



Using a Collective Brain to Defeat the Deadliest Brain Tumor

Sometimes referred to as the “terminator,” glioblastoma (GBM) is one of the deadliest forms of brain cancer.¹ Drug developers and clinical trial sponsors in oncology have described the glioblastoma research and development (R&D) landscape as a “graveyard” because of the many failed trials.² The disease takes around 16,000 Americans from their families and friends each year.³ Glioblastoma is the most common—and lethal—form of brain cancer, yet virtually no effective treatment options exist, despite such high-profile passings as those of U.S. Senator Edward Kennedy and Delaware Attorney General Beau Biden, and the recent diagnosis of Senator John McCain.

The Defeat GBM Research Collaborative launched in 2013 with an eye toward transforming the clinical landscape for this complex, adaptable, and aggressive cancer.

The idea was simple: change the way we fund and conduct glioblastoma research and change the calculus behind years of heartbreaking disappointments and achingly slow progress against these tumors. The ultimate intervention designed, however, would need to be as sophisticated as the adversary, and would require the input and buy-in of many of the top minds in neuro-oncology—a “collective brain”—in the quest to overcome one of cancer’s most challenging puzzles.

Past is Prologue

The traditional R&D process for cancer drugs is lengthy and filled with challenges, risks, bottlenecks, and inefficiencies. For example, one-off treatments are discovered and then developed in a highly-sequential, time-consuming manner. While the typical drug development process in oncology is estimated to take about 10 years, glioblastoma patients continue to be diagnosed with life expectancies of less than two years.

After analyzing the state of the science in glioblastoma research, it was determined that the scope of the scientific endeavor needed to cover the entire spectrum of preclinical research—from basic science and target discovery to translational research to drug discovery and development.

In brain cancer, thousands of interventional clinical trials have been conducted over the past four decades, with only a handful of new drug approvals succeeding in extending life—and in each case only by a few months. Since 1994, the failure ratio in brain cancer clinical trials has been more than 25:1.⁴

Glioblastoma was first described in the medical literature in 1926.⁵ At that time, patients who were not operated on lived around three months beyond diagnosis. With the addition of surgery, patients’ lives would be extended by a few short months. That prognosis remained for nearly 50 years, until the mid-to-late 1970s when radiation became the standard treatment for gliomas, increasing life expectancy for patients to an average of nine months.⁶ Survival would persist at around nine months for 20 more years, until chemotherapy was first successfully added to the standard of care for

glioblastoma patients, improving survival to a median of around 12 months.⁶ From 1993, incremental advances in the type, delivery, and doses of chemotherapy (including nitrosoureas and temozolomide) and radiation, combined with improved imaging and surgical techniques, extended the overall survival to 12 to 15 months. Finally, from 2008 to 2016, the introduction of bevacizumab and Optune has pushed that range to between 12 and 18 months on average.

All told, there are four FDA-approved drugs (temozolomide, bevacizumab, carmustine wafer, and lomustine), and one FDA-approved device to treat glioblastoma, along with surgery and radiation. Ninety years of research have yielded only enough improvements to extend life by, at most, a year and a half. Meanwhile, certain forms of breast, prostate, blood, and skin cancers are now curable or at least manageable as chronic diseases.

Further, the glioblastoma research field is filled with some of the greatest scientific minds in the world, and has benefited from massive government-funded efforts like The Cancer Genome Atlas, which chose glioblastoma as its first tumor type for genomic sequencing.

When The Cancer Genome Atlas published its findings on glioblastoma in 2008, the research and patient advocacy field was certain that with this tumor's genome decoded, we were on the cusp of a massive breakthrough in treatment development. Yet nearly a decade later, very little has changed in the glioblastoma therapy landscape.

“The knowledge base is incredibly deep in many ways,” says Paul Mischel, MD, a principle investigator in the Defeat GBM Research Collaborative from the Ludwig Institute for Cancer Research, San Diego. “The map of the genes that make proteins and their alterations in this cancer has largely been identified, so one would expect or anticipate that this would actually make a difference in the lives of patients. But for a variety of reasons... that information has yet to really benefit patients.”

Despite great effort from many different funders as well as labs across the field of neuro-oncology, we were not making enough progress against this disease, motivating leaders in this field to begin conversations with the National Brain Tumor Society about the need for fresh approaches to this difficult disease.

In 2012, we took a step back and asked ourselves: “*Why isn't more progress being made? What is stopping great science from becoming great medicine?*”

“This is a devastating cancer and there hadn't really been any advances in the field,” says Dr. Mischel. “Now, in the past 20 years there's really been a sea-change where our understanding of the biology of the disease is really quite sophisticated. The challenge in front of us now is to be able to use those advances for the benefit of patients.”

Forging A New Path

We needed systemic change in the way that limited funds were being distributed and spent for glioblastoma research, as well as



Members of the Defeat GBM Research Collaborative and Cure GBM, LLC, at the National Brain Tumor Society's 2015 Scientific Summit.

the approaches and incentives for moving science through the lab and to the clinic.

The National Brain Tumor Society had been following the lead of our nation's biggest biomedical research funders, the National Institutes of Health, using R01-style grants as a gold standard for seeding research projects. This strategy alone was not working well enough to move the needle for glioblastoma patients. In many ways, it encouraged labs to compete against one another with single-investigator projects.

We could not fund transformative research solely through discreet grants, handed out each year to a cadre of different researchers working on different projects. This process would only perpetuate the traditional model of one-off research efforts by individual labs slogging through the clunky, step-by-step process to move the science forward toward new treatments.

It wasn't that past grant-funding hadn't been impactful—in fact, it had laid a great foundation of knowledge that underpins future research efforts—but rather, we wanted to create a model that would capitalize on advances in biomedical science and technology as we moved deeper into the second decade of the 21st century and the so-called “precision medicine” era. It was about speeding the pace with which discoveries were being made—and ensuring their ability to be moved further down the entire pipeline, from the lab to the clinic with minimal interruption.

With a team of visionaries in the field we created a new model: our “Defeat” model for research.⁷ Instead of funding more individual grants, we would establish and lead a large, directed, broad-based multidisciplinary collaborative capable of converting basic research into drug candidates in coordination with one another. Thus the idea for the Defeat GBM Research Collaborative was born.

Building a New Foundation

We knew that our concept would not easily align with the traditional research system. Researchers might want to work together, they might want to share data and materials, but if their institutions' legal departments wrapped them in red tape, our concept could not move forward.

We began by building a framework that would facilitate true collaboration. We needed a sophisticated business approach to managing scientific research that would bring institutes representing our key principle investigators on as “research partners” to a neutral, central organization. With that, the National Brain Tumor Society created a subsidiary: Cure GBM, LLC.

Cure GBM, LLC, is managed by a board of directors and president separate from that of the National Brain Tumor Society Board of Directors and executive leadership (though some overlap). The LLC manages, operates, and facilitates all activities between participants in the Defeat GBM Research Collaborative, such as:

- Managing the budget and finances
- Marketing, communications, and fundraising
- Providing data and infrastructure support
- Coordinating meetings and research reviews.



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Defeat GBM Research Collaborative

Driving research to new brain cancer therapies

Each partner institution representing researchers within the Collaborative would sign “collaborative agreements” with the LLC, allowing Cure GBM to act as a clearinghouse to help overcome legal barriers to data and material sharing and transfer. Once an institution had signed an agreement with Cure GBM, LLC, their researchers could share raw data and materials with other participants in the Collaborative in real-time without needing to wait for their institutions' legal department to execute a new Material Transfer Agreement or Memorandum of Understanding in each instance. Finally, the fact that an impartial corporation governed the Collaborative gave confidence to participating organizations and individuals that no singular entity would solely benefit from the work of the group.

After analyzing the state of the science in glioblastoma research, the Collaborative determined that the scope of the scientific endeavor needed to cover the entire spectrum of preclinical research—from basic science and target discovery to translational research to drug discovery and development. With the right individuals and structure, we believed we could take on all these areas at once in a coordinated and synergistic approach. To do so, we broke down the scientific plan into four integrated “Core” projects and teams: Discovery, Drug Development, Biomarkers, and “SMART”⁸ Clinical Trials led by experts in each particular discipline (target discovery/genomics/molecular biology; preclinical modeling; biomarker identification and validation; drug screening; and clinical trial operations), all in close collaboration to enable swift scientific translation.

Finally, the Collaborative needed to ensure that its efforts were accountable, milestone-based, and subject to rigorous and frequent review. To do so, the Collaborative decided that a scientific director would join the president and Managing Board to establish and



David Arons speaks at the National Brain Tumor Society's 2016 Scientific Summit.

lead a Strategic Scientific Advisory Council. The council would provide oversight to the scientific projects, manage the research portfolio (including development of a Scientific Research Plan), nominate individuals or entities to conduct research, and establish and evaluate annual research milestones.

Alfred Yung, MD, (at the time, chair of the Neuro-Oncology Department at MD Anderson Cancer Center) was named the scientific director. Several of the early advisors to the Defeat GBM Research Collaborative were named to the Strategic Scientific Advisory Council, including Webster Cavenee, PhD, of the Ludwig Institute for Cancer Research, and Anna Barker, PhD, formerly of the NCI, and now at Arizona State University and the National Biomarker Development Alliance.

Putting the Pieces Together

With a basic infrastructure and model in place, and a diverse and distinguished panel of cancer research experts from multiple fields comprising the Strategic Scientific Advisory Council, the task shifted toward identifying the right projects, institutions, and investigators needed to fill out the Defeat GBM Research Collaborative.

The Power of the “Defeat” Model

The Defeat model, on which the LLC and Collaborative are built, harnesses an infrastructure that facilitates collaboration and data and information sharing, putting scientists to work in areas where they can leverage their expertise while coordinating across a multidisciplinary team all working toward a singular goal. The Defeat model is defined by two major characteristics:

1. A “Cores” design (see below) that allows new findings in one area of the Collaborative to move quickly and efficiently on to the next stage of research without barriers or typical delays seen in single-investigator funding models. In short, much of

the traditional sequential process required in translating basic discovery from lab to clinical testing can be accelerated by enabling seamless integration across cores to execute on research priorities in synchrony.

2. A business and research management model that facilitates all the Collaborative's operational and administrative needs so that researchers can spend more time in the lab and less time doing paperwork. Cure GBM, LLC, serves as a “command-and-control” structure, as well as an administrative hub to enable glioblastoma research at institutions across the country.

Further, the infrastructure is designed to move multiple findings continuously through the “Cores,” thus avoiding an “all the eggs in one basket” scenario. With top labs from around the United States working together, quality and well-researched data is produced at a level requisite for beginning first-in-human trials. In short, participating world-class researchers leverage their strengths and expertise, and the National Brain Tumor Society, via Cure GBM, LLC, provides the infrastructure to move the science forward.

In 2013, with Strategic Scientific Advisory Council guidance, Defeat GBM's four “Cores” were established with scientists/physicians in each area of research selected to lead each of the four Core project teams.

- **Core 1. Target Discovery** was assigned to the Ludwig Institute for Cancer Research, San Diego, where Dr. Frank Furnari's lab would work on identifying high-value treatment targets and associated treatment resistance mechanisms.
- **Core 2. Drug Development** would be led by Drs. John de Groot and Erik Sulman of MD Anderson Cancer Center, who would focus on drug testing across cellular and animal models representative of different classes of glioblastoma subtypes. They would be joined by genomics and computational biology expert Roel Verhaak, PhD, of the Jackson Laboratory and Ingo Mellinghoff, MD, a physician-scientist and expert in brain tumor molecular pathogenesis and clinical trial investigation from Memorial Sloan Kettering Cancer Center.
- **Core 3. Predictive Markers (Biomarkers)** would be led by Dr. Paul Mischel of Ludwig Institute for Cancer Research, University of San Diego, and Timothy Cloughesy, MD, of University of California, Los Angeles, as co-principal investigators (co-PIs) to investigate clinical biomarkers that predict response and resistance to treatment in glioblastoma patients.
- **Core 4. Innovative, Adaptive Clinical Trials** is intended to support biomarker-driven, early-phase clinical trials investigating promising agents identified from preclinical work in the other cores.

This research plan was designed to get the top minds in the field working together—yet within their own areas of expertise—to accelerate the translation of basic research into clinical candidates for human trials.

Making Progress: Moving toward the Clinic

In 2014, funding for the Collaborative raised through philanthropic contributions began flowing to the principal investigators and scientific experiments began. Now, nearing the halfway point

of Defeat GBM's five-year, \$10 million commitment, the Collaborative is bringing forth a host of both new therapeutic targets as well as drugs of interest to be evaluated in the clinic.

While the scientific research underlying the Collaborative is intense, sophisticated, and truly leading-edge, the theory behind it is quite simple: Advance our understanding of tumor biology and gain a deeper understanding of why treatments—that were expected to work—have failed to provide benefit for glioblastoma patients. To develop new, effective treatment strategies for these patients, the Collaborative seeks to:

- Discover how these tumors are protecting themselves from, or escaping, the effects of current treatments.
- Find vulnerabilities in these tumors (their Achilles' heel).
- Create better laboratory models to recreate these effects for use in studies.
- Test potential drugs against these mechanisms with the goal of identifying drugs that can stop them.

So far, Defeat GBM researchers have been able to identify new ways in which glioblastoma tumor cells evade drugs that try to stop them. Collectively, nearly 20 new discoveries have been made that present a multitude of potential new approaches for treating glioblastoma.

Further, Defeat GBM's Drug Development Core has successfully identified potential new drug candidates for further evaluation and testing as possible future glioblastoma treatments. Importantly, these tests have been conducted in newly-developed laboratory models that are better at mimicking how a glioblastoma will actually behave in human patients. In total, the Defeat GBM teams are working on further testing for 11 encouraging drug candidates—some in combinations with current and other therapies—in addition to 21 drugs identified from initial screens that researchers would like to analyze further, which they've identified and prioritized.

“We are poised to move into the clinic soon, and we're very excited about working with NBTS to translate our latest discoveries into the clinic,” says John de Groot, MD, a principle investigator and head of the Drug Development Core.

Next Steps

Operationally, the Defeat GBM Research Collaborative is still a relatively young initiative. Yet, the convergence of the findings made to date has the group already talking about the clinic. The design and makeup of the Collaborative have allowed a portfolio of novel and actionable precision medicine therapeutic targets and biomarkers, and potential clinical candidates, to be developed at a particularly rapid rate.

Several next steps involving close collaboration across different research Cores are now underway with the goal of advancing top scientific findings to go/no-go decisions for clinical trials in glioblastoma patients.

Organizationally, the Defeat GBM Research Collaborative is poised for continued and expanded collaboration with stakeholders who share a common purpose in accelerating brain tumor research in a dynamic team environment. The model is designed to be scalable with new Cores being added, as well as additional investment partners and scientific endeavors, as appropriate,

depending on how the research efforts progress and on guidance provided by the Strategic Scientific Advisory Council.

The ultimate goal is to improve survival for glioblastoma patients—a critical, unmet need. Yet, we also hope the Defeat GBM Research Collaborative can serve as a demonstration project that illustrates how to optimize research efforts through novel models for collaborative, multidisciplinary science. There is real opportunity to transform the landscape of one of the world's deadliest cancers, and the field owes it to glioblastoma patients past, present, and future to capitalize on it.

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