UCSF Brain Tumor Center

Spring/Summer 2024

New Focused Ultrasound Clinical Trial

A Biomarker for Predicting Meningioma Recurrence and Radiotherapy Response

Precision Medicine for Glioblastoma

Whole-Tumor Perspective

How 3D representations of individual patients' glioblastomas are revealing origins, new potential vulnerabilities

UCSF

A 3D Perspective on How Glioblastomas Develop

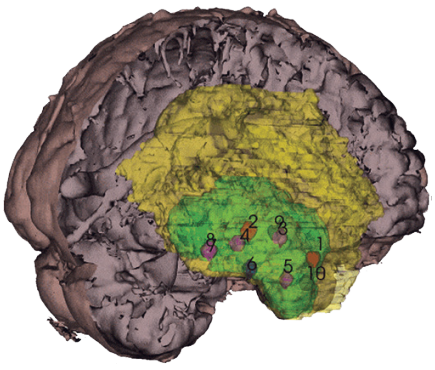
Glioblastomas often grow back after initial treatment because the currently available therapies only manage to attack a portion of cells present within the tumor. Identifying more targeted treatment strategies requires a more complete understanding of the whole tumor landscape.

Researchers and clinicians at UC San Francisco in collaboration with scientists at Northwestern University have charted the unique patterns of genetic and epigenetic alterations present throughout the tumor. Their study, published in *Cell,* offers a comprehensive map showing how these malignant tumors form and continue growing.

“If we could develop a therapy based on the knowledge that the target is everywhere on the tumor, then we get around that major concern about intratumoral heterogeneity,” said Joseph Costello, PhD, a neurosurgery professor at UCSF and one of the study’s co-senior authors.

By coordinating with neurosurgeons at the UCSF Brain Tumor Center and scientists at the Neurosurgery Biorepository, Costello and his colleagues obtained at least 10 samples each from 10 patients with newly diagnosed glioblastoma. They also asked the surgeons for samples widely distributed across the tumor — from the core all the way out to the periphery. With the neuroimaging expertise of radiology professor Janine Lupo, PhD, the researchers then generated 3D models of each individual patient’s tumor using the coordinates from the surgical neuronavigation software and pre-operative MRI scans.

“Our spatial sampling approach was very unique because most people only have one sample, and then they try to extrapolate from that to the whole tumor,” said Radhika Mathur, PhD, a postdoctoral scholar in the Costello lab and the study’s first author.



3D model of an individual patient’s tumor showing where samples were taken for subsequent analyses. Image by the Costello lab.

The scientists used these 3D representations of each patient’s tumor to situate their data about genetic and epigenetic alterations present in each sample within the context of the whole tumor. By controlling for how many cancer cells were in each sample, Mathur says their map also more accurately distinguishes between the tumor and its microenvironment.

This approach allowed the scientists to tease out features common among all the samples from the patients’ tumors.

Mathur says their data shows that genes important in neurodevelopment are active in the tumor cells. These results build on the large body research showing the cells from which glioblastomas originate, specifically outer radial glial differentiation into oligodendrocyte precursor cells.

To better understand what causes the cell-of-origin to undergo transformation into a cancer cell, he and his team applied a specialized genomics technique called Hi-C to examine the structure of the DNA in the cells from each sample.

“It is pretty striking because large portions of the chromosome are shattered and misassembled,” Mathur said.

Although these types of DNA variants have been described in glioblastoma before, Costello says that their presence in every sample of the tumor indicates that chromosome shattering is one of the earliest events in tumor formation.

The structural changes in the DNA also result in fusion genes that can generate small proteins or peptides, which he says present new potential therapeutic opportunities. For example, cancer vaccines against these proteins could be used stimulate the immune system to attack to the tumor.

“We are really excited about the possibility of personalized immunotherapy,” Costello said, adding that his lab is collaborating on projects led by the laboratory of Hideho Okada, MD, PhD, to jump start the process.

Moving from the center to the edges of the tumor, the scientists could also see that cells expressed genes facilitating the communication with the surrounding healthy neurons, identifying many more genes than previous cancer neuroscience studies.

The researchers have created a free online resource for other scientists to find other possible tumor-wide drug targets and see where specific genes, programs, and cell types are active across glioblastomas.

This dataset is also just the beginning for Costello and his colleagues as they continue investigating the cellular events that cause malignant brain tumors to form. The next phase of the project will incorporate tumor samples from patients with lower-grade gliomas as well as patients with recurrent tumors.

Mathur R et al. Glioblastoma evolution and heterogeneity from a 3D whole-tumor perspective. Cell. 2024 Jan 18;187(2):446-463.e16.

By Alejandra Canales

Can Gene Expression Predict if a Brain Tumor Is Likely to Grow Back?

Doctors often prescribe radiation along with surgery to treat a brain tumor called meningioma that originates in the protective membranes surrounding the brain. But side effects from radiation can be serious, including memory loss and cognitive decline, so it's important to know which patients really need it.

Now, researchers at UC San Francisco and Northwestern Medicine, in collaboration with 10 other medical centers, have found a highly accurate way to predict the best treatment for patients based on patterns of gene expression – which genes are turned on and off – in their tumors.

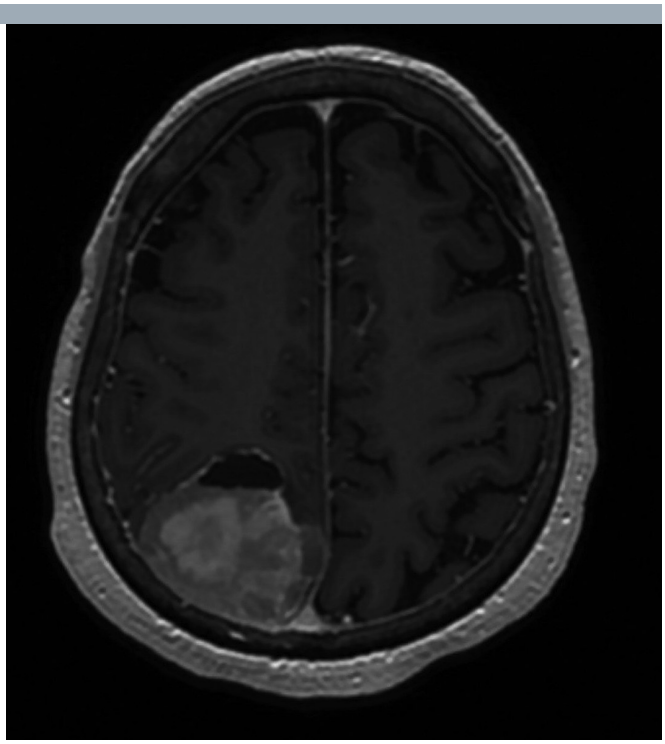
Screening tumors using this new approach could change the course of treatment for nearly 1 in 3 people with meningioma, the most common form of brain tumor diagnosed in 42,000 Americans each year. Unlike other brain tumors, meningiomas occur most often in female, Black and elderly patients.

In a paper appearing in *Nature Medicine,* the team concluded that just 1 in 5 patients with low-grade tumors may need radiation, while around 2 in 5 with higher-grade tumors may be better off without radiation, based on the results of the new gene-expression test.

"There's been a lot of controversy in the field in terms of who should receive radiotherapy and who shouldn't," said David Raleigh, MD, PhD, a radiation oncologist in the UCSF Brain Tumor Center and a senior author of the study, along with Stephen Magill, MD, PhD, assistant professor of neurological surgery at Northwestern University Feinberg School of Medicine. "Our biomarker takes the guessing game out of this and shows us which patients are likely to benefit from radiotherapy and which may get toxicity and possibly no benefit from radiation."

Pathologists currently classify meningiomas by looking at them under a microscope for features that indicate whether they may grow back, a system that is very good but not perfect. Patients with Grade 1 tumors don't usually receive radiation treatment if their tumors can be removed completely during surgery. Yet approximately 20% of the time, the tumors recur. Those with Grade 2 and 3 tumors, which are much more aggressive and more likely to grow back after surgery, are often treated with radiation after surgery. It has been unclear how many of these patients, particularly those with Grade 2 tumors, actually need radiation treatment.

Raleigh, along with Magill and lead author William Chen, MD, decided to look at classifying tumors according to which of their genes are turned on and off, thereby offering clues to how aggressive they might be.



MRI scan showing a meningioma. Image by Raleigh lab.

"Gene-expression tests like this, that analyze a small number of genes at a time, are widely available for breast, prostate and some other cancers, and they've proven to be a very accurate and inexpensive alternative to other types of tests," said Chen.

Raleigh and Chen and their multidisciplinary team suspected that gene expression could more accurately point out the patients who would be helped by radiotherapy. Using samples from 1,856 meningioma patients at 12 medical centers in the U.S., Europe and Hong Kong, Raleigh's team came up with a set of 34 genes whose gene expression patterns had the potential to predict whether a tumor would return.

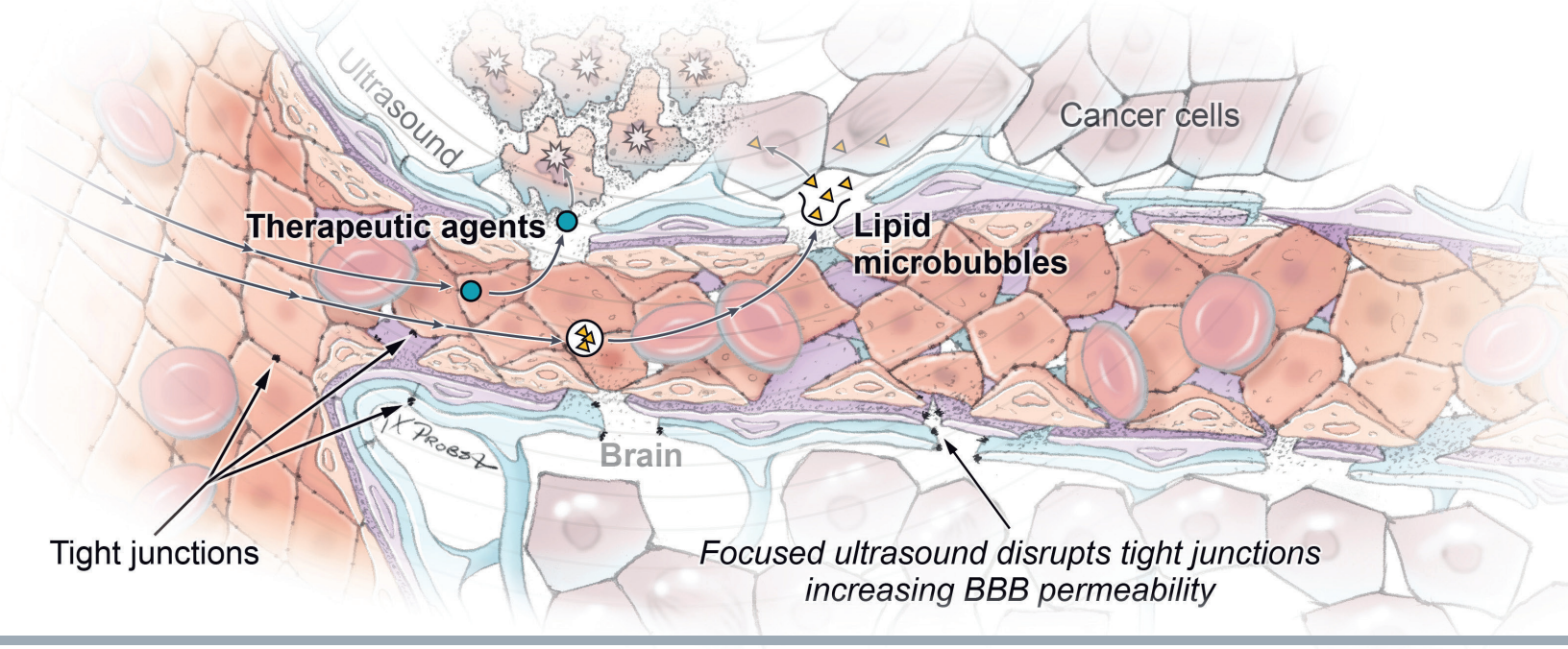
One-fifth of the Grade 1 tumors – the same number that grow back after surgery – expressed the patterns that Raleigh's team found could predict a tumor's regrowth. This fraction of patients may benefit from radiation. The researchers also found that two-fifths of patients with Grade 2 and 3 tumors did not have a recurrence, and this, too, could be predicted by the tumor's gene expression.

"When to proceed with additional surgery, radiotherapy or simply to observe a small residual meningioma is not always clear," said Magill. "This test adds information that can let us tailor our surgical and radiation approach to provide the best outcome for each patient and maximize both quality and quantity of life."

The team's next step is to test the approach in two clinical trials currently being developed.

Chen WC et al (2023). Targeted gene expression profiling predicts meningioma outcomes and radiotherapy responses. Nat Med. 2023 Dec;29(12):3067-3076.

By Robin Marks



The combination of ultrasound waves and an injection of microbubbles into the blood disrupt the blood-brain barrier, allowing therapeutic molecules to penetrate the tumor. *Illustration by Ken Probst.*

New Clinical Trial Uses Focused Ultrasound to Improve Drug Delivery in Glioblastoma

Many drugs used to treat other types of types of cancers do not reach brain tumors due to the blood-brain barrier.

The UCSF Brain Tumor Center is now recruiting patients with recurrent glioblastoma for a clinical trial with an implanted focused ultrasound device to safely disrupt the blood-brain barrier to enhance chemotherapy drug delivery to the tumor.

"The goal is to help the chemotherapy drug combination of carboplatin and paclitaxel reach therapeutic levels in the glioblastoma tumor," said John de Groot, MD, Chief of the Division of Neuro-Oncology within the Department of Neurological Surgery. "This drug combination is an effective chemotherapy treatment for many solid tumors."

The Carthera device being studied in this trial is inserted in place of the skull after the patient's tumor resection. From there, the device generates localized low-intensity pulses of sound waves. The ultrasound waves from the device's nine emitters when combined with an injection of microbubbles into the blood safely open the blood-brain barrier for a brief period.

As part of the phase II portion of this trial, participants will now be receiving an IV infusion of carboplatin followed by the focused ultrasound treatment and the albumin-bound paclitaxel once they have recovered from surgery.

This trial is a collaborative effort with Northwestern University's Robert H. Lurie Comprehensive Cancer Center that builds on previous clinical studies using this approach to disrupt the blood-brain barrier. Results from a phase I clinical trial, published last year in *The Lancet Oncology,* first demonstrated that the ultrasound device was well-tolerated by patients with recurrent glioblastoma and was able to increase the concentration of albumin-bound paclitaxel in the brain.

Researchers have further demonstrated in a phase I/II clinical trial that the focused ultrasound device safely disrupts the blood-brain barrier in the area surrounding the tumor and increases the concentration of carboplatin in that region of the brain. Preliminary findings in the cohort of 12 patients with recurrent glioblastoma who received carboplatin immediately before the focused ultrasound treatment had a median overall survival of 14 months, which is longer than expected for this patient population. These results were published earlier this spring in *Nature Communications.*

With continued investigations on the use of focused ultrasound for brain tumors, researchers are exploring how the technology could improve the efficacies of novel therapies. de Groot says that UCSF researchers are also interested in focused ultrasound's effects on the tumor microenvironment and the passage of antibodies and immune cells into the tumor.

For More Information on Enrollment

Phase I/II Trial of Blood-Brain Barrier Opening With an Implantable Ultrasound Device SonoCloud-9 and Treatment With Albumin-bound Paclitaxel and Carboplatin in Patients With Recurrent Glioblastoma

(415) 353-2193

By Alejandra Canales

Clinical Trials

The UCSF Brain Tumor Center has one of the largest clinical trials portfolios in the nation and is part of several national clinical trials consortia. Our involvement in national cooperative clinical trials ensures that our patients have access to the latest techniques and the newest concepts for treatment of brain tumors.

Select Adult Trials

NCT04528680	A Phase I/II Trial of Blood-Brain Barrier Opening with an Implantable Ultrasound Device SonoCloud-9 and Treatment with Albumin-Bound Paclitaxel in Patients with Recurrent Glioblastoma
NCT05303467	A Feasibility Study to Evaluate the Safety of the TheraSphere Glioblastoma (GBM) Device in Patients with Recurrent GBM (FRONTIER)
NCT04656535	A Multi-Center Phase 0/I trial of anti-TIGIT antibody AB154 in combination with anti-PD1 antibody AB122 for recurrent glioblastoma
NCT05383872	Blood-Brain Barrier Disruption for Liquid Biopsy in Subjects with Glioblastoma
NCT05503797	A Study to Assess the Safety and Efficacy of FORE8394 in Participants with Cancer Harboring a BRAF mutation
NCT05417594	A Study of AZD9574 as Monotherapy and in Combination with Anti-Cancer Agents in Participants with Advanced Solid Malignancies (CERTIS1)
NCT06186401	Anti-EGFRvIII synNotch Receptor Induced Anti-EphA2/ IL-13Ralpha2 CAR (E-SYNC) T Cells
NCT04135807	A Pilot Study of an Implantable Microdevice for In Situ Evaluation of Drug Response in Patients with Primary Brain Tumors
NCT04659811	A phase II study of stereotactic radiosurgery in conjunction with the PD-1 inhibitor, pembrolizumab for the treatment of recurrent meningioma
NCT05753007	A Randomized, Double-blind, Clinical Trial of a Hemp-Derived, High Cannabidiol Product for Anxiety in Glioblastoma Patients
NCT05484622	Study of Vorasidenib and Pembrolizumab Combination in Recurrent or Progressive Enhancing IDH-1 Mutant Astrocytomas

Select Trials for Children

NCT05169944	Magrolimab in Children and Adults with Recurrent or Progressive Malignant Brain Tumors (PNOC025)
NCT05057702	Individualized Treatment Plan in Children and Young Adults with Relapsed Medulloblastoma (PNOC027)
NCT05465174	Nivolumab and DAY101 for the treatment of newly diagnosed or recurrent craniopharyngioma in children and young adults (PNOC029)
NCT04732065	ONC206 for Treatment of Newly Diagnosed, or Recurrent Diffuse Midline Gliomas, and Other Recurrent Malignant Brain Tumors (PNOC023)
NCT04485559	A Phase I Trial Evaluating the Combination of Trametinib and Everolimus in Pediatric and Young Adult Patients with Recurrent Low Grade Gliomas (PNOC021)
NCT05478837	Genetically Modified Cells (KIND T Cells) for the Treatment of HLA-A*0201-Positive Patients With H3.3K27M-Mutated Glioma (PNOC018)

Browse the full list of clinical trials, and sign up to have the list delivered to your inbox at braintumorcenter.ucsf.edu/clinicaltrials

Uncovering Better Glioblastoma Treatment Approaches with Genomics

Part of what makes glioblastoma difficult to treat lies in the variation, or heterogeneity, between individuals who seemingly have the same type of tumor.

Using genomic sequencing, researchers at the UC San Francisco Brain Tumor Center have discovered a rare new glioblastoma subtype with unique biological properties that distinguish it from typical glioblastoma. Their findings, published in *Acta Neuropathologica,* suggest that these tumors may be more responsive to immunotherapy.

The study is the second in a series characterizing the molecular features of glioblastoma. The team previously found that some tumors that may resemble low-grade glioma under the microscope, are, in fact, aggressive tumors similar to glioblastoma that require multimodal therapy including radiation and chemotherapy for best patient outcomes.

“Tumors of the central nervous system have definitely been leading the way in terms of recognizing how molecular diagnostics is such an important part of the treatment workup,” said David Solomon, MD, PhD, an assistant professor in Department of Pathology and senior co-author of the study.

As part of the philanthropically-supported UCSF Glioblastoma Precision Medicine Program, Solomon and co-senior author Annette Molinaro, PhD, analyzed the sequencing data from 459 newly diagnosed glioblastoma patients who were studied using the UCSF500 Cancer Gene Panel. The scientists, led by UCSF postdoctoral scholar Sara Hadad, PhD, from the Molinaro lab, identified nine patients whose tumors lacked genetic mutations characteristic of glioblastoma.

Glioblastomas typically have few somatic mutations, but these unique tumors stood out to the researchers because they had a very large quantity of mutations. Closer examination revealed that these hypermutated tumors have completely different biological properties than what’s typically considered glioblastoma.

“All that’s the same is how they look on an MRI and how they look under a microscope,” said Solomon. “But our molecular profiling revealed that have unique DNA mutations, epigenetic patterns, chromosomal copy number patterns, and immune cell microenvironment.”

The scientists found that this new subtype of glioblastoma is caused by mutations in genes that are normally responsible for fixing mistakes that often occur during DNA replication. As a result of this “replication repair deficiency”, tumor cells end up acquiring many mutations across their genome, including in tumor suppressor genes that normally limit cell growth.

All those many mutations result in tumor formation but can also confer an advantage when it comes to immunotherapies.

“Basically, now there’s a whole bunch of neoantigens or neoepitopes that are being expressed on the tumor cell surface that the immune system can recognize,” said Solomon. “This leads to a different immune cell composition in these tumors compared to conventional glioblastomas.”

The researchers next wanted to see if these differences could result in better outcomes for patients treated with immune checkpoint inhibitors. They turned to the Brain Tumor Center Database, which has the complete clinical records of each glioblastoma patient’s health history.

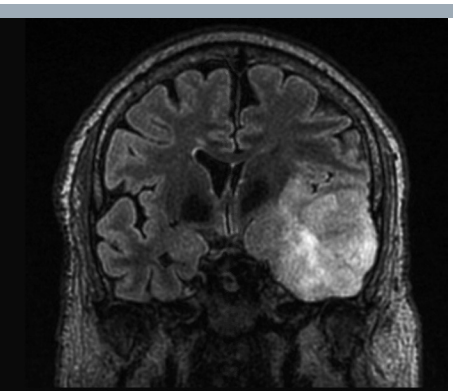
“The reason that we have this detailed data on which drugs the patients received and which trials they participated in is because of the database,” said Molinaro, who is also the director of the Division of Biomedical Statistics and Informatics within the Department of Neurological Surgery.

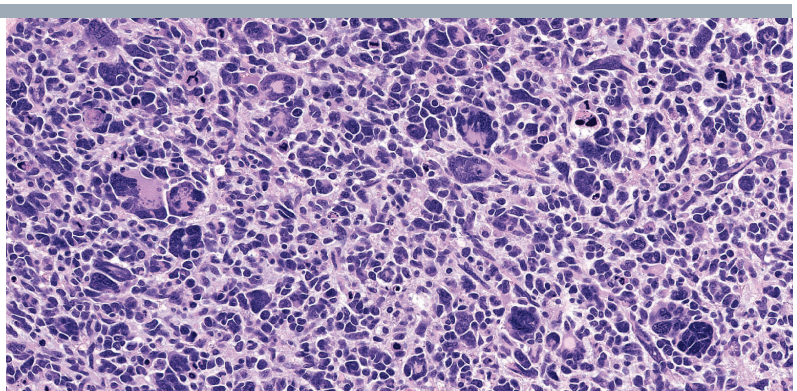
Although only five patients with this tumor subtype received immune checkpoint inhibitors, preliminary evidence indicates that the immunotherapy drugs may be more effective for them. Hypermutated tumors are also generally more resistant to the chemotherapy drug temozolomide, suggesting that these patients could benefit from other chemotherapies.

Solomon says these findings underscore the importance of prospectively identifying the unique molecular features in each patient’s tumor. The team is now working to develop more sophisticated prognostic models that incorporate all this information about a patient’s tumor.

“The fundamental goal of precision medicine is to recognize that each patient’s tumor is different and may likely respond best to a uniquely tailored treatment regimen as directed by molecular profiling,” Solomon said.

By Alejandra Canales

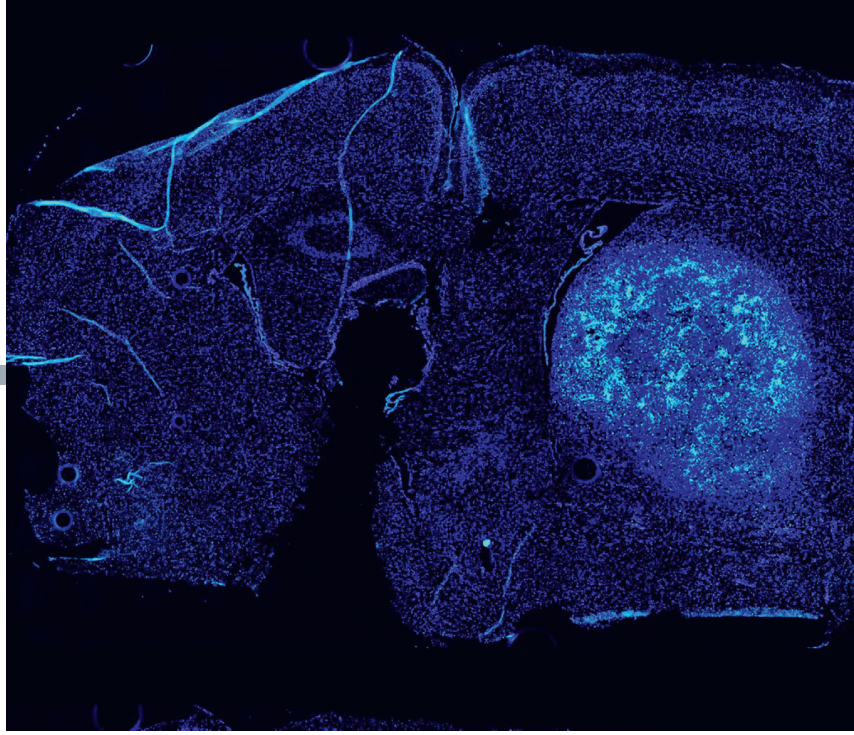




MRI and histology images of de novo replication repair deficient glioblastoma, a new tumor subtype discovered at the UCSF Brain Tumor Center as part of the UCSF Glioblastoma Precision Medicine Program. *Images by the Solomon lab.*

Hadad S, Gupta R, et al (2023). “De novo replication repair deficient glioblastoma, IDH-wildtype” is a distinct glioblastoma subtype in adults that may benefit from immune checkpoint blockade. Acta Neuropathol 147(1):3.

UCSF Scientists Build a Molecular 'GPS' to Guide Cell Therapies



In an early experiment, these engineered T cells (cyan) successfully found and treated a glioblastoma in laboratory mice. Image by Payal Watchmaker from the Okada lab.

The ideal therapy for a disease works exclusively at the site of the disease.

But when it comes to the brain, which is wrapped in a protective barrier and contains thousands of different cell types, this ideal is very hard to achieve.

Now, scientists at UC San Francisco have been awarded more than $30 million by the Advanced Research Projects Agency for Health (ARPA-H) to lead the Cell Therapies for Neuroinflammation and Neurodegeneration (CT-NEURO) project, which will develop a new technology dubbed "tissue GPS." The system uses engineered T cells to guide therapies directly to their targets in the brain to treat neurological diseases, like the deadly brain cancer glioblastoma, multiple sclerosis and Alzheimer's.

These immune cells navigate by detecting molecular markers called antigens that appear on the surface of target cells like street addresses, replete with nine-digit zip codes. They only transfer their payload of anti-inflammatories or cancer-killing molecules once they have arrived at the right location.

The tissue GPS system may give immune cells the ability to pass through molecular gates in the blood brain barrier; find and stick to target cells; and safely deliver a tailored therapy. With such an exacting approach, the hope is that patients will be spared many of the uncomfortable or even dangerous side effects associated with other therapies.

"The field has many molecular tools that could potentially address conditions like neuroinflammation or Alzheimer's, but it is challenging to know how to use these tools in a way that would precisely target the brain," said Wendell Lim, PhD, project lead, UCSF Byers Distinguished Professor of Cellular and Molecular Pharmacology, and director of the UCSF Cell Design Institute. "Tissue GPS will ensure that therapies have a maximal effect in the right parts of the brain, making it much easier to treat complex disease."

Disbursed over five years, the funds will support Lim and UCSF colleagues Scott Zamvil, MD, PhD; Hideho Okada, MD, PhD; Dean Sheppard, MD; and Anna Molofsky, MD, PhD, in developing the system.

The UCSF researchers will test the system's delivery of therapies for brain tumors; neuroinflammation; demyelination (the loss of insulation on neural wires, like in multiple sclerosis); and neurodegeneration. They also will test its ability to reach other specific organs, like the lungs.

The team has mapped out antigens that are present throughout the brain, as well as the molecular sensors required for the tissue GPS to navigate to various brain regions. In an early experiment, their approach enabled engineered T-cells to treat brain tumors in mice.

"Immune cells are incredibly adept at traversing the body to reach a target," Lim said. "These living cells could provide a powerful way to get therapies to where they need to be."

By Levi Gadye

Register Now for Neuro-Oncology Update Course

Course# MNS25005

Join us on Saturday, August 3, at Cavallo Point for this year's neuro-oncology update. This CME course, chaired by Nancy Ann Oberheim Bush, MD, PhD, and Steve Braunstein, MD, PhD, provides updates on disease management as well as recent advances in neuroimaging, surgical approaches, and novel immunotherapies.

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