UCCAA University of California Center for Animal Alternatives

The Mouse in Science: Cancer Research

Mice have been used in cancer research since 1894. Initially, mice were used for same-species tumor transplantations and drug treatment studies. In 1921, inbred strains that were predisposed to getting tumors were started and disseminated among cancer researchers. Many more strains of mice were originated beginning in 1929 with the founding of the Jackson Laboratory in Bar Harbor, Maine, now the largest supplier of mice.

In 1962, the discovery of a mutant mouse with low immunity led to human tumor transplantations, a valuable breakthrough for cancer research. A further breakthrough in the late 1980s led to transgenic mice, those whose genes have been altered to produce a desired characteristic. Oncogenes, or genes that cause cancer, could then be studied in greater detail.

Life in the Laboratory.
Mice adapt well to laboratory housing and can be housed socially or individually. Significant numbers can be housed in relatively little space because of their small body size. They possess a surprising genetic similarity to humans. These features, combined with a rapid rate of reproduction, make mice the mammal of choice for fine-tuned genetic manipulation. Mice with many different special features have been bred or created, including some described here.

Inbred Strains.
The inbreeding of mice predisposed to developing cancer has led to a variety of specialized strains. In 1921, Leonell Strong established many inbred strains that frequently and spontaneously developed cancer. Serving as a virtually unlimited source of many types of tumors, these inbred mice have made it possible to study the growth and general characteristics of tumors.

Nude Mice.
The nude mouse is a major breakthrough for cancer research because it allows human tumors to be studied in another animal. The nude mouse, a hairless mutant discovered in 1962, is immunodeficient, and thus does not reject tumor transplantations from other species. It lacks a thymus, which is essential for the

production of T-cells, **lymphocytes** that are essential to the immune system. iBy transplanting an actual human tumor into a nude mouse, the tumor can be studied in a whole animal system.

Before discovery of the nude mouse, human tumors were grafted and grown in immune-privileged sites, such as the anterior chamber of the eye, the brain and the cheek pouch. These locations are inconvenient, and the tumors are eventually rejected. The recessive nu gene, which is responsible for the lack of a thymus in nude mice, has since been introduced into many types of inbred strains of mice with other immunodeficiencies.

SCID Mice.
In 1983, mice with severe combined immune deficiency (SCID) were discovered. SCID mice are even more immunodeficient than nude mice. Tumors from other species are easily transplanted into SCID mice and will grow without being rejected. For certain specific tumors, SCID mice show improved transplantability over nude mice. In addition, SCID mice are ideal for the growth of **hybridomas** *in vivo* to produce a continuous supply of antibody (Ab). Sometimes referred to as a reagent, Ab is necessary for a wide range of diagnostic, clinical and experimental procedures.

Transgenic Mice.
In the late 1980s the methodology for engineering transgenic mice made it possible to create mice to address specific questions and problems. Transgenic mice result from genetically altered embryos: a gene or combination of genes is microinjected into developing oocytes. The genetic alteration affects the germ plasm, and subsequently can be transmitted to progeny. Through selective breeding, it then is possible to maintain a strain of mice consisting of individuals with particular traits of interest.

A specific trait, such as a predisposition to develop a particular type of tumor, can be introduced into a mouse strain by injecting into the embryo an oncogene, a gene that causes cancer. Transgenic mice permit the study of cancer in specific tissues, including initial tumor development.

Uses.
The purpose of cancer research is to understand tumor initiation and growth. This information helps researchers develop treatments, and eventually cures, for cancer. Many aspects of cancer research use mice, including:

*** Production of Tumors.**
Different: Types of cancer are induced through inbreeding or transgenic techniques (e.g., breast cancer).

Specific: Specific tumors from humans are transplanted into nude and SCID mice.

*** Therapy Testing.**
Chemotherapy: Mice with tumors are treated with different compounds to see if their tumors regress. Cancer cells from humans are also cultured in vitro to screen possible useful compounds.

Radiotherapy: Mice with tumors are exposed to radiation to see whether their tumors regress.

Immunotherapy: The immune system in whole animals is stimulated to treat cancer.

1. Monoclonal Antibodies (MAbs): MAbs are used to target cancer cells selectively.

2. Interferons: A species-specific, natural body substance that is secreted to fight viral infections, mouse interferon has been used against mouse leukemia and has been shown to stop cell division. Interferon shows promise in treating hairy-cell leukemia, non-Hodgkin's lymphoma, and other cancers.

3. Interleukins (IL): Mostly focusing on IL-2, researchers have tested its ability in vivo to kill tumor cells in mice. IL-2 appears to increase T-cell immune properties along with a generalized immune effect against cancer.

Carcinogenicity Testing.
Mice and other animals are used to test the cancer-causing ability of substances. Although mice are still widely used for these tests, the number of whole animals used in carcinogenicity testing has diminished. Faster, short-term tests are now used to screen substances. One such test uses cells growing in vitro to measure the ability of a substance to change cellular DNA. If it causes changes in DNA, it is considered a mutagen, or potential carcinogen.

Alternatives in Cancer Research.
Although no alternatives could completely replace the use of mice in current cancer research, uses of mice have already been reduced and refined. *In vitro* systems such as cell and tissue culture are the primary alternatives. Cell culture is less expensive than the use of whole animals and is easier to manipulate. For example, cancer-causing effects of radiation have been studied in cell culture. If whole animals (*in vivo*) were used, they would have to be irradiated and observed throughout their lifetime for tumor development -- a more costly and time-consuming procedure than the use of cell cultures. Changes in the growth of cells are good indicators for revealing when normal cells become tumor-producing.

Some aspects of cancer research require whole animal studies cells cannot mimic the physiology of a live animal. Clinical studies involving humans are another alternative. *In vivo, in vitro,* and clinical studies all combined produce the most informative results.

Recent Breakthroughs.

Research with both human patients and animal models is in progress, seeking to devise improved methods of treating cancer. With the development of recombinant DNA technology and gene therapy, a functioning gene is inserted into the cells of a patient in order to correct a genetic defect or to introduce a new function into the cell. This technique was approved for clinical trials in the late 1980s. It may become possible to use retroviruses as vectors to deliver the particular desirable genes into defective cells.

Adenoviruses are a type of virus that attack human cells; recently it has been found that they "turn off" the cancer- suppressing p53 gene. In cancerous cells, the p53 gene is defective: it fails to suppress cancer. Researchers have genetically engineered an adenovirus that attacks the defective p53 gene and protects the normal p53 gene. When human tumors in mice were injected with this adenovirus, the tumors regressed and disappeared. These initial results suggest that the method might also be effective in humans.

Glossary.

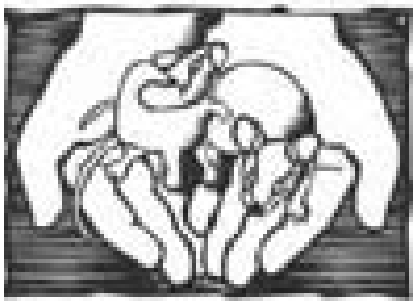
antibody a protein formed in reaction to an antigen, which it then attacks and destroys.

hybridoma. the cell produced by the fusion of an antibody- producing cell and a tumor cell.

interleukins. specialized substances that help to produce cellular immunity.

lymphocyte a type of white blood cell.

The Mouse in Science is published by the UC Center for Animal Alternatives. The UCCAA mission is to disseminate information concerning animal alternatives so as to improve the well-being and quality of life of animals wherever possible, and to optimize their contribution to education and research.



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