A career in cancer research? Computational skills wanted

Cancer researchers are generating mounds of molecular data on tumor biology. Scientists with molecular and computational backgrounds are needed to move the growing field of precision oncology forward. Researchers with both skill sets, however, have a leg up. By Gunjan Sinha

When William Pao was a medical oncology fellow at Memorial Sloan Kettering Cancer Center (MSKCC) during the early 2000s, treating patients with metastatic non-small cell lung cancer (NSCLC) was rote: Every patient received the same chemotherapy regimen. But the odds of benefiting were hit or miss: “Only about 20% could expect to see their tumors shrink,” Pao says. “There was no way to know ahead of time who was going to benefit.” Even more nerve-racking for the patients was the fact that typically six weeks would pass before he could assess tumor response.

Today, depending on the mutations found in individual tumors, there are several unique drugs available to treat metastatic NSCLC. Therapies can be tailored, and for many patients the odds of surviving have gone from months to years. The success of “targeted therapies” in oncology—so named because they disable cancer cells in very specific ways—is being hailed a watershed moment in cancer therapy. Basic research on cancer mechanisms has led to over 40 targeted cancer therapies currently on the market, which take the form of monoclonal antibodies, small molecule drugs, and immunotherapies.

As targeted therapies take center stage in cancer treatment, they are profoundly changing the way research is done. Like many other medical research disciplines, oncology is going molecular. The success of such drugs has fueled a push toward studying basic molecular mechanisms of cancer growth, which has brought with it “a crush of data so large that no human brain alone would be able to make heads or tails of it,” says Levi Garraway, assistant professor of medicine at the Dana-Farber Cancer Institute in Boston, Massachusetts. The complexity of the technology and tasks required to design targeted drugs and study their efficacy has grown so great that groups of scientists with varied expertise are required to continue to move the field forward, he adds. Although scientists working in the field today have largely picked up skills along the way, there will be a massive increase in demand for translational researchers with computational, analytical, and clinical trial expertise who can turn data into concrete knowledge.

Future oncologists will need to have a much deeper understanding of tumor biology on a molecular level than their predecessors. “That is where the breakthroughs have been and will continue to be,” Garraway says.

The rise of molecular oncology

Lung cancer in particular has become the “poster child” for how research and treatment have changed, says Charles Swanton, a research oncologist at the Francis Crick Institute in London, England. The advent of therapies directed at tumors with mutations in epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and B-Raf proto-oncogene (BRAF) genes over the past decade have dramatically changed outcomes, he says. These therapies were born out of a deep understanding of the potent genetic drivers of lung cancer, particularly in nonsmokers.

Pao was involved in studies of EGFR tyrosine-kinase inhibitors while at MSKCC, where he trained in medical oncology. He was part of a team that recognized that only about 10% of patients with NSCLC responded to the small molecule erlotinib—those whose tumors harbored mutations in the gene encoding EGFR. Those patients can benefit from the drug for years, says Pao. “Just being able to pinpoint patients has been a significant achievement.”

Pao’s career trajectory has paralleled the rise of molecular oncology. As a student at Yale University in New Haven, Connecticut, he earned his M.D. and Ph.D. degrees and trained in a basic immunology lab. He then studied cancer cell signaling, discovering mechanisms of sensitivity and resistance to targeted agents. Today Pao heads the Oncology Discovery and Translational Area at Hoffman-La Roche, cont.>
based in Basel, Switzerland. He is now tasked with developing new drugs that harness immune cells to attack cancer cells or target cancer cells directly. As part of its push toward precision oncology, the company announced early last year that it would spend $1.03 billion to buy a 56.3% stake in Cambridge, Massachusetts-based Foundation Medicine, a company that uses genetics to help select drugs for cancer patients. One project involves probing Foundation Medicine’s growing database of tumors profiles for specific mutations and using that information to either design drugs or to parse patients into clinical trials of the company’s drugs, says Pao.

Similarly, Wendy Winckler’s career path in oncology research “followed the genomic era,” she says. Winckler is executive director of Next Generation Diagnostics at the Novartis Institutes for BioMedical Research in Cambridge, Massachusetts. She came to the company three years ago from the Broad Institute in Cambridge. Prior to that, she earned her Ph.D. in genomics at Harvard University and then landed her first job helping to build The Cancer Genome Atlas. She then became director of the Genetic Analysis Platform at Broad—a technology group that collaborated with both Broad and external scientists to generate and analyze diverse types of genomic data. “Having come from the science side, I was able to get experience in technology and also in being head of a large group.”

Computational skills a plus

At Novartis, Winckler leads a department of 37 people. One early project was to help Genoptix—a Novartis daughter-company acquired in 2011 and located in Carlsbad, California—to commercialize a diagnostic test for lung cancer patients. That particular assay tests for “actionable mutations”—changes to those genes in a lung cancer sample that have been identified to date as helping guide treatment. Another major project is to characterize the tumors of patients across the company’s ongoing cancer clinical trials to try to understand how genetic changes may influence response.

In Winckler’s lab, about half of the scientists have computational expertise, and the other half have extensive wet lab skills. The most successful people, however, engage in both realms, she says. “Exposure to lab environments helps computational biologists have a more intuitive understanding of the data and an easier time planning sequencing experiments; lab scientists familiar with data analysis approaches can provide important insights while interpreting results.”

Dual training has certainly benefited Marcin Imieliński, a molecular pathologist at Weill Cornell Medicine in New York City. “Where I am right now is exactly where I hoped I would be,” he says. “I feel like I have a single career instead of two, which I think is a big challenge for all M.D.-Ph.Ds.” Imieliński earned his undergraduate degree in computer science and then entered a newly christened M.D.-Ph.D. program in genomics and computational biology at the University of Pennsylvania in Philadelphia in 2001. He then chose pathology for his clinical training because he wanted “synergy between his research and his future clinical role,” he says. At Weill Cornell, Imieliński is participating in the precision oncology effort, which will sequence tumor DNA to match patients to particular therapies.

Imieliński is also building his own lab, which will focus on understanding the role of complex DNA rearrangements in cancer. Part of his task is to develop analytical and computational tools to make sense of the data. He also plans to leverage the latest sequencing technologies to understand how complex rearrangements impact the tumor epigenome and perturb cancer genome structure over time.

Technology leads the way

Clearly, next-generation sequencing (NGS) technologies have had a trailblazing effect on career opportunities. Since the first targeted cancer therapy to treat chronic myelogenous leukemia became available in 2001, there has been an explosion in genomic technology. Where once it was possible to test tumor samples for only one mutation or genomic rearrangement at a time, NGS technology now enables testing for multiple gene mutations in multiple samples simultaneously. This technology has influenced not only the type and speed of cancer research being conducted, but it has also radically changed clinical practice. Recently, San Diego, California-based Illumina, one of largest manufacturers of sequencing machines, teamed up with Dana-Farber, MSKCC, and two other major U.S. cancer centers to define the “cancer actionable genome” to help tailor cancer therapies. Moreover, such technology is enabling research toward the next step in targeted therapy: understanding why cancers grow resistant to drugs.

At the Crick, Swanton’s lab is focused on exactly that. In collaboration with the University College London (UCL) Cancer Trials Centre and the UCL Cancer Institute, Swanton’s research group will be following about 850 patients with NSCLC from diagnosis to death as part of a clinical trial to understand tumor evolution. Tumors that are surgically removed as part of routine care will be dissected and different regions sequenced to build phylogenetic maps of the genomic events that drive cancer growth. cont.>
About half of NSCLC patients go on to develop metastatic disease. As part of a second trial, Swanton's lab will also study what happens to tumors under the selective pressure of various types of cancer therapies, from traditional chemotherapy to targeted drugs.

As successful as targeted therapies are, “they aren’t curing people,” Swanton says. Resistance to therapy is inevitable. Research questions in his lab are driven by “what we see happening in human tumors,” he says. The hope is that even better second- and third-generation therapies can be developed that can potentially limit the acquisition of resistance. “It’s a very exciting time where laboratory-based molecular analyses are underpinning drug discovery and development.”

At the German Cancer Research Center, (Deutsches Krebsforschungszentrum, or DKFZ) in Heidelberg, scientists working in precision oncology are also taking full advantage of advances in genomic technology. In 2012, the DKFZ formed the Heidelberg Center for Personalized Oncology (DKFZ-HIPO). The goal is to develop a clinical program for personalized oncology that will translate “the latest research and technologies from functional genomics and systems biology into clinical routine.”

The initiative is “very ambitious,” says Roland Eils, professor of functional genomics and bioinformatics and the codirector of DKFZ-HIPO. Of the several thousand cancer patients treated annually at the Heidelberg National Center for Tumor Diseases (NCT), whole-genome sequencing of tumors is offered to all patients who might benefit, says Eils. But DKFZ is taking research a giant step further. The cost of whole-genome sequencing is now comparable to exome sequencing, says Eils. So DKFZ-HIPO made a strategic decision to collect whole-tumor genome sequencing data for future research. If a patient consents, the sequence data is added to a database developed in-house. The database is designed to hold clinical annotations about patient progress and can perform multiple data analyses. So far, the database holds data from roughly 3,000 patients. The plan is to scale up to collecting whole-tumor genome sequence data from 3,000 to 4,000 patients annually. “That’s an awful lot of data that poses a variety of challenges,” says Eils. What’s more, the researchers hope to be able to add other types of ‘omics data such as RNA sequencing, epigenetic information, and histone modifications.

Obviously there is a huge need for experts in data management who have computational skills, Eils says. In collaboration with Heidelberg University, the DKFZ does indeed train many students and physicians in informatics and data management. But regrettably there is a demand for such experts in other industries such as banking that pay better, says Eils. Hopefully scientists will be drawn to work in cancer research because of “interest and excitement.”

Precision medicine creates opportunities

A candidate’s enthusiasm about the future of cancer research is certainly a huge plus when Swanton is searching for new hires. Important questions he asks himself include, “How do they think? Does this person bring fascination and interest? How can they contribute?” With the goal to translate insights from his lab into the clinic, Swanton's lab holds a full spectrum of expertise, from “bench to bedside,” including people with regulatory and clinical-trial experience.

The demand for such qualified people is set to grow, and not only within oncology. In January 2015, President Obama announced the Precision Medicine Initiative. Launched with a $215 million investment in the President's 2016 budget, the initiative aims to “give clinicians tools to better understand the complex mechanisms underlying a patient’s health, disease, or condition, and to better predict which treatments will be most effective,” according to a statement issued by the White House. The bulk of the funding, $130 million, will go to the National Institutes of Health to launch a population study that will follow 1 million Americans over many years to track their health; the National Cancer Institute will receive $70 million to develop more effective personalized approaches to cancer treatment; the U.S. Food and Drug Administration will receive $10 million to develop a database to advance innovation in precision medicine; and the Office of the National Coordinator for Health Information Technology will receive $5 million to develop interoperability standards and address privacy and secure data exchange issues.

The amount of funding relative to the task is small, says Mark Rubin, head of the Institute for Precision Medicine at Weill Cornell Medicine and New York-Presbyterian Hospital, but “we are at the beginning,” he adds. “That this is coming down from the government tells us that patients want access to their data to improve outcomes and that the government and regulatory agencies are going to make sure we find ways to make it happen.” Moving forward, working in precision medicine could be an option for anyone with a scientific or mathematical background, he adds. For example, engineers who design devices will be needed as well as experts in population biology and epidemiology. “The opportunities will only expand.”

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