Going after the tough ones: Modeling and targeting the "resistors" in glioblastoma brain cancer

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Glioblastoma (GBM) is the most common cancer that originates in the brain. Unfortunately, it is also one of the deadliest cancers. There are several reasons for this. First, these tumors invade into the normal brain and cannot be fully removed surgically. Second, most anti-cancer therapies (chemotherapy drugs) cannot penetrate the brain very well which limits options. Third, GBM tumors quickly develop resistance to our existing non-surgical therapies, namely, temozolomide chemotherapy, radiation treatment, and tumor-treating fields wearable device (TTFields or "Optune"). Scientists are trying to understand why GBM becomes resistant to therapy and are trying to identify new targets/vulnerabilities to overcome resistance and improve patient outcomes.

Can we do better?

For 80 years, scientists have been studying GBM, but outcomes are still poor with an average life-span of only 15-20 months after diagnosis, despite receiving surgery, temozolomide, radiation and TTFields. In recent years, we have figured out that most historical lab research models were missing the complexity of actual patient tumors such that when laboratory discoveries were tried on patients, the therapies provided no benefit. Newer models called **patient-derived xenografts (PDX)**, sometimes referred to as patient "**avatars**," are better able to capture the complexity of actual patient tumors since they are developed and maintained under more natural conditions than the historical models.

What should we be going after?

GBM avatars are improved models, but they are usually generated from the material removed during the original surgery at time of diagnosis (before the standard of care treatments like temozolomide and radiation). ***The real clinical problem is not the tumor that the patient starts with, but the tumor that comes back after the standard of care treatments.*** Since repeat surgery is usually very difficult when the tumor returns, there are very few models that exist from these "resistant" tumors.

Making GBM avatar resistors could help us identify new targets to attack

Our lab has spent the past decade developing therapy-resistant GBM avatars, by taking initially treatment-sensitive avatars, and doing repeated treatments (such as multiple courses of radiation) until the tumor avatars can withstand those treatments. We then examine these resistant tumors through molecular testing and find out what changed from the original tumor condition. We believe that the molecular changes we identify in the resistant GBM avatars should be our research focus. We are testing drug therapies that target the unique biology of the resistant tumors.

The Bottom Line

We believe that by changing our focus to studying the tumors that resist and persist standard therapies will help us identify and prioritize the best therapy to give patients when the GBM tumors, inevitably, return.