National Brain Tumor Society

Defeat GBM Research Collaborative

Driving research to new brain cancer therapies

BACKGROUND

The Defeat GBM Research Collaborative was established by the National Brain Tumor Society to employ a team-science approach to transform how brain tumor research is funded and conducted. This world-class team of glioblastoma (GBM) experts are collaborating to accelerate the translation from cutting-edge science to treatment-focused development programs. Key focus areas of the program span from discovery science (including target discovery and validation), to translational research (including drug screening and biomarker identification) and into clinical development (including clinical trial design). Extraordinary research has already been produced that will serve as the basis for translating these scientific findings into potential new treatment approaches for patients with GBM.

PROGRESS MADE

Defeat GBM's scientific endeavours have led to new discoveries about how glioblastoma tumors function and evolve, how they evade current treatments, as well as potential new strategies, methods, and drugs to prevent these tumors from continuing to grow out of control. The Defeat GBM team has tested thousands of drugs preclinically (in laboratory models) as single-agents, and in different combinations, and identified a number of useful "biomarkers" to predict which drugs – or types of drugs – are most likely to benefit subgroups of GBM patients.

LATEST UPDATES: 2018 & 2019

Making Existing Treatments More Effective

Together, the NBTS-funded Defeat GBM teams from Ludwig Cancer Research in San Diego and MD Anderson Cancer Center have discovered, tested, and advanced a new approach to "supercharge" the effects of radiation treatment for GBM patients. They found that combining radiation with a type of drug known as an "FGFR inhibitor" could prevent tumors from repairing themselves following radiation treatment. The team developed laboratory models to test and compare multiple types of these drugs and are planning a clinical trial with the most promising of those tested.

Defeat GBM Research Collaborative Key Personnel:

PRINCIPAL INVESTIGATORS

- **Tim Cloughesy, MD**
  University of California, Los Angeles
- **John de Groot, MD**
  MD Anderson Cancer Center
- **Frank Furnari, PhD**
  Ludwig Cancer Research, University of California, San Diego
- **Dimpy Koul, PhD**
  MD Anderson Cancer Center
- **Ingo Mellinghoff, MD**
  Memorial Sloan Kettering Cancer Center
- **Paul Mischel, MD**
  Ludwig Cancer Research, University of California, San Diego
- **Erik Sulman, MD, PhD**
  NYU Langone's Perlmutter Cancer Center
- **Roel Verhaak, PhD**
  The Jackson Laboratory

STRATEGIC SCIENTIFIC ADVISORY COUNCIL

- **Scientific Director: W. K. Alfred Yung, MD**
  MD Anderson Cancer Center
- **Anna Barker, PhD**
  Arizona State University
- **Mitchel S. Berger MD, FACS, FAANS**
  University of California, San Francisco
- **Lewis Cantley, PhD**
  Weill Cornell Medical College
- **Webster Cavenee, PhD**
  Ludwig Cancer Research
- **William C. Hahn, MD, PhD**
  Dana Farber Cancer Institute/ Harvard Medical School

Another team from the collaborative discovered that administering a type of immunotherapy (immune checkpoint inhibitors) to patients with GBM prior to surgery (neoadjuvant) could improve the activity of these promising treatments. This research has shown that immune checkpoint inhibitors (like pembrolizumab), could be effective for brain cancer patients if used in the neoadjuvant setting. Importantly, this now provides a rational way to develop immunotherapies for the treatment of brain tumors in future clinical trial programs.

> *"Over the past four years, we made major progress towards our goals…our findings are poised to generate clinical impact for patients."*
>
> *– Drs. Paul Mischel and Timothy Cloughesy*

Identifying New, Promising Treatments

The Defeat GBM team at MD Anderson Cancer Center has created 70 new model systems that mimic human GBM tumors with superior reliability compared to existing laboratory models. These models have been deployed across the Defeat GBM teams to identify and validate a host of novel disease targets that new treatments could attack and enabled testing of massive libraries of drugs against these targets.

> *"The focus…is to validate and accelerate the translation of high-value targets and pharmaceuticals into the clinic," said the MD Anderson Defeat GBM team in their progress report. "Over the last year, we have continued to identify and validate multiple drugs for the treatment of subgroups of patients with GBM."*

These potential new treatment approaches fall into three major categories::

- Precision Medicine
- Targeting Vulnerabilities in Tumor Metabolism
- Revealing the Hiding Places of Tumor-Causing Genes

Precision Medicine

Defeat GBM researchers have established multiple potential strategies for combining specific classes of drugs to block the multiple escape routes GBM tumors use to avoid treatment with a single drug.

- Identified a combination of drugs (CLK2 inhibitors with PI3K/mTOR or FGFR inhibitors) that can overcome resistance to targeted GBM treatments.
- Identified a major signaling pathway (Aurora A kinase/PLK1/CDK1) that drives resistance to PI3K inhibiting drugs.
- Identified several targets that could be exploited for potential new treatment approaches in patients with a particularly aggressive subset of GBM tumors (mesenchymal), including one target (LAYN) that looks especially promising.
- Discovered that inhibiting a particular protein (DAXX) leads to increased survival in GBM laboratory models missing a specific gene (PTEN). The team is currently screening for drugs that can knockout the protein in relevant lab models.
- Found that two different members from a family of drugs (PARP inhibitors) were highly active in killing tumor cells in laboratory studies, and that one of these (pamiparib) has demonstrated the ability to cross the blood-brain barrier — a major hurdle in the treatment of brain tumors.

Collectively, these results offer actionable precision medicine strategies that can be followed up on by the field of neuro-oncology research.

Defeat GBM investigators

Targeting Vulnerabilities in Tumor Metabolism

Previously, Defeat GBM researchers have shown that glioblastoma tumors require vast amounts of cholesterol to fuel their growth, and that shutting down their ability to manufacture and retain cholesterol could be a new treatment strategy. The team has now identified at least two other ways in which glioblastoma cells become dependent, or addicted, to certain molecules to fuel their metabolism:

- The first involves an enzyme which GBM is dependent on to keep growing (LPCAT1). Knocking-out LPCAT1 in laboratory models led to significant tumor cell death indicating an encouraging new drug target.
- The second involves a molecule that is so important to a cell's metabolism and other functions that healthy cells have three different ways of generating it (NAD). Cancer cells, however, can use only one NAD production pathway, rendering them highly vulnerable to targeted treatments that block that pathway.

Revealing the Hiding Places of Tumor-causing Genes

In our last Defeat GBM update, we highlighted the discovery that tumor-causing genes in GBM (oncogenes) are able to "hide" on extrachromosomal DNA (ecDNA). Further research since has revealed additional information about this process, which could lead to new approaches to attack and kill cancer cells.

"I've been lucky," says eight-year GBM survivor, Karen Turner. "But we must continue research to improve treatments, provide a better quality of life for patients, and, of course, find a cure."

Enable More Personalized Treatments by Gathering Tumor Information via Novel & Less Invasive Techniques
The Defeat GBM Research Collaborative is focused on understanding how GBM tumors change and adapt during treatment with the goal of unveiling new therapeutic targets and informing clinical treatment decisions.

To do this type of tracking and analysis, researchers and doctors need to perform tests on tumor samples taken via biopsies. However, for brain tumor patients, the prospect of repeated biopsies is often not only extremely risky, but simply not feasible. Accordingly, Defeat GBM researchers have been developing a number of innovative, less invasive approaches to extract more information about how glioblastoma tumors function than ever before:

- A method to isolate small fragments of DNA shed from tumors (circulating tumor DNA) in a patient's cerebrospinal fluid which largely reflect the same mutational profile as the original tumor. This method could lead to more routine and less invasive lumbar punctures ("spinal taps") to track tumor evolution during treatment.
- Imaging approaches to determine the rate of tumor growth in glioma patients. This approach could measure the effectiveness of a potential new treatment earlier and in a less invasive manner than a biopsy.
- A novel molecular diagnostic platform using machine learning that allows researchers to more easily and efficiently determine which mutations are driving glioma patients' tumors.

> *"The Defeat GBM Research Collaborative has catalyzed a body of work that has been published at the highest levels of science and has led to the identification of new, targetable mechanisms in GBM, coupled with promising compounds for clinical development and testing in patients."*
>
> *- Drs. Tim Cloughesy and Paul Mischel in their latest progress report*

LOOKING AHEAD

Work continues for all teams within the Defeat GBM Research Collaborative. The group is continuing its efforts to identify or create potential treatments that effectively target implicated biological pathways and successfully kill tumor cells displaying specific mutations. This includes pushing forward on some of the leads described previously in this report, as well as other areas of potential promise. National Brain Tumor Society looks forward to continuing to advance these discoveries and sharing the results with our dedicated supporters.