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「ラットES細胞の樹立・遺伝子改変ラットの作製」

Return of the rat Nature 460, 2009

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."

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.

Two things have happened in the past few years that make a major assault on the rat feasible and worthwhile, says Hüb-

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

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-

"The rat is a better model than the mouse for many complex disorders that are common in humans."

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.

A. ZVOZNIKOV/ARIFA.COM

25年間：不可能

ラット研究は100年の歴史
発がん実験、薬理実験、10倍のサイズ

"The rat is a better model than the mouse for many complex disorders that are common in humans."

ヒトの複合疾患
マウスよりも優れたモデル

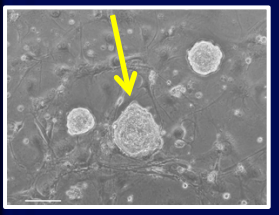
- ラットは発がん実験を始め、実験動物として非常に長い歴史を持っております。
- Natureにも記されているように実はヒトの複合疾患を考える上で、ラットはマウスよりも優れたモデルであると言われております。
- マウスで確立されて以来、25年間・・・。

→ひとたび遺伝子改変技術が確立すれば基礎や臨床に向けた研究の飛躍が期待できます。

世界中の研究者との競争

1981　1986　2008　2010

ES 細胞　遺伝子改変マウス　ES 細胞　遺伝子改変ラット



Capture of Authentic Embryonic Stem Cells from Rat Blastocysts　UK

Austin Smith's group, 2008 *Cell*

Germline Competent Embryonic Stem Cells Derived from Rat Blastocysts　USA

Qi-Long Ying's group, 2008 *Cell*

研究業績

2010-2011年

Generation of genetically modified rats from embryonic stem cells

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Kawamata & Ochiya, *Methods Mol Biol*, 597, 169-77 (2010) Impact Factor: 13.9

Kawamata & Ochiya, *Cell Mol Life Sci*, 68, 1911-5 (2011) Impact Factor: 7.047

Kawamata & Ochiya, *InTech*, p383-96 (2011) Open access book

・2008年には遺伝子改変に必須のラットES細胞を競争相手に樹立されてしまい、絶望的な状況に陥りました。しかし、彼らのES細胞は長期培養で染色体異常が起きてしまうのに対し、我々が独自の方法で樹立したES細胞は非常に安定しており、彼らよりも1ヶ月早く遺伝子改変ラットの作製に成功しました。