Pediatric high-grade gliomas (pHGG) comprise a group of particularly aggressive and deadly brain tumors. The lack of progress in treating pHGGs is one of the main reasons why brain tumors have surpassed leukemias as the leading cause of cancer-related death in children ages 19 and younger. It was also a driving factor in making high-grade gliomas the initial focus of the National Brain Tumor Society’s flagship pediatric research initiative, the Defeat Pediatric Brain Tumors Research Collaborative (DPBT).

The Defeat Pediatric Brain Tumors Research Collaborative has brought together some of the world’s best pediatric brain tumor research teams from St. Jude Children’s Research Hospital, Montreal Children’s Hospital/McGill University Health Centre, and the German Cancer Research Center to work in a team environment and share data and other resources to speed the scientific discovery process and ultimately develop better treatments for patients.

PROGRESS MADE

Over the last several years, major discoveries — often led by members of DPBT — have dramatically increased our understanding of the underlying mutations that fuel pediatric high-grade gliomas. These breakthroughs highlighted important differences between high-grade gliomas that occur in children versus their adult counterparts. They also found significant variability in the mutations these tumors may carry, depending on the age of the patient and the location of the tumor.

These advances were a significant first step toward developing new and better treatments. Yet, there is still a lot of work to be done to understand how these mutations cause a cell to become cancerous, as well as strategies for interrupting those processes with medical interventions.

Developing the Tools for Translational Research

Model systems (cells from patient tumor samples that can be grown in a laboratory dish or in a mouse) are important tools for cancer research. Models that represent the variety of different changes seen in these tumors can be used to both study the functional role of different mutations within the cell, as well as test potential new drugs to see if they can kill the pHGG tumor cells.

DPBT researchers have created 17 new model systems for use in research. In addition to making new, useful models, the team has also been compiling a list of as many other existing models of pHGG in the field as possible and adding them to an easily accessible table with detailed information about each.

“By sharing models across the DPBT team, we can expand the number of tools available to the Collaborative’s researchers”, said Dr. Baker, one of the leading Principal Investigators of the DPBT Collaborative from St. Jude’s. “Sharing model systems and the data derived from them is one of the strongest aspects of the Defeat Pediatric Brain Tumors program.”
The underlying mutations in pHGGs can change over time, including after initial treatment, with some mutations vanishing and new ones appearing. Finding simple ways to detect and track these mutations in patients could unveil new targets for drugs as well as inform ongoing treatment plans and strategies.

To do this type of tracking and analysis, researchers and doctors need to perform tests on samples of a tumor taken by biopsy. However, for pHGG patients, the prospect of repeated surgical biopsies is often not only extremely risky, but simply out of the question.

So, DPBT researchers want to see if it’s possible to use a “liquid biopsy” to collect fragments of DNA shed from the main tumor (called ctDNA, or circulating tumor DNA) from more easily accessible bodily fluids like blood, urine, and/or cerebrospinal fluid (CSF) for mutational analysis in pHGG patients.

In the first year of the project, techniques (called “custom capture”) were developed to detect mutations from ctDNA in different biofluids. The techniques were tested on blood, urine, and CSF samples from pHGG patients. This work found that detecting and analyzing ctDNA from CSF is the most reliable and promising method to refine moving forward, which is where Dr. Nada Jabado’s lab at McGill University/Montreal Children’s Hospital will focus their research in the coming year.

Researchers from DPBT got access to 120 tumor tissue samples and corresponding data that had been taken and archived from patients participating in a pHGG clinical trial. The team has begun analyzing these samples and data to learn more about how specific mutations found in the tumor samples may influence how the corresponding patient fared. This will help stratify patients for future clinical trials evaluating potential new treatments, as well as in regular clinical practice for determining which patients to give which drug(s).

DPBT researchers took some of the most promising results from prior testing of more than 1,300 potential drugs in pHGG cell cultures and conducted more focused evaluations and analyses of these drugs (and combination of drugs) in the new models they’ve been creating.

Doing so, they’ve identified some encouraging candidates that they want to further analyze as possible treatments to evaluate in human clinical trials (translational research):
In 2019, DPBT researchers are continuing to prioritize drug candidates for further testing in the mouse models that have been created. In addition to the GDC0084/PD0325901 and AZD1390/radiation combination treatments, other potential new drugs will be prioritized to better understand their therapeutic development opportunities. Special attention will be given to candidates that act on rationally selected targets for these drugs, that represent potential vulnerabilities, have mechanisms of relevance to pHGG, and have the ability to reach and engage their target across the blood-brain barrier. Particular interest will continue to be given to drugs that act on novel targets identified by other labs in the Collaborative, drugs that are considered “epigenetic regulators,” and drugs that might have synergistic effects when combined with radiation.

Other research teams will continue to refine liquid biopsy approaches for pHGG, including partnering with researchers outside of the Collaborative who are conducting clinical trials and plan to collect sequential samples of CSF from participating patients. Secondarily, they’ll seek to develop methods to detect other materials shed from tumors that could be analyzed for mutations, including fragments called “extracellular vesicles,” as well as attempting to isolate cells from the immune system via liquid biopsy approaches, which could potentially lead to new strategies for immunotherapy.

Finally, the team will conduct new studies to identify parts of the DNA sequences of pHGG subtypes that play critical roles in controlling which genes (and how) get switched on and off within the tumor cells. Identifying these regions of the genome — called “enhancers” — that are controlling the activity of key genes in each pHGG subgroup will help researchers identify possible new treatment targets that could be shared with the drug discovery and testing teams.

**LOOKING AHEAD**

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“**The use of model systems accelerates the search for a cure by allowing us to test many different therapies so that we can select only the most promising ones to treat children with HGG in clinical trials.**”

– Dr. Suzanne Baker, St. Jude Children’s Research Hospital