

# New strategy likely to speed drug development for rare cancers

September 15 2011

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Researchers have identified promising new therapies for ependymoma, a rare tumor with few treatment options. St. Jude Children's Research Hospital investigators led the effort, which used a new, faster drug development system that combines the latest drug screening technology with the first accurate animal model of the tumor.

Investigators identified several dozen new and existing drugs as possible ependymoma treatment candidates. The drugs were found by screening 5,303 existing medicines, natural products and other compounds for activity against the tumor, which develops in the brain and spine of children and adults. The work is published in the current edition of the scientific journal *Cancer Cell*.

The list of candidate drugs included 5-fluorouracil (5-FU). 5-FU has been widely used to treat a variety of adult cancers but has not been formally tested against ependymoma. Based on study results, St. Jude is planning a clinical trial of 5-FU in young ependymoma patients, said senior author Richard Gilbertson, M.D., Ph.D., director of the St. Jude Comprehensive Cancer Center. Gilbertson credited the method used in this study with highlighting 5-FU's potential.

Researchers hope to use the same system to expand chemotherapy options for patients with other cancers. "This approach should significantly advance the efficiency and speed with which we discover and develop new treatments for rare cancers and cancer subtypes," the investigators noted. Jennifer Atkinson, Ph.D., a former St. Jude

postdoctoral fellow, is the first author. R. Kiplin Guy, Ph.D., chair of the St. Jude Department of Chemical Biology and Therapeutics, and Gilbertson are corresponding authors.

Rather than waiting years for clinical trial results, this system promises to take just months to provide key information about a drug's effectiveness and optimal administration, Gilbertson said.

The results are good news for patients with ependymoma and other cancers where treatment options are limited and the outlook remains bleak. While overall childhood cancer survival rates are now almost 80 percent, ependymoma remains incurable in up to 40 percent of patients. The tumor is found in 150 to 200 U.S. children annually, making it the third most common pediatric brain tumor. Treatment has changed little in the past 40 years and is limited to surgery and radiation.

Along with identifying and prioritizing drug development candidates against ependymoma, the research provided insight into the tumor's biology. The screening identified several messenger proteins, known as kinases, as possible new regulators of the tumor cell proliferation that makes cancer deadly. The abnormal tumor kinase activity occurred in certain pathways in tumor cells, including the insulin-signaling pathway and the centrosome cycle.

This study builds on earlier research led by Gilbertson that showed ependymoma includes nine different tumor subtypes. Each begins when particular mutations occur in stem cells from different regions of the brain or spine. Stem cells are the specialized cells that can divide and take on more specific functions.

For this project, investigators focused on a subtype D ependymoma. In earlier research, Gilbertson and his colleagues showed that extra copies of the EPHB2 gene caused this tumor subtype. The investigators used

this information to develop an accurate model of subtype D ependymomas in mice. The mouse model includes the same mutation in the same neural stem cell responsible for the human disease and was crucial for speeding drug development.

Researchers used an automated system to check 5,303 existing drugs, natural products and other compounds for activity against four different types of mouse brain cells, including normal neural stem cells, subtype D ependymoma tumor cells and cells from a different brain tumor.

Of the 634 compounds that showed activity against subtype D ependymoma cells, four demonstrated a two-fold greater ability to block the growth of the tumor cells, but not normal cells. The drugs included 5-FU and two closely related compounds. The fourth was beta-escin, which belongs to a family of drugs that are generating interest as potential chemotherapy agents.

5-FU also proved more effective than four other chemotherapy drugs in slowing tumor growth and extending the lives of mice with subtype D ependymoma. 5-FU also appeared less toxic to normal mouse brain cells than another drug, bortezomib, included in the study. The findings provided preliminary evidence that the screening system might provide an early indication of drug toxicity. The information could help guide treatment and prioritize drugs for development, researchers said.

The screening also highlighted a possible role for kinase inhibitors. Those are drugs that block activity of proteins that help drive cell division and sustain tumors. More than 18 inhibitors are in clinical trials that target the kinases this study tied to proliferation of both normal and ependymoma [tumor cells](#).

Provided by St. Jude Children's Research Hospital

Citation: New strategy likely to speed drug development for rare cancers (2011, September 15)  
retrieved 9 March 2023 from

<https://medicalxpress.com/news/2011-09-strategy-drug-rare-cancers.html>

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