Subtyping lessons in brain cancer

By Joanne Kotz, Senior Editor

A team at **St. Jude Children's Research Hospital** believes a screening approach based on disease subtypes will be important for identifying therapeutics for brain cancer patients. As a proof of principle, the researchers conducted a small molecule screen in a neural stem cell model of one subtype of ependymoma, a rare brain cancer.¹

On the basis of the data, the investigators plan to start a Phase I trial of 5-fluorouracil (5-FU) in pediatric ependymoma this year. The Phase I trial will be open to all patients, with stratification for subsequent trials to be determined on the basis of the Phase I trial results and preclinical testing of 5-FU in other ependymoma subtypes as more models become available.

Ependymoma is a rare form of glioma that develops leads to tumors in the brain and spinal cord. The cancer typically is treated with surgery and radiation; no chemotherapeutic has increased overall survival in clinical trials.

"We think that a key issue is that we have been treating all patients with ependymoma as if they had the same type of disease. We know now that this is not correct and we have to develop better ways of matching the right patients with the right therapies," said Richard Gilbertson, director of the comprehensive cancer center and of the division of brain tumor research at St. Jude.

As part of an ongoing program to develop therapies for pediatric brain tumors, a team led by Gilbertson has been focused on ependymoma on the basis of the team's recent progress in identifying molecularly distinct subpopulations of patients.

Last year Gilbertson reported in *Nature* that ependymomas could be grouped by transcriptional profiling into nine subtypes that were characterized by distinct oncogenic mutations in neural stem cells (NSCs) from different regions of the CNS. The team showed that mice implanted with embryonic cerebral NSCs engineered to overexpress *Eph* receptor B2 (*Ephb2*) developed brain tumors that resembled the D subtype.²

Now, Gilbertson and colleagues have teamed up with R. Kiplin Guy and used this first mouse model of an ependymoma subtype to identify potential therapies. Guy is chair of the department of chemical biology and therapeutics at St. Jude.

Initially, the researchers conducted a high throughput screen of about 5,300 small molecules in cultured subtype D ependymoma NSCs. In parallel, the researchers ran a control screen in normal mouse embryonic cerebral NSCs to weed out compounds that were cytotoxic to normal NSCs.

The top prospect from those two screens was the generic chemotherapeutic 5-FU, which was about ten times more selective against ependymoma NSCs than against normal NSCs.

In the mouse model of subtype D ependymoma, intravenous 5-FU increased survival in comparison with vehicle. No models for other ependymoma subtypes are available yet for cross comparisons.

Data were published in *Cancer Cell*.

"This study suggests that a combination of high throughput screening and *in vivo* efficacy studies can identify drug candidates that act specifically against a subtype of ependymoma," said Virginie Clément-Schatlo, cofounder and CSO of **Stemergie Biotechnology S.A.**, which is developing therapeutics and diagnostics targeting cancer stem cells.

"This work not only illustrates the importance of identifying ependymoma subtypes but also underscores the fact that there are likely to be subtype-specific treatments," agreed Mark Gilbert, professor in the department of neuro-oncology at **The University of Texas MD Anderson Cancer Center**.

"It is important information that good old conventional therapeutics such as 5-FU, for which we have a lot of clinical experience, may be highly effective in distinct subsets of tumors," noted Stefan Pfister, who investigates the molecular genetics of pediatric brain tumors.

Pfister is a professor in the department of molecular genetics at the **German Cancer Research Center (DKFZ)** and a physician in the department of pediatric oncology, hematology and immunology at **Heidelberg University**.

Gilbert, who also is CMO of the **Collaborative Ependymoma Research Network (CERN)**, added that 5-FU has not been previously tested in ependymoma. He said the disease's annual incidence is 500 patients in the U.S. and as a result it is difficult to run a prospective clinical trial for all patients and even a greater challenge to test ependymoma subtype-specific therapies.

Clinical test

The St. Jude team is planning to put the screening results to the test in the clinic. Gilbertson noted that although 5-FU is an approved drug, a Phase I trial is necessary because the route of administration and schedule planned for ependymoma will be different from that previously used to treat children with cancer.

An open question is whether 5-FU has efficacy beyond ependymoma subtype D.

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Heidelberg University**

Gilbertson agreed, saying the St. Jude team is planning to test the effects of 5-FU and other small molecules in mouse models of more subtypes of the disease. “We are developing new models for similar screens in other subtypes and already have two models generated,” he said.

If 5-FU proves to be effective only in the D subtype, running a sufficiently powered trial will be challenging, added Gilbert. He told SciBX that in addition to funding the Phase I trial, CERN is organizing a “concerted multi-institutional effort” to ensure that enough patients with subtype D are enrolled.

Next step, medulloblastoma

This subtype-based screening approach may be applicable to other brain cancers.

“This study is certainly paving the way for similar studies in other brain cancers for which driver mutations as well as corresponding cells of origin for distinct biological subtypes are known,” said Pfister.

He said a number of *in vitro* and *in vivo* models have been developed that could be used for this subtype screening approach, including in medulloblastoma, low-grade astrocytoma and glioblastoma.

Indeed, Gilbertson told SciBX, “we are using the same approach to screen our models of medulloblastoma subtypes.”

The results reported in the paper are unpatented and not available for licensing.

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