CAREERS

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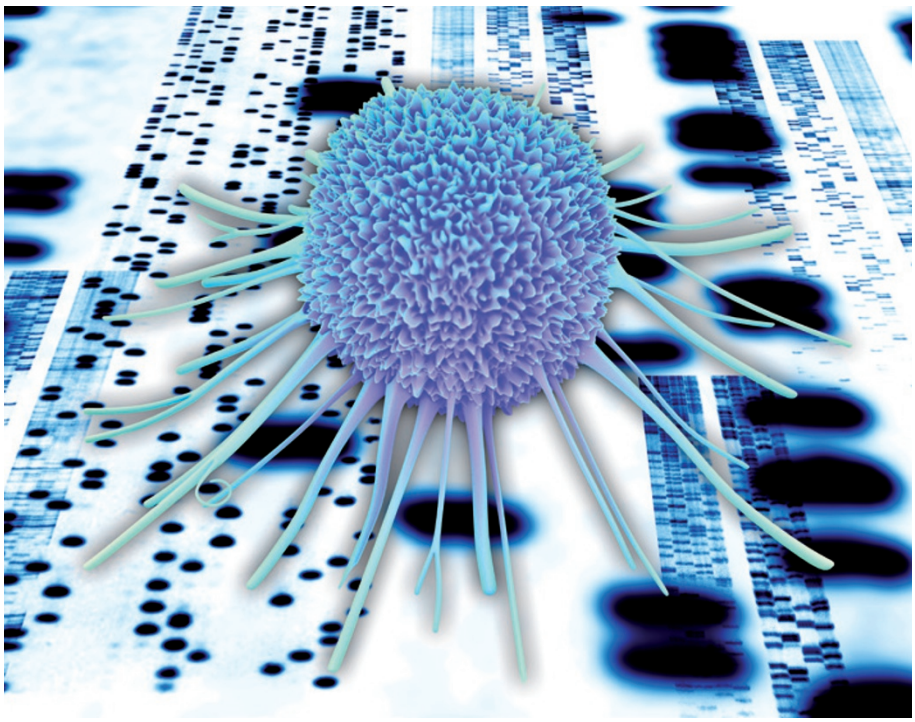


Computer reconstruction of a cancer cell on a DNA autoradiogram.

EPIGENETICS

Marked for success

The growing field of cancer epigenetics demands computational expertise and translational research experience. Qualified practitioners are in high demand.

BY HEIDI LEDFORD

When Constellation Pharmaceuticals first called to recruit venture capitalist Mark Goldsmith to be its chief executive in 2009, he was sceptical. Although Goldsmith was looking to change careers, he worried that the young biopharmaceutical company was heading into murky waters. The firm in Cambridge, Massachusetts, was focusing on epigenetics — the study of heritable changes in gene expression that are not due to changes in DNA sequence. It planned to create cancer treatments that correct the abnormal patterns of epigenetic DNA modifications seen in tumours. "I took some convincing," he says. "This was not an easy class of targets to go after; they were all unprecedented targets with incompletely understood biology."

Despite his qualms, Goldsmith took the helm and, nearly three years later, epigenetics has become a hot topic in oncology drug discovery. In January, biotechnology giant Genentech in South San Francisco, California, added its own vote of confidence to the field by investing US$95 million in a partnership with Constellation, which is now hoping to add another 10 scientists to its current roster of 70.

Epigenetics, and cancer epigenetics in particular, is a bright spot in an otherwise stark biomedical-research funding and jobs landscape. Those with the right skills and background — computational and bioinformatics training, familiarity with and interest in translational research, and an intimate knowledge of molecular biology and cancer research techniques — have plenty of opportunities from which to choose. In particular, computational skills are so sought after that they alone could be a bridge to the sub-discipline. "It's a really hot field," says Benjamin Garcia, a chemist at Princeton University in New Jersey. "I wouldn't be surprised if in five to ten years, you're going to see a lot of universities with epigenetics departments."

COMING OF AGE

Genetic mutations are not the only way to alter gene expression and protein function. Methyl groups added to DNA can silence a gene, as can chemical changes made to proteins called histones, which package the DNA in chromosomes. The modifications are exquisitely complex: the effect of one epigenetic change can be shaped by other modifications found nearby, and the epigenetic state of a cell will vary depending on the cell's identity and maturity.

By the 1990s, researchers knew that the epigenetic state of a cancer cell was often in disarray. DNA methylation, for example, was markedly reduced in some tumours, unleashing gene-expression programs that were normally kept under lock and key. "The cancer genome was grossly different," says Susan Clark, an epigeneticist at the University of New South Wales in Australia. "It was an amazing discovery."

But many in the field needed further convincing before accepting that this epigenetic 'chaos' promoted changes in gene expression and, ultimately, led to cancer. That scepticism was not limited to industry; academics also worried that a career in the field would bring funding struggles and rejections from high-impact journals. "Clearly it was a risk, even ten years ago, to somebody's career to dedicate themselves to an area that seemed to have a lot of hand-waving," says Clark. "Now that's changed; it is certainly a growth area for young scientists."

As mounting evidence pointed to the importance of epigenetic changes in cancer, government funders began making significant investments in the field. The US National ▶

DIVERSITY

PhD completion rates

In the hope of boosting degree completion rates, the US Council of Graduate Schools (CGS) in Washington DC is to examine attrition of minority students in science, technology, engineering and maths (STEM) programmes. The CGS will analyse data from 21 public and private universities for those entering programmes between 1992 and 2012. It aims to visit sites and interview students, faculty members and administrators to identify impediments to completion, and develop tools to remove them. Previous studies found that completion rates of minority students for STEM PhDs were significantly lower than those of non-minority students, notes Robert Sowell, vice-president for programmes and operations at CGS.

UNITED STATES

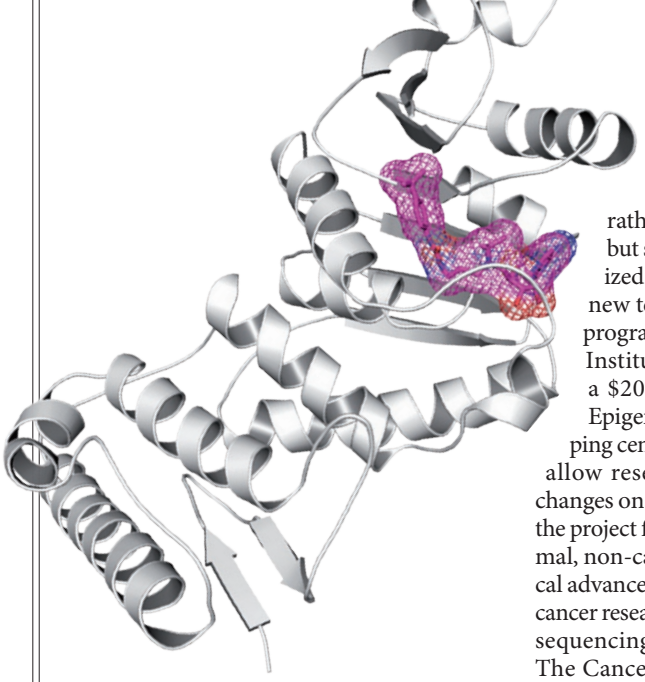
Unions banned

Michigan Governor Rick Snyder has banned graduate-student research assistants in public universities from unionizing following the efforts of 1,200 students to organize a union in April 2011. Snyder said in a statement that research assistants are students and giving them public-employee status and union representation would alter the student–teacher relationship. This is the latest action against US graduate-student unions. In 2004, New York University's union was disbanded under a state labour-board decision. Student representatives from Michigan State University in East Lansing and University of Michigan in Ann Arbor did not respond to interview requests.

PARTNERSHIPS

Postdoc opportunities

The California Institute for Quantitative Biosciences (QB3), part of the University of California, will hire up to 15 postdocs in a collaboration with drug firm Pfizer that expands a 2009 agreement to discover and develop technologies and drugs. Postdocs will be funded for two years in areas such as cardiovascular disease, immunology, neuroscience and oncology. They will learn to work with industry, says QB3 director Regis Kelly, who notes that this is a key activity given that many will go on to seek industry positions. Pfizer contributed US$9.5 million to the original partnership and will provide at least the same level of funding again, says Ron Newbold, Pfizer's vice-president for strategic research partnerships.



L. JIN/EPIZYME

An example of one of Epizyme's inhibitors interacting with an epigenetic enzyme.

Cancer Institute (NCI) in Bethesda, Maryland, has several programmes dedicated to epigenetics, including the Epigenetic Approaches in Cancer Epidemiology programme, which funds about 30 projects at a total of $45 million. In 2011, the US National Institute of Environmental Health Sciences awarded about $11 million in grants for epigenetics-related research. The institute has a strong interest in the environment's effect on epigenetics and how that influences diseases such as cancer, notes Edward Kang, a spokesman for the institute, which is based in Research Triangle Park, North Carolina.

Government investment has also fuelled the shift to large, genome-wide epigenomics studies. In October 2011, the European Commission launched its €39.9-million (US$52.1-million) BLUEPRINT project, which brings together 41 institutes and companies to generate at least 100 reference epigenomes from healthy and leukaemic cells. Just over €2 million of that is still to be doled out, says project coordinator Henk Stunnenberg of Radboud University in Nijmegen, the Netherlands. The project's team hopes to recruit at least five more groups from academia and industry. The European Commission support of epigenetics research helped to woo Manel Esteller, an epigenetics researcher at the Bellvitge Biomedical Research Institute in Barcelona, Spain, back to his home country from the United States. Esteller now participates in the BLUEPRINT project and coordinates CURELUNG, another programme funded by the European Commission, which unites 11 institutions and companies and has analysed DNA methylation in nearly 1,000 human lung tumours thus far. "The European Commission offered the opportunity to apply for different grants that were able to complement local funding," he says. "This extra help has been critical in the success of my projects."

Many of the biggest investments in epigenomics directly fund the larger sequencing centres rather than individual investigators, but smaller laboratories have capitalized on the steady stream of data and new technologies emerging from the programmes. In 2008, the US National Institutes of Health (NIH) launched a $200-million, ten-year Roadmap Epigenomics Project to develop mapping centres and technologies that would allow researchers to survey epigenetic changes on a genome-wide scale. Although the project focuses on the epigenetics of normal, non-cancerous tissue, the technological advances and large data sets have helped cancer research as well. Many cancer genome sequencing projects, including the NCI's The Cancer Genome Atlas (TCGA) programme, include a partial focus on cataloguing epigenetic changes. Kenna Shaw, director of the TCGA programme office in Bethesda, says that the programme has funded around 200 jobs. The bulk of the funding for these large-scale programmes is already dedicated to the larger sequencing centres, but smaller teams are using the data from these projects to generate individual-investigator grant applications, Shaw adds.

These data have helped to persuade investors in industry that epigenetic abnormalities in cancer could provide a wealth of new drug targets. The finding that mutations in epigenetics-related genes may be driving some cancers offers the tantalizing possibility of taking a personalized approach to cancer treatment, a tack that is rapidly gaining ground in industry, says Robert Gould, chief executive of Epizyme, an epigenetics focused biotechnology firm based in Cambridge, Massachusetts. This evidence, plus the successful approval of a first generation of drugs intended to target epigenetic pathways, has convinced almost every major drug company to invest in cancer epigenetics, says Mukesh Verma, a programme officer at the NCI. For example, Novartis, a pharmaceutical firm with its headquarters in Basel, Switzerland, has more than 200 employees working in epigenetics, most of them in cancer, says En Li, head of China Novartis Institutes for Biomedical Research, based in Shanghai. Last year, GlaxoSmithKline in London, in addition to funding its own epigenetics team, paid $20 million to partner with Epizyme in a deal

M. MCKEE/EPIZYME

Personalized treatment for cancer is rapidly gaining ground in industry.
Robert Gould

in which Epizyme could ultimately receive as much as $630 million. "GSK's group is partnering with us and is also competing with us on other programmes," says Epizyme's chief scientific officer, Robert Copeland. "It makes for an interesting dynamic."

With so much excitement, competition in the field can be fierce. Data from large government projects can be a boon to smaller labs, says Clark, but individual investigators and those new to the field need to carve their own niche. "In the face of those big initiatives, smaller labs have the challenge of asking smaller and more unique questions as to the basic mechanisms underlying these epigenetic changes," she says. Christopher Vakoc, an epigenetics researcher at Cold Spring Harbor Laboratory in New York, notes that the "tiny" lab he started in 2008 directly competed with several big pharmaceutical companies to discover a role for Brd4 — a 'reader' protein that binds to certain modified histones and modulates gene expression — in acute myeloid leukaemia (J. Zuber *et al. Nature* **478,** 524–528; 2011). After his team's paper was published, Vakoc heard rumours that ten companies were racing to capitalize on the results.

There is also an intense demand for talent. In particular, epigenetics companies and individual labs need bioinformaticians as sequencing projects continue to dump terabytes of data into public databases (see *Nature* **482,** 263–265; 2012). Although this is an opportunity for job hunters with computational training, it creates challenges for those opening labs for the first time, says Jun Song, a computational biologist who opened his lab at the University of California, San Francisco, in 2009. Song has struggled to compete with bigger labs to recruit graduate students and postdoctoral researchers, who often prefer the proven track-record and extensive connections offered by a well-established principal investigator. "We battle to get a talented bioinformatician," says Clark. "Everybody wants their own."

Ultimately, Song looked outside biology to recruit three postdocs, two of whom he lured away from high-energy particle physics and the third from applied mathematics. Song himself was trained as a physicist, and says that epigenetics and epigenomics offer a range of challenging computational questions that can entice researchers from other fields. "It would be great to have someone already trained in both biology and computation," he says. "But as biology becomes more quantitative as a field, I also believe that it's important to bring in new computational scientists and train them in biology."

The opportunity for cross-disciplinary training in epigenetics can be an advantage for bioinformaticians and molecular biologists alike, says Garcia. "It makes you a more well-rounded scientist," he says. "And that's what you need these days to compete in the job market." ■

Heidi Ledford *writes for* Nature *from Cambridge, Massachusetts.*

COLUMN

A tough climb

Challenging your own ideas and opinions takes more than just a change of scenery, says **Andrew Peterman**.

It was 4:00 a.m., and I was sure I was getting close to the top. The wind had pelted my face with snow and ice for the past three hours. Every few steps, the train of people stopped. Below me, hundreds of specks of light from climbers' lamps clung to the mountainside in a zigzag pattern. At each pause, I shut my eyes.

When I opened them again, I was looking down at the half-metre between my feet and the heels of my former college roommate. The short respite hardly counteracted the fact that each breath contained less than half of the oxygen I am used to back at home. I looked at my altimeter — I still had a couple of hours to go.

Last February, I decided to climb Mount Kilimanjaro in Tanzania, which stands 5,895 metres above sea level. I embarked on the 3-week trip to challenge myself to embrace a different culture. But I found that it takes more than a change of scenery to challenge one's perceptions.

I wanted to broaden my landscape, test my own conventions and walk away feeling as if I had pushed myself physically and mentally. I wanted to create an unconventional forum for discussion, as different as possible from that of the engineering department at Stanford University, California. I invited my closest friends who had gone on to pursue different areas of study or practice from my own. In academia, we often interact with the same people, hear and speak the same language, and attend the same presentations. We surround ourselves with people just like ourselves. I assumed that an unfamiliar location and culture would challenge my ideas and opinions.

But researchers such as Miller McPherson, a sociologist at Duke University in Durham, North Carolina, have shown that similarity breeds connection — the homophily principle (M. McPherson *et al. Annu. Rev. Sociol.* **27,** 415–444; 2001). Individuals' relationships tend towards homogeneity. In other words, we develop contacts with greater frequency among individuals who have sociodemographic and behavioural characteristics and attitudes similar to our own.

Despite the fact that my friends have pursued careers in other fields, they are still more like me than are other people. We are all males and are mostly white, Stanford alumni, from middle-upper-class families, in our late 20s who share similar political views. Perhaps

R. STEIER

Andrew Peterman and friends climb Kilimanjaro.

forming the group was, by my own subconscious design, a way to avoid the unfamiliar in a trying and scary environment, and perhaps the research is correct.

The experience has made me realize that homophily is also a tough mountain to overcome. I found that by stepping outside my comfort zone physically — braving the cold, harsh conditions of Kilimanjaro — I had clung to the familiar opinions of my close friends.

As much of the research in this area shows, homophily has serious implications for the development of new ideas. If you surround yourself with people who share your opinions, attitudes, beliefs and even experiences, how can you learn anything new? Who will challenge your ideas?

I aim to keep looking for that interdisciplinary environment. The first step is engaging with people with whom I do not always agree — embracing the conflict and uncomfortable nature of working with those with starkly different opinions. I believe that all scientists, especially those with interdisciplinary aspirations, should strive to break away from the familiar in search of the unfamiliar. Doing so may uncover a new approach to an old problem.

Creating these situations requires an active effort to push through the discomfort of difference. And, despite what the research suggests, it does not always have to be the case that 'birds of a feather flock together'. ■

Andrew Peterman *is a doctoral candidate in civil engineering at Stanford University in California.*