2017 Progress Report: Reaching a Tipping Point

NBTS launched the Defeat GBM Research Collaborative to connect a team of expert cancer researchers in a collaborative infrastructure to work together to accelerate progress in treatment development for patients with glioblastoma (GBM) - the most common, complex, treatment-resistant, and deadliest type of brain cancer. Now, halfway through 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.

Paradigm-Shifting Discoveries & New Possibilities for Treatment Strategies

While the scientific research underlying the Collaborative is intense, sophisticated, and truly leading-edge, the theory behind it is actually quite simple: advance our understanding of tumor biology and gain a deeper understanding of why treatments, which were expected to work, have failed to provide benefit for GBM patients. In order to develop new, effective treatment strategies for GBM patients, the Collaborative seeks to discover how these tumors were 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; and then test potential drugs against these mechanisms with the goal of identifying ones that could stop them.

1. **New Research Discoveries Lead to New Therapeutic Targets** Defeat GBM researchers have been able to identify completely new ways in which GBM tumor cells evade drugs that try to stop them:

   - Defeat GBM researchers discovered that levels of a protein critical for bringing about cell death, known as "Bim," decreases when GBMs become resistant to drugs that target one of these tumors' most common mutations (the "EGFR" mutation). Importantly, researchers found that by using drugs that mimic the activity of Bim, there is an opportunity to restore the critical role Bim plays in promoting tumor cell death.
   - Researchers discovered that tumor cells can use an increased uptake of the nutrients glucose and acetate to fuel tumor growth even in the face of treatment. Thus, modifying the production and uptake of these nutrients could be a new way to impact tumor growth and resistance.
   - Researchers believe they have uncovered how GBM cells repair themselves after treatment with radiation – a standard treatment – and are now screening for potential drugs that could act as so-called "radio-sensitizers," which would make GBM tumor more sensitive and less resistant to radiation.
   - Defeat GBM-funded research discovered that depriving tumor cells of cholesterol may be another new strategy to treat glioblastoma, and importantly, the team has identified a drug of interest to test.
   - Researchers discovered fragments of DNA are not on chromosomes (where DNA is usually located) can be found in high-frequencies in tumor, but not normal, cells. These pieces of "extrachromosomal" DNA (ecDNA) are now believed to be major contributors to tumor growth and treatment resistance. This has the potential to significantly change the way we treat GBM based on where cancer-fueling genes are found.
   - Findings, made possible through the funding and network of Defeat GBM, provide a new direction for developing treatments for GBM patients whose tumors are driven by the loss of the tumor suppressor gene PTEN.
   - Researchers have discovered that a common mutation in GBM cells – the "EGFRvIII" mutation changes the landscape of gene activity in the tumor by altering specific regions of DNA that are critical to how genes are "regulated" – or switched on or off – in cells. One of the genes "switched on" as a result of this altered landscape is the "BRD4" gene, which creates a protein by the same name and controls the expression and activity of another protein called "cMyc," which plays a central role in reprogramming tumor metabolism to fuel growth of GBM cells.

Collectively, these discoveries present a multitude of potential new approaches for treating GBM.

2. **Screening & Testing New Drugs Identify Compounds of Interest** Defeat GBM's Drug Development Core has successfully identified potential new drug candidates for further evaluation and testing as possible future GBM treatments. Importantly, these tests have been conducted in newly developed laboratory models that are better at mimicking how a GBM will actually behave in human patients:
    - The team has created, characterized, and validated 71 new Glioma Stem Cell (GSCs) lines – a type of laboratory model – using tissue samples taken from GBM patients.
    - In these GSCs, the team has screened over 1,000 different drugs (and 75,000 combinations) to see if they exhibit signs of effectiveness. From these initial screens, the team has chosen 12 of the drugs that had the most potent anti-tumor effect for further testing and analysis.
    - Additionally, the team has been working with the other researchers in the collaborative to evaluate 4 additional potential classes of drugs that target the novel therapeutic targets identified through their respective research.
    - Finally, the team, through creating and analyzing their new models and how they react when exposed to drugs, have preliminarily identified an additional 10 new targets of interest that may play a role in GBM treatment resistance.

In total, the Defeat GBM teams are working on further testing for 16 encouraging drug (some in combinations with current and other therapies) candidates – with 8 prioritized for evaluation, and 4 further categorized as clinical candidates.

3. **Biomarkers to Monitor Response to Treatment** Because GBM tumors are often "heterogeneous" – meaning different tumors can have different sets of mutations and alterations driving them – and they progress very quickly, it's important for researchers to begin identifying biological markers (biomarkers) that can give doctors a better idea of which treatments will, or will not, work for individual patients, as well as a way to determine early in treatment if a therapy is not working or is creating new mutations.
    - Defeat GBM researchers have identified a potential biomarker that could indicate which patients might benefit from a certain class of drugs called PI3K inhibitors
    - Researchers have identified two potential biomarkers that could indicate which patients might respond to a combination of drugs called FGFR and CDK4/6 inhibitors.
    - Researchers demonstrated it may be possible to use a medical imaging technique that detects a metabolite produced by tumor cells to monitor, and identify early, if GBM patients with a certain mutation to a gene called IDH are responding to IDH inhibitors or not.
    - Researchers have demonstrated the possibility of using a patient's cerebrospinal fluid for a "liquid biopsy" or "liquid biomarker" to monitor how a tumor is responding to treatment in a less-invasive way than surgical biopsy of the tumor.

These advancements could help better match the right treatments to the right patients (precision medicine) as well as help determine early in the course of treatment if a drug is truly working or not, so doctors can make a more informed decision on whether a patient should stay on that treatment or try another.

Looking Ahead: Translating Science into Survival

Growing sentiment from both the Defeat GBM researchers and the independent Strategic Scientific Advisory Council – experts who review and advise the program – is that the program is reaching a tipping point.

The team is currently focused on four categories of drugs for near-term translation. All candidates will need preclinical testing to ensure only those with the most robust potency and best drug properties will be advanced for evaluation in actual patients via clinical trials. Additionally, six key areas of scientific endeavors represent areas ripe for further study and unraveling. These include further development of models that mimic human GBMs; the role of metabolic codependency in GBM tumors; the role of the tumor microenvironment and epigenetics in GBM growth; the mechanisms and consequences of ecDNA generation, and how it might be targeted therapeutically; additional radio-sensitizers; and using cerebrospinal fluid to monitor GBM tumor response to treatment and evolution.