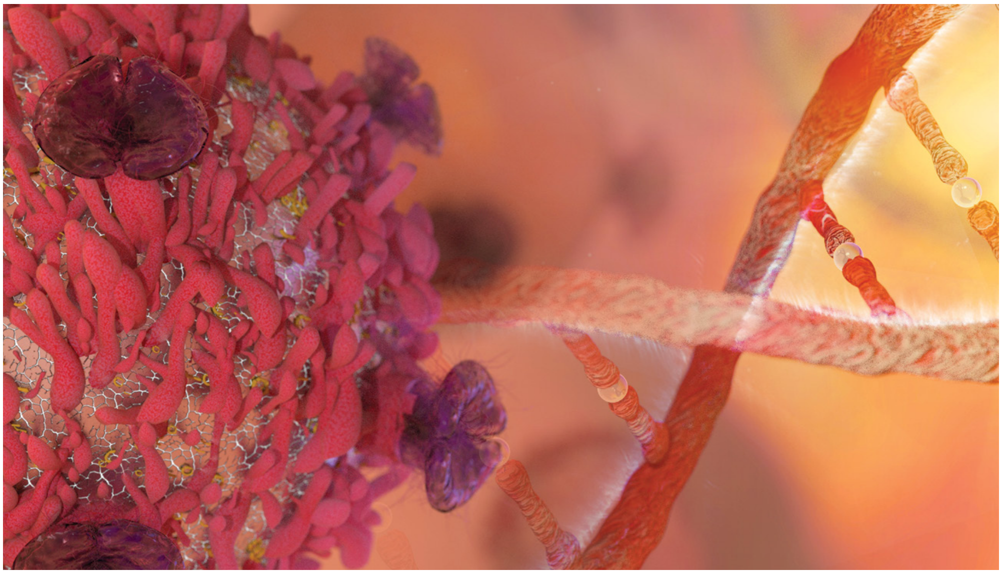

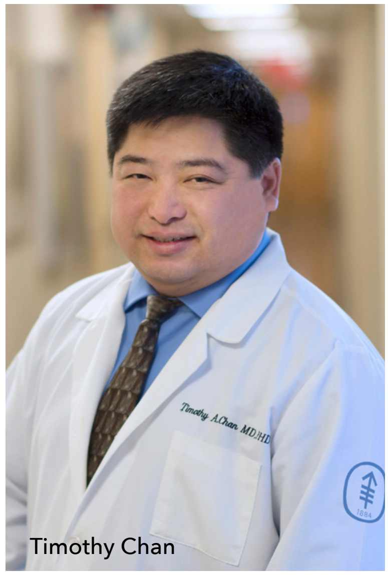

Timothy Chan

Cancer genomics and immunotherapy: Opportunities at the intersection

Clinical progress in cancer immunotherapy is driving career, collaboration, and leadership opportunities. Along with that progress comes a need for people with many different skills. Academic institutions, research hospitals, and life science companies large and small are seeking scientists who are fluent, or at least conversant, in fields such as genetics, oncology, immunology—and especially informatics. **By Chris Tachibana**

Eye-catching cancer immunotherapy headlines arrived in 2017 with nearly every season. In the spring, the U.S. Food and Drug Administration approved an antibody that is the first cancer therapy based on a tumor genetic biomarker instead of a location in the body. Summer and fall brought approval of chimeric antigen receptor (CAR) T-cell therapies for forms of leukemia and lymphoma. These attention-getting stories about cancer immunotherapy underline the vast career opportunities in academic, clinical, and industry research for those entering this field.

We're at a scientific crossroads, says physician-scientist **Timothy Chan,** director of the Immunogenomics and Precision Oncology Platform at Memorial Sloan Kettering Cancer Center in New York City. "Only a few years ago, cancer genomics and immunology were separate fields," he says. "That's changed with evidence that immunotherapy can work, and with the realization that cancer genomes and mutations influence how well it works." The result is the reinvigorated, integrated field of precision immuno-oncology. "It's one of the most fast-paced, active areas in cancer research," Chan says, "because it's at the intersection of fields, where breakthroughs happen."

Immuno-oncology is data-driven, creating a high demand for informaticians, says Professor **Zemin Zhang,** a principal investigator at the Beijing Advanced Innovation Center for Genomics, College of Life Sciences, Peking University. Since they often have many collaborators from diverse fields, Zhang says, "Bioinformaticians are in the best position to connect fields for truly novel findings."

Current landscape and new directions

Recent immunotherapy approvals are in two areas. Immune checkpoint blockade therapies use antibodies to counter the defensive tactics of tumor cells. CAR T cells target and kill cancer cells via bioengineered T-cell receptors. Much current research in immuno-oncology focuses on improving these treatments, for example, by finding new immunotherapy targets and identifying biomarkers that predict a patient's response.

We have a lot to learn about improving therapeutic effectiveness, Chan says: "Immunotherapy isn't magic. It's just another family of cancer therapies with rules that are still relatively undefined." In addition, since combination therapy that includes multiple immunotherapies and traditional chemotherapy and radiation looks clinically promising, researchers are working to develop new immunotherapy options based on completely novel strategies.

Chan's laboratory uses genomic analyses to identify neoantigens—novel peptides found only in tumors that arise from mutations accumulated by cancerous cells. According to Chan, neoantigens have two advantages: First, they look very foreign to the immune system and second, they don't appear in normal cells. The foreignness of neoantigens means therapies based on them could induce strong, specific antitumor responses. These responses should target only tumors and not normal tissues, resulting in low toxicity. Another focus in Chan's group is personalized vaccines that are based on neoantigens identified by sequencing a patient's tumor. cont.>

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"Targeted vaccines have a lot of promise," Chan says, "and could be used in combination with immune checkpoint inhibitors."

More precise application of immunotherapies and the development of new approaches requires knowing the detailed immune landscape of individual patients and tumors. Zhang's group is moving beyond bulk sequencing of tumor samples and is now conducting genomics on single cells. Tumor tissue is a diverse mix of cell types and states, so Zhang and others are characterizing the individual genomes, expression patterns, and mutational status of thousands of cells from a single tumor. By comparing the results to cells from paired normal tissue, researchers get a detailed molecular picture of the tumor environment, including the types and activity levels of T cells that are critical to the immunotherapy response. "Single-cell analysis is helping us find new genomic patterns and biomarkers that tell us the functional status of T cells associated with tumors," Zhang says. "This type of analysis is one of the most exciting developments in biomedicine. It will drive the study of cancer immunotherapy in the future."

Zhang's work aligns with what **Liselotte Brix** hears from cancer genomicists about leading-edge research in the field. Brix is chief scientific officer and cofounder of Immudex, a small company headquartered in Denmark that supplies reagents and tools for disease-specific T-cell research and diagnostics. "Researchers are using newer technologies to look directly into tumors," she says, "to make sure immunotherapies induce a response that works in the tumor." She says demand is high for biomarkers backed by clinical evidence, to determine which patients will likely respond to therapeutics and also to monitor treatment progress. To make their work more efficient, scientists are interested in developing multiplexed assays and clinical tests that provide information on several factors at once, such as T-cell type, specificity, and activation level. "The idea," she says, "is taking biomarkers from being merely tools for research to becoming a way to make immunotherapy more personalized."

Cancer genomics overall is becoming more translational, and is moving toward "bringing results to patients," says **Jean Claude Zenklusen.** He directs The Cancer Genome Atlas (TCGA), an initiative of the U.S. National Cancer Institute (NCI) and the U.S. National Human Genome Research Institute. For example, TCGA, with genomic data on 33 tumor types taken from samples from 11,000 patients, is finishing 2018 by publishing a series of papers and holding a symposium. Future resources from the NCI Center for Cancer Genomics (CCG), which oversees TCGA and other activities, will support more translationally focused research, including databases with genomic information on clinical samples linked to outcomes of their patient donors. CCG is also developing cell lines that are cultured to represent tumor behavior in vivo, and computational methods that will help researchers understand tumor behavior and apply the resulting data to diagnoses, treatments, and cures.

Catherine Sabatos-Peyton, Novartis Institutes for BioMedical Research

Sabatos-Peyton recommends preparing for an industry career by "learning good basic research and scientific interrogation skills."

TCGA data, which has been the foundation of many immuno-oncology hypotheses and discoveries, will still be available for research. "TCGA is a valid model for a genomics resource," Zenklusen says, "but by no means juices the whole fruit." CCG will be 'squeezing' more clinically meaningful information out of cancer genomics, to understand at the molecular level how genes and mutations drive cancer and determine response to treatment. CCG will also continue its collaboration with the International Cancer Genome Consortium, Zenklusen says. Even small projects with other countries contribute important information on how genetic backgrounds and cultural factors such as diet affect cancer development, he adds. Global cancer genomics research also helps us understand geographical hotspots for certain tumor types.

Developing skills and finding a niche

Early career scientists have opportunities in basic and clinical research and in both small and large industries, Zenklusen says. Researchers who want to participate in large-scale projects like CCG initiatives should look at government and academic laboratories. To use genomics resources to benefit patients, consider research hospitals that do clinical trials, he advises; to turn discoveries into diagnostic tools and medicines, look for opportunities in the life science industry.

Catherine Sabatos-Peyton endorses an industry career for the rewards of seeing scientific discoveries translate into clinical practice. She studied T cells, including the role of a checkpoint inhibitor, for her Ph.D. and postdoctoral projects and at a startup company that was acquired by Novartis. She is now a director in Exploratory Immuno-Oncology at the Novartis Institutes for BioMedical Research (NIBR), where she relies on her basic research background. Her team works on new immune-modulating therapies. Their approach is to make a detailed exploration of tumors. "We're interrogating the tumor microenvironment," she says, "by looking at suppressive cues as well as cells and secreted proteins that protect tumors from the immune response."

NIBR is similar to an academic setting, Sabatos-Peyton says, because scientists do in-depth, foundational research on a topic, for example the validity of a potential therapeutic target. But sometimes, they also have the privilege of seeing a therapy they worked on go to clinical trials or even to patients.

When hiring, Sabatos-Peyton looks for scientists with deep knowledge in their field and an ability to apply that knowledge to translational research. Novartis uses a collaborative model with teams of people from many disciplines—including genetics, immunology, informatics, and chemistry—so Sabatos-Peyton recommends preparing for an industry career by "learning good basic research and scientific interrogation skills." Early career scientists can get industry experience through the NIBR postdoctoral program. The goals are the same as an academic postdoc, she explains: "To publish and establish an independent body of work." NIBR cont.>

PHOTO: NOVARTIS

Ph.D. students and postdocs in the Zemin Zhang lab

Featured participants

Center for Cancer Genomics
www.cancer.gov/about-nci/organization/ccg

Immudex
www.immudex.com

Immunogenomics and Precision Oncology Platform, Memorial Sloan Kettering Cancer Center
www.mskcc.org/research-areas/programs-centers/immunogenomics-and-precision-oncology-platform

Novartis Institutes for BioMedical Research
www.novartis.com/our-science/novartis-institutes-biomedical-research

Peking University
english.pku.edu.cn

The Cancer Genome Atlas
cancergenome.nih.gov

U.S. National Cancer Institute
www.cancer.gova

postdocs either continue in industry or return to academia, she says. For established immuno-oncology researchers, academic–industry partnerships are an opportunity to move findings closer to clinical applications.

Sabatos-Peyton says immuno-oncology will offer career opportunities for years to come. "The clinical success is exciting," she says, "but still limited. We have so much more biology to understand when it comes to immunotherapy and patient response at a molecular level."

For all scientists, Zenklusen recommends getting solid, basic science training. Don't specialize too early, he cautions, because science is constantly changing thanks to emerging new technologies, discoveries, and even research fields. Adaptability is a strength, as Zenklusen's own career shows. He trained as a chemist, but says, "Whatever techniques I learned 20 years ago are prehistoric." The most important factor in education is a reliable scientific foundation that can be applied to any field, he says: "Generalists can move from one area to another."

Zenklusen was not the only expert to promote flexibility through moving between different fields. Zhang says multifunctional team members who can take samples from wet-lab assays to dry-lab data analysis are increasingly valued for their varied skill sets. "The next wave of researchers," he says, "is versed in two languages, biological and computational." Zenklusen agrees. "You don't have to be an expert in every facet of cancer genomics," he says, "but you need to be conversant."

Scientists in small companies need to be exceptionally versatile, Brix says. Immudex researchers must understand not only the scientific details about the products they are developing, but also the process of bringing those products to market, including manufacturing, marketing, and costs. "Industry needs creative scientists who can overcome challenges throughout the development process," she says.

At a small company, people wear many hats, Brix notes: "One moment I'm talking with scientists about new research and the next, I'm working on marketing, sales, or regulatory issues." Scientists at big companies don't usually worry about these issues because specialists or entire departments handle these matters. However, Brix says, "At a small company, you have more direct influence on the products that reach the market"—although you also might have to take out the garbage, she jokes.

For young scientists interested in industry, Brix suggests a student internship or part-time job at a small company. "It's a good way to find out if you're comfortable with the constantly changing environment," she says. If you want to run your own company, she says, "Just start. You need money and protection for your idea and a business development plan. If you need to, find a partner who can help with those areas."

Preparing for the future: Embrace new technologies and data

Regardless of career path, one thing is certain: New technologies will continue to bring more and different types of data to cancer genomics and immunotherapy. "Being able to deal with a lot of data is critical," Chan emphasizes. Students and postdocs should use their training time to get wide-ranging experience with large-scale data. "In translational work," he says, "the more tools and experiences you can add during training, the better." Get familiar with data-analysis methods, he advises, and with best practices such as how to normalize data properly. Scientists who are no longer trainees can learn genomic analyses on the job by trying out the tools of the trade, interacting with colleagues (e.g., in genomics core facilities), and taking short courses and workshops.

Scientists who anticipate technological advances and think about how to apply the data they generate are positioned for a career of discoveries, Zhang says. "As an informatics person, I'm banking on new technologies coming along that will generate tons of data." Being able to quickly process and add new data to existing information positions a scientist to see patterns, similarities, and differences in a way that advances the field. "Our best projects combine data from different technologies," he says.

Zhang has noticed a keen interest in people with dual experience in biology and informatics. He often gets calls from recruiters looking for bioinformaticians. "They call from everywhere," he says, "big pharma, small startups, clinical labs, and research teams. Researchers with biology and computational expertise are in high demand, and in a position to take leadership roles," he says. "If you go for an informatics career, you have a bright future ahead of you."

Chris Tachibana is a science writer based in Seattle, USA, and Copenhagen, Denmark.

PHOTO: PEKING UNIVERSITY STAFF