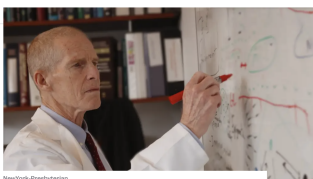


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Breaking decades of stagnation in brain cancer research

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Jun 30, 2025, 6:57 PM GMT+1



Cancer care has changed dramatically over the last fifty years. For millions of people, advances in screening, surgery, precision medicine, and immunotherapy have transformed what a diagnosis can mean, bringing far better odds and genuine reason for hope.

Glioblastoma, an aggressive brain cancer, is a notable exception.

"When I was a medical oncology fellow at Harvard back in the 80s, the median survival of a person with a glioblastoma was about 12 to 13 months," says Dr. Howard Fine, founding director of the Brain Tumor Center at NewYork-Presbyterian. "Four decades later, that has increased to just 15 months."

The stagnation is not due to a lack of effort. Hundreds of millions of dollars have been spent on research — but Temozolomide, the only medication added to standard therapy in recent years, only extends median survival by six weeks. More than 2,000 glioblastoma clinical trials have been conducted over the last 25 years, but promising preclinical studies ultimately faltered when tested in patients.

Fine said the lack of progress points to a deeper problem: Too many potential treatments have been tested against lab models that don't resemble the disease doctors see in people.

To find therapies that stand a better chance of helping patients, researchers first need a more accurate replica of the disease. At NewYork-Presbyterian, that work centers on a glioma cerebral organoid, known as GLICO — a patient-specific platform designed to mimic how glioblastoma grows, invades, and resists treatment inside the brain.

The limitations of older models

Glioblastoma is difficult to treat partly because it does not stay neatly contained. By the time a scan reveals a visible tumor, microscopic cells have often already moved into surrounding brain tissue. Surgeons can remove the main mass, but the scattered tumor deposits left behind can seed the disease again.

That would be hard enough in almost any part of the body — but in the brain, the margin for error is razor thin. Treatment must avoid areas responsible for speech, movement, memory, and personality, while the blood-brain barrier, a protective filter between the bloodstream and the brain, prevents many drugs from reaching the tumor.

The disease also has an unusual survival strategy, which Fine describes as an "internet" of tumor cells threaded through functioning brain tissue.

Glioblastoma cells form synaptic and electrical connections with normal neurons and brain support cells known as glia, creating networks that help them withstand chemotherapy, radiation, and other stressors.

This is what older lab systems have struggled to recreate. Tumor cells grown in a dish, or as a compact mass in a mouse brain, do not behave like those embedded in human neural tissue. A therapy that kills isolated tumor cells tells researchers only so much; what matters is whether it works when those cells are woven into the brain-like networks that help glioblastoma survive.

Creating a more realistic environment

GLICO combines glioma stem cells from a patient's tumor with cerebral organoids, lab-grown structures that mimic aspects of a developing human brain. When the two are combined, the tumor cells attach to the organoid and invade. Drawn to the brain-like tissue around them, they form intrinsic networked connections with normal brain cells, which in part accounts for the tumor's aggressiveness and resistance to treatment.

Working in this more realistic environment, Fine's team can observe how glioblastoma tumor cells spread, communicate, and form pathways to resist treatment, rather than watching them behave in an artificial environment. The result, Fine says, is more accurate modeling that could not only improve the preclinical odds of finding drugs and treatment strategies that ultimately benefit patients in clinical trials, but also spare "the expense, time, and effort of negative clinical trials" and most importantly, protect patients from studies that "had no chance of working."

The model also points researchers toward new ways of combating the disease. Because glioblastoma cells use synapses and electrical signaling to communicate with the brain, medications developed for epilepsy, psychiatric conditions, or cardiac disease could become relevant. Disrupting synaptic and electrical connections may make tumor cells more vulnerable to standard treatments, Fine says, opening "new therapeutic targets and ultimately new classes of drugs."

The path ahead

The GLICO team's next goal is to turn drug-screening results into a broader system for predicting treatment response. The plan, Fine says, is to test thousands of drugs and drug combinations against patient-derived tumor samples, then combine those results with genomic, molecular, imaging, and clinical data. AI could help identify patterns across that volume of information, pointing toward therapies that fit the biology of a future patient's tumor more precisely than older approaches allowed.

Clinical studies still need to confirm that GLICO can select treatments more accurately than current approaches. It's clear, however, that better models create better data — and better data could support more personalized decisions for a disease that has offered patients few meaningful options for too long.

For Fine, that possibility now feels closer than it did for much of his career. "For years, I didn't know where the future was for glioblastoma," he says. "Now, I can see a more concrete path ahead and focus my science on something that has a chance of making a difference to patients. That's what drives me."

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