NCI

The move reverses a decade of declines in NCI paylines for new R01 grants, which were at the 16th percentile in 2009. However, competition for funding is likely to remain intense until paylines increase further, says Ruth Keri, PhD, associate director for basic research at the Case Comprehensive Cancer Center in Cleveland, OH.

"Expect to see a steady rise in grant submissions to NCI, partly due to great excitement around recent advances in interdisciplinary cancer research, but also with the clear understanding that nine of 10 grant submissions are going to miss the payline," she says. "Most investigators feel they must submit multiple applications continuously to increase their chances of success."

An additional boost in the payline to 15% in 2021—the NCI's goal, according to an October 2019 blog post by L. Michelle Bennett, PhD, director of the NCI's Center for Research Strategy—would go a long way toward reducing pressure on researchers, says Keri (accessible at www.cancer.gov).

For now, investigators can meet the challenge of stringent paylines by adjusting to emerging research questions and paying attention to the NCI's special areas of emphasis, which tend to be funded higher than the standard payline, she says. For example, Bennett's blog post singles out three priority funding areas: the immune system and microbiome; artificial intelligence; and implementation science, which focuses on integrating effective interventions into routine health care.

Another approach is to develop interdisciplinary, multi-investigator teams, says Keri, which can apply for larger grants and take advantage of economies of scale. In addition, the ESI MERIT program now allows early-stage investigators to receive up to 7 years of funding instead of the standard 5 years.

"The trend is certainly in the right direction, and it is safe to say that congressional bodies are highly supportive of cancer research," Keri says. "As scientists, we need to be wise about how we position ourselves to be competitive for the funding that is available." *–Janet Colwell* ■

Initiative Suggests Angiosarcoma Therapies

In an analysis published in *Nature Medicine*, researchers report details on the molecular underpinnings of angiosarcoma and suggest possible therapeutic options (Nat Med 2020;26:181–7). The findings also suggest that a research model based on engaging patients through social media and patient networks can overcome common barriers to studying rare diseases.

The insights are the first from the Angiosarcoma Project, in which patients in the United States and Canada can enroll online and submit their medical history and biospecimens remotely (see https://ascproject.org). For this study, researchers conducted whole-exome sequencing on 47 donated tumor samples and discovered several recurrently mutated genes, including some—such as *PIK3CA, GRIN2A,* and *NOTCH2*—that had not been associated with angiosarcoma.

PIK3CA was one of the most frequently mutated genes, with alterations showing up in 10 of the samples, nine of which were from patients with breast angiosarcoma, suggesting that a PI3K inhibitor might be a viable therapeutic option for them. In addition, because *PIK3CA* mutations frequently arise in breast adenocarcinoma, researchers hypothesized in their report that "the site of tumor origin (breast), independent of tumor lineage, may be permissive for PI3K pathway activation and may aid tumor formation within breast tissue, perhaps due to interaction with the breast microenvironment."

This "suggests a rationale for potentially treating these patients with a PI3K inhibitor recently approved for breast cancers [alpelisib (Piqray; Novartis)] with this mutation," says senior investigator Nikhil Wagle, MD, of Dana-Farber Cancer Institute in Boston, MA.

Investigators also observed a high tumor mutation burden (TMB) in angiosarcomas of the head, neck, face, and scalp (HNFS), a molecular signature linked to ultraviolet radiation and sun exposure. High TMB is a possible biomarker of response to immune checkpoint inhibitors, and the researchers noted that three patients in the study with refractory metastatic HNFS angiosarcoma had been treated off-label with the PD-1 inhibitor pembrolizumab (Keytruda; Merck). Two of them have remained disease-free for 2 years, even after discontinuing the drug. The third patient did not have a durable response and stopped the drug after a single dose due to side effects.

"The fact that multiple targets were identified in a large set like this is very encouraging from a therapy standpoint," says Vinod Ravi, MD, of The University of Texas MD Anderson Cancer Center in Houston. "It suggests we should start investigating the activity of these agents in select angiosarcoma patients."

The Angiosarcoma Project is part of Count Me In, an initiative that aims to advance treatment for several types of cancer by engaging directly with patients to build extensive online databases of clinical and genomic information (see https://joincountmein.org). The approach can be particularly effective for studying cancers affecting relatively few patients across a large geographic area, which can limit enrollment in a traditional research study.

"There is a huge amount we can learn by studying tumor samples directly contributed by patients, particularly when accompanied by detailed clinical information," says Wagle, who directs Count Me In. "This approach allows us to reach patients at community oncology clinics and hospitals throughout the country—where the vast majority receive their care—thus overcoming a major barrier of the traditional approaches."

The take-home message of the Angiosarcoma Project, says Ravi, is that tailoring treatment for patients holds tremendous value. "These results suggest that we should consider checkpoint inhibitors for patients with high mutational burden

when standard therapies fail," he notes. "In terms of future research, we should think [about] separating patients into their respective molecular buckets in order to match them to appropriate targeted therapies." *–Janet Colwell*

Imaging Technique Reveals New Breast Cancer Subtypes

Prognosis and treatment decisions for patients with breast cancer are often determined with just a handful of molecular markers and genetic tests, meaning potentially rich information in pathology slides from tumor samples may be underutilized. Using imaging mass cytometry (IMC), a technique recently developed by his own research group, Bernd Bodenmiller, PhD, of the Department of Quantitative Biomedicine at the University of Zurich in Switzerland, and his team have demonstrated how to extract and use some of this information.

The work identified previously uncharacterized subtypes of breast cancer, each defined by the spatial organization of cells in the tumor microenvironment expressing certain cancer-linked molecular markers, such as hormone receptors and cell-cycle proteins (Nature 2020;578:615–20). Dividing tumors into single-cell pathology groups based on expression of these markers revealed strong predictors of prognosis. "I was surprised to see how strong the differences in survival are among some of the single-cell pathology groups," Bodenmiller says.

For example, neither the poor prognosis associated with triple-negative breast cancer (TNBC) nor the favorable prognosis associated with hormone receptor–positive breast cancer is universal, and IMC predicted which patients in each group would defy the trends. Patients who would traditionally be classified as having TNBC but whose tumors expressed the cell-cycle protein p53 and apoptotic markers had a 100% survival rate after approximately 10 years, whereas patients with TNBC divided into another subtype by IMC had a survival rate of 33% over the same period. Further work using IMC may illuminate the basic biology underlying the disparities.

This computationally intensive technique involves treating tissue sections with a panel of isotope-labeled antibodies that bind proteins of interest—such as estrogen receptor in breast cancer—and then ablating the tissue with a laser and subjecting the vaporized particles to mass cytometry. This process allows the spatial relationships among cells and the proteins they express to be discerned. Fabian Theis, PhD, head of the Institute of Computational Biology at Helmholtz Zentrum München in Germany, expressed excitement about the work, saying that the study techniques were robust and "will enable quite a few methods papers that build upon this IMC dataset."

However, there are some caveats, including the panel of antibodies used (which included only 35 antibodies), the limited ability to consider different histologic subtypes of breast cancer, and the study's retrospective nature and inability to control for prior treatments. Future and ongoing work, including drug screens under way in Bodenmiller's group, will address some of these concerns.

When it comes to clinical applications, ICM lags behind traditional pathology labs' techniques in its ability to rapidly sift through specimens, and it requires specialized equipment and dedicated staff. However, "I wouldn't be surprised if, 2 or 3 years from now, this was miniaturized and simplified in a way that you can do it in pathology labs," says Steffi Oesterreich, PhD, of the University of Pittsburgh in Pennsylvania.

"This is the start of more to come," says Adrian Lee, PhD, who leads a research group with Oesterreich. "This is showing the power of the technique and the complexity of the data." *–Nicole Haloupek* ■

NOTED

Researchers reported that **T cells edited with CRISPR/Cas9 and reinfused into three patients persisted for up to 9 months** (Science 2020;367:eaba7365). Researchers removed two genes that code for the T-cell receptor so the cells could be reprogrammed to express a synthetic receptor, as well as a third gene that encodes PD-1, to improve antitumor immunity. Although the editing process appears safe, outcomes in patients were modest.

Merck's HIF2α inhibitor **MK-6482 may be effective in patients with advanced clear cell renal cell carcinoma** who received at least one prior therapy, according to findings presented at the 2020 Genitourinary Cancers Symposium in San Francisco, CA, February 13–15. In a phase I/II trial of 55 patients, 23.6% responded to the drug and an additional 56.4% had stable disease.

Cardiovascular problems that happen during oncology clinical trials are often not reported (J Am Coll Cardiol 2020;75:620–8). Researchers analyzed data from 189 phase II and III cancer trials and found that only 62.4% reported cardiovascular events. Further, these trials had a lower rate of such events than would be expected in the general population (542 versus 1,408, respectively, per 100,000 person-years), suggesting that problems are underreported.

Genentech will pay Bicycle Therapeutics $30 million up front in a deal that could be worth up to $1.7 billion in milestone payments. Together, the companies will develop and commercialize immunotherapies for cancer that use Bicycle's bicyclic peptide technology. Bicycle will focus on discovery and early development, and Genentech will tackle additional development and commercialization.

Abbreviated MRI may be more effective than digital breast tomosynthesis (DBT), also called 3-D mammography, at detecting breast cancer in certain women (JAMA 2020;323:746–56). Using both MRI and DBT, researchers screened 1,444 women ages 40 to 75 found to have dense breasts during prior screening. They found that MRI detected 22 out of 23 cases of breast cancer, whereas DBT detected only nine cases.

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