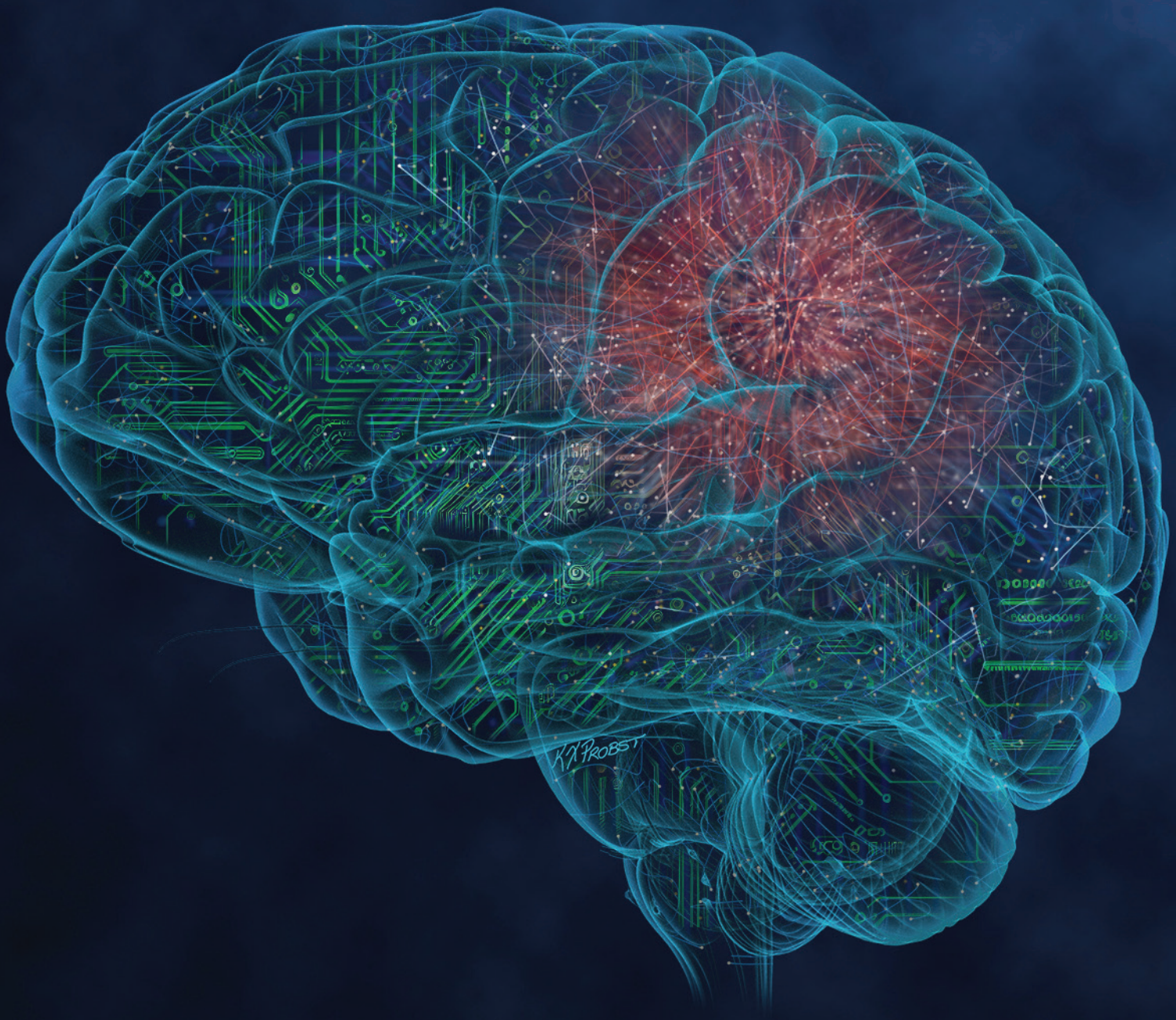
UCSF Brain Tumor Center

Fall 2023

Renewed Funding of SPORE Grant

Neurocognitive Rehabilitation

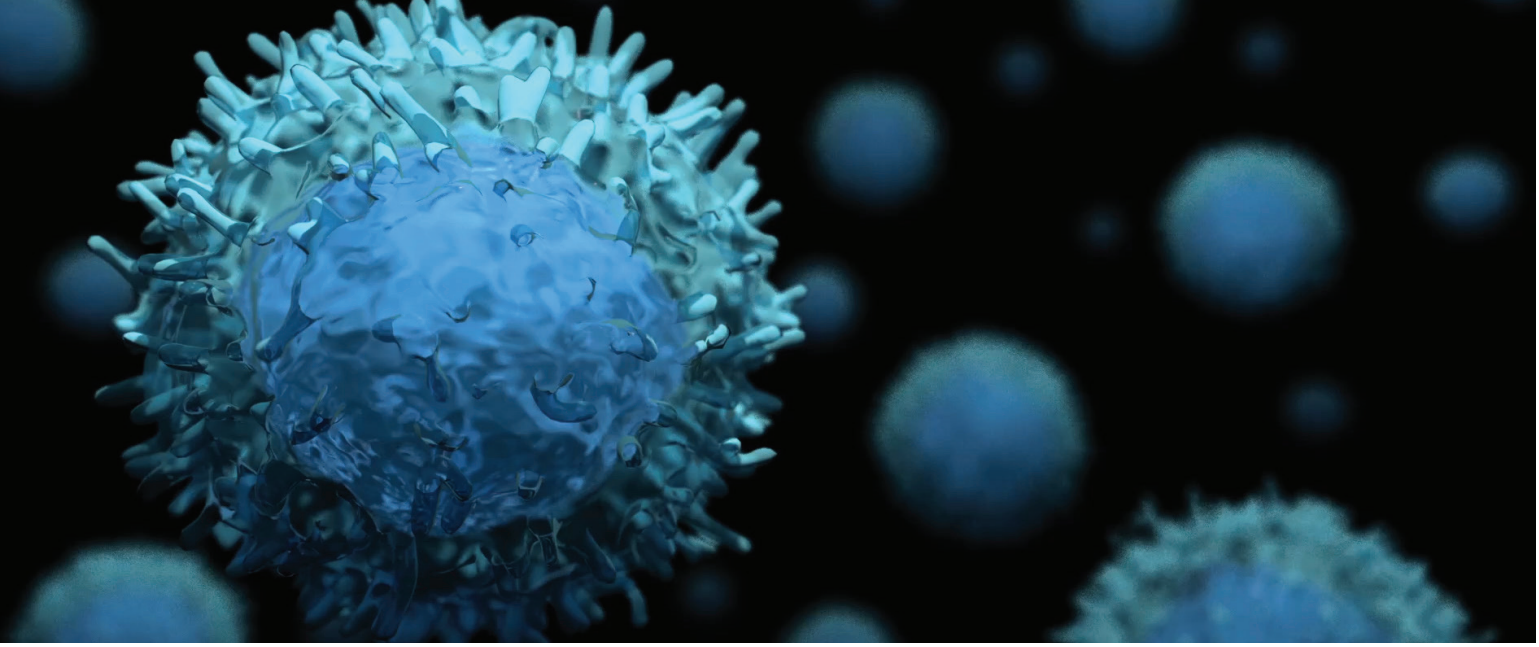
Susan Chang on Her Role as Editor-in-Chief of *Neuro-Oncology*



Short Circuit

How gliomas integrate into neuronal networks to impair cognition

UCSF



Brain Tumor SPORE at UCSF Receives $12 Million Renewal from NCI

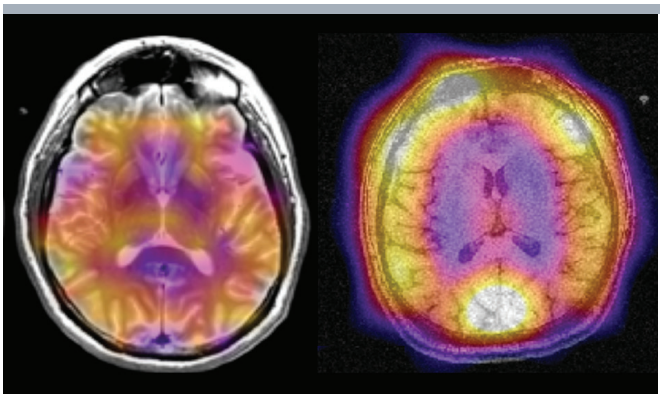
With a renewed Specialized Program of Research Excellence (SPORE) grant, the UC San Francisco Brain Tumor Center is receiving $12 million over five years to translate scientific findings into improved care for people with brain tumors.

The award marks the fifth cycle of continuous support for the UCSF Brain Tumor SPORE program since the National Cancer Institute (NCI) first established brain tumor SPOREs in 2002.

This SPORE grant — led by UCSF Brain Tumor Center director Mitchel Berger, MD — funds three projects focused on developing noninvasive ways to better predict patient outcomes and a new immunotherapy for glioma.

The first project is testing an innovative new technique pioneered at UCSF called immunomethylomics. It characterizes unique DNA methylation patterns on immune cells circulating in the blood, and could be used to measure immune suppression. Led by Annette Molinaro, PhD, John Wiencke, PhD, and Jennie Taylor, MD, MPH, the research aims to develop a non-invasive blood test that can assess response to tumor therapies and give more accurate prognosis by analyzing a patient's immune system profile.

Hyperpolarized C-13 imaging can show early changes in the tumor's metabolism, making it a promising noninvasive way to assess tumor burden and response to therapy. *Image courtesy of Daniel Vigeron, PhD.*



The scientists working on the second project — led by Pavithra Viswanath, PhD, Yan Li, MD, PhD, and Susan Chang, MD — are also using a novel approach to evaluate the response to brain tumor therapies. With an advanced medical imaging technology called hyperpolarized C-13 imaging, researchers can track dynamic changes in the tumor's metabolism. The goal of this project is to characterize tumor burden by monitoring the metabolism of gliomas with mutations in isocitrate dehydrogenase (IDH) — an enzyme which normally makes α-ketoglutarate but instead produces the oncometabolite 2-hydroxyglutarate when mutated.

The third project aims to develop a novel immunotherapy for glioblastoma. Using CAR T-cells specifically engineered to identify and kill only the tumors cells, this new therapy is poised to overcome several of the current challenges of adapting immunotherapy to brain tumors. This project is led by Hideho Okada, MD, PhD, and Jennifer Clarke, MD, MPH.

In addition to supporting these three translational research projects, the SPORE grant funds three resource cores: Administrative (Leaders: Mitchel Berger, MD, Susan Chang, MD, and Hideho Okdada, MD, PhD); Biostatistics and Clinical (Leaders: Annette Molinaro, PhD, John de Groot, MD); and Biospecimen and Pathology (Leader: Joanna Phillips, MD, PhD). The Career Enhancement Project and Developmental Research Project — managed by Joseph Costello, PhD — also serve to support early career investigators and foster innovative research projects.

How Gliomas Integrate Into Neuronal Networks to Impair Cognition

Krishna S et al. (2023) Glioblastoma remodelling of human neural circuits decreases survival. Nature 617(7961):599-607.

The difficult-to-treat brain cancer glioblastoma steals a person's mental faculties as it spreads, yet the tumor's insidious ability to infiltrate neighboring networks in the brain could also prove its undoing.

Scientists at UC San Francisco have discovered that neural activity in these deadly tumors can restructure connections in surrounding brain tissue, causing the cognitive decline associated with the disease, and that the drug gabapentin, commonly used to prevent seizures, could block this growth-causing activity in mice with glioblastoma.

The findings, appearing in *Nature,* provide a hopeful new direction for research on a disease that has defied even the most modern and sophisticated types of cancer drugs.

"Glioblastoma needs a win," said neurosurgeon Shawn Hervey-Jumper, MD, who led the study along with postdoctoral scholar Saritha Krishna, PhD. "This study opens the door to a whole world of treatment possibilities for these patients and a new way of thinking about brain cancer."

When Hervey-Jumper was beginning his study, scientists had recently discovered that brain tumors are fueled by a positive-feedback loop. It begins when cancer cells produce substances that can act as neurotransmitters. This "extra" supply of neurotransmitters spurs neurons to become hyperactive, which in turn stimulates the growth of the cancer cells.

Building on earlier studies done on mice and brain organoids (small bundles of neurons derived from human stem cells grown in petri dishes), Hervey-Jumper focused on what the feedback loop meant for human behavior and cognition in brain cancer.

The team recruited volunteers awaiting surgery for glioblastoma whose tumors had infiltrated the brain region controlling speech. Just before operating on the tumor, Hervey-Jumper placed a grid of tiny electrodes on the surface of the speech region, showed the volunteers pictures and asked them to name what they saw.

The research team then compared the results with normal-appearing non-tumor regions of the brain from the same participants. They found that the tumor-infiltrated brain regions used a broader neural network of brain area in the effort to identify what they were seeing.

Hervey-Jumper attributes this to degradation of information-processing power in that region of the brain. He likens it to an orchestra where it's the musicians playing in synchrony that makes the music work.

"If you lose the cellos and the woodwinds, the remaining players just can't carry the piece the way they could otherwise," he said. The brain cells bound up in the tumor are so damaged that others must be recruited from farther out to perform the tasks that used to be controlled by a smaller area.

The study shows that it's this interaction between cells that causes the cognitive decline associated with brain cancer, rather than inflammation and pressure from tumor growth, as scientists had thought.

"A brain tumor isn't just sitting there dying," said Hervey-Jumper. "It's being regulated by the nervous system. It's having conversations with the cells around it and actively integrating into brain circuits, remodeling the way they behave."

Now, the researchers knew that the tumors were taking advantage of the brain's networks. So, they turned to gabapentin, which controls seizures by tamping down excess electrical activity in the brain, testing it in mice engrafted with human glioblastoma cells.

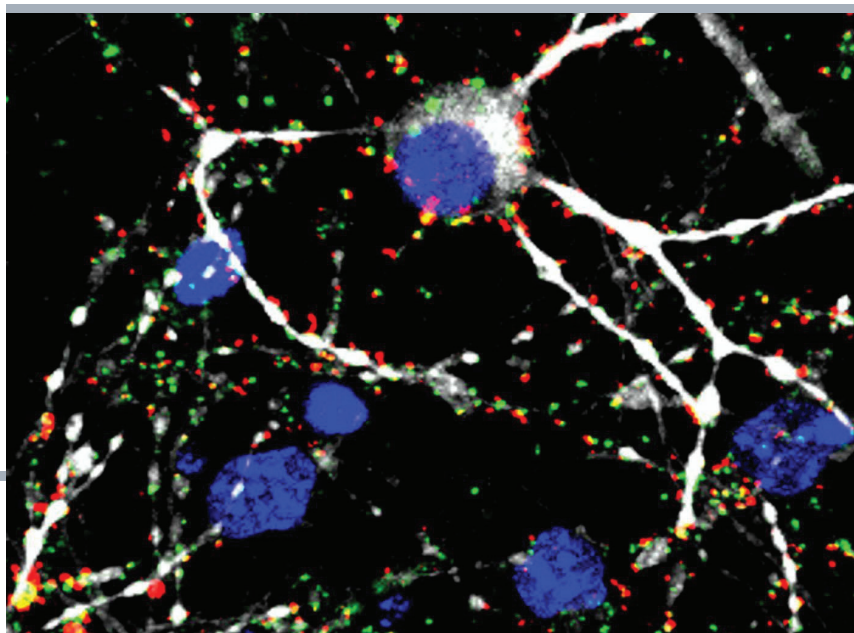
"Gabapentin actually kept the tumor from expanding," said Krishna. "This makes us hopeful that combining gabapentin with other glioblastoma therapies could stave off some of the cognitive decline we see in patients and perhaps extend their lives."

The findings will likely translate to other neural cancers, such as those of the spine, and may help explain why the brain is the first site of metastasis in many cancers.

Hervey-Jumper said the study encourages cancer specialists to consider communication networks between cells, like the positive-feedback loop in glioblastoma, as potential targets for treatments, along with genetic and immunological approaches.

"We haven't thought about cancers in this way before," he said. "The idea that there's conversation between cancer cells and healthy brain cells is something of a paradigm shift."

Human glioblastoma cells showing areas where new connections between cells are being formed at an accelerated rate. Image by Hervey-Jumper Lab.



This story was written by Robin Marks and first appeared in the UCSF News Center (ucsf.edu/news) on May 10, 2023.

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

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
NCT05163080	Prospective Randomized Placebo-Controlled Trial of SurVaxM Plus Adjuvant Temozolomide for Newly Diagnosed Glioblastoma (SURVIVE)
NCT05267106	Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants with Previously Treated Glioblastoma or Other Primary Central Nervous System Tumors Harboring Activating FGFR1-3 Alterations (FIGHT-209)
NCT05023551	A Phase I Study of DSP-0390 in Patients with Recurrent High-Grade Glioma
	Development of Liquid Biomarkers for Temozolomide Induced Hypermutation in Patients with Glioma
NCT04762069	A Study of Berubicin in Adult Subjects with Recurrent Glioblastoma Multiforme
NCT03561207	3D-Prediction of Patient-Specific Response (3D-PREDICT)
NCT04659811	A phase II study of stereotactic radiosurgery in conjunction with the PD-1 inhibitor, pembrolizumab for the treatment of recurrent meningioma
NCT03948490	Rehabilitation and Longitudinal Follow-up of Cognition in Adult Lower Grade Gliomas
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)
NCT05478837	Genetically Modified Cells (KIND T Cells) for the Treatment of HLA-A*0201-Positive Patients With H3.3K27M-Mutated Glioma (PNOC018)
NCT03749187	BGB-290 and Temozolomide in Treating Isocitrate Dehydrogenase (IDH) 1/2-Mutant Grade I-IV Gliomas (PNOC017)
NCT04732065	ONC206 for Treatment of Newly Diagnosed, or Recurrent Diffuse Midline Gliomas, and Other Recurrent Malignant Brain Tumors (PNOC023)

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

Susan Chang on Serving as Editor-in-Chief for *Neuro-Oncology*

Last March, the Society for Neuro-Oncology (SNO) and Oxford University Press named UCSF neuro-oncologist Susan Chang, MD, Editor-in-Chief of its flagship journal *Neuro-Oncology.* Since then, she has overseen an increase in the journal's impact factor from 13.029 to 15.9, making it among the most influential journals in clinical neurology and oncology.

She also helped launch SNO's Editorial Scholars Program to offer training on the peer-review process and mentoring to early career researchers. The program recruited its first cohort of 17 junior faculty members in July.

We spoke with Dr. Chang about her role, SNO's educational mission, and the landscape of scientific publishing.

What motivated you to start the Editorial Scholars Program?

There is no question that scientific publishing benefits many stakeholders – the field and neuro-oncology community, publishers and sponsors, authors, reviewers, the editorial team and, of course, the patient. Some of the biggest challenges in scientific publishing that junior faculty often face include not having the appropriate training and time to dedicate to the review process and not having knowledge of the publishing enterprise. Personally, I did not have an opportunity to learn about the publishing enterprise except through my positions as Editor-in-Chief for both *Neuro-Oncology Practice* and *Neuro-Oncology.* Similarly, I learned about the peer review process informally.

I have two major goals for the program: to provide opportunities for early career investigators to engage in the publishing enterprise and to enhance their skills as peer reviewers. I think being a good reviewer will translate into being a better writer and contributes immensely to enhancing the overall quality of the work that is published. Ultimately, I want to foster the next generation of investigators to be engaged in the publishing enterprise so we can continue to publish high impact papers that advance the field.

What have been some highlights of the program so far?

The interest in the program from the editorial team and mentors and the enthusiasm from applicants has been the greatest highlight. Forty-one people applied, which was an unexpected and fantastic start to an inaugural program. We thought the first class would consist of about 10 scholars, but because the response to the announcement was so positive, we have 18 scholars this year.

What do you feel is most contributing to the program's success?

The need, I think, is great, as well as the interest in understanding and contributing to the journal. The willingness of the editorial team to serve as mentors for one-on-one training is also a major draw.

How would you like to see the program grow in the next year?

I would like to expand to all major disciplines in neuro-oncology and across diverse early career investigators, so we can ensure that we have experienced reviewers for all the areas in which research is conducted. Articles in *Neuro-Oncology* span basic science, clinical, and translational research in both adult and pediatric populations. As our multidisciplinary field continues to grow, we need experts to be engaged in the process. For example, this year we added expertise in pediatric neuro-oncology, cancer neuroscience, and artificial intelligence to the editorial board. We need the program to continue to support investigators with a multitude of perspectives.

In her role as Editor-in-Chief of *Neuro-Oncology,* UCSF neuro-oncologist Susan Chang, MD, is raising the impact factor of the journal and spearheading a new educational initative for early-career faculty.

Beating the Odds: 21-Year Survivor on How to Live Well with Brain Cancer

Michael Dunbar had been getting frequent headaches for months before his family and friends finally convinced him to seek out medical care. After a neurological exam, his physician ordered an MRI for the next day.

But Dunbar would not make it to that appointment. Later that evening his wife rushed him to the ER upon noticing that the left side of his face was drooping. He got the brain scan at the hospital, which revealed that he had a tumor known as a glioblastoma. A nurse there advised him to get to UC San Francisco.

After his tumor was removed, Dunbar and his wife learned that the prognosis for patients with glioblastoma could be as short as six to 12 months. They wondered what they should tell their three small children.

That was now more than 21 years ago.

“I tell people who ask, ignore any of the statistics,” Dunbar said. “They don’t apply to any one person.”

Four years ago, he experienced another rare event — a small stroke caused by the radiation therapy to treat his cancer. As he was recovering, UCSF neuropsychologist Christina Weyer Jamora, PhD, RN, told him about the Sheri Sobrato Brain Cancer Survivorship Program.

The program takes a holistic approach to supporting brain tumor survivors in managing the lasting impacts of cancer and treatment. Through generous philanthropic support, the program offers a wide array of services — ranging from support groups and peer mentoring to exercise classes and neurocognitive care.

For Dunbar, the program has provided exactly the kind of satisfaction and fulfillment he was looking for after he had to stop working. He now tries to immerse himself in many of the survivorship program’s events, including the monthly brain tumor support group.

“The Sheri Sobrato Brain Cancer Survivorship Program not only offers information, wellness classes, community connections and direct support, but it also offers opportunities for survivors like Michael to contribute in very meaningful ways,” said program manager Naomi Hoffer. “Michael and others are here to offer deep understanding and perspective, and together they have created a web of community support that reaches far beyond the walls of what any program could offer.”

UCSF Thrivers Dace Hines and Michael Dunbar. Photo by Dace Hines.

For the last year and a half, Dunbar has also been volunteering as a member of the UCSF Thrivers, a group of trained peer support mentors. Thrivers meet weekly over Zoom to support each other and practice their skills for supporting others who are struggling to cope with brain cancer and its treatment.

Hoffer says that through volunteer roles as panelists, mentors, editors and advisors, the UCSF Thriver community has helped thousands of others who are newly diagnosed.

“When people tell me that I give them hope,” Dunbar said, “that’s the best thing I can hear.”

He advises other survivors to take advantage of all the services the UCSF Brain Tumor Center offers to both patients and their caregivers, emphasizing how important his wife’s support has been throughout his journey.

Dunbar, who previously wrote and edited documents about products for engineers, was glad to put his skills to use in helping review a manual detailing cognitive strategies for people with brain cancer.

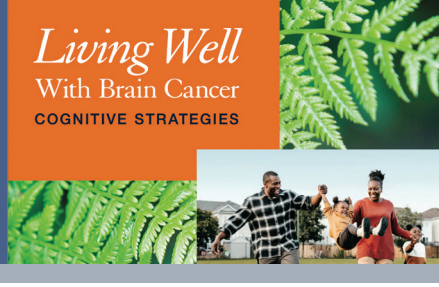
He appreciates getting tools he can incorporate into his daily life that are from a patient perspective. For example, fellow Thriver Kat Shotz leads a 4-week meditation and yoga class for the UCSF neuro-oncology patient community and has served as a panelist on the monthly Living Well After Brain Cancer Treatment webinars.

Shotz, who was a yoga instructor for years before she was diagnosed with a brain tumor, is open about how her practice has changed to embrace a gentler approach that has helped her feel more peace and compassion. Having to work through the anxiety that often accompanies going through treatment and follow-up brain scans resonates with survivors like Dunbar.

“I want to do whatever I can to get better and stronger, whether that’s mind or body,” he said.

Dunbar does physical therapy exercises and goes out for daily walks in his neighborhood in Alamo. He also solves jigsaw puzzles — a hobby he has had since childhood that now doubles as part of his ongoing cognitive rehabilitation therapy. The puzzles help with his spatial awareness, and many are of photos that remind him of what matters most in his life.

“It’s not about breathing life; it’s about living life,” Dunbar said on being a long-term survivor. “I want to make sure that I’m living fully.”



Neurocognitive Care Takes Patient-Centered, Research-Driven Approach

Cancer patients can experience changes in their cognitive abilities, but for people with brain tumors, difficulties with memory, concentration, and executive function are unfortunately, more common.

In 2018, the UC San Francisco Brain Tumor Center began offering neurocognitive care services through the Sheri Sobrato Brain Cancer Survivorship Program to meet the growing need of brain tumor patients.

“Patients don’t want to just be told the challenges they have,” says UCSF neuropsychologist Christina Weyer Jamora, PhD. “They want a pathway to managing these changes.”

Weyer Jamora and her growing team of neuropsychologists take a holistic, personalized approach that emphasizes building on the patients’ cognitive strengths. The neuropsychologists are also key members of UCSF’s Neuro-Oncology Interdisciplinary Team — a group of experts across different fields that work together to figure out the care brain tumor patients need after surgery.

“The neuro-oncologist, the neuropsychologist, the health psychologist, the social worker, palliative care — all these people come together to try to think through the best way to meet the patient’s goals of care and help them live and thrive in the ways that are meaningful to them,” Weyer Jamora said.

Many factors can influence the presentation and severity of cognitive symptoms in brain tumors patients, including the tumor type and location, which stage of treatment a patient is in, and fatigue.

The process of managing cognitive symptoms is about learning what works best for the patient and providing them tools to cope with the changes they are experiencing, said UCSF neuropsychologist Melissa Brie, PsyD, during a recent Living Well After Brain Cancer Treatment webinar.

Cognitive rehabilitation approaches have been used for years as part of the recovery for people who suffer traumatic brain injuries or a stroke. The strategies often involve cognitive retraining, where a person practices certain cognitive exercises to try and improve their skills. On the other hand, compensatory strategies focus on modifying the environment or adjusting patient and family expectations to facilitate better cognitive outcomes.

“We call it ‘minding the gap’ between what the environment requires and what skills they have,” Weyer Jamora said.

Through an ongoing clinical trial, UCSF researchers are testing out different interventions in people with lower grade gliomas, a younger patient population that reports cognitive impairments that decrease their quality of life.

Last fall at the Society for Neuro-Oncology Annual Meeting, the team presented their initial findings showing that patients generally liked and completed the interventions, which included in-person, app-based, and texting-based modalities. The patients’ working memory, verbal learning, and memory skills also improved after three months of cognitive rehabilitation.

“It’s encouraging to see that we can improve certain aspects of cognition even in the midst of neurodegenerative disease,” Weyer Jamora said.

Now, she and her colleagues are trying to understand more about which patients may benefit most from cognitive rehabilitation in the context of returning to work, as well as the best time to intervene during the course of the disease.

“It’s really that balance between wanting to make these areas of cognition improve while also not losing sight of what’s important to the patient in the process,” Weyer Jamora said.

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