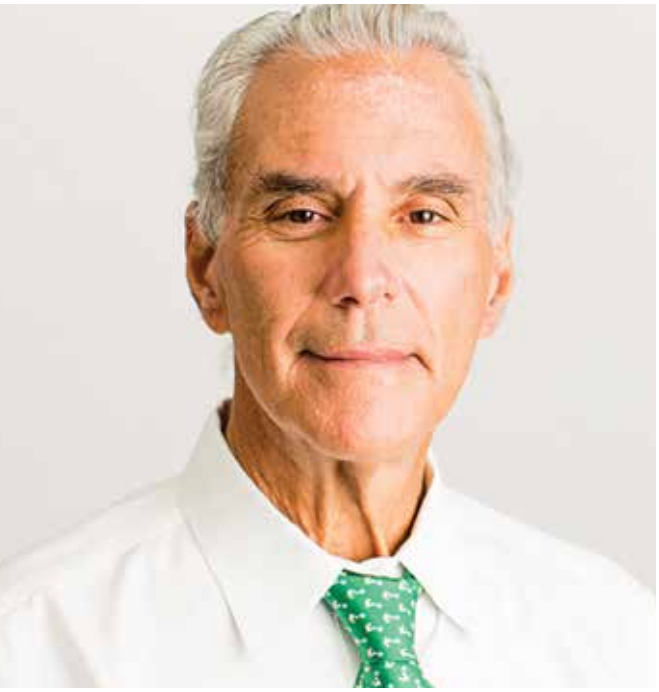
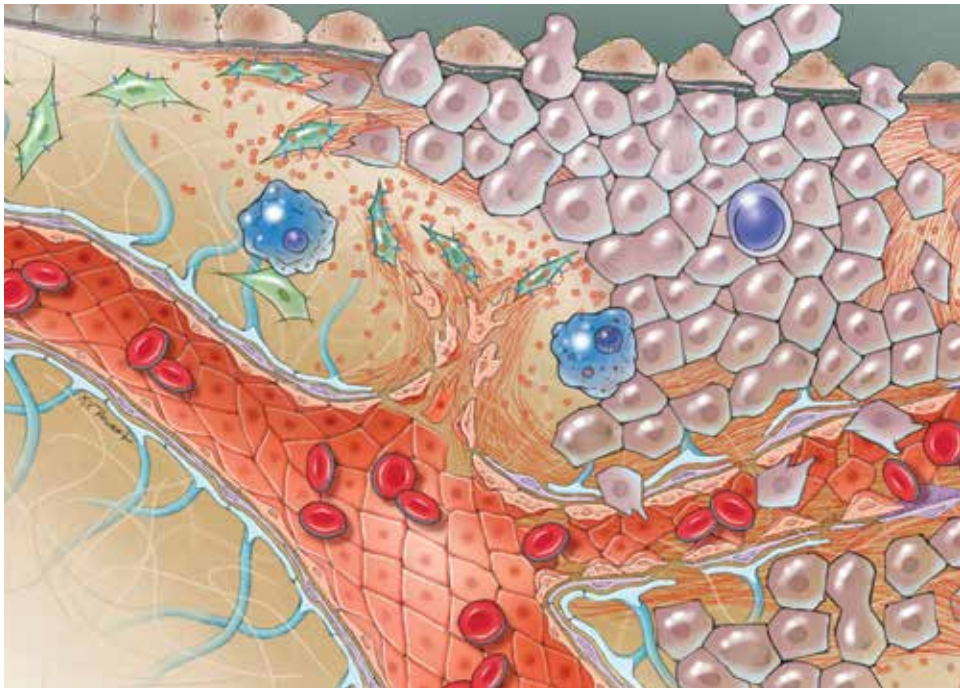
UCSF Brain Tumor Center News





Message from the Director

Dear Colleague:

I am pleased to introduce the first issue of the UCSF Brain Tumor Center newsletter. This biannual publication is designed to keep you up to date with developments in research and clinical care for brain tumors, and I hope it will be a source of useful information for your practice as well as a look into some of the exciting new developments emerging in this area of oncology.

The UCSF Brain Tumor Center is a comprehensive, interdisciplinary program that integrates neurosurgery, neuro-oncology, radiation oncology, neuropathology, and neuroimaging with basic science and clinical research. We also have innovative programs geared towards improving quality of life for our patients, as well as a program exclusively focused on the well-being of their caregivers. I am proud to say that over the past 50 years, we have established a reputation among both patients and physicians for providing the highest quality of care and most advanced clinical trials.

Another goal of the Brain Tumor Center is to serve as a regional resource for physicians and allied health professionals. From surgical consults to questions about clinical trial eligibility, we strive to provide physicians in our community with a fast, high-quality referral process.

As always, we are grateful to partner with you in the care of your patients.

Mitchel S. Berger, MD

Berthold and Belle N. Guggenhime Professor and Chair

Department of Neurological Surgery

Director, UCSF Brain Tumor Center

UCSF

University of California
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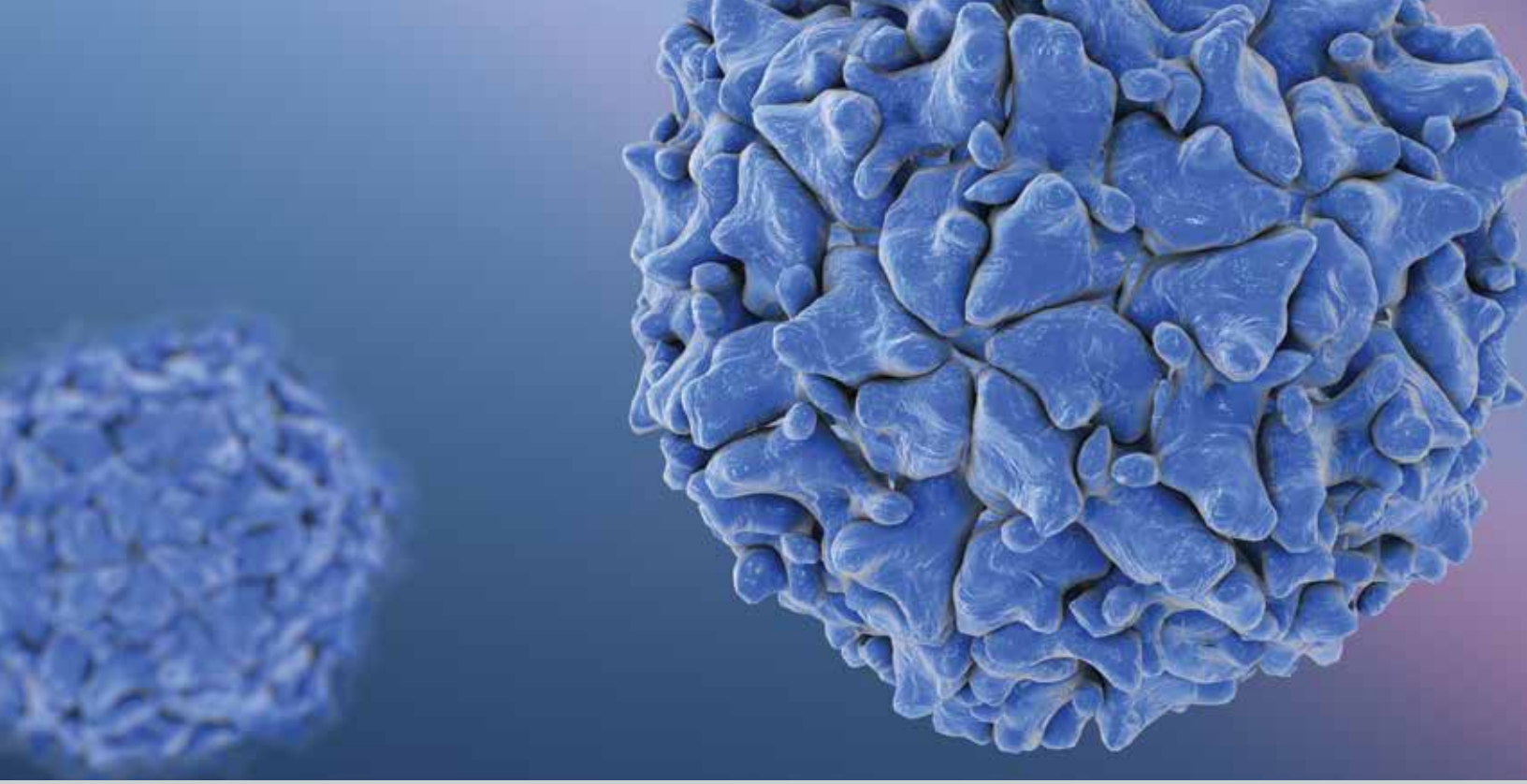


New Surgical Clinical Trial Uses Modified Poliovirus Against Glioblastoma

Nicholas Butowski, MD, director of translational research

"We hope that by this time next year, we will have some preliminary indications of how the therapy is working."

– Nicholas Butowski, MD

The UCSF Brain Tumor Center is one of four sites in the country testing a modified version of a poliovirus that had encouraging results against glioblastoma (GBM) in a recent phase I clinical trial.

In this trial, neurosurgeons infuse a genetically modified, non-pathogenic version of poliovirus into patients' tumors. Normally, poliovirus can only infect and enter cells by binding to CD155, a protein on the surface of certain cells. This approach takes advantage of the observation that CD155 levels are high in certain cancer cells, like GBM. Additional modifications ensure that the modified poliovirus only replicates and goes on to lyse non-neuronal cells. This directly kills tumor cells and also stimulates the immune system to attack the tumor.

Using convection-enhanced delivery (CED), the modified poliovirus is administered directly to the tumor site through a surgically implanted catheter. Half of the patients will receive the study virus only; the other half will also receive a course of the chemotherapy lomustine, which will begin eight weeks after the one-time polio treatment.

To be eligible for the trial, patients must have a recurrent tumor, located in an area that is amenable to CED. UCSF is the only West Coast site for this trial. "We will enroll 31 in each arm, and we hope that by this time next year, we will have some preliminary indications of how the therapy is working," says neuro-oncologist Nicholas Butowski, MD, who is co-leading the study at UCSF with Mitchel Berger, MD, and Manish Aghi, MD, PhD.

New Precision Medicine Trials Offer Individualized Therapy Based on Tumor Genetics

The UCSF Brain Tumor Center is currently leading several clinical trials to investigate a new personalized medicine strategy for both adult and pediatric patients.

A new pilot precision medicine trial, led by UCSF neuro-oncologist Jennifer Clarke, MD, is currently enrolling for adult patients with recurrent glioblastoma. In the trial, 15 eligible participants will undergo surgery as part of their standard of care, with sufficient tumor tissue collected for analysis. Their tumor samples will be analyzed using the UCSF500 Gene Panel to identify genetic changes in the DNA of each patient's cancer. The UCSF500 Gene Panel test analyzes nearly 500 different genes, including the majority of known cancer genes.

A multidisciplinary genomic tumor board then reviews the profile and looks for already-FDA-approved drugs that may target the abnormalities found in the patients' tumors, such as overactive tyrosine kinases or growth factors. The tumor board then recommends an individualized regimen of up to four FDA-approved drugs. Repurposing existing drugs in this fashion is one way to more quickly offer alternative therapies to patients with life-limiting illness who may not be eligible for other clinical trials.

"In a prior pilot study, we confirmed feasibility of generating an individualized treatment plan in a timely, efficient manner," said Clarke. "With this new trial, we are excited to actually implement the individualized treatments, to start to assess the efficacy of this approach."

A similar pilot study is underway for pediatric patients with newly diagnosed high-grade glioma. In the trial, UCSF pediatric neuro-oncologist Sabine Mueller, MD, PhD, and her colleagues in the Pacific Pediatric Neuro-Oncology Consortium will treat up to 44 children and young adults.

Again, the UCSF500 Gene Panel will be used, alongside other techniques, to analyze each patient's tumor profile. With this information, genetic alterations may be matched with existing targeted therapies or investigational new drug (IND) study agents that block the growth of cancer by interfering with the molecular targets that drive progression.

The treatment will be based on each child's individual tumor profile and will include up to four FDA-approved medications and, in special circumstances, IND study agents.

"We have learned a lot about the molecular makeup of high-grade gliomas in recent years and we recognize that their heterogeneity means that a blanket treatment approach fails to reach most patients," said Mueller. "We hope that this personalized strategy may lead the way to life-saving treatments for children with high-grade gliomas, as well as other treatment-resistant brain tumors."

"With this new trial, we are excited to actually implement the individualized treatments, to start to assess the efficacy of this approach."

– Jennifer Clarke, MD

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	
NCT02022644	Study of Convection-Enhanced, Image-Assisted Delivery of Liposomal-Irinotecan In Recurrent High Grade Glioma
NCT02986178	A Randomized, Multicenter, Phase 2 Study of Oncolytic Polio/Rhinovirus Recombinant (PVSRIPO) Alone or in Combination with Lomustine in Recurrent WHO Grade IV Malignant Glioma Patients
NCT02658279	Pembrolizumab (MK-3475) in Patients With Recurrent Malignant Glioma With a Hypermutator Phenotype
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)
NCT03295396	ONC201 in Adults With Recurrent H3 K27M-mutant Glioma
NCT03681028	Feasibility of Individualized Therapy for Recurrent GBM
NCT02655601	Trial of Newly Diagnosed High Grade Glioma Treated With Concurrent Radiation Therapy, Temozolomide and BMX-001 (BMX-HGG)
	Impact of Cannabis and Synthetic Cannabinoid Use on Quality of Life of Patients with Central Nervous System Tumors (ICANCNS-QOL)

Select Trials for Children	
NCT03086616	CED With Irinotecan Liposome Injection Using Real Time Imaging in Children With DIPG
NCT03245151	Study of Lenvatinib in Combination With Everolimus in Recurrent and Refractory Pediatric Solid Tumors, Including Central Nervous System Tumors
NCT02650401	Study of RXDX-101 in Children With Recurrent or Refractory Solid Tumors and Primary CNS Tumors, With or Without TRK, ROS1, or ALK Fusions
NCT01734512	Phase II Study of Everolimus for Recurrent or Progressive Low-grade Gliomas in Children
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
NCT03330197	A Phase I Study of Ad-RTS-hIL-12, an Inducible Adenoviral Vector Engineered to Express hIL-12 in the Presence of the Activator Ligand Veledimex in Pediatric Brain Tumor Subjects
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)
NCT03231306	A Phase II Study of Binimetinib in Children and Adults With NF1 Associated Plexiform Neurofibromas (PNOC010)
NCT03893487	Fimepinostat in Treating Brain Tumors in Children and Young Adults (PNOC016)
NCT02962167	Modified Measles Virus (MV-NIS) for Children and Young Adults With Recurrent Medulloblastoma or Recurrent ATRT

At the **UCSF Brain Tumor Center**, clinicians & scientists are involved in

27 ongoing clinical trials for **adults**

24 ongoing clinical trials for **children**

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

Annual Caregiver Retreat Focuses on Caregiver Wellness

In May, nearly 30 caregivers of patients with brain tumors joined us for an event dedicated to their well-being. Organized by the UCSF Neuro-Oncology Gordon Murray Caregiver Program, the annual Caregiver Retreat is designed as a restorative day where caregivers can connect with each other and receive practical advice.

This year, the day-long event included:

- Educational sessions, including information on how brain tumors affect patients
- Emotional support sessions
- Self-care activities including chair massages and an exercise workshop

Additional workshops highlighted the importance of self-care as a caregiver. “You may think you have to set aside your own needs as a caregiver, but the truth is, that’s not sustainable,” said Margaretta Page, RN.

Educational videos from the 2019 Caregiver Retreat can be found on our website at: http://tiny.ucsf.edu/aFxJY9

At this annual event, caregivers consistently report that the most meaningful part of the day is the opportunity to connect with others going through similar experiences. Especially given the unique and rare nature of brain tumors, the caregivers were grateful and took comfort in finding a community of people that understood their daily challenges.

The day-long event is provided at no cost to caregivers of UCSF Neuro-Oncology patients, and is supported through philanthropic donations to the UCSF Neuro-Oncology Gordon Murray Caregiver Program.

“The impact of a glioblastoma on a family is enormous. Not only are they facing an illness that is life-threatening, but one that threatens the very essence of who the patient is.”

Margaretta Page, RN

UCSF Neuro-Oncology Gordon Murray Caregiver Program

"Increasingly, there's a shift towards treating cancers using a precision medicine approach by matching specific targeted therapies based on their exact genetic mutations. This work lays the foundation for such targeted therapies for STAG2-mutant cancers."

– David Solomon, MD, PhD

Researchers Identify a New Therapeutic Target for Glioblastoma and Other Cancers

UCSF researchers have discovered that STAG2 – a gene commonly mutated in several human cancers – plays an essential role in DNA replication, revealing potential mechanisms for therapeutically targeting glioblastoma and other cancers.

As part of a multi-protein complex called cohesin, the STAG2 protein has been implicated in numerous cellular functions. The cohesin complex, which forms a ring-like structure that encircles DNA molecules, was first identified for its role in regulating the separation of DNA chromatids during mitosis.

Published in *Nature Communications,* UCSF neuropathologist and cancer biologist David Solomon, MD, PhD, and colleagues identify a new role for STAG2. "We found that STAG2 is required for replication fork progression, which can be exploited as a therapeutic vulnerability in STAG2-mutant cancers," said Solomon.

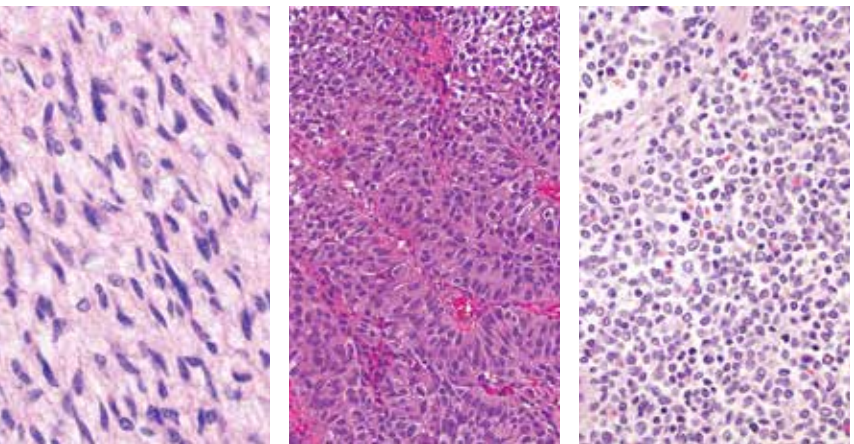
The Solomon Lab reports that loss of STAG2, in normal cells, causes the replication fork to stall by disrupting interactions between the cohesin complex and DNA replication proteins. This leads to replication fork collapse and causes double-strand breaks in the DNA; consequent activation of DNA damage signaling pathways ultimately halts the cell cycle, thus preventing cell proliferation.

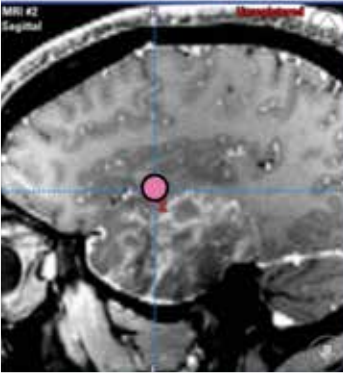
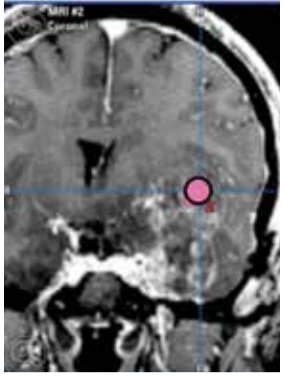
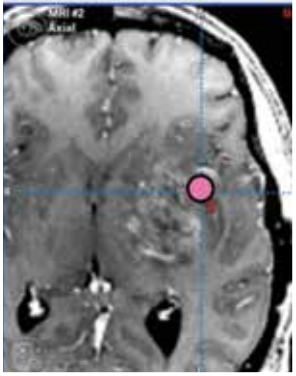
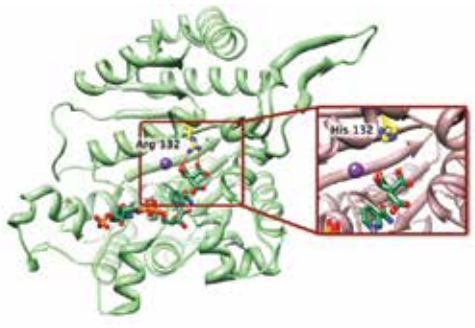
However, STAG2 inactivation behaves differently in tumor cells. "STAG2 inactivation is often associated with TP53 mutations, and in some cancers such as Ewing sarcoma, the combination of these mutations is associated with worse prognosis," said Solomon. When they tested the combined loss of STAG2 and p53, those cells escape cell cycle arrest. Instead, the DNA double-strand breaks caused by STAG2 deficiency likely contributes to further gene mutations and rearrangements that promote tumorigenesis.

Given the accumulation of DNA double-strand breaks with STAG2 inactivation, Solomon and colleagues speculated that STAG2-deficient cancer cells might heavily rely on DNA damage repair proteins for survival. Indeed, the combined loss of STAG2 and certain DNA repair factors (e.g. ATR, PARP1, BRCA1) results in synthetic lethality, a condition in which the combination of two or more deficiencies leads to cell death.

When testing a panel of chemotherapy drugs, Solomon also found that STAG2-mutant cancer cells (including glioblastoma and Ewing sarcoma) are more sensitive to cytotoxic chemotherapeutic agents that induce double-strand breaks. They also have lower survival rates when exposed to gamma radiation. Presumably, loss of STAG2 sensitizes tumor cells such that an even greater accumulation of DNA damage is catastrophic.

STAG2 is one of the most commonly mutated genes in (left to right) glioblastoma, bladder cancer, and the bone cancer Ewing sarcoma.



UCSF Brain Tumor Center Is Awarded Renewal of Program Project Grant for Gliomas

This year marked the ninth cycle of Program Project Grant funding for the UCSF Brain Tumor Center from the NIH. The Center's first Program Project Grant was awarded in 1979 to study the biology and therapy of malignant brain tumors. Since then, the program has evolved to focus on developing and applying novel noninvasive neuroimaging techniques to clinical problems in neuro-oncology

In the last decade, delineation of histopathological and molecular subgroups of glioma has revolutionized the field of neuro-oncology by improving diagnosis and prognosis. Interrogating metabolic and physiologic signatures of these subgroups will be one of the next critical advances in the field of neuroimaging. For the next four years, the program will focus on four projects aimed at improving the management of patients with different subgroups of glioma.

Project 1: Improved Strategies for Noninvasive Imaging of Patients with Glioma

This project will link metabolic and physiological imaging data with histological characteristics from 2000 image-guided tissue samples obtained from 750 patients in our previous funding cycle and will validate them prospectively in a new cohort of patients. This multi-parametric approach will produce metrics tailored to each molecular subgroup of glioma.

Project 2: Investigating Mechanisms that Regulate Tumor Cell Immortality in TERT-promoter-mutant Glioma

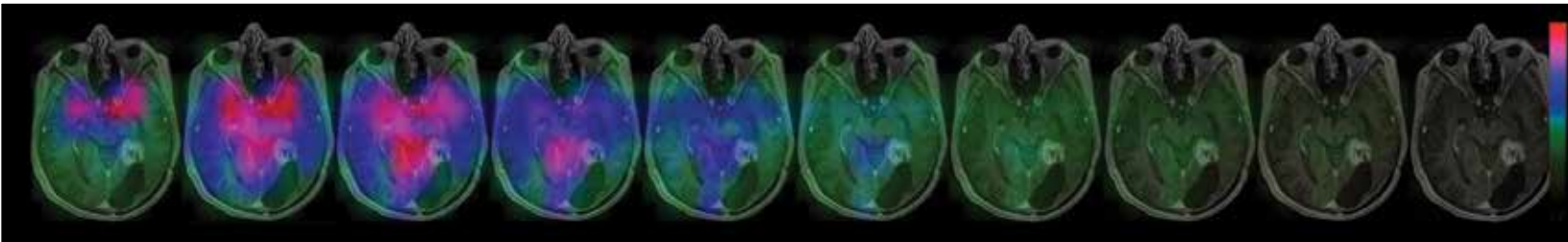
Delineating the regulators of tumor immortalization that are associated with TERT promoter mutations is highly significant for providing a better understanding of the formation and evolution of glioma. Project 2 aims to identify subgroup-specific and shared factors that influence how the TERT promoter mutation impacts tumor progression for glioblastoma and oligodendroglioma, which have such divergent clinical outcomes.

Project 3: Defining Metabolic Signatures for Monitoring TERT Expression in Glioma

Project 3 will use 1H and hyperpolarized 13C MR spectroscopy in cell and pre-clinical models to identify signatures of TERT expression that could be used for monitoring tumor progression and assessing response to therapy. This would be highly significant for the initial screening of promising therapeutic agents aimed at TERT-promoter-mutant cells.

Project 4: Translating 1H and Hyperpolarized 13C Metabolic Imaging Techniques to Patients

Combined 1H and hyperpolarized 13C metabolic imaging techniques can resolve ambiguities associated with current anatomic imaging methods and evaluate metabolic signatures that are specific for different glioma subgroups. Project 4 will conduct the first patient studies using two new hyperpolarized agents that are associated with changes in metabolism in IDH+ glioma. The most appropriate parameters for acquiring the metabolic data will be determined and applied to patients from the three most common glioma subgroups.



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