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Embracing the rat

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In the past fifty years, the role of the rat has shifted from a bane on society – eater of harvests, carrier of disease – to an animal of great utility, as the best physiological model for research. Now the rat's value to researchers is poised to skyrocket with the recently completed sequencing of the rat genome. Richard Gibbs, Director of the Human Genome Sequencing Center at Baylor College of Medicine (http://www.hgsc.bcm.tmc.edu/), headed up the enormous consortium of researchers from over 20 institutions worldwide. Gibbs says that the sequence will be valuable to many areas of biology, but its greatest potential lies in the development of models of complex human disease.

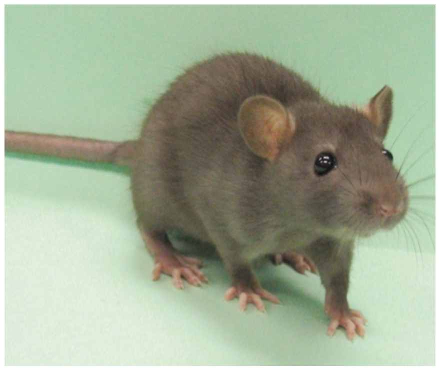

Image courtesy of the National Human Genome Research Institute (http://www.nhgri.nih.gov)

An ideal model for complex disease

The mouse has been a favorite tool of geneticists. Knock-out technology has allowed them to insert or delete individual genes in mice, providing a useful model for mendelian disease. The difficulty with manipulation of rat genes, though, has been 'the Achilles heel for rat in genetics,' says Gibbs. But the rat has been the darling of physiologists. Allen Cowley, Jr, Chair of the Physiology Department at the Medical College of Wisconsin (http://www.mcw.edu/pathol/ed/), points out that the rat's size has allowed for 'meaningful physiological organ and whole animal studies,' which has made them such a valuable animal model.

Cowley, who was not involved in the sequencing project, sees great potential for the rat genome in disease research. 'The mouse has been of tremendous use, but not for complex diseases.' The rat, in contrast, has been bred into hundreds of model strains for diseases like diabetes, cardiac disease, and obesity. For example, notes Cowley, there are over a dozen rat models for hypertension alone, each of which represents the biology of some portion of the human disease population. Researchers have used these rat models to identify large regions of a chromosome – or quantitative trait loci – that contribute to a condition. When it comes to quantitative genetics, says Gibbs, 'the rat really has such a huge head start.' But the individual genes that contribute to a disease are in most cases unknown. The genome sequence will allow one to 'straight away go to the rat and look at the orthologues' to human disease genes. Cowley too is enthusiastic that the genome will 'simplify the search for genes in complex disease.' Both are hoping that the improved rat model of disease will eventually lead to better therapeutic targets, and lower the current 90% failure rate in drug development.

Mammalian evolution

Along with the mouse and human, this third mammalian genome sequence provides a key data point from an evolutionary standpoint. By comparing the sequences of all three organisms, researchers will be able to determine when certain events occurred on an evolutionary time scale, and get a better picture of our common mammalian ancestor – that organism that 'scurried around the dinosaur eggs' and survived when dinosaurs died out, says Gibbs. The evolutionary data, he adds, 'is icing on the cake, but has turned out to be very exciting.' Some evolutionary biologists argued that, with limited sequencing resources, the rat – so closely related to mouse – was not a worthy endeavor. But for physiologists, 'it's not about evolution, it's about consummating the model' of disease. 'From the rat people's point of view, there was never a question.'

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