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Center News

Mouse Models Provide Insights

"Just because a cancer treatment works in mice doesn't mean it will work in human patients." This has long been a lament of cancer researchers. Now, several MSKCC laboratories are trying to change that by developing mouse models that have tumors that are more like human tumors — both in the way they grow and spread and in their genetic behavior. These models not only contribute to a deeper understanding of what causes many cancers, but they provide a better way to test therapies for some of the most intractable, deadly tumors.

Mice have been used in cancer research for decades. Because of their size, they are easy to keep

Mouse-Model Research

continued from page 1

in large numbers, and their short life span allows the study of how disease develops over time. But more-traditional mouse models often do not yield the results researchers hope for. Treatments that show promise in these models commonly fail in people.

Advances in cancer genetics are changing that. Now that more genes related to human cancers are being identified, scientists are testing those genes in mice — inserting different combinations and comparing responses — to determine which genes are actually involved in tumor formation.

MSK geneticist Pier Paolo Pandolfi developed a mouse model for acute promyelocytic leukemia (APL) that contributed to a new treatment, arsenic trioxide. This mouse model is made by inserting a faulty gene called *PML-RARα*, which causes APL in humans, into mice. *PML-RARα* doesn't cause APL immediately but sets in motion the genetic chain reaction that leads to disease. This allows study of the disease's progression. The mouse disease also is very similar to the human leukemia in responding to specific therapies known to be effective in human APL.

"Mouse models allow us to validate that a certain gene is involved in tumor formation," said Dr. Pandolfi. "They also allow us to unravel further the genetic pathways to disease." He notes that models allow researchers to study how the tumor reacts to its environment. "The tumor is not a killer in a bottle but in the body. The drugs we develop may not affect the tumor directly but instead elicit a favorable response from the surrounding tissue. That's something we wouldn't find if we were doing everything in a test tube."

Most recently, Dr. Pandolfi's laboratory developed a mouse model for prostate cancer. Using this model, he found that mice with one defective copy of the *PTEN* gene and one or two defective copies of the *p27* gene always develop prostate cancer. Because there are many genes involved in prostate cancer, he plans to develop more mouse models, allowing for targeted treatments for different forms of the disease.

Molecular geneticist and neurosurgeon Eric C. Holland has developed models for eight subtypes of gliomas, the most common brain cancers. While working as a fellow at the National Institutes of Health with Harold Varmus (now MSKCC President) in the mid-1990s, Dr. Holland took advantage of a new technique that employs as a gene delivery system in mice a virus normally found only in birds. Mice can be genetically altered to produce a receptor for the virus in certain cell types — brain cells, in this case. The cancer gene is packaged into the virus, which carries it to the target cells, where tumors then form.

Now, Dr. Varmus's laboratory continues to use the gene-delivery methods in liver, ovarian, breast, lung, and pancreatic cancers.

The need for better cancer therapies will continue to make mouse models important. "Treatments for glioblastomas are not very effective," said Dr. Holland. "Because most of my patients die, that drives me to find better therapies."

Animal Research Requires Oversight

All animal research at MSK must be approved by the Institutional Animal Care and Use Committee. Experiment protocols must include specifics on the number of animals involved and how they will be used and cared for.

Animal care is overseen by the Research Animal Resource Center (RARC), which includes animal care technicians, animal veterinary technicians, and veterinarians. There is also a diagnostic and clinical laboratory that specializes in laboratory animal diseases.

"My staff has a major impact on research," RARC Director Neil S. Lipman said. "They monitor the animals' health on a daily basis and keep an eye out for clinical problems that may alter the experiments' results."