capable of clearing tumors. Those cells might be less common and less diverse, but they're there—and they bear TCRs that can be introduced into engineered T cells, grown in the lab, and given back to patients in sufficient numbers to have a therapeutic effect.

"Those patients can potentially be helped," says PACT Chief Scientific Officer Stefanie Mandl, PhD. "You don't need to have hundreds of different TCR specificities if you have the right ones."

The UCLA and PACT researchers validated that idea for each patient in their study. They created bespoke TCR T cells using a nonviral CRISPR gene-editing technique to insert neoantigen-reactive TCRs into healthy donor T cells for each individual, including the four who did not respond to anti–PD-1 therapy. The reconstituted T cells demonstrated cytotoxic activity against patient-matched melanoma cell lines in every case.

"It really demonstrates that the T cells and the associated TCRs that we isolate with our technology are meaningful," Mandl says.

Buoyed by results like those, PACT moved forward with trials of its first clinical-stage product, a personalized TCR T-cell therapy named NeoTCR-P1 that uses the same methods for isolating and expressing TCRs in autologous cells as described in the latest article. That product showed promise in early clinical testing (Nature 2022;615:687–96). However, the individualized nature of that therapy created manufacturing challenges, and PACT is now advancing a shared neoantigen platform instead. *–Elie Dolgin* ■

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PD-1 Blockade Falls Short (Repeatedly) in Prostate Cancer

Over and over, trials evaluating PD-1/PD-L1 inhibitors in advanced prostate cancer have missed the mark. The failures have led to questions as to why—and have prompted oncologists to conclude that new treatment strategies are needed.

Two phase III trials of the PD-1 inhibitor pembrolizumab (Keytruda; Merck) were halted earlier this year after interim analyses showed that adding it to the antiandrogen drug enzalutamide (Xtandi; Astellas) and androgen deprivation therapy (ADT) failed to extend survival compared with placebo plus enzalutamide and ADT in men with metastatic castration-resistant prostate cancer (mCRPC; KEYNOTE-641) or metastatic hormone-sensitive disease (KEYNOTE-991).

Trials for mCRPC evaluating pembrolizumab plus docetaxel and pembrolizumab plus the PARP inhibitor olaparib (Lynparza; AstraZeneca)—KEYNOTE-921 and KEYLYNK-010, respectively—had previously come up short as well.

"It's incredibly disappointing," says William Oh, MD, of the Icahn School of Medicine at Mount Sinai in New York, NY, and chief medical officer of the Prostate Cancer Foundation, based in Santa Monica, CA. "With these four pembrolizumab trials being negative, I think it continues that trend of immune checkpoint inhibitor therapy benefiting only a small percentage of prostate cancer patients."

"I am optimistic that we will be treating more and more patients with immune checkpoint inhibitors in the future," Oh adds, "but we have to do it in a smart way."

Prostate cancer specialists say that checkpoint inhibitors should now be avoided for molecularly unselected patients except for the few cases in which prostate tumors carry inactivating mutations in mismatch repair genes or exhibit microsatellite instability.

"Definitive negative studies are very important to the field," says Emmanuel Antonarakis, MD, of the University of Minnesota's Masonic Cancer Center in Minneapolis, who worked on KEYLYNK-010. The use of a PD-1 or PD-L1 inhibitor with standard systemic therapies "is not likely to be fruitful," he adds, "and probably should not be pursued in unselected advanced prostate cancer patients" outside of a clinical trial.

Merck continues to look for subtypes of prostate cancer—for example, treatment-emergent neuroendocrine prostate carcinoma—that might be more responsive to PD-1 blockade. Plus, a phase III trial of Bristol Myers Squibb's PD-1–targeted agent, nivolumab (Opdivo), paired with docetaxel continues in the broader mCRPC patient population.

A team co-led by Russell Pachynski, MD, of Washington University School of Medicine in St. Louis, MO, previously showed that nivolumab plus docetaxel has clinical activity in men with chemotherapy-naive mCRPC (Eur J Cancer 2022;160:61–71).

But expectations for success are diminishing, especially when factoring in last year's report that another inhibitor of the same pathway—the PD-L1 blocker atezolizumab (Tecentriq; Genentech)—offered no survival benefits over placebo when added to enzalutamide in a phase III mCRPC trial (Nat Med 2022;28:144–53).

"One of the problems," says Julie Graff, MD, of the Veterans Affairs Portland Health Care System in Oregon, who led KEYNOTE-641, "is that the immune cells in the prostate tumors are very few and far between"—especially in metastatic lesions found within the bone microenvironment.

Those tumors are typically chockfull of myeloid-derived suppressor cells and M2 macrophages, both of which suppress immune responses. To overcome that and help recruit $CD8^+$ T cells to the tumor bed, researchers are investigating PD-1 inhibitors with T cell–redirecting agents, costimulatory antibodies, mRNA cancer vaccines, bifunctional fusion proteins, and other strategies in clinical trials.

Molecular stratification could be another avenue forward. Studies show that certain biomarkers, such as tumor mutational burden, are linked to response rates to checkpoint inhibitors, even when administered as single agents (JAMA Netw Open 2022;5:e225394). And, as Antonarakis points out: "There might be other tumor- or host-specific genomic or transcriptomic signatures, especially at baseline, that can predict an immune-activated prostate cancer subtype or a conducive host environment."

Careful patient selection could therefore help maximize the benefit of checkpoint inhibitors for prostate cancer. But novel, rational drug combinations are likely needed to benefit a broad population, according to Pachynski, who was also involved in KEYNOTE-921. "As we do more of the basic preclinical,

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.