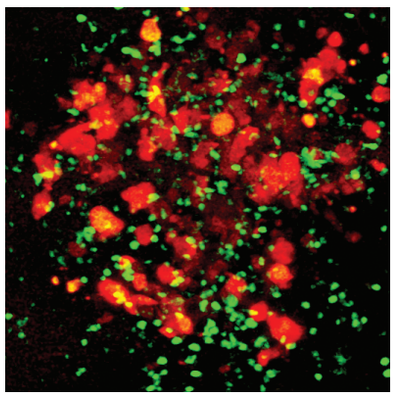
and clear the tumor cells' debris before they metastasize," says senior author Catherine Hedrick, PhD, of the La Jolla Institute for Allergy and Immunology in La Jolla, CA.

Hedrick and lead author Richard Hanna, PhD, had long investigated the role of monocytes in atherosclerosis, but shifted their focus to cancer after research from Jeffrey Pollard, PhD, director of the MRC Center for Reproductive Health at the University of Edinburgh, United Kingdom, suggested that classic monocytes promote tumor growth and metastasis (Nature 2011;475:222–5). Meanwhile, others had shown that PMo could clear damaged endothelial cells, and Hanna observed a striking enrichment of PMo in the lung—a common site of metastasis (Cell 2013;153:362–75). This got him wondering if PMo might play a clean-up role in cancer, perhaps helping remove tumor cells within the lung.

Hanna, Hedrick, and their team tested this idea in three mouse models. First, they injected mice with lung carcinoma cells and saw that PMo swarmed to tumor sites, preventing tumor cells from attaching to lung blood vessels. Next, the researchers injected melanoma cells into PMo-deficient mice, which developed lung metastases earlier and in greater numbers compared to control mice.

A third line of evidence for PMo's role in preventing metastasis came from experiments with mice that spontaneously develop breast tumors that spread to the lung. When the immune system in these animals was replaced with that of PMo-deficient mice, the number of spontaneous lung metastases rose dramatically, suggesting that PMo guard against metastasis. This was confirmed with "rescue" experiments where, prior to tumor injection, PMo were reconstituted in mice that lacked these immune cells; in this setting, very few lung metastases formed.

The researchers suspect CX3CL1 (fractalkine) is important for drawing PMo to the lung. This protein is highly expressed in lung epithelial and tumor cells, and its receptor, CX3CR1, is abundant on the surface of monocytes. In the lung, it's hard to tell if PMo are directly killing tumor cells.



Dr. Richard Hanna

Patrolling monocytes (green), a subgroup of white blood cell, block breakaway tumor cells (red) from gaining a foothold in blood vessel walls, where they could gain access to lung tissue and establish metastases.

But "we know they orchestrate it," says Hedrick. "They make a lot of the chemokines that recruit natural killer cells," which are known for their ability to kill tumor cells.

All told, the new research suggests there is a balance of protumor and antitumor activities within the innate immune system, says Pollard, who wasn't involved with this study. "From a therapeutic point of view, enhancing patrolling monocytes might help tilt the balance toward an antimetastatic role." *–Esther Landhuis* ■

CRUK Launches "Grand Challenges"

Cancer Research UK (CRUK) plans to invest £100 million, or about $150 million, over the next 5 years in an ambitious grant program aimed at tackling some of the most vexing unsolved problems in cancer research. The group has issued seven initial challenges and aims to present its first award next fall.

Each year, the "Grand Challenges" program will award at least one 5-year grant of up to £20 million (approximately $30 million) to teams chosen by an international panel of nine accomplished scientists, which also set the initial challenges. Expressions of interest are due in February, with select teams making final submissions by the end of July. The winner will be announced in September.

"We are looking for scientists to approach these problems from multiple coordinated angles and to make use of the latest technologies," says panel member Suzanne Cory, PhD, laboratory head in the Division of Molecular Genetics of Cancer at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia. "In developing these challenges, we deliberately looked for things that would provoke researchers to think outside the box."

Although CRUK's grants have traditionally supported UK-based projects, the Grand Challenges initiative requires only that teams have a strong UK component, and encourages international collaboration, says Nic Jones, PhD, CRUK's chief scientist. Teams are also expected to cross disciplines, have a principal investigator and up to seven co-investigators from academic institutions or industry, and include a patient advocate.

"We'd like to see 25% of overall activity occur in the UK, but the rest could be based and led from elsewhere—and that's a very different approach for CRUK," Jones says. "Our main goal is to have the very best people apply their knowledge and expertise towards these challenges."

While similar in spirit to the National Institutes of Health's Provocative Questions grant program, Grand Challenges is larger in scale and more focused on teams versus individual investigators, says Jones. The NIH recently committed $40 million to fund Provocative Questions grants over the next 2 years (Cancer Discov 2015;5:569–70).

CRUK hopes to attract other funding partners as the project gains momentum. With the participation of other organizations, the group may eventually be able to sponsor more than one challenge per year, Jones adds.

During the selection process, the panel will look for new or unusual collaborations involving multiple disciplines, says Cory. For example, teams might include biomedical researchers, software developers, engineers, and experts in the physical, behavioral, health, population, and social sciences.

Proposals must provide details on how team members will communicate and work together effectively, she adds. "These should be very real teams, not just collections of individuals."

These are the seven initial challenges:

- Develop vaccines to prevent non-viral cancers
- Eradicate Epstein-Barr virus–induced cancers worldwide
- Discover how unusual patterns of mutation are induced by different cancer-causing events
- Distinguish between lethal cancers that need treating and nonlethal cancers that don't
- Find a way of mapping tumors at the molecular and cellular level
- Develop innovative approaches to target the cancer super-controller MYC
- Deliver biologically active macromolecules to any and all cells in the body

Information about how to apply for a Grand Challenges grant is available at www.cancerresearchuk.org/funding-for-researchers. *–Janet Colwell* ■

T Cells Target Pancreatic Tumors

Engineered T cells that recognize the protein mesothelin on the surface of tumor cells can attack and shrink pancreatic tumors in mice, a recent study reveals. Researchers plan to start a clinical trial with human versions of the cells.

So far, checkpoint inhibitors and other immunotherapies haven't worked against pancreatic ductal adenocarcinoma, the most common kind of pancreatic cancer. Several characteristics of the tumors explain why: Their stroma serves as a barrier, and they have few blood vessels to admit drugs or therapeutic cells. In addition, the extracellular matrix in pancreatic tumors absorbs large amounts of water, creating a high internal pressure that may exclude T cells. Even if T cells do manage to slip in, the tumors suppress them in several ways, such as producing the inhibitory cytokine TGFβ.

A team led by Sunil Hingorani, MD, PhD, and Philip Greenberg, MD, of the Fred Hutchinson Cancer Research Center in Seattle, WA, tested whether T cells that target mesothelin, which pancreatic tumors produce in abundance, could overcome these obstacles. To generate these T cells, the researchers immunized two kinds of mice against mesothelin: animals that lack the protein and normal mice, which produce mesothelin in a few tissues. Both kinds of animals generated T cells with a receptor that recognized a short segment of mesothelin. The researchers then engineered mouse T cells to produce this receptor.

Next, the scientists infused the engineered T cells into mice that spontaneously developed pancreatic tumors. The T cells entered the tumors and began to kill cancer cells. However, their potency declined quickly. Within a month of the infusion, most of the tumor-infiltrating T cells had died, and many of the remaining T cells carried proteins, such as PD-1, that indicated they were no longer functional.

Aiming to overcome that challenge, Hingorani and colleagues tested whether repeated infusions of T cells would work better. When they gave mice the T cells every 2 weeks, the treatment's effectiveness didn't tail off. Tumors shrank in 63% of the mice, and the animals' overall survival increased from 54 days to 96 days, the researchers reported (Cancer Cell 2015;5:638–52). Although other tissues, such as the pleura and pericardium, produce mesothelin, the researchers saw no signs that the engineered T cells were attacking these sites.

Along with a few other recent studies, the work "changes the impression that this is an impregnable cancer and suggests there are ways to target it," says Hingorani.

The study "makes the point that T cells can enter pancreatic cancer tumors and that their stroma and poor vascularity are not barriers," says Gregory Beatty, MD, PhD, of the University of Pennsylvania in Philadelphia, who wasn't connected to the study. He's part of a group that recently launched a clinical trial of a slightly different approach that involves chimeric antigen receptor T cells targeted against mesothelin. "They are different strategies, but both might be efficacious," says Beatty.

Hingorani says that he and his colleagues hope to begin a clinical trial of their engineered T cells by the end of 2016. *–Mitch Leslie* ■

NOTED

- **Pfizer and Allergan announced that they will merge operations** in a deal worth $160 billion, creating the world's largest drugmaker. Because Pfizer, an American corporation, is combining with a company headquartered in Ireland, which has a lower tax rate, Pfizer could save millions of dollars in U.S. taxes annually.
- **Bristol-Myers Squibb's immunotherapeutic nivolumab (Opdivo) received FDA approval for two more indications**: the treatment of patients with metastatic renal cell carcinoma after they have received an antiangiogenic agent, and as a single agent for patients with previously untreated BRAF wild-type advanced melanoma. Nivolumab is a PD-1 inhibitor.
- Genentech's **cobimetinib (Cotellic), in combination with vemurafenib (Zelboraf), received FDA approval for the treatment of patients with inoperable or metastatic melanoma** with the BRAF V600E or V600K mutation. Cobimetinib is not indicated for treatment of patients with BRAF wild-type melanoma.
- **The FDA also approved Eli Lilly's necitumumab (Portrazza)** in combination with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous non–small cell lung cancer (NSCLC); the drug is not indicated for the treatment of nonsquamous NSCLC.
- Data from the 2014 National Health Interview Survey, reported by the Centers for Disease Control and Prevention (CDC), indicate that **the prevalence of cigarette smoking among U.S. adults declined from 20.9% to 16.8% between 2005 and 2014**, including a decline of 1% between 2013 and 2014.
- Scientists from the CDC reported that **cancer cells originating in a common tapeworm can take root in people with a weakened immune system**, causing the development of cancer-like tumors (N Engl J Med 2015;373:1845–52). The report raises concern that similar cases, if they occur, may be misdiagnosed as human cancer—especially in less-developed countries where this tapeworm and immune system–suppressing illnesses like HIV are widespread.

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