

Defeat GBM: How It Works

Defeat GBM is an accelerator of progress. The four “cores” of research work simultaneously and in connection with one another, so that laboratory discoveries can be more rapidly advanced to the clinic.

Defeat GBM enables research efficiency. Defeat GBM has an unparalleled and comprehensive process for testing drugs, including cutting-edge screening techniques and disease models. This allows the teams to begin to predict whether a patient will respond to a given drug, all before clinical trials begin – leading to greater potential for success in clinical trials.

Defeat GBM unites world-class researchers with proven success. By assembling a group of highly-accomplished, leading researchers driven to deliver clinical impact, traditional scientific silos are broken down, resulting in an incredible opportunity to make more progress, and faster.

Defeat GBM: On the Road to Impact

Launched in 2014, the Defeat GBM Research Collaborative is already making progress toward its goal:

- Defeat GBM research demonstrated for the first time that GBM cells’ resistance to current targeted treatments could be overcome by restoring the levels of a protein called Bim.
- Defeat GBM research discovered that GBM cells might use an increased uptake of two nutrients to reprogram their metabolism to fuel their aggressive growth. This raises the possibility that interventions that alter metabolism could potentially have an impact on the response to treatments in GBM.
- Defeat GBM research has shown that a specific mutation to a protein known as EGFR that frequently occurs in GBM cells changes the processes in which the genetic code, stored in DNA, is transcribed into the instructions that regulate cell functions – this provides another avenue to exploit for developing new treatments.
- Defeat GBM-funded research discovered that depriving tumor cells of cholesterol may be a useful strategy to treat glioblastoma, and importantly, the team has identified a drug of interest to test.
- Defeat GBM researchers discovered that small fragments of DNA that are not part of chromosomes (where DNA is usually found in human cells) can be found in high-frequencies in brain tumors, but not normal cells. These circular stretches of “extrachromosomal” DNA were revealed to have a high-likelihood of driving tumors and making them difficult to treat. This has the potential to significantly change the way we view, understand, and treat cancer based on where cancer-fueling genes are found.
- Findings, made possible through the funding and network of the Defeat GBM Research Collaborative, provide a new direction for developing a therapeutic for PTEN-mutated glioblastomas.

These findings set up researchers to take the **next steps** toward further preclinical and clinical development of new types of treatments (and combinations of treatments) that could lead to increased survival.

Your Support Will Help Defeat GBM Maximize Its Potential

Defeat GBM can be made even stronger through your participation. National Brain Tumor Society invested in the core infrastructure, but Defeat GBM embraces partners and contributors. We would welcome your interest, participation, and support in helping to propel these initiatives forward. **Together we CAN achieve our goal.**

“GBM needs targets. It needs new discoveries and new ideas. And you’re doing that. Only thing like it.”

– Dr. Anna Barker,
Arizona State University
and the National Biomarker
Development Alliance

*“These are the best institutions
in the world...this is the
brain trust in the field”*

– Dr. Bill Hahn,
Dana-Farber Cancer Institute

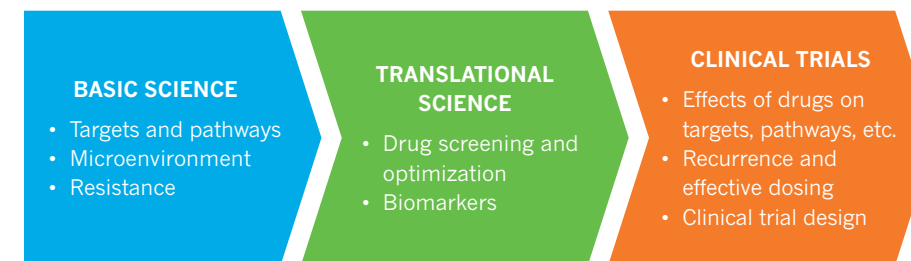
Defeat GBM Research Collaborative: Increasing Survival for GBM Patients

Overview

Defeat GBM (Glioblastoma) Research Collaborative is a multi-disciplinary research program taking a precision medicine approach to develop new treatments for GBM patients. Four cores (see more in right column) made-up of world-class research teams work synergistically to accelerate the translation of discovery to the clinic. The cores operate without “borders” allowing pre-published data to be shared among participating institutions and scientists, speeding the research process.

Objective: To double the percentage of GBM patients surviving five years or more after diagnosis.

Key Areas to Target in GBM



GBM Facts & Figures

- GBM is the most common, and most deadly, malignant brain tumor – or brain cancer.
- GBM forms in the glial tissue of the brain – the supportive “gluey” tissue that keeps neurons in place and functioning correctly. As such, GBM is part of a group of tumor referred to as gliomas. Gliomas account for 75% of all malignant brain tumors.
- GBM is the most common glioma, and is considered a “high-grade glioma” because it is the most aggressive. GBM accounts for 55% of all gliomas
- GBM can also be classified as a WHO grade IV astrocytoma, as they originate in astrocyte cells.
- GBM is one of the most complex, aggressive and heterogeneous cancers.
- 12,390 estimated new cases of GBM will be diagnosed in 2017.
- Mean age at diagnosis is 64.
- Mean survival after diagnosis is ~16 months.
- Five-year survival rate is only 5-10%.

Defeat GBM Cores, Project Teams, and Goals

CORE 1: Discovery

Led by Ludwig Cancer Research, San Diego

Identify high-value treatment target(s) and understand any associated resistance mechanisms (i.e. how the tumors escape or resist treatment).

CORE 2: Drug Development

Led by University of Texas MD Anderson Cancer Center

Identify potential treatments that demonstrate acceptable safety and effectiveness in targeting biologic drivers of GBM progression and that also inhibit resistance mechanisms. A **systems biology project** led by a team at Memorial Sloan Kettering Cancer Center will complete the drug discovery efforts of the MD Anderson researchers by screening potential therapies for molecular and biological response at the systems level to develop rational combination treatments.

CORE 3: Predictive Markers (biomarkers)

Led by Ludwig Cancer Research, San Diego

Identify clinical biomarkers to predict response and resistance in GBM patients.

CORE 4: Innovative Clinical Trials

Led by multiple collaborators

Take advantage of the study of genetic alterations, systems biology, and molecular profiling of GBM patients to develop trials that are faster, more focused, and less costly so that the right therapies can be delivered to the right patients quickly.

Defeat GBM Strategic Scientific Advisors

A team of senior brain cancer experts acting as the Strategic Scientific Advisory Council will help guide the Defeat GBM Research Collaborative.

- **Dr. Anna Barker**
Arizona State University
- **Dr. Mitch Berger**
University of California, San Francisco
- **Dr. Lewis Cantley**
Weill Cornell Medical College
- **Dr. Webster Cavenee**
Ludwig Cancer Research
- **Dr. William Hahn**
Broad Institute of Harvard and MIT
- **Dr. W.K. Alfred Yung**
The University of Texas MD Anderson Cancer Center

History of Impact in GBM Research

Years of previous funding and advocacy in the field of GBM research and drug development, provided insights and helped shape the principles on which Defeat GBM was developed... it also led to a number of critical discoveries that form the foundation of our knowledge of, and treatment strategies for, GBM to date:

- National Brain Tumor Society (NBTS) funding has led to the discovery of numerous biomarkers and molecular targets that could open potential avenues for future therapeutic approaches.
- NBTS advocacy helped convince the National Cancer Institute to make GBM the first tumor-type sequenced by The Cancer Genome Atlas, one of the most transformative projects in the history of cancer research.
- NBTS funding has helped advance five of the most promising treatments that are currently in clinical trials for GBM:
 - » A gene therapy developed by Tocagen, which is currently in multiple clinical trials for both newly diagnosed and recurrent GBM patients.
 - » The Heat Shock Protein vaccine, which is now being evaluated in clinical trials by the biotechnology company Agenus, as well as the National Cancer Institute.
 - » The poliovirus to treat GBM, which is in clinical trials at Duke University and was featured on “60 Minutes” for its promising early-stage results.
 - » CMV-based GBM immunotherapies, which are now being explored in multiple clinical trials.
 - » The adenovirus, which is now in clinical trials at MD Anderson and was featured on the HBO program VICE for its early positive results.

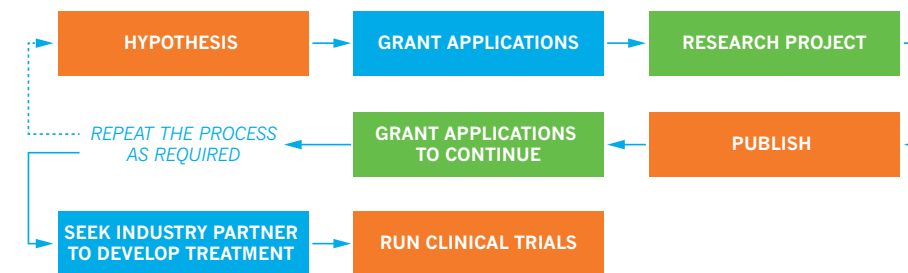
The Cost is Too High To Not Act Now

- Only four FDA approved drugs to treat GBM, which have provided only incremental survival benefits over decades.
- The cost of developing a new cancer drug now is estimated to cost more than \$1 billion and take upwards of 15 years.
- It costs approximately \$1,000 to sequence the genome of one brain tumor patient.
- It costs approximately \$40,000 to fund the development of one new mouse model of brain cancer.
- It can cost more than \$10,000 to fund a month of laboratory research.
- The clinical trial process alone can cost well in the hundreds-of-millions of dollars range.

The real word affect of these alarming statistics is that the survival rate for GBM patients has remained unacceptably low for decades with only incremental advances. **The Defeat GBM Research Collaborative is changing that!**

Defeat GBM Research Collaborative: The Rationale

An individual researcher or research lab - even at top cancer centers - does not have the time, resources, or expertise to, alone, increase the pace of progress for GBM patients. Collaboration is necessary to make the big leap forward that NBTS intends with the Defeat GBM Research Collaborative. Take for example, a typical process a researcher would likely go through to make a discovery and then turn it into a treatment that could help patients:



This process can take many years, and force talented researchers to spend an undue amount of time on administrative-like tasks (e.g. writing grant applications) when they could be in the lab.

Defeat GBM Research Collaborative, through its unique infrastructure to facilitate research, allows scientists from different teams to conduct multiple research efforts simultaneously, share more data in real-time, and spend more time in the lab focused on finding and developing new treatments. It is estimated that this approach can shave two-years of the traditional research process.



Infrastructure Bolsters Investment

Cure GBM, LLC, a subsidiary of NBTS, provides an infrastructure that de-risks Industry engagement, boasts an aggressive IP (intellectual property) policy to protect discoveries, and redefines traditional funding with Founding Research Partners matching NBTS “grants” dollar-to-dollar.

“One of the reasons that the scientific process is often slow in turning knowledge into outcomes for patients is because the ecosystem of science is a complicated one. It’s very hard to be able to have the pieces in place to interact rapidly. The Defeat GBM program is almost like a catalyst - it puts together the pieces that allow progress to move much more quickly. So it’s been thrilled to be a part of it and I really congratulate the NBTS for being so forward thinking in developing this program.”

– Dr. Paul Mischel, Ludwig Cancer Research



Best of the Best: Defeat GBM researchers include some of the world’s top experts in neuro-oncology and cancer research:
 L-R: Michael Nathanson, NBTS; Dr. Timothy Cloughsey, UCLA; David Arons, NBTS; Dr. Frank Furnari, Ludwig Cancer Research; Dr. Alfred Yung, MD Anderson Cancer Center; Dr. John de Groot, MD Anderson Cancer Center; Dr. Erik Sulman, MD Anderson Cancer Center; Dr. Ingo Mellinghoff, Memorial Sloan Kettering Cancer Center; Dr. Paul Mischel, Ludwig Cancer Research; Dr. Robert Strausberg, Ludwig Cancer Research; and Carrie Treadwell, NBTS