The rat is a better model than the mouse for many complex disorders that are so common in humans, like cardiovascular and psychiatric disease," says EURATRANS coordinator Norbert Hübner, a geneticist at the Max Delbrück Center for Molecular Medicine in Berlin. "The project will help rat genetics catch up with the many-years head start that mouse genetics has enjoyed."

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A Europe-led project could push the lab rat back into the spotlight.

In the late 1980s, researchers developed a technique to knock out single genes from mice using embryonic stem cells as a starting material, making it possible for geneticists to engineer the mutant strains needed to model human disease. Rat genetics proved trickier to manipulate, and the mouse's popularity as a lab animal soared.

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Two things have happened in the past few years that make a major assault on the rat feasible and worthwhile, says Hübner. "First, the huge advances in sequencing and other molecular technologies, and second, the problem which was preventing the development of gene knock-out technology in rats has been overcome." Last year, Austin Smith, director of the Wellcome Trust Centre for Stem Cell Research at the University of Cambridge, UK, and his colleagues achieved this by altering the culture medium conditions used to grow embryonic cells *in vitro*[1]. Knock-out rats have not yet been created using these cells, but this is one of the aims of the EURATRANS project, in which Smith is also a participant.

The 16 institutions participating in EURATRANS will receive a total of €10.5 million (US$14.9 million) from the commission, which they will match from their own resources. The money will be used to create detailed genome sequences of the eight progenitor strains of rat that gave rise to the stock rats generated at the US National Institutes of Health (NIH) laboratories in Bethesda, Maryland, the diverse genetics of which mirrors that of human populations.

The project will also apply state-of-the-art technologies in order to generate data on rat functional genomics. Thirty additional 'recombinant inbred strains' created at the Prague-based Institute of Physiology, part of the Academy of Sciences of the Czech Republic, will also get this treatment. These rats were made by crossing the two strains of rat that have already had their genomes sequenced — the Norwegian brown rat (*Rattus norvegicus*)[2] and the albino spontaneously hypertensive rat, which develops high blood pressure early in life. The crosses display a range of clinical phenotypes, such as variations in blood pressure and glucose tolerance, and resistance to insulin, so studying them may help researchers to unpick the many genes involved in these pathologies.

But identifying genes is not enough to understand complex diseases, stresses Hübner. "It is a question of what happens to those genes." For example, a recent genome-wide association study in thousands of people implicated the gene for the enzyme HMGCoA reductase as a risk factor in cardiovascular disease — but found the risk to be small[3]. Yet the statin drugs that target this enzyme are among the most effective for cardiovascular disease. "That's why we need to integrate genomic information with other molecular information and learn more about entire molecular pathways in cells that may go wrong in disease," says Hübner.

The systems-biology approach of EURATRANS aims to integrate terabytes of information — on gene sequences, gene transcription and chemical modification, as well as proteomic and metabolomic data — in order to identify these molecular networks. The consortium will then confirm the networks' involvement in disease using appropriately engineered rats.

Smith points out that the growing use of mutant rats will come at a cost. Being larger than mice and taking longer to reach maturity, rats are more expensive to keep, although their size can also make them easier to work with. "Funding agencies will need to be persuaded that it is worth the investment," he says.

EURATRANS is one of the first projects to be approved under a reciprocal funding arrangement agreed in late 2008 between the European Union and the NIH. This means that a consortium does not have to prove, as it still does for other non-EU countries, that no laboratory with the same skills exists in Europe.

EURATRANS participant Tadao Serikawa of Kyoto University in Japan, who heads the National BioResource Project–Rat initiative, says that the global nature of the EU project is important both for exchange of skills and information, and because "it avoids redundant experiments, which saves animals, time and money and accelerates biomedical progress". ■

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1. Buehr, M. *et al. Cell* **135,** 1287–1298 (2008).
2. Rat Genome Sequencing Project Consortium *Nature* **428,** 493–521 (2004).
3. Kathiresan, S. *et al. Nature Genet.* **40,** 189–197 (2008).