UCSF Brain Tumor Center

Spring 2020

Updated Surgical Strategy for Newly Diagnosed Glioblastoma

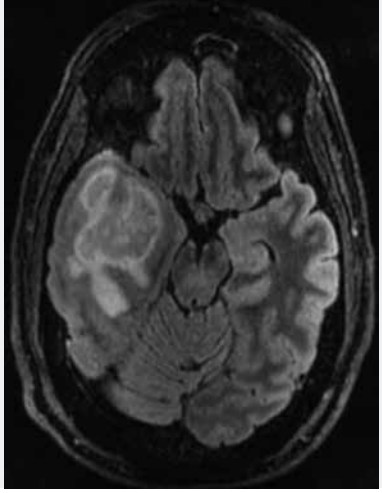
New Clinical Trial Targets Mutant IDH

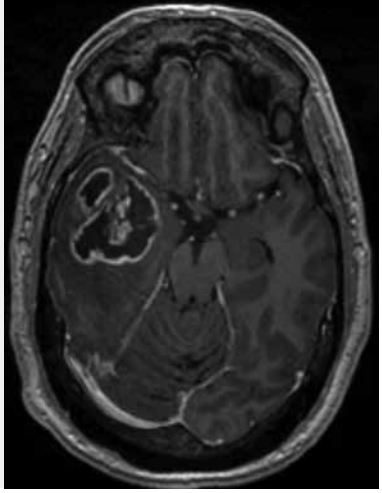
UCSF Brain Metastases Clinic Opens

Brain Organoids

How organized 3-D cultures of brain cells are advancing glioblastoma research

UCSF





Left: Annette Molinaro, PhD.

Right: Pre-operative MRIs showing contrast-enhanced tumor (T1-weighted MRI) and non-contrast-enhanced tumor (FLAIR MRI)

Cover: Glioblastoma cells (red) invade a brain organoid, a 3D culture of brain cells including neurons (green) and astrocytes (blue). Illustration by Ken Probst.

Brain Tumor Surgery that Pushes Boundaries Boosts Patients' Survival

Survival may more than double for adults with glioblastoma, the most common and malignant brain tumor, if neurosurgeons remove the surrounding tissue as aggressively as they remove the cancerous core of the tumor.

Removing the "non-contrast enhancing tumor" – so called because it does not light up on MRI when a contrast agent is injected into the vein – represents a paradigm shift for neurosurgeons, according to senior author and neurosurgeon Mitchel Berger, MD, director of the UCSF Brain Tumor Center.

"Traditionally, the goal of neurosurgeons has been to achieve total resection, the complete removal of contrast-enhancing tumor," said Berger. "This study shows that we have to recalibrate the way we have been doing things and, when safe, include non-contrast-enhancing tumor to achieve maximal resection."

In their study, published in *JAMA Oncology* on February 6, 2020, the researchers tracked the outcomes of 761 newly diagnosed patients at UCSF who had been treated from 1997 through 2017. The patients, whose average age was 60, were divided into four groups with varying risk based on age, treatment protocols, and extent of resections of both contrast-enhancing and non-contrast-enhancing tumor.

They identified a group of 62 patients whose average survival was 37.3 months (3.1 years). These patients had IDH-mutant tumors, or were under 65 with IDH-wild-type tumors and had undergone both radiation and chemotherapy with temozolomide in virtually all cases. Each had resections with a median of 100 percent of contrast-enhancing tumor and a median of 90 percent of non-contrast-enhancing tumor.

In comparison, their counterparts – 212 patients under 65 who had received the same therapies, but had more modest resections of the non-enhancing tumor – survived only 16.5 months (1.4 years) on average, or about half as long. These results were verified with patient cohorts at the Mayo Clinic, University Hospitals and Case Western Reserve University School of Medicine.

Among the group of longer-surviving patients, those with IDH-wild-type tumor did approximately as well as those with the IDH-mutant variant when a portion of the non-contrast enhancing tumor was removed, the authors noted. "The difference was that the patients with IDH-wild-type tumor declined more rapidly after the three-year mark," said first author Annette Molinaro, PhD, from the UCSF Department of Neurological Surgery,

The researchers caution that maximal resection should only be achieved when it can be safely performed using techniques such as intraoperative brain mapping. This means that areas of the brain responsible for speech, motor, sensory and cognition are tested during surgery to ensure that these functional areas are preserved.

"Although these data show a survival benefit associated with maximal resection, it remains critically important that we do our best to remove tumor in a manner that will not harm the patient," said co-author and UCSF neurosurgeson Shawn Hervey-Jumper, MD, noting that about 80 percent of medical centers do not offer brain mapping.

Molinaro AM et al. (2020) Association of Maximal Extent of Resection of Contrast-Enhanced and Non-Contrast-Enhanced Tumor With Survival Within Molecular Subgroups of Patients With Newly Diagnosed Glioblastoma. *JAMA Oncol.* [Epub ahead of print]

This story was written by Suzanne Leigh and first appeared in the UCSF News Center (ucsf.edu/news) on February 6, 2020.

Brain Organoids Reveal Glioblastoma Origins

Glioblastomas are the most aggressive form of brain cancer – they grow and spread rapidly through the brain and are virtually impossible to eradicate, typically leading to death within one or two years of diagnosis. Scientists are constantly seeking more powerful targeted therapies, but so far without success – in part because glioblastomas are challenging to study in a laboratory setting.

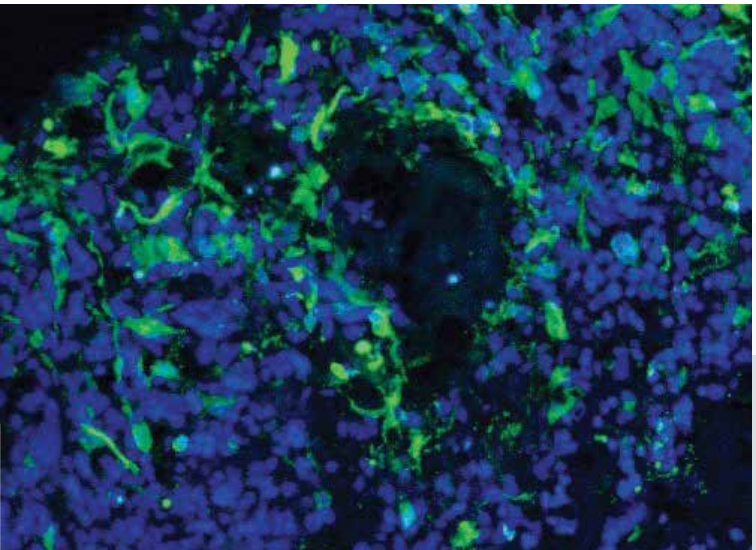
"Glioblastomas are aggressive and tenacious in patients, but have always been very difficult to keep alive in the lab," said UC San Francisco postdoctoral researcher Aparna Bhaduri, PhD. "In previous attempts to study glioblastomas in mice, only 5 to 10 percent of human tumors survive transplantation into the animals, making us suspect that these tumors may differ in important ways from the ones that don't survive."

Now Bhaduri and Elizabeth Di Lullo, PhD, a fellow postdoctoral researcher in the laboratory of Arnold Kriegstein, MD, PhD, have for the first time succeeded in keeping a diverse array of glioblastomas alive in the lab using brain organoids – balls of simple brain tissue grown from human stem cells.

In a study published January 2, 2020, in *Cell Stem Cell,* Bhaduri, Di Lullo, and colleagues first created an atlas of glioblastomas taken from surgical treatment of human patients, cataloguing dozens of distinct cell types and these cells' expression of distinctive patterns of genes. They then used organoids grown from human stem cells to model how these genetically identified cancer cell types behave in human brain tissue.

They discovered that glioblastomas do not appear to originate from a single cell type – what other researchers have called a "glioblastoma stem cell" – but instead arise from multiple kinds of seed cells, including one that looks and behaves very much like a neuronal stem cell Kriegstein's lab discovered a decade ago, called an outer radial glia (oRG) cell.

Glioblastoma cells (green) invade a brain organoid grown from human stem cells (blue). Credit: Aparna Bhaduri, Keiegstein Lab



Aparna Bhaduri, PhD, received the second place award for her research talk at the 2019 UCSF Postdoc Slam.

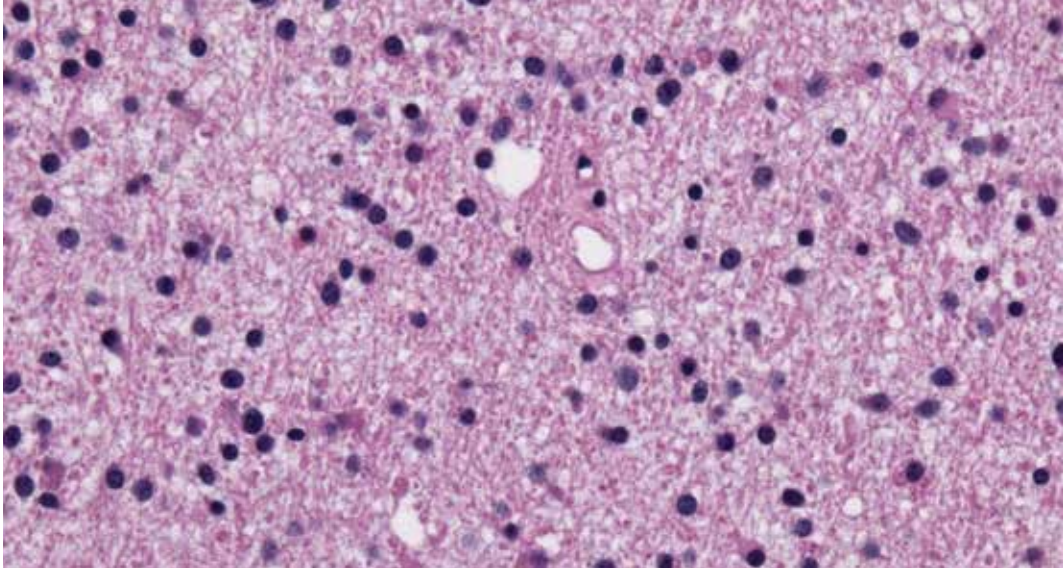
These cells normally disappear as the brain matures, but the new results suggest that they may reappear in glioblastomas and could help drive the tumors' ability to rapidly grow and spread through the brain.

"Our study raises a number of important questions for the field, including how a stem cell present only in the developing brain re-emerges in an adult tumor," said Kriegstein. "Fortunately, Aparna and Elizabeth have now developed a model system in which we can begin to find the answers."

"This research combines numerous complimentary techniques to provide comprehensive evidence that glioblastomas revive stem cell programs from early brain development, including migratory behavior that may to contribute to their rapid spread," added co-author David Raleigh, MD, PhD, a UCSF radiation oncologist and brain tumor researcher. "This gives me confidence that the findings are not only scientifically robust but also will translate to human patients, with the potential to lead to new targeted therapies."

Bhaduri et al. (2020) Outer Radial Glia-like Cancer Stem Cells Contribute to Heterogeneity of Glioblastoma. *Cell Stem Cell* 26(1):48-63.e6.

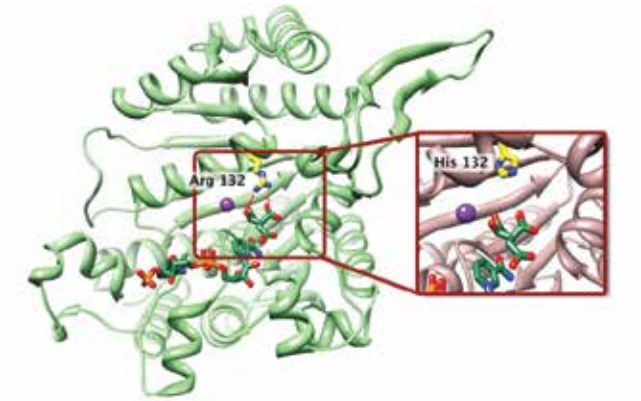
This story was written by Nicholas Weiler and first appeared in the UCSF News Center (ucsf.edu/news) on January 3, 2020.



New Clinical Trial Targets Mutations Commonly Found in Lower Grade Gliomas

Within the next few months, the UCSF Brain Tumor Center will begin recruiting for a multi-center clinical trial to evaluate AG-881, a small molecule drug, for treatment of residual or recurrent IDH-mutant grade II glioma.

AG-881 is a drug that inhibits the mutated forms of the isocitrate dehydrogenase (IDH) 1 and 2 proteins. IDH1 and IDH2 gene mutations are commonly found across a variety of cancers, including glioma. In the last decade, the discovery of these mutations and their role in brain tumor growth and biology has led to a sweeping re-organization of the World Health Organization (WHO) classification system. Now, certain glioma subtypes are further defined based on their IDH mutation status – a distinction that greatly impacts tumor biology and patient outcomes.



IDH mutations are known to be an early driver of glioma development, though the exact mechanism by which that occurs remains elusive. AG-881 acts to counter the overactive proteins produced within tumor cells carrying either of those mutations. “With IDH mutations present in the majority of low-grade gliomas, being able to specifically target this known driver of tumor development could have enormous impact,” says UCSF neuro-oncologist Jennifer Clarke, MD, who is leading the study at UCSF.

Preliminary findings from a phase I study of AG-881 show promising results for patients with IDH-mutant glioma. For patients with non-enhancing tumor, average six-month volumetric tumor growth was 6.8% following AG-881 treatment, compared to 24.5% in a similar glioma population without treatment. In addition, preliminary findings from a second, surgical study of AG-881 showed good brain penetration of the drug.

In this phase III trial, approximately 360 participants across multiple study sites will receive daily doses of the orally administered drug (or a placebo), with their treatment response followed. To be eligible, patients must have residual or recurrent grade II astrocytoma or oligodendroglioma with confirmed mutation(s) in IDH1 or IDH2, and be between 1 and 5 years from their most recent surgery.

For More Information on Enrollment

Study of AG-881 in Participants With Residual or Recurrent Grade 2 Glioma With an IDH1 or IDH2 Mutation

(415) 353-2966

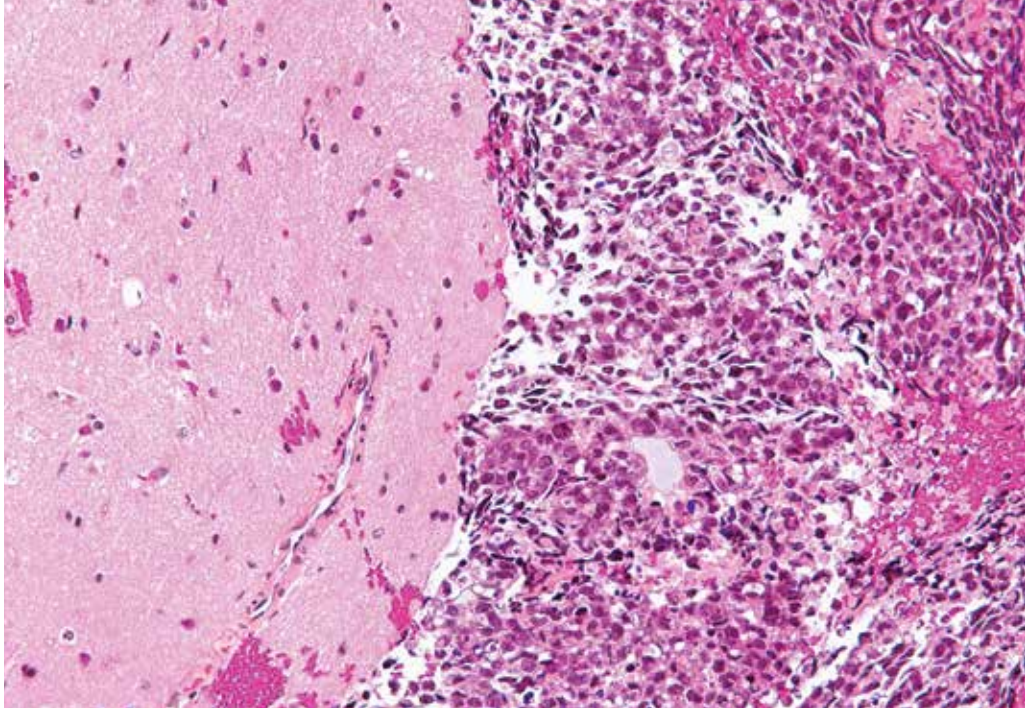
Clinical Trials

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 Trials for Adults	
NCT03345095	A Phase III Trial of Marizomib in Combination With Standard Temozolomide-based Radiochemotherapy Versus Standard Temozolomide-based Radiochemotherapy Alone in Patients With Newly Diagnosed Glioblastoma
NCT02655601	Trial of Newly Diagnosed High Grade Glioma Treated With Concurrent Radiation Therapy, Temozolomide and BMX-001 (BMX-HGG)
	Molecular Genetic, Host-derived and Clinical Determinants of Long-term Survival in Glioblastoma
NCT02796261	Study to Evaluate Eflornithine + Lomustine vs Lomustine in Recurrent Anaplastic Astrocytoma (AA) Patients (STELLAR)
NCT02549833	Neo-adjuvant Evaluation of Glioma Lysate Vaccines in WHO Grade II Glioma
NCT02924038	A Study of Varlilumab and IMA950 Vaccine Plus Poly-ICLC in Patients With WHO Grade II Low-Grade Glioma (LGG)
NCT03948490	Rehabilitation and Longitudinal Follow-up of Cognition in Adult Lower Grade Gliomas
NCT03561207	3D-PREDICT REGISTRY: 3D Prediction of Patient-specific Response using Ex vivo Interrogation of Live Cells from Tumors
	Impact of Cannabis and Synthetic Cannabinoid Use on Quality of Life of Patients with Central Nervous System Tumors (ICANCNS-QOL)

Select Trials for Children	
NCT02960230	H3.3K27M Peptide Vaccine for Children With Newly Diagnosed DIPG and Other Gliomas
NCT03566199	An Open Label Single Arm Phase I/II study of MTX110 Delivered by Convection-enhanced Delivery (CED) in Patients With Diffuse Intrinsic Pontine Glioma (DIPG) Previously Treated With External Beam Radiation Therapy
NCT03416530	ONC201 in Newly Diagnosed Diffuse Intrinsic Pontine Glioma and Recurrent/Refractory Pediatric H3 K27M Gliomas
NCT03086616	CED With Irinotecan Liposome Injection Using Real Time Imaging in Children With DIPG
NCT03749187	BGB-290 and Temozolomide in Treating Isocitrate Dehydrogenase (IDH)1/2-Mutant Grade I-IV Gliomas (PNOC017)
NCT03739372	Clinical Benefit of Using Molecular Profiling to Determine an Individualized Treatment Plan for Patients With High Grade Glioma (PNOC008)
NCT03919071	ACNS1723: A Phase 2 Study of Dabrafenib with Trametinib after Local Irradiation in Newly-Diagnosed BRAFV600-Mutant High-Grade Glioma (HGG)
NCT02962167	Modified Measles Virus (MV-NIS) for Children and Young Adults With Recurrent Medulloblastoma or Recurrent ATRT
NCT02724579	A Phase 2 Study of Reduced Therapy for Newly Diagnosed Average-Risk WNT-Driven Medulloblastoma Patients
NCT03893487	Fimepinostat in Treating Brain Tumors in Children and Young Adults (PNOC016)
NCT03579602	A Randomized, Blinded Study of Fluorescence Detection of Pediatric Primary Central Nervous System Tumors in Subjects Receiving Tozuleristide and Imaged With the Canvas System
NCT03690869	REGN2810 in Pediatric Patients With Relapsed, Refractory Solid, or Central Nervous System (CNS) Tumors and Safety and Efficacy of REGN2810 in Combination With Radiotherapy in Pediatric Patients With Newly Diagnosed or Recurrent Glioma
NCT00772200	Neuropsychological and Behavioral Testing in Younger Patients With Cancer

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



UCSF Offers New Clinical Service for Patients with Brain Metastases

Neuro-oncologist Mariza Daras, MD, has joined the UCSF Brain Tumor Center to lead a new service that coordinates care for patients with CNS metastases. Daras has spent the last six years at Memorial Sloan Kettering's Brain Tumor Center, treating primary tumors and metastatic disease.

"One goal for me at UCSF will be to help medical oncologists provide more comprehensive care for people with CNS metastases by creating an infrastructure specifically for these patients, whose metastatic disease tends to have very specific characteristics," says Daras.

Given the increasing complexity of care for patients with metastatic brain tumors, the new clinical service will help with the following:

- Facilitating access to care
- Integrating treatments among different specialties, including neuro-oncology, neurology, neurosurgery, and radiation oncology
- Bridging inpatient to outpatient treatment
- Collaborating in the development of clinical and translational research in the area of CNS metastases

"My role will be to tie together all the expert pieces available at UCSF into a dedicated consultative service that supports medical oncologists as they treat metastases involving the brain," said Daras.

The clinic will be geared toward patients with brain and/or leptomeningeal metastases with new or progressive CNS disease and for any associated neurologic complications, including radiation necrosis, cerebral edema, headaches, seizures, cognitive difficulties, paraneoplastic complications, gait balance difficulties. Lung and breast cancer are among the most common cancers to metastasize to the brain, so this clinical service will coordinate with the Thoracic and Breast Oncology clinics at UCSF.

Daras will also work with medical oncologists and other expert UCSF specialties and resources to develop new clinical trials designed specifically for patients with metastatic brain tumors. "The goal is to personalize care," she says. "If we join forces for everything from preclinical modeling through collection of biospecimens and biobanking, perhaps we can offer more targeted approaches."

Mariza Daras, MD, will be leading the new clinical service for patients with metastatic brain tumors.

UCSF Brain Tumor Center Celebrates 50th Anniversary

On February 18, 2020, over 150 guests gathered at the top of San Francisco's Salesforce Tower to raise funds and celebrate the 50th anniversary of UCSF's Brain Tumor Center.

Hosted by long-time supporters Alan and Ashley Dabbiere, the event also paid tribute to the pioneering work of the Center's director, Mitchel Berger, MD.

"I'm very, very proud of the achievements that we come here to celebrate tonight. Patients like Ashley come from all over the country as well as all over the world to receive what's turned out to be the highest quality of care along with the most advanced clinical trials offered by any center," said Berger.

Host Ashley Dabbiere shared her experience as a brain tumor survivor and together with her husband, Alan Dabbiere, gave a moving speech about the need for philanthropic support for brain tumor research.

"This team is known all over the world for being on the cutting edge of research, imaging, surgery, finding new therapies, but I know Dr. Berger and the Brain Tumor Center as something more – I know them as the devoted team that not only saved my life, but gave me quality of life," said Ashley.

The event raised funds for clinical care and research and paid tribute to 50 years of accomplishments by BTC investigators, including:

- Pioneering surgical techniques that are now standard care, including awake brain mapping and transsphenoidal surgery for pituitary tumors
- Identifying the first drug combination to be effective for brain tumors
- Introducing radiosurgery to the west coast
- Establishing one of the world's largest biorepositories of brain tumor tissue for research
- Publishing 2,000+ academic research articles that continue to drive advances towards improved therapies

Top left: Director of the UCSF Division of Neuro-Oncology, Susan Chang, MD, with Willie Brown, former Mayor of San Francisco.

Top right: Hosts Alan and Ashley Dabbiere with Joan Berger and UCSF Brain Tumor Center Director Mitchel Berger, MD.

Bottom left: Chancellor Sam Hawgood, MBBS

Bottom right: Marc Weill and Talmadge King, Dean of the UCSF School of Medicine

"I congratulate the Brain Tumor Center for 50 years of work," said Sam Hawgood, MBBS, Chancellor of UCSF. "I look forward to an exponential increase in discovery and benefits to patients over the next 10 years."

UCSF Department of Neurological Surgery
505 Parnassus Avenue, M779
San Francisco, CA 94143-0112

Nonprofit Org
U.S. Postage
PAID
University of
California
San Francisco

Referrals for Adult Patients

Phone: (415) 353-7500
Fax: (415) 353-2889

Referrals for Pediatric Patients

Phone: (415) 353-7500
Fax: (415) 502-5477

Request an online
peer-to-peer consult:
braintumorcenter.ucsf.edu/consult

@neurosurgUCSF @ucsfneurosurgery facebook.com/ucsfneurosurgery