Molecular Therapy
Beyond Molecular Therapy

Turning cancer against itself: Programmable genetic medicines for glioblastoma

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Glioblastoma (GBM) is among the most formidable of all human cancers. Despite decades of effort, patient outcomes have changed little. The reasons are now all too familiar: extensive genetic heterogeneity, diffuse infiltration into normal brain, profound immune suppression, and the challenge of delivering therapies safely within the central nervous system. Even when targetable mutations are identified, tumors rapidly evolve around them, undermining precision oncology.

Yet beneath this genetic chaos lies a more conserved biology. Increasingly, GBM—and many other solid cancers—are understood not simply as collections of proliferating mutant cells but as distorted developmental and regenerative programs maintained by malignant stem cell-like states. These malignant cells, which can exist in either quiescent or proliferating states, drive tumor growth and lie at the apex of a differentiation hierarchy; they are the critical cellular targets. The challenge is therefore how to eliminate these corrupted cancer stem cell-like states without being compromised by diverse and evolving genotypes or off-target toxicities.

Neurodevelopmental transcription factors (TFs) such as SOX2 are master regulators of GBM identity. Together with signaling-responsive TFs downstream of oncogenic pathways, they maintain stem-like and plastic states that underpin tumor growth, infiltration, and therapeutic resistance. These gene regulatory networks are compelling targets yet are intrinsically difficult to inhibit pharmacologically and display redundancy across TF families.

In our recent publication in *Nature*,[1] we sought to invert this paradigm. Rather than attempting to inhibit the transcriptional circuitry defining GBM stem cell identity, we asked whether this activity could instead be harnessed. Could the molecular machinery defining the identity of the most aggressive tumor cells be exploited to eradicate them?

To address this, we engineered synthetic super-enhancers (SSEs). These compact regulatory elements function as transcriptional logic gates, reading out the combinatorial TF network grammar that defines the aggressive GBM cell states. The resulting SSEs combine exceptional tumor selectivity and very strong expression but are compact enough for viral gene therapy vectors.

Mechanistically, these SSEs were found to bind the dominant neurodevelopmental regulators such as SOX2 and SOX9, integrating these with signaling pathway-responsive TFs including MAPK hyperactivation. The SSEs remain largely silent in normal adult tissues but become strongly activated within immature malignant tumor cells, triggering strong expression of the transgene payloads and providing the level of precision required for effective cancer gene therapy: an engineered biological cell-state sensor.

Glioma was among the first solid tumors to reach phase 3 testing with viral gene therapies in the 1990s, using retroviral or adenoviral vectors to deliver cytotoxic enzyme/prodrug systems such as HSV-tk/ganciclovir.[2] Despite some encouraging patient responses, overall survival did not improve significantly. The field then shifted attention to oncolytic viral vectors, with the hope that they would propagate through the tumor mass and kill via oncolysis. But these also failed to impact patient survival as initially hoped. However, many lessons were learned—particularly the potential for viral vectors and their payloads to stimulate an anti-tumor immune response.[3]

Against this backdrop, it is curious that adeno-associated viruses (AAVs), arguably the most successful gene therapy vector for monogenic disease,[4] have remained relatively overlooked in oncology. Yet AAVs possess several properties that appear ideally suited to GBM: small physical size, durable episomal persistence in non-dividing cancer cells, lower immunogenicity of the vector capsid (compared to oncolytic viruses), manufacturing scalability, and vast opportunities for rational vector engineering (capsid and transgene). Prior preclinical attempts using AAV9 with interferon beta showed promise but struggled to achieve efficacy and were too toxic without appropriate control of the payload.[5]

Local administration of viral gene therapies has also been problematic in the past. Viruses directly injected into the walls of the resection cavity with handheld syringes distribute poorly and spill into the cavity "sink." Improved delivery came from convection-enhanced delivery (CED) technology. This image-guided neurosurgical approach enables predictable distribution of AAV vectors throughout the human brain. Clinical studies in Parkinson's and Huntington's disease have already demonstrated reliable CNS delivery.[6] For GBM, where infiltration and the blood-brain barrier remain major obstacles, the combination of AAV and local delivery via CED may prove transformative.

Accurate disease-relevant experimental models remain critical for development of

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