mechanistic work," he says, "we'll start to figure out better combinations" that should aid patients. *–Elie Dolgin* ■

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Researchers Invited to Tackle New "Grand Challenges"

Cancer Grand Challenges, an initiative of the NCI and Cancer Research UK, is again inviting international teams to apply for up to $25 million each to tackle some of the most intractable questions in cancer research. The latest set of nine challenges was winnowed down from more than 300 ideas submitted by scientists and others across the cancer community.

"This year's challenges cover a wide range of issues, from aging and social determinants of health to fundamental science questions, such as understanding cancer cell plasticity," says Sir David Lane, PhD, chair of the Cancer Grand Challenges Scientific Committee. "They also include topics that have been under-researched in the past, such as understanding and preventing side effects of chemotherapy."

Teams have until June 22 to submit expressions of interest in one of the challenges, after which a short list of teams will be asked to submit full proposals, with winners announced in March 2024. (For more information, visit https://cancergrandchallenges.org/new-challenges-2023.)

For now, previous winners are making strides in addressing past years' challenges, says Lane (Cancer Discov 2022;12:2010–11). For example, the Mutographs team seeks to understand the causes—such as lifestyle habits or environmental exposures—of unusual mutational fingerprints associated with cancer in different parts of the world.

The team is collecting samples from 5,000 people in countries with either a high or low incidence of certain cancers, starting with pancreatic, kidney, esophageal, and bowel cancers. Researchers use advanced duplex sequencing—a next-generation method that independently tracks both strands of DNA—to detect mutations with higher accuracy.

Broad patterns have emerged so far, says team lead Sir Mike Stratton, MBBS, PhD, of the Wellcome Sanger Institute in Hinxton, UK. For instance, esophageal squamous carcinomas show no difference in mutational loads across regions with high or low incidence, while studies in regions with high versus low risk of renal cancer reveal striking differences in mutational signatures, probably due to varying prevalence of environmental or lifestyle factors linked to cancer.

"What we're seeing in these two classes of carcinogen is that one causes cancer through mutations, while the other doesn't cause mutations but is nevertheless carcinogenic through some other mode of action," says Stratton. "These types of studies may help us answer the question of what causes variation in cancer incidence around the world."

Another example is the NexTGen team, which is making inroads into understanding the barriers to treating pediatric solid tumors and developing new chimeric antigen receptor (CAR) T-cell therapies.

"Progress on treating relapsed, refractory disease in children has stalled over the past two to three decades, with very little improvement in outcomes and survivors facing long-term comorbidities and second cancers," says team co-lead Catherine Bollard, MBChB, MD, of The George Washington University and Children's National Hospital in Washington, DC. "CAR T-cell therapy has really changed the playing field and created hope for successfully treating these patients."

The team is divided into five work "packages" with synergistic and interconnected goals: identifying surface targets or antigens; understanding the tumor microenvironment; engineering novel receptors that target identified surface antigens; developing preclinical models using novel methods, such as tumor-on-a-chip and mathematical models; and clinical testing.

New CAR T-cell therapies are already in development, says Bollard, with about 40 children to be enrolled in three phase I trials at sites in the United States and the UK. Findings from the trials will inform ongoing basic science investigations, says Bollard. For example, tumor samples from patients enrolled on the trials can be used in tests that employ tumor-on-a-chip and other *in vitro* assay models, allowing researchers to gain a better understanding of what's happening in the tumor microenvironment.

"This approach helps us answer questions in real time both in the lab and in the clinic," she says. "The trials help us understand a bit more about what's happening in the tumor microenvironment for a particular patient, which will help us better assess the potency of the new therapies we are developing for children with relapsed/refractory solid tumors." *–Janet Colwell* ■

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What's Next for Sotorasib in NSCLC?

In 2021, the FDA greenlighted the KRAS inhibitor sotorasib (Lumakras; Amgen) for previously treated *KRAS*^{G12C}-mutated non–small cell lung cancer (NSCLC). But based on the recently published results of the phase III CodeBreaK 200 trial, experts say that it and perhaps other KRAS inhibitors have yet to achieve their full potential.

In the study, 345 patients whose disease recurred after initial treatment were randomly assigned to receive either sotorasib or docetaxel. The trial met its primary endpoint of a statistically significant increase in progression-free survival (PFS; Lancet 2023;401:733–46). Median PFS was 5.6 months for sotorasib compared with 4.5 months with docetaxel. The overall response rate was also higher—28.1% versus 13.2%, respectively—with sotorasib also yielding more durable responses at 12 months. In addition, sotorasib led to a 34% decrease in relative risk of disease progression or death when compared with docetaxel.

However, there was no significant increase in overall survival with sotorasib. "It's not going to cure anyone," says Roy Herbst, MD, PhD, deputy director and chief of medical oncology at Yale Cancer Center and Smilow Cancer Hospital in New Haven, CT, who also noted that "it's incredibly expensive."

A 1-month supply of sotorasib costs about $20,000, whereas docetaxel runs just a few hundred dollars. Insurance companies generally cover the expense, but given that difference and the lack of a survival benefit, should sotorasib be prescribed?

Herbst says yes. "I think we should use it because it's much less toxic." It can also be taken orally at home, eliminating the need for regular intravenous infusions. Even so, "we need more science," Herbst adds.

The next step should be "looking at drug combinations and trying to understand what genomic alterations are implicated in resistance or potential benefit to sotorasib in NSCLC tumors that harbor *KRAS*^{G12C}," says Abdul Rafeh Naqash, MD, of the Stephenson Cancer Center at the University of Oklahoma in Norman, who was not involved in the study. "Teasing out these signals will be crucial to find the right patients for the appropriate combination approaches."

"It is important to recognize that non–small cell lung cancer is very heterogeneous, even within this group of patients that all have *KRAS*^{G12C} mutations," says Melissa Johnson, MD, of Sarah Cannon Research Institute in Nashville, TN, and a CodeBreaK 200 investigator. "Some have secondary *STK11* and *KEAP* co-alterations, while others have a secondary *p53* mutation. In prior studies with chemotherapy and immunotherapy, it was these co-mutations which predicted a different prognosis. Those subgroup analyses from CodeBreaK 200 are ongoing."

Additional clinical trials are evaluating KRAS inhibitors in combination with other treatments. A phase II trial is assessing sotorasib and RMC-4630 (Revolution Medicines), a SHP2 inhibitor, as a second-line therapy for *KRAS*^{G12C}-mutated NSCLC. The phase III KRYSTAL-7 study is evaluating adagrasib (Krazati; Mirati) plus the PD-1 inhibitor pembrolizumab (Keytruda; Merck) compared with pembrolizumab plus chemotherapy as an initial treatment for inoperable, locally advanced or metastatic NSCLC with a *KRAS*^{G12C} mutation and a PD-L1 tumor proportion score of less than 50%. Adagrasib received FDA approval in December for advanced *KRAS*^{G12C}-mutated NSCLC.

Other questions about sotorasib, adagrasib, and KRAS inhibitors in development need to be answered as well, says Johnson. For example: Does the extent of the disease correlate with response? How might radiation therapy augment the drugs' activity? Another area ripe for exploration is whether the agents can be administered as initial therapy for patients with newly diagnosed or early-stage disease.

"We are beginning to ask research questions about how to incorporate these drugs earlier in a patient's disease course, but you've got to start somewhere," Johnson says. *–Aaron Tallent and Suzanne Rose* ■

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For more news on cancer research, visit *Cancer Discovery* online at https://aacrjournals.org/CDNews.

NOTED

The U.S. Centers for Disease Control and Prevention called for all adults to be screened for hepatitis B infection at least once, saying that testing "is cost-effective compared with risk-based screening" because most people living with the infection don't know that they have it (MMWR Recomm Rep 2023;72:1–25). A cure is not available, but early diagnosis and treatment of infections reduce the risk of liver cancer and other conditions.

As of September 2024, **mammography facilities must tell patients whether they have dense breasts,** according to a final rule issued by the FDA. Dense breast tissue makes it more difficult to spot breast cancer on a mammogram and raises the risk of developing the disease.

An FDA advisory panel voted 11–2 in favor of approving polatuzumab vedotin (Polivy; Roche) as an initial treatment for diffuse large B-cell lymphoma based on the findings of the phase III POLARIX trial. The drug, a first-in-class anti-CD79b antibody–drug conjugate, would be combined with rituximab, an anti-CD20 monoclonal antibody, and chemotherapy. The final decision rests with the FDA.

Clinical trial data show that immune checkpoint blockade can prompt lymph nodes to produce cancer-fighting T cells, suggesting that **leaving lymph nodes near a tumor intact could boost the drugs' effectiveness** (Cell 2023;186:1127–43).

Drugmakers that raised prices faster than the rate of inflation on 27 medicines will be fined, the Biden administration announced, and will have to pay back the difference to Medicare. Six of the drugs treat blood cancers, one treats lung cancer, one treats bladder cancer, and one is used to prevent chemotherapy-induced nausea and vomiting.

Novartis announced that **the FDA approved dabrafenib (Tafinlar) with trametinib (Mekinist) for children age 1 and older with low-grade glioma** with a *BRAF*^{V600E} mutation. The agency also OK'd new oral formulations of both drugs for patients who cannot swallow pills. This is the first approval of a systemic therapy as an initial treatment for children with this condition.

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