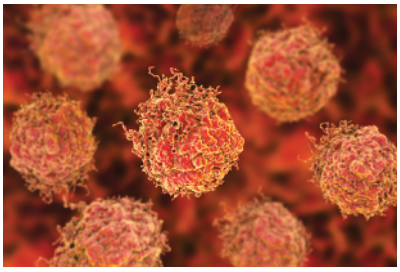


"A strength of the study is an active control arm using cabazitaxel, a validated life-prolonging therapy," Hofman said. He concluded that ^{177}Lu-PSMA-617 appears to be significantly more active than cabazitaxel, and thus "represents a new class of effective therapy for men with castration-resistant prostate cancer." TheraP will continue to gather OS data, and ^{177}Lu-PSMA-617 will undergo additional testing in the upcoming phase III VISION trial.

Anthony D'Amico, MD, PhD, of Brigham and Women's Hospital in Boston, MA, who was not involved in the trial, is "cautiously optimistic" about the results. "I think the science is valid, and I think it's a wonderful targeted treatment," he said, noting the agent's minimal toxicity.

He added that "there probably is a benefit over cabazitaxel," but several limitations associated with the relatively small size of a phase II trial make it difficult to assess the magnitude of the difference. Chiefly, patients in the cabazitaxel group had a higher dropout rate than those in the ^{177}Lu-PSMA-617 group, and they were almost twice as likely to have visceral metastases going into the trial—factors that may have contributed to their poorer outcomes.

Thus, D'Amico said, OS data and results from the phase III trial will be key. "I'd like to see it work. We just need the level one evidence to move it forward." *–Catherine Caruso* ■

Break Through Cancer Launches with $250M

Five major cancer centers have formed a foundation aimed at accelerating progress against some of the most hard-to-treat cancers. Break Through Cancer, launched recently with an initial pledge of $250 million from philanthropists Alice T. and William H. Goodwin Jr., is expected to begin awarding grants to research teams within the next few months (see http://breakthroughcancer.org).

"We've created Break Through Cancer to take the concept of collaboration significantly further than ever before," said the foundation's president, Tyler Jacks, PhD, at a news conference. "We hope to develop proof of concept for new ways to rapidly integrate the best of science and the most powerful technologies into clinical research and cancer treatments, resulting in dramatic improvements for patients."

The five founding institutions have long-standing philanthropic ties to the Goodwins, whose son, Hunter Goodwin III, died from cancer last year at age 51. Participants include: Dana-Farber Cancer Institute in Boston, MA, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD, Memorial Sloan Kettering Cancer Center in New York, NY, the Koch Institute for Integrative Cancer Research at MIT in Cambridge, MA, and The University of Texas MD Anderson Cancer Center in Houston.

Grants of up to several million dollars each will support multidisciplinary teams of researchers from across the five centers, and possibly scientists at other institutions in the future, said Jacks, who is also the founding director of the Koch Institute and a former president of the American Association for Cancer Research. The foundation—which aims to raise $500 million over the next 10 years—will initially fund translational projects that focus on four difficult-to-treat malignancies: pancreatic cancer, ovarian cancer, glioblastoma, and acute myelogenous leukemia.

Break Through Cancer's chief science officer, Jesse Boehm, PhD, formerly of the Broad Institute of MIT and Harvard in Cambridge, and its scientific advisory board—comprised of experts from nonparticipating institutions—will take a much more active role in planning and executing projects than has traditionally occurred in cancer research, Jacks noted.

"Our leaders and board members will work closely with institutions from the outset to form innovative teams and shape bold, potentially transformative research plans," he said. "They will monitor progress of these teams closely, help them clear hurdles, pivot if research warrants, and drive faster, smarter, and ideally more successful clinical studies."

According to Boehm, leaders also plan to tackle challenges around sharing clinical, genomic, and laboratory data across institutions without compromising patient privacy. "Often, there are funding barriers to creating and maintaining high-quality software tools that actually make sharing data easy and useful," he said. "We will explore this in detail, as we suspect that adequately incentivizing and resourcing data sharing will go a long way toward making collaborations work."

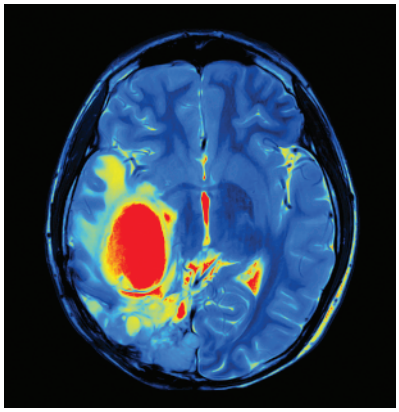
The group will work closely with the NCI and other major funders, as well as biotechnology and pharmaceutical companies. "Our goal is to get new medications out there as fast as possible," said board member Laurie Gilmcher, MD, of Dana-Farber. "Our industry partners can facilitate a path from discovery to treatment."

The foundation's commitment to collaboration is inspired in part by the scientific community's robust response to COVID-19, Jacks said. During the COVID-19 pandemic, "there's been a sense that progress—as opposed to individual accomplishment—is the most important thing," he said. "We want to bring that same sense of urgency to the problems that we face in cancer." *–Janet Colwell* ■

"A Complete Molecular Atlas of Glioblastoma"

A detailed examination of the genes, proteins, metabolites, regulatory RNAs, post-translational modifications, and epigenetic markers active in glioblastoma has revealed new molecular drivers and immune subtypes of the deadly brain cancer. The findings, from the largest multi-omics investigation of glioblastoma conducted to date, should inform treatment strategies and clinical trial design (Cancer Cell 2021;39:509–28.E20).

"This is a huge resource—a complete molecular atlas of glioblastoma," says Karin Rodland, PhD, of the Pacific Northwest National Laboratory (PNNL) in Richland, WA, and the Oregon Health & Science University in Portland, who co-led the research.



Neuro-oncologists currently rely on genomic mutation profiles and gene expression signatures to identify subtypes of glioblastoma, but such differential diagnoses have not dramatically altered therapeutic management of the disease—usually some combination of surgery, chemotherapy, and radiotherapy. Cancer biologists have thus remained on the hunt for molecular features to better stratify glioblastomas and select the likeliest effective treatment for each patient.

To that end, Rodland and her collaborators, including co-lead investigators Li Ding, PhD, of Washington University in St. Louis, MO, and PNNL's Tao Liu, PhD, threw the kitchen sink of analytic tools at 99 treatment-naïve glioblastomas and 10 unmatched healthy samples. Their study formed part of the NCI's Clinical Proteomic Tumor Analysis Consortium (CPTAC), an effort launched 10 years ago to add a new protein-based layer of biological understanding to genomically characterized tumors (Cancer Discov 2013;3:1108–12).

Combining 10 different omics platforms, the researchers filled in molecular details about the three known subtypes of glioblastoma, each originally defined by gene expression patterns alone. Focusing on protein acetylation patterns, for example, they found that the "classical" subtype was enriched for post-translational modification on chromatin modifiers and DNA repair proteins. And using single-cell RNA sequencing, they showed that the "mesenchymal" subtype was defined by transcriptomic patterns expressed by the tumor cells themselves, rather than the surrounding stroma.

The team also discovered four new subtypes of glioblastoma characterized by distinct immune cell infiltrates. Plus, they identified phosphorylation events linked to two proteins—PTPN11 and PLCG1—proposed to act downstream of oncogenic mutations in frequently altered genes to fuel tumor growth.

Those two phosphorylated proteins, and the signaling hub they collectively form, now provide promising new drug targets, says Hyun-Seok Kim, PhD, of Yonsei University College of Medicine in Seoul, South Korea, who was not involved in the work. Also, Kim is intrigued by the suggestion that the four new immune subtypes of glioblastoma outlined in the paper might affect patient responses to checkpoint blockade. But, he says, "it would be important to test those hypotheses experimentally in relevant *in vitro* and *in vivo* models."

According to Rodland, various CPTAC-affiliated researchers are engaged in such follow-up studies.

Investigators from the consortium also recently described a proteogenomic characterization of 218 pediatric brain tumors across seven histologic types (Cell 2020;183:1962–85.E31). They found druggable pathways that span histologic boundaries, as well as proteomic features that help explain why particular treatments work only for certain childhood brain cancers.

All the data from both brain cancer studies and the CPTAC's investigations of more than a dozen other tumor types are now publicly available on the consortium's Data Portal, notes Liu (see http://cptac-data-portal.georgetown.edu/cptacpublic). "These are resources that other people can test their hypotheses on," he says. *–Elie Dolgin* ■

Stool Swap Overcomes PD-1 Resistance

Fecal transplants can make immunotherapy-refractory melanomas sensitive to checkpoint blockade. The finding, from a pair of small clinical trials—the first of their kind—highlights the potential of manipulating gut bacteria to boost response rates to anti–PD-1 agents (Science 2021;371:595–602; Science 2021;371:602–9). Yet, the best strategy for modulating the microbiome—whether with capsules or colonoscopies, fecal material from healthy donors or cancer survivors, or even fecal matter versus lab-grown microbes—remains a matter of active debate.

"The results from both groups are really exciting," says John Lenehan, MD, of London Regional Cancer Program in Canada, who is leading a trial to evaluate fecal microbial transplantation (FMT) in patients with treatment-naive melanoma [J Immunother Cancer 2020;8(Suppl 1):A11–A12]. "There is much that we don't yet know," he adds, "and hopefully we will learn a great deal from the similarities and differences in our approaches."

In the two reports, both groups obtained stool samples from donors who experienced durable responses to anti–PD-1 drugs, such as nivolumab (Opdivo; Bristol Myers Squibb) and pembrolizumab (Keytruda; Merck), and administered the fecal matter to patients with refractory metastatic disease. There were some notable methodologic differences, though.

One group, led by researchers at the NCI and the University of Pittsburgh Medical Center in Pennsylvania, performed the FMT by colonoscopy on the same day that they administered an initial course of pembrolizumab to patients, followed by additional immunotherapy until disease progression or intolerable toxicity. None of the recipients had responded to prior anti–PD-1 therapy. The combination was well tolerated and produced clinical benefits in six of 15 individuals: One had a complete response (CR), two had partial responses (PR), and three experienced stable disease lasting a year or longer.

The other group, led by clinicians at the Sheba Medical Center in Tel-HaShomer, Israel, prescribed antibiotics before treatment to clear native intestinal microflora. Focusing on patients who developed resistance to anti–PD-1 therapy, they administered FMT via both ends of the GI tract—by colonoscopy and feces-filled capsules—for 2 weeks before starting patients on nivolumab. Of the 10 individuals treated, one had a CR and two experienced PRs lasting at least 6 months.

Both studies detailed how the stool swaps led to favorable shifts in