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Making the most of transgenic mice

Genetically modified mice are unquestionably a powerful tool for the study of biology. In particular they have contributed enormously to our understanding of development, largely because developmental genetics had a well established conceptual framework that could accomodate the new technology. In contrast, their application to adult brain function has proven more complicated. Whereas developmental biologists tend to study cellular effects or well defined cell–cell interactions (for instance, those that affect cell fate), interpreting mutant brain phenotypes requires understanding higher-level phenomena, such as a neural circuit and the behavior it generates.

One problem with almost any adult phenotype is the potential confounding effect of developmental compensation. Plastic mechanisms are particularly common in the brain, which wires and rewires itself in response to experience. If the brain lacks a particular gene, development itself is likely to be affected, so the mutant phenotype may not clearly reflect the missing gene's normal function. Thus, even though genetics offers a degree of specificity that pharmacologists may envy, the gene knockout approach is not a replacement for pharmacology, but a complementary technique with its own interpretational problems. Indeed, Steven Hyman, director of the National Institute for Mental Health (NIMH), argues that the confounds may often be even greater for genetic than for pharmacological methods. Peter Seeburg, a molecular neurobiologist at the Max-Planck Institute in Heidelberg, is even more blunt; many of the conclusions about brain function from knockout studies, he says, must be taken "not just with a grain of salt, but with a rock."

The best current hope for overcoming these obstacles is conditional knockouts, in which genes can be turned on or off at specific times in particular brain regions or cell types. This techology is still in its infancy, however, and many problems remain to be overcome. Rigorous approaches such as timed rescue of mutant phenotypes are well established among (for instance) *Drosophila* geneticists, but analogous manipulations of mutant mice are currently impossible and will probably remain so for some time to come.

These issues seem likely to become more acute as the number of transgenic studies continues to grow. NIMH has expressed strong support for mouse genetics and expects that much of the behavioral and physiological work that has traditionally been done in rats will need to be transferred to mice to take advantage of molecular genetic technologies. NIMH and the National Institute for Neurological Diseases and Stroke, along with several other institutes, have already committed themselves to what has been termed the Brain Molecular Anatomy Project (BMAP) and are reviewing proposals for a large-scale characterization of gene expression in the mouse brain.

A recent workshop at NIMH[1] addressed many of these issues, with a view to defining strategic priorities for future funding. The recommendations from the panel have yet to be finalized, but are likely to include a proposal for large-scale mutagenesis, with a view to identifying new genes that affect behavior. Random mutagenesis is a standard approach in invertebrate genetics (and more recently in zebra fish), but it has not yet been widely applied in mice, mainly for cost regions. It has, however, had several recent successes (notably the identification of *clock*, a gene that affects circadian rhythms), and mouse mutagenesis programs are now underway in both Germany and Britain. NIMH hopes that large-scale random mutagenesis and behavioral screening will identify new genes that affect a variety of mammalian brain functions. In particular, they expect to emphasize functions such as memory, emotion and motivation, which may provide insights into the pathogenesis of human psychiatric conditions. One key will be to select and define appropriate strains for analysis, as genetic background can strongly affect mutant phenotype. Another goal will be to develop a large battery of behavioral tests that are both sophisticated and standardized and to get away from the simplistic tendency, as Hyman puts it, "to equate learning with the water-maze and fear with the open-field test."

This ambitious research program will not come cheap; although the budget has not yet been finalized, Hyman expects that NIMH will spend $2.5 million in the coming fiscal year and that this will be part of a larger National Institutes of Health (NIH) initiative that will involve well over $10 million per year. Critics will raise concerns about the rise of the 'big science mentality' and the possible impact on funding of individual labs. Yet there is no doubt that genetic research benefits from economies of scale, and NIMH intends that the benefits be spread throughout the neuroscience community.

For this to happen, however, one urgent priority is to develop a better system for archiving and distribution of mutant mouse strains[2]. The Jackson Laboratory in Maine has set the standard in this respect, but it cannot handle every mutant that is created, and many potentially valuable strains are languishing unstudied in laboratories around the world or—worse still—dying out for lack of resources for their maintenance and distribution. A broad-based system of access will be essential, not least because the laboratories with the expertise to make mutant mice are not always the best placed to analyze them. The necessary combination of expertise in molecular biology, mouse genetics, electrophysiology and behavior is difficult to assemble for even the largest and best-funded laboratories, and although smaller groups can sometimes collaborate, they are often unable to either create for themselves or obtain from others the mouse strains that might advance their own research programs. By centralizing and scaling up the production and characterization of new mutants, Hyman and other proponents of the NIH initiative hope to create a platform that will support individual investigator-led projects, and thereby provide unprecedented access to this powerful technology.

1. NIMH workshop, Mouse genetics: brain and behavior, August 31 to September 1, 1998.
2. *Nature Genetics* **18**, 299–300 (1998).

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