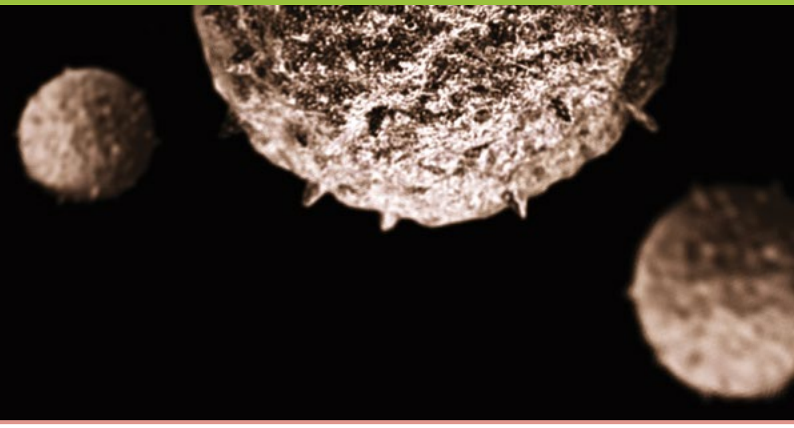
# A New Breed of Cancer Researcher



As our understanding of cancer has gone from simplistic to complex, so too has research on treatment and detection. In a field once dominated by scientists with biomedical backgrounds, cancer research today includes engineers, chemists, and physicists. To land a job in any emerging area of cancer research, interdisciplinary training is becoming increasingly important. Luckily for job seekers, educational institutions are rising to meet the need. **By Gunjan Sinha**

When **Martin Pule** landed a Fulbright scholarship 14 years ago to study at the Center for Cell and Gene Therapy in Baylor College of Medicine, he never anticipated that he would be working in one of the hottest fields of cancer research today: immunotherapy. At Baylor, Pule began training in Malcolm Brenner's laboratory—one of the pioneers of engineered T-cell treatments. In 2008, Brenner's team published one of the first studies demonstrating that T cells could be taken from a patient with neuroblastoma, engineered to express tumor-specific receptors, and then administered back to the patient as a treatment. At the time most cancer researchers considered T-cell therapy a "fantastical and unrealistic thing to do," Pule recalls. It was "cumbersome and seemed a lot less feasible than treating patients with cancer-fighting antibodies." Fast-forward to 2014 and immunotherapy is one of the most promising, novel ways to treat cancer to emerge in over a decade.

Pule's career path is typical of many scientists working at the crossroads of immunology, gene therapy, and cancer. Trained in medicine, his research focus came from a coalescing of chance decisions with the march of scientific progress. While Pule largely acquired his varied expertise along the way, interdisciplinary training is the catch phrase for scientists entering emerging fields of cancer research today.

"There's a strong perceived need among cancer research funding bodies that new modes of education and skill sets are necessary," says **Bennett Goldberg,** director of Boston University's (BU) Center for Nanoscience and Nanobiotechnology, an interdisciplinary center that brings together academic and industrial scientists and engineers to develop nanotechnology applications in biomedicine. "There's been a huge push over the past five years to apply more physical science and engineering to biomedicine in general."

BU's center was jump started by a $2 million grant from the National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer in 2010 and is one of six cancer nanotechnology training programs supported by NCI. NCI has spearheaded several additional initiatives to promote research on nanotechnology applications in cancer, which include funding centers of nanotechnology excellence and cancer nanotechnology platform partnerships.

NCI isn't alone in promoting cross-disciplinary approaches to developing new cancer treatments. Memorial Sloan Kettering Cancer Center (MSKCC) in New York City has set up several collaborative research centers focused on promoting research across scientific disciplines; the Massachusetts Institute of Technology's (MIT's) David H. Koch Institute for Integrative Cancer Research in Cambridge, Massachusetts has been fully operational since 2010; and other institutions, such as the Fred Hutchinson Cancer Research Center in Seattle, Washington, offer dual-mentor fellowships in cancer research. While the approach to interdisciplinary training or research may differ by institution, the goal is the same: to encourage and facilitate collaboration across different areas of science to develop novel approaches for cancer detection and treatment. Some of the most fervent activity is in the fields of immunotherapy, nanotechnology, and epigenetics.

## IMMUNOTHERAPY

Scientists have tried for decades to coax the body's immune system to stamp out cancer cells but have had little clinical success. After years of setbacks, promising results finally began flowing out of clinical trials a few years ago with a therapy that uses chimeric antigen receptors (CAR)—receptors engineered to recognize specific targets on cancer cells.

CARs typically contain a portion of a monoclonal antibody, which recognizes a specific tumor antigen, and are linked to signaling molecules inside the T cell. To use these receptors as a therapy, T cells must first be isolated from a patient's blood and engineered ex vivo using gene-therapy vectors. Once returned to the patient, the T cells recognize and bind to target antigens on cancer cells, stimulating the signaling molecules that in turn instruct the T cell to activate, divide, and attack cancer cells.

Recently, stunning clinical trial results showing that CAR therapy could help dramatically shrink tumors in patients who had failed to respond to conventional treatments led to cancer immunotherapy being dubbed *Science*'s "Breakthrough of the Year" in December 2013 (news.sciencemag.org/breakthrough-of-the-year-2013).

The excitement isn't restricted to the scientific community; industry continued>

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Angela Belcher

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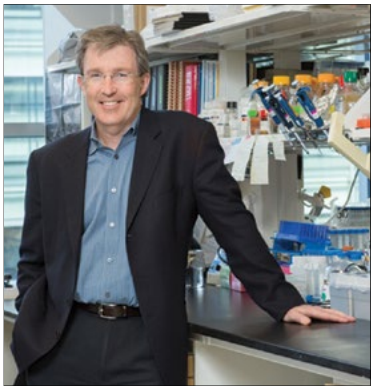
**Any type of interdisciplinary training is "a good way to position yourself for something that is growing in importance."**
**—Tyler Jacks**



is also on board. In December, The Fred Hutchinson Cancer Research Center, MSKCC, along with pediatric partner Seattle Children's Research Institute teamed up to form Juno Therapeutics, a Seattle-based biotechnology company aiming to develop novel cancer immunotherapies. Juno was launched with an initial investment of $120 million—one of the largest pots of seed funding for a biotech startup in history. Juno's incarnation followed Novartis' 2012 exclusive global collaboration agreement with the University of Pennsylvania to research, develop, and commercialize targeted CAR immunotherapies to treat different types of cancer.

"T-cell engineering has gone from being something of a cottage industry with a small group of investigators tinkering along to a field that has completely exploded," says Pule.

After Baylor, Pule returned to Europe to finish his clinical training and to set up his own lab at University College London (UCL), where he is now a clinician scientist in the UCL Cancer Institute's Department of Hematology. Pule's lab is coordinating the Advanced T-cell Engineered for Cancer Therapy (ATECT) consortium—a €6 million ($8.13 million) five-year research collaboration funded by the European Commission that is aimed at improving CAR therapy.

Most T-cell engineering approaches are designed to simply introduce genes into cells using viral vectors, Pule explains. But ATECT scientists have combined viral vector technology with a proprietary genome-engineering tool developed by Paris, France-based Cellectis, an ATECT partner, called transcription activator-like effector nuclease (TALENs), enabling them to also disrupt or delete genes. Using this gene editing technology, researchers have the potential to disrupt the genes that cause a patient's body to attack or reject donated T cells.

Currently, to avoid immune system rejection, CAR T cells are made for each patient individually using their own cells. An "off the shelf" T-cell cancer therapy, however, would eliminate the need to personalize every treatment. It would also enable CAR therapy to be mass-produced and would greatly facilitate access to what remains a highly complex experimental therapy. Cellectis is currently developing several off-the-shelf CAR T-cell products.

For job seekers, the immunotherapy's success means opportunities. "The easiest way to get into this field now would be to land a position in one of centers that are doing this kind of work," says Pule. "A wide range of people are needed." Among them are molecular biologists and protein engineers who make the receptors, immunologists who do the in vitro and preclinical research, virologists who make the viral vectors, and skilled specialists who can manufacture vectors and cells according to Good Manufacturing Practice guidelines. That said, "a lot of know-how and skills are just learned on the job," he adds.

**Seth A. Ettenberg,** head of biologics for oncology at Novartis Institutes for Biomedical Research in Cambridge, Massachusetts, agrees. Ettenberg is in the process of assembling a team of scientists to interface with researchers at the University of Pennsylvania with whom the company is co-developing CAR immunotherapies. "The main question that we ask job applicants is: 'Do you have a story to tell?'" In hiring early career scientists, Novartis looks for candidates who have demonstrated that they ask big picture questions and do rigorous hypothesis driven research, he says. Ideally, job candidates will also have published in a top journal, he adds, although this criterion generally extends across all areas of the company. A more unique skill required for the cancer immunotherapy group is the ability for intense teamwork. Because cell-based therapies are still experimental, Novartis has immunologists and cell manufacturing specialists working side-by-side. This differs from their development process for small molecules and antibody-based drugs, where manufacturing practices are well understood, says Ettenberg. Therefore, a candidate's communication skills are of the utmost importance.

Novartis' hiring managers typically speak to candidates several times over the phone before inviting them to give a presentation. The presentation can make or break a person's prospects, Ettenberg adds. "We really look at how well thought out the presentation is and how they handle questions. Are they dismissive, aloof, do they say 'I don't know' when they really don't know?" If it goes well, candidates are then invited for a full day of interviews. For senior scientists, interdisciplinary training is important for the tasks they will be required to do. For creative and excited scientists just starting out, however, there are many skills one can learn on the job, Ettenberg says.

## NANOTECHNOLOGY

Engineered T cells aren't the only emerging technology promising to transform cancer treatment. Nanotechnology—the science of manipulating matter at the nanoscale to create devices with novel chemical, physical, and biological properties—also has the potential to radically change how cancer is diagnosed and treated. From new imaging agents to new modes of drug delivery, "cancer nanomedicine" is another exploding field of cancer research.

NCI recognized the potential of nanotechnology to improve cancer treatment and detection as early as 2004 when it formed the NCI Alliance for Nanotechnology in Cancer. In addition to several other nanotechnology projects, NCI Alliance currently supports nine centers of cancer nanotechnology excellence, six cancer nanotechnology training programs, and 12 cancer nanotechnology platform research partnerships aimed at addressing major barriers and fundamental questions in cancer.

At the Koch Institute for Integrative Cancer Research, a recipient of NCI Alliance grant money, **Angela Belcher,** works on improving nano-based imaging of cancerous tissue. Current practices employ computed tomography, magnetic resonance imaging, or ultrasound to image soft tissues. Belcher's lab is trying to develop a less expensive method that will enable smaller tumors to be imaged at greater tissue depths than is currently possible with these technologies. Her approach uses genetically modified bacteriophages that bind specific cancer cell receptors and that carry a single carbon nanotube which fluoresces when exposed to near-infrared light. Her team has already demonstrated that the technique enables imaging of tissues as deep as 3 cm in animals, but should be able to image up to 10 cm, she says.

"Angie is a very good example of the type of people we like to have working here," says **Tyler Jacks,** director of the Koch Institute. "She has a deep background in materials science but is working at the convergence of life science and engineering."

Belcher, who has a joint appointment at the MIT Department of Materials Science and Biological Engineering, is a materials chemist by training. She accepted the joint appointment two and a half years ago after she collaborated on a cancer-related project with MIT biomedical engineer Bob Langer. At the Koch Institute, her task is to use engineering to solve challenges facing cancer researchers. The interdisciplinary environment at Koch is a good fit for her, says Belcher, since she has had interdisciplinary training from early on—she designed her own major as an undergraduate at the University of California, Santa Barbara. "I've always asked the question: What different disciplines are helpful for addressing the problem you want to solve?" she explains. continued>

## FEATURED PARTICIPANTS

**Center for Nanoscience and Nanobiotechnology, Boston University**
nanoscience.bu.edu

**David H. Koch Institute, Massachusetts Institute of Technology**
ki.mit.edu

**Novartis Institutes for BioMedical Research**
www.nibr.com

**Memorial Sloan Kettering Cancer Center**
www.mskcc.org/research/ski

**The Gurdon Institute, University of Cambridge**
www.gurdon.cam.ac.uk

**University College London**
www.ucl.ac.uk

**Daniel Heller,** on the other hand, came to cancer nanomedicine with a background almost exclusively steeped in physical science. Heller came to the Molecular Pharmacology and Chemistry Program at MSKCC after finishing his Ph.D. in chemistry at the University of Illinois at Urbana-Champaign. Except for a brief stint as a postdoc in Bob Langer's lab at MIT, he had never worked in biomedicine.

Heller landed at MSKCC almost by accident. While at MIT, he met his future MSKCC head, who suggested that he apply for a job, at a meeting. "I had no idea that Sloan Kettering was even an option," recalls Heller, who had had been applying exclusively to universities. In retrospect, "not only is it the best place for me, but it is probably the best place for a lot of people who don't even know it," he says.

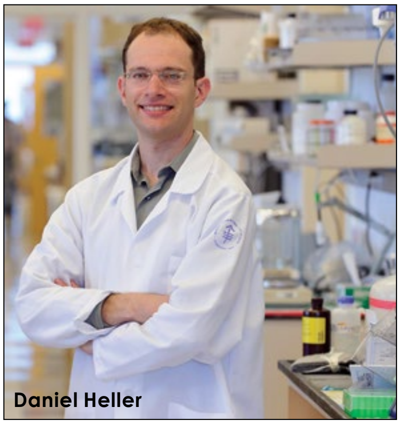
The reason: need. In most engineering departments "there are a lot of people making hammers, but there aren't a lot of nails nearby," explains Heller. "Now, I'm in a place where there are a lot of nails, and I'm one of a few hammers. That's an exceptional position to be in."

At MSKCC, Heller focuses on developing nanoscale molecular sensors and targeted therapeutics. For example, his team is currently making optical sensors from carbon nanotubes in order to quantify metabolite levels in living cells—a tool that has no existing counterpart. Indeed most of the projects in his lab involve creating tools that enable scientists to study what had not been previously possible because the technology was nonexistent. In coming up with project ideas, Heller has found that the ability to have on-going dialogues with cancer clinicians who also work on site makes it easier for him to understand the problems he is tasked with solving.

Heller's lab consists of a hodge-podge of expertise, including physicists, chemists, and biologists. This type of interdisciplinary team often poses language barriers at first, but these can break down over time through working together. Teamwork is key, he says. "You can't be too introverted." For scientists working in any discipline and looking for a job in cancer research, there are opportunities in areas and places that are not obvious. "Talk to people and look at alternative places to work that are far outside of your field," advises Heller.

## EPIGENETICS

Interventions that alter the epigenome of cancer cells present yet another novel cancer treatment approach. A cell's epigenome is a secondary level of genetic modification that does not affect the integrity of genes, but impacts when and where they will be expressed. As with the mutations that change the genetic code, epigenetic abnormalities can also drive cancer. However, unlike genetic mutations, epigenetic changes are reversible, and as such, potentially correctable with therapeutics. There are already four U.S. Food and Drug Administration (FDA)-approved drugs that alter the epigenetic profile of cells to treat cancer and at least 30 more investigational drugs in on-going cancer clinical trials, according to current data available on clinicaltrials.gov.


Daniel Heller

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At the Gurdon Institute at the University of Cambridge in England, **Tony Kouzarides** works with two different pharmaceutical companies developing epigenetic drugs to treat cancer. His partnerships with industry came about after a successful collaboration with pharmaceutical giant GlaxoSmithKline (GSK) a few years ago during which he showed that an epigenetic drug the company was developing to treat inflammation was actually active against leukemia cells, specifically mixed-lineage leukemia, the most common form of leukemia in babies. The drug mimics an epigenetic tag in bone marrow cells that prevents leukemia-causing genes from being activated and is now in clinical trials. "We helped [GSK] understand the drug's mechanism of action," says Kouzarides, "when the company didn't have the expertise in this area."

Kouzarides is a biologist by training, having earned a Ph.D. studying viruses in the Department of Pathology at the University of Cambridge. Over the years, however, he became specialized in cancer genetics. Today his laboratory focuses on the epigenetics of histone proteins, which package DNA, and how epigenetic mechanisms regulate gene expression in cancer cells. The work done in his group today requires a very broad range of skills, he says. For example, if one of his researchers identifies an important cancer-related signaling pathway, they would benefit from a knowledge of chemistry so they can communicate their needs to companies that have libraries of molecules that might target their pathway of interest, explains Kouzarides. They might also have to interact with cancer clinicians as well as generate models of the disease to better understand the pathway.

Kouzarides isn't suggesting that people interested in working in the field of cancer epigenetics become a "jack of all trades." In fact, quite the opposite: "everyone has a type of science that they do, and no one can do everything," he explains. "Certainly having one or two major skills is important, but the rest you can pick up from collaborations."

BU's Goldberg concurs: "You have to have depth in one area to develop scientific acumen," he says, "since there's a confidence that comes with depth in one field." Only then can one go on to develop breadth across several areas, he explains, which is something nanotechnology training programs help to provide.

While epigenetics, cancer nanomedicine, and immunotherapy are important new directions for cancer research, they certainly are not the only ones. The Koch Institute, for example, received NCI funds to establish interdisciplinary training programs in cancer systems biology and a physical sciences oncology center in which network theory and mathematical and computational modeling are being brought to bear on cancer research. To work at the crossroads of any of these areas, "having a very broad perspective is becoming increasingly attractive," says Jacks.

For Ph.D. graduates in any of the sciences who are interested in cancer research, there are many ways to gain that broad perspective including interdisciplinary fellowships that require students to choose mentors from different disciplines, postdoctoral training programs outside of one's field, and institutional training programs. According to Jacks, any type of interdisciplinary training is "a good way to position yourself for something that is growing in importance."

*Gunjan Sinha is a freelance writer living in Berlin, Germany.*

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