Over the past five years, the Defeat GBM Research Collaborative has stood as a testament to the power of ideas, collaboration, and the philanthropic partnership between patient advocacy nonprofits like NBTS and a dedicated community of supporters.

When we launched Defeat GBM as our flagship research initiative in 2014, we sought to do something different. Decades of grant-making in the traditional form of funding separate, individual research projects (one- to two-year grants to a single Principle Investigator) had produced extraordinary knowledge of the biology of glioblastoma cells, but not nearly enough of this work was primed to move out of research laboratories and into clinical trials for patients.

NBTS wanted to see what could be accomplished if, instead of continuing this traditional model of research funding, we deep-funded a team of expert researchers, over a five-year period, to work collaboratively. This team would be charged with working across the continuum of research to translate a scientific discovery into an actionable treatment strategy and/or medical product that could be tested in clinical trials, and hopefully become an approved new therapeutic option for patients. In short, we wanted to change the way glioblastoma research was funded and conducted. It was a big bet, but we believed it would be critical to accelerating the pace at which we discover, develop, and evaluate new therapies for patients. We made a $10 million commitment to our team of world-class Defeat GBM researchers, hopeful that our community would share our vision and enthusiasm for an innovative, unconventional initiative aimed at speeding progress against glioblastoma. We are humbled and profoundly grateful that you did.

Thanks to your generous support, Defeat GBM’s scientific endeavours have led to new discoveries about how glioblastoma tumors function and evolve, and how they evade current treatments — as well as potential new strategies, methods, and drugs to prevent these tumors from continuing to grow. The Defeat GBM team has tested thousands of drugs preclinically, and identified a number of useful “biomarkers” to predict which drugs – or types of drugs – are most likely to benefit subgroups of GBM patients. Together, we’ve demonstrated what fresh thinking, a shared vision, and novel, responsive philanthropy can accomplish. We are proud to share these accomplishments with you in the following report.

With sincere gratitude,
David F. Arons, Chief Executive Officer
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

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.

These potential new treatment approaches fall into three major categories: precision medicine, targeting vulnerabilities in tumor metabolism, and 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.
Defeat GBM investigators

“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.”

Defeat GBM investigators

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.

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.
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

The research described above has created a foundation that will soon serve as the next generation of treatment development initiatives within NBTS’s Defeat Brain Tumors Program. While the current projects within Defeat GBM will wrap-up in their current iterations over the course of the next 12 months, much of the work will continue to advance and/or inform even more focused efforts to facilitate clinical trials to evaluate new therapies for patients. Specifically, the advances in attacking metabolic co-dependencies, improving the effects of radiation (and other DNA-damaging agents), and using the neoadjuvant setting as a platform to develop more effective immunotherapies, will all likely continue to progress toward new treatment strategies primed for clinical evaluation.

None of this pioneering work would have been possible without your generous philanthropic support. We again thank you for sharing our vision for change, and for trusting NBTS to put your generosity to the best use in the fight against glioblastoma. Together, we made a big bet and it has paid off. By investing in Defeat GBM’s unique concept, structure, and scientific plan, you’ve fueled remarkable discoveries, seeded new, promising treatment strategies, and proved the value of a collaborative research model.

National Brain Tumor Society looks forward to continuing to advance these discoveries and sharing the results with our dedicated supporters.