Rats!

New genetic technologies in the rat open new research opportunities and call for more careful choice of the most suitable model organism before embarking on a study.

Although 'lab rat' entered the English lexicon after its introduction as a laboratory animal in the mid-1800s, recently the laboratory mouse has received most of the accolades. Since 1990, the number of yearly scientific publications indexed by PubMed devoted to the mouse increased threefold, overtaking the number of papers devoted to the rat in 2002.

The outward similarity of mice and rats can give the false impression that mice are essentially smaller, faster-breeding substitutes for rats. The evolutionary distance between mice and rats, however, may be as great as that between humans and Old World monkeys. The rat's larger size and better characterized and more human-like physiology has maintained the rat as the model of choice in areas of research where this difference is crucial. In the 1980s, however, mouse embryonic stem cell technology began allowing the creation of genetically engineered mouse lines with specific genes added or removed, and because this technology eluded the rat, the mouse became the model of choice for vertebrate genetic research.

But rat genetics began to catch up after the report of the first cloned rat in 2003 and sequencing of the rat genome in 2004. Zinc-finger nuclease technology has now been used to create dozens of knockout rat lines, and embryonic stem cell–based technologies are on the cusp of delivering their first knockout rats. On page 443 of this issue, researchers report the use of transposon-mediated mutagenesis to knock out genes in rat spermatogonial stem cells and create 35 mutant rat lines. This method will greatly simplify high-throughput generation of rat knockout lines.

Although targeted mutants are invaluable for studies in which you know or have a good idea what genes are involved in a disease, when this is not the case, it is often better to use models that naturally mimic the disease phenotype. Years have been devoted to phenotype-guided breeding of hundreds of inbred rat strains that mimic the phenotypes and physiological progression of complex human diseases. Each strain may have dozens of quantitative trait loci containing genes associated with a disease phenotype. Mice have many more spontaneous mutant lines, ~2,000 at the Jackson Laboratory alone, but these are usually composed of one major gene and one or two modifying genes, and efforts at phenotype-guided breeding in the mouse have been limited.

The arrival of these genetic technologies provides new opportunities to probe these disease models, and large collaborative projects, such as the international EURATRANS consortium, are taking advantage of them. Funded under the 7th European Framework Program, EURATRANS intends to identify the major pathways in rat models of inflammatory, cardiovascular and metabolic, and behavioral disorders by genome sequencing, genome-wide transcriptional and epigenetic profiling, and proteomic and metabonomic characterization of nine rat strains. Functional pathways derived from these data will be validated by generating knockout lines and then integrated with results from human genome-wide association studies.

The advantages the rat offers should not be ignored by researchers considering a new project. Outreach efforts are crucial for educating researchers who may be unfamiliar with the established benefits of rats for particular studies. In addition, efforts are needed to transfer the genetic technologies available in the rat to investigators who already use this organism in their studies but may be unfamiliar with the new technical opportunities. Funding institutions and grant reviewers need to be aware that rats are the best choice for some studies and that the higher animal facility costs are justified.

Preliminary evidence indicates that development of genetically engineered model rat lines will occur much faster than it did for the mouse, offering challenges and opportunities for the community. Officials at the Rat Resource and Research Center (RRRC)—a National Institutes of Health–funded repository service for importing, storing and distributing hundreds of high-value rat strains—anticipate that the number of available rat lines will quadruple by 2014. By maintaining the majority of strains as cryopreserved materials, keeping only commonly requested strains as live colonies and allowing very highly requested strains to be distributed by commercial providers, the RRRC has the capacity to archive approximately 2,500 rat lines per year while still fulfilling their distribution mandate.

Recently the mouse was often the best or safest choice for new projects. Now that genetic technologies are catching up in the rat and other organisms, it is becoming more crucial that researchers educate themselves regarding the most suitable organism for their study. See *methagora* for additional information and links.