Mighty mice

Clarence Little's brainwave gave biomedical researchers their best friend.

Michael F. W. Festing and Elizabeth M. C. Fisher

In 1909 Clarence Cook Little, an undergraduate at Harvard, wanted to study coat-colour inheritance in mice. He got some brown mice, and produced a pure line by mating brother with sister. At least 17 Nobel prizes, two major scientific tools (monoclonal antibodies and gene-targeted strains), profound scientific insights into the immune system, retroviruses, oncogenes, cancer, the inheritance of complex traits, and countless scientific experiments have flowed from his inbred, or 'isogenic', strains.

Others also saw the potential value of pure lines. Sewall Wright inbred guinea pigs, and Helen King inbred rats at about the same time. However, Little's master-stroke was to found, in 1929, the Roscoe B. Jackson Memorial Laboratory in Bar Harbor, Maine. He had the foresight to make it a multidisciplinary laboratory doing research into all aspects of mouse biology, with a special emphasis on genetics. It also spread its influence by supplying mice and offering training to other researchers. Two Nobel prizewinners (David Baltimore and Howard Temin) ascribe their interest in research to spending a summer there as high-school students.

Scientific advances are often unpredictable. One of the Jackson Laboratory's obscure mouse strains, called '129', developed testicular teratomas with a bizarre mixture of differentiated tissues. Elsewhere, 'embryonic carcinoma' stem cells from these mice were isolated, grown in tissue culture, and fused with normal pre-implantation embryos to make chimaeric mice. Unfortunately, these all developed tumours.

However, embryonic stem-cell lines from pre-implantation embryos of strain 129 were established and used to make chimaeras which transmitted the 129 genotype to their offspring. The final step was the development of a homologous recombination technique for targeting individual genes in the stem cells. The knockout mouse was born.

Good stem cells are difficult to obtain with other mouse strains, and none have yet been developed for rats. Whether the genes that lead to the development of testicular teratomas are the same ones that allow the establishment of useful embryonic stem cells remains an open question, but no one could have foreseen such a breakthrough from this low-key start.

Mice of strain BALB/c, developed largely at the Jackson Laboratory, develop myelomas when treated with mineral oil intraperitoneally. Immortal cell lines derived from these leukaemias were fused, by George Köhler and César Milstein, with lymphocytes from immunized animals. The resulting hybridomas produced monoclonal antibodies which can now be produced on a vast scale *in vitro*. These are valuable research tools, and have enormous therapeutic potential.

JACKSON MEMORIAL LABORATORY

Little's helper: Clarence Little, and the inbred mice that can lay claim to 17 Nobel prizes.

In 1932, mammary tumours found in some mouse strains at the Jackson Laboratory, including one known as C3H, were found to be due to a virus passed from mother to offspring through her milk. This was the first of several oncogenic viruses to be found in mammals, although Peyton Rous had found his sarcoma virus of chickens some years earlier. Some oncogenic viruses were found to carry nucleotide sequences homologous to normal, highly conserved cellular genes. These 'proto-oncogenes' turned out to code for a large number of signalling molecules associated with cell-cycle regulation, growth and programmed cell death (apoptosis). When diseases such as cancer and AIDS are eventually conquered, isogenic mice and the understanding of oncogenes will have played an important part in the battle.

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The genetic uniformity of each isogenic strain and the differences between strains has been used to study the architecture of the immune system. As early as 1903, it was found that tumours could sometimes be transplanted to other mice, but were often rejected. The laws of transplantation genetics were initially proposed by Little and E. E. Tyzzer, based on the very first experiments ever done with inbred strains.

It fell to George Snell at the Jackson Laboratory to characterize the mouse major histocompatibility complex, using classical genetic backcrossing techniques, for which he received a share of the 1980 Nobel prize. These studies, and those of some eight to ten other Nobel prizewinning immunologists who used isogenic strains, have led to enormous advances in immunology and the saving of many lives, through organ and tissue transplantation.

Yet there are disciplines where the value of these rodents is only beginning to be appreciated. Humans vary in susceptibility to chemicals and environmental toxins, with several major Mendelian loci already identified. The pharmaceutical and chemical industries could use isogenic strains to develop animal models and identify genes for susceptibility to chemicals and side effects of drugs, using strategies pioneered by immunologists and, more recently, by geneticists studying complex traits.

Potentially dangerous chemicals, and drugs that help some people but damage others, cannot be studied ethically in humans. Yet, incredibly, most toxicological research, for example, is still done on 'white' mice and rats, with no attempt to control for genetic variation. Pharmacologists and toxicologists should wake up and embrace modern genetics, including Clarence Cook Little's isogenic strains. ■

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