However, Bruce Gordon, MD, a pediatric hematologist-oncologist and executive chairman of the University of Nebraska Medical Center’s IRB in Omaha, worries that the NIH is rushing to implement its single IRB policy—which had been slated to go into effect in May but has been pushed back to September 25—without giving institutions the time to figure out how best to integrate off-site IRBs with other considerations of their Human Research Protection Program, such as biosafety, conflicts of interest, and patient privacy.

“With that said, I’m in favor of cooperative review and single-IRB models,” adds Gordon, who once chaired the NCF’s pediatric CIRB. “For the most part, it’s going to be better than the system we have now, but it’s not a panacea, and it does require thinking about these other considerations.” —Elie Dolgin

Exploiting Defective DNA Repair in IDH-Mutant Cancers

Findings from a preclinical study suggest a better strategy for treating tumors with IDH1 or IDH2 mutations: taking advantage of their vulnerability to PARP inhibition, rather than suppressing the function of altered IDH1/2. The data were presented on April 4 by Ranjit Bindra, MD, PhD, of Yale Cancer Center in New Haven, CT, during the American Association for Cancer Research Annual Meeting 2017 in Washington, DC.

Neomorphic IDH1/2 mutations completely rewire part of the citric acid cycle, resulting in the conversion of α-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG), which competitively inhibits α-KG-dependent enzymes downstream. Because 2-HG is thought to be an oncometabolite driving cell proliferation, much effort has been spent on developing drugs that block its production by selectively inhibiting mutant IDH1/2. “The idea is that suppressing 2-HG will cause rapid cell-cycle arrest and halt tumor progression,” Bindra explained. “This ‘oncometabolite hypothesis’ has been the basis for nearly all trials evaluating IDH inhibitors in gliomas, about 70% of which have IDH1/2 mutations.”

Investigational IDH1/2 inhibitors have been described as potentially having a “broad, profound impact on the glioma landscape,” Bindra noted, but as a clinician specializing in this disease, he’s unimpressed by the efficacy data so far. The agents being evaluated have had “nearly zero effect against aggressive, high-grade gliomas,” he said, and have yielded no regression of low-grade tumors, only stable disease.

Exploiting 2-HG–induced defective homologous recombination in IDH1/2-mutant tumors, and their resulting dependence on PARP for DNA repair, may be a better therapeutic strategy, Bindra suggested. His team recently reported this “BRCAness” phenotype in a variety of IDH1/2-mutant preclinical models (Cancer Discov 2017;7:OF4).

“We’ve observed marked PARP inhibitor sensitivity across these models, both in vitro and in vivo,” he said. “We also have unpublished data showing significant synergy with combinations of different DNA-repair blockers [PARP plus ATR inhibition], or when [DNA-damaging] platinum chemotherapy is added to PARP inhibition.”

Overall, there is now “substantial” preclinical evidence—from Bindra’s group and others—that IDH1/2 inhibitors not only are ineffective against tumor cell growth, but rapidly reverse the cells’ “BRCAness” phenotype, he said. As such, these agents are unlikely to be a home run, at least in gliomas. “We may need to rethink the ‘oncometabolite hypothesis’ and, in IDH-mutant tumors, capitalize on targeting defective DNA repair instead, which we know to be a powerful, cytotoxic approach.”

Bindra and his colleagues will soon launch a multicenter phase II study, sponsored by the NCI, to evaluate the PARP inhibitor olaparib (Lynparza; AstraZeneca) in patients with various IDH1/2-mutant tumors, including gliomas, cholangiocarcinomas, and a small subset of breast cancers. Patients in this “all-comers” basket trial will be identified using the NCI-developed Ion AmpliSeq Cancer Hotspot Panel.

The preclinical data from Bindra’s team could have “revolutionary implications” for treating IDH1/2-mutant cancer, noted Louis Weiner, MD, director of the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC. “It’s intriguing that the reflex approach within oncology—focusing on what’s assumed to be a driver mutation—may be exactly the wrong thing to do here. Confirming these findings in the basket trial could provide an interesting twist on how we interpret [tumor] molecular profiles in the future.” —Alissa Poh

Four Groups Win CRUK “Grand Challenge”

Cancer Research UK (CRUK) has announced the winners of its first “Grand Challenge” competition, in which investigators from around the world were invited to propose novel approaches to unsolved problems in cancer research. Based on the quality of the entries, the judges awarded between £15–£20 million, or $19–$25 million, over 5 years to each of four winning teams, instead of one as was originally planned.

“We were bowled over by the insight, creativity, and advances these teams had already made in putting their proposals together,” says Edward Harlow, PhD, professor of biological chemistry and molecular pharmacology at Harvard Medical School in Boston, MA, and a member of the Grand Challenge advisory panel that reviewed the proposals. “They offered us new ways of thinking about problems in cancer that were quite exhilarating.”
For example, two teams will focus on the challenge of how to map tumors in greater detail at the cellular and molecular level by using advanced imaging technologies, including mass spectrometry and cytometry, as well as virtual reality headsets. The contest drew a total of 56 applicants, each addressing one of seven challenges (Cancer Discov 2016;6:7–8).

Following are brief descriptions of the four winning proposals, which will receive a combined total of over £70 million, or about $87 million:

- Studying cancer-associated mutational fingerprints to attain a deeper understanding of what causes DNA damage, how it leads to cancer, and whether the damage can be prevented (led by Sir Michael Stratton, PhD, of the Wellcome Trust Sanger Institute in the UK)
- Analyzing tissue samples taken from women with ductal carcinoma in situ to identify biomarkers of breast cancer (led by Jelle Wesseling, MD, PhD, at the Netherlands Cancer Institute in Amsterdam)
- Using mass spectrometry imaging to create detailed maps of the entire molecular makeup of breast, bowel, and pancreatic tumors (led by Josephine Bunch, PhD, at the National Physical Laboratory in the UK)
- Creating 3-D models of breast cancer that can be studied using virtual reality headsets (led by Gregory Hannon, PhD, at the University of Cambridge in the UK)

The winning investigators will collaborate across many geographic borders and fields of study. The 14-member team led by Hannon, for example, draws upon the combined expertise of molecular biologists, astronomers, and game developers from the UK, Switzerland, the United States, Canada, and Ireland.

Hannon’s team will focus on creating “extremely faithful, anatomical models of tumors with deep molecular annotation,” says Hannon. “Our initial goal is to study the 10 subtypes of breast cancer previously described, and collect enough tumors from each subtype to establish patterns that occur within the subtypes and across multiple incidences of the disease.”

They have already started collecting thousands of pieces of information about every cell in a tumor to discover exactly where cells are positioned, he explains. Using tissue samples from women involved in the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) study, they will annotate entire transcriptionome—or all of the RNA contained in a cell (Nature 2012;486:346–52). They will also use mass cytometry coupled with approximately 50 metal-tagged antibodies to study the location and abundance of proteins in a tumor.

The team has already created a prototype that allows scientists to experience—via virtual reality headsets—what it’s like to walk around inside a breast tumor and to observe how individual cells interact and influence each other.

“Virtual reality allows us to ‘fly’ inside a tumor and look at every cell,” Hannon explains. “We are able to see whether the same cell types behave differently depending on where they are located in the tumor and to recognize patterns and characteristics that are very difficult to see in 2-D.”

Ultimately, says Hannon, the goal of the research is to create a blueprint for studying all types of tumors that can be used in the clinic for education and diagnostic purposes.

“We will try to capitalize on the multiuser experience developed by the video game industry to put researchers, doctors, and patients in the same virtual space at the same time,” he says. “Our ultimate dream is that this becomes part of modern molecular pathology.” —Janet Colwell

For more news on cancer research, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.
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