

Mouse model tightly matches pediatric tumor syndrome, will speed drug hunt

By Michael C. Purdy

March 1, 2008 — Frustrated by the slow pace of new drug development for a condition that causes pediatric brain tumors, a neurologist at Washington University School of Medicine in St. Louis decided to try to fine-tune the animal models used to test new drugs.

Instead of studying one mouse model of the disease causing the brain tumors, the laboratory of David Gutmann, M.D., Ph.D., the Donald O. Schnuck Family Professor of Neurology, evaluated three. They "auditioned" the three models to see which was the best match for neurofibromatosis 1, a genetic condition that increases the risk of brain tumors and afflicts more than 100,000 people in the United States.

Animal models have long been used to explore the basic physiology underlying disease and to tentatively try out new remedies, but Gutmann believes that creating a tighter match between the animal models and the human disorder will allow more extensive and more accurate preclinical testing of potential therapies.

"If you think of how we move drugs from testing in the laboratory to testing in humans, this is an exciting step that's likely to speed the translation from bench to bedside," says Gutmann, the senior author of a report in the March 1 *Cancer Research*. "With more extensive preclinical testing in the mice, we can make sure a new drug is reaching its target protein in tumor cells, we can learn whether the drug is killing tumor cells or shutting off their growth, and we can get some indication of whether the drug is likely to have an adverse effect on the developing brain."

For the new study, Gutmann and colleagues Joshua Rubin, M.D., Ph.D., assistant professor of pediatrics, neurology and of neurobiology, and Joel Garbow, Ph.D., research associate professor of radiology, compared three mouse brain tumor models of neurofibromatosis 1. One of the models was the line his lab has previously used to study basic tumor biology.

To compare the mouse lines to the human disorder, researchers analyzed where the mice developed tumors, determined how quickly the tumor cells were dividing, and assessed when the tumors ceased growing. Based on these criteria, they learned that the model they had used earlier most faithfully reproduced the important features of the human condition. Researchers hope that this means the model will also give them the most accurate picture of how human patients are likely to respond to new treatments.

To test this theory, they gave the mice doses of a chemotherapy agent, temozolomide, currently in use clinically. Temozolomide slowed the growth and reduced the size of tumors in the mice, as it does in human patients.

Next researchers gave the mice rapamycin, an experimental drug currently in clinical trials as a treatment for other cancers. They found the drug was not killing tumor cells but preventing them from growing while the mice received regular doses of the drug. Higher doses could shut off tumor growth in a more long-lasting fashion, but also produced harmful side effects.

Because the trials were in mice, researchers could use a variety of invasive techniques to learn additional details about the effects of the drugs. For example, brain development is ongoing in young children, making the introduction of drugs that kill cells or stop their replication cause for significant concern. The mouse model let researchers look at developmental hotspots in the brain to see if temozolomide or rapamycin was adversely affecting the creation of new brain cells. They found that neither drug was.

Gutmann plans to use the mouse model in a new collaborative network funded by the Children's Tumor Foundation. His group and four other labs will test a variety of compounds against specific tumor types found in individuals affected with neurofibromatosis 1.

"We want to learn if these new drugs work the same in all aspects of the disease," Gutmann says. "We will be using what we learn to provide an efficient, rigorous pipeline for moving promising new drugs from the laboratory to clinical trials."

Hegedus B, Banerjee D, Yeh T-H, Rothermich S, Perry A, Rubin JB, Garbow JR, Gutmann DH. Preclinical cancer therapy in a mouse model of neurofibromatosis 1 optic glioma. *Cancer Research*, March 1, 2008.