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

doi: 10.1158/2159-8290.CD-NB2023-0017

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* ■

doi: 10.1158/2159-8290.CD-NB2023-0020

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.