

# Translating Cancer Research In The New Millennium

Cancer research now reaches far beyond questions of uncontrolled cell division into a more broadly focused 'total picture' perspective of a tumor's proteomic, genomic, and metabolomic landscape. With the dawn of personalized medicine and new technologies allowing next generation sequencing of individual patients' tumors, a burst of information has been brought forth that needs wrangling in order to advance cancer diagnosis and treatment. This shift has opened new areas of fundamental exploration, and presented scientists with new career opportunities and challenges as they try to navigate the information overload. **By Kendall Powell**

**E**ven in tough economic times, cancer research has more government backing and private philanthropy donations than many other fields. The National Cancer Institute's 2010 budget at \$3.1 billion is almost double that of the National Institute for General Medical Sciences. "If I were to bet on a stable or growth area against the financial background at the moment, I would be backing biomedical research in cancer," says **Hamish Ryder**, director of drug discovery at Cancer Research Technology in London, United Kingdom.

Still, the academic job market has become ultracompetitive as universities struggle to find the funds for starting up new laboratories, notes **Karl Saxe**, cell biologist and scientific program director of cancer cell biology and metastasis for the American Cancer Society in Atlanta, Georgia. Saxe, who also oversees the peer review of postdoctoral fellowship applications, sees a noteworthy trend—that more lab heads are demanding postdocs arrive with their funding already in hand.

With this current hiring slowdown, researchers need to be creative about looking for posts. But, the good news is that almost any cellular and molecular training can prepare scientists for a career in cancer research. And researchers who pair a strong scientific background—especially in areas such as cell signaling, metabolic pathways, epigenetics, or small RNAs—with the ability to make sense of large data sets gain a leg up on a career in cancer research. This combination of skills easily translates into success in areas beyond the academic realm, too.

For those making job transitions, "I definitely recommend thinking about all the different options, including government and the pharmaceutical world, which has long shed its big, bad evil image," says Saxe. "And people with really good doctoral degrees [in biomedical fields] should be thinking about how to turn themselves into informaticists as well."

Information specialists with sophisticated scientific training will be essential in the push for personalized medicine, Saxe notes. Large, patient-generated genomic data sets are already the rule at some major cancer centers, and increasingly proteomic and metabolomic data are being added. In addition, clinical testing of new, mutation-specific therapies demand more sophisticated patient-selection

From Left: Karl Saxe, Cheryl Jones, Diana Caracino



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David Plas

strategies. In such settings, both drug developers and regulators "will need to be able to talk to each other intelligently," explains Saxe.

He predicts that "people who are really good at combining 'omics and mathematical modeling into their own thinking [about biological processes]" will have the best chance at success in the individualized medicine age.

## GETTING BACK TO METABOLISM BASICS

The new 'omics buzzword is metabolomics. But, **David Plas**, a cancer researcher at University of Cincinnati in Ohio, says metabolomics is a tool in the larger, burgeoning field of cancer metabolism research. Plas studies how dysregulation of AKT signaling impacts cell metabolism and how this leads to apoptosis resistance in cancer cells. He and others hope to capitalize on a renewed interest in the role of metabolism in cancer. **continued »**

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Craig Thompson



Jim Maher

**“Almost everything you could do to understand how cells effectively live together will impinge on cancer treatment and diagnosis. The challenge is going to be using a systems biology approach to deconvolute the goals of multicellular life.” —Craig Thompson**

In the 1920s, the Nobel Laureate Otto Warburg proposed that aberrant cellular metabolism might be the cause of cancer, after observing that cancer cells consume more glucose than normal cells through the anaerobic glycolysis process even when oxygen is plentiful. But his ideas were overshadowed by the molecular biology revolution of the 1970s that led to the traditional view that cancer results from an imbalance between oncogene drivers and tumor suppressor genes.

Plas says that the last decade of research has made cancer cell biologists realize that signal transduction pathways control metabolism in more sophisticated ways than a simple response to energy supply and demand. And, Plas explains, similar to the way current therapies attack signaling pathways that control cell cycle and metastasis, targeting the regulation of metabolism signaling pathways has the potential to serve as an avenue for cancer treatments. “We’ve needed to reunify these two sides—[signaling and metabolism]—of cancer biology,” he says.

While Plas works on the metabolism-apoptosis connection, other researchers, from both academia and industry, are probing how cancer cell metabolism affects cell growth and metastasis. One major question: Why does oncogenesis favor glycolysis over the Krebs cycle and oxidative phosphorylation? The answer, perhaps, lies in the fact that glycolysis produces many more of the precursor building blocks that rapidly dividing cells need to synthesize daughter cells.

“How do cells acquire enough nutrients to maintain homeostasis and live another day?” asks **Craig Thompson**, president of Memorial Sloan-Kettering Cancer Center (MSKCC) in New York. “Even normal cells have to go into net growth, where the problem isn’t ATP, but rather the [availability of the necessary] building blocks for making nucleotides, lipids, and proteins all over again.”

This question of biosynthesis is pulling another basic cell biology field, autophagy, into the cancer spotlight. Autophagy—literally ‘self eating’—is a process by which cells digest their own internal organelles to recycle their building block components. Once thought only critical for single-cell organisms like yeast, now, Thompson notes, mammalian cells are thought to turn to this desperate measure to get through energetically stressful times, like metastasis.

Plas says scientists need to not only brush up on their biochemistry equations, reactions, and kinetics, but also be able to handle large data sets and, ideally, have mathematical modeling skills. “I’d

hire that person in an instant,” says Plas. “I’ll give them the biological problem, they bring the math [skills], and then we’d do some interesting things.”

Ryder notes that his own organization and other academic institutes have recently recruited metabolism experts for their research efforts. “We were looking for [researchers with] an excellent background in biochemistry—but one broader than just a focus on glycolysis and the Krebs cycle. A knowledge of the biosynthesis of lipids, nucleotides, and proteins, and how catabolism and anabolism are linked is also needed,” says Ryder.

For example, to build upon the observation that some cancer cells seem addicted to particular nutrients, such as specific amino acids, Ryder depends upon his team’s knowledge of the biochemical processes that occur as nutrients enter the cell, including the key intermediates and enzymes in pathways, to identify proteins that could serve as potential drug targets.

Ryder also finds experience with cell culture, gene knockdown technologies, apoptosis assays, and metabolite profiling methods—such as mass spectrometry, quantifying metabolites from cell lysates, and the ability to identify key nodes in signaling pathways regulating metabolism—essential for researchers working on his drug discovery projects at the subsidiary of the Cancer Research UK charity.

He notes that the cancer metabolism field is likely to have a long shelf life—with some 1,500–2,000 genes playing a role in metabolism—and has a strong potential for cross-purposed discoveries in the pharmaceutical industry between cancer and metabolic disease.

“Cancer is a horrible example of what can go wrong in multicellular life,” says Thompson. “Almost everything you could do to understand how cells effectively live together will impinge on cancer treatment and diagnosis. The challenge is going to be using a systems biology approach to deconstruct the complexities of multicellular life.”

### TAKING ‘OMICS TO THE NEXT LEVEL

Such a systems approach will require scientists who can weave together large and disparate data sets from the various realms on the ‘omics map—genomes, proteomes, transcriptomes, and metabolomes. Researchers grappling with all that data will be **Gustavo Salem’s** main clients. As vice-president of the Biological Systems Division of Agilent Technologies in Santa **continued »**

Clara, California, Salem is ahead of the curve in integrating the ‘omics sciences.

Traditionally, he says, cancer experts have either been doing discrete genomics or proteomics experiments and then collaborating with groups using different approaches, or they have tried a systems biology approach to ask what is changing across the entire biological system for a specific type of cancer. “Under either scenario, it becomes a bioinformatics nightmare to bring all that information together,” says Salem.

Gathering data from multiple vendors’ instruments and then visualizing or analyzing all the data sets simultaneously is not always possible. But, Agilent is hoping to step into that void by providing tools for visualization and analysis across genomics, next generation sequencing, proteomics, and metabolomics. For example, the Mass Profiler Professional (for mass spec data) and the Gene Spring GX (for genomic data) are written on the same software platform so that protein hits and gene lists can be compared directly.

“This integrated biology approach is really gaining a lot of attention and a lot of steam,” says Salem. “There will be a need for people who can really speak about bioinformatics and computational biology, and who know how to use mass spectrometers and microarrays.”

And the information flood has not even begun to crest, as major worldwide projects such as the International Cancer Genome Consortium (based at the Ontario Institute for Cancer Research in Toronto), the Cancer Genome Atlas (based at the National Cancer Institute in Bethesda, Maryland), and the Cancer Genome Project (based at the Wellcome Trust Sanger Institute in Hinxton, United Kingdom) get under way. The genome consortium, for example, aims to catalog the genetic mutations, changes in gene expression, and epigenetic changes across 500 cancer samples from each of 50 different cancer sites.

From those reams of data, says **Jim Maher**, a cancer researcher and associate dean of the Mayo Graduate School in Rochester, Minnesota, the ultimate challenge will be pulling out which changes are actually causative. “Even with comparative genomics and arrays, there will be a lot of information that is not indicative of what’s really going on,” he explains. “To sort that out, we’re going to need really clever biologists.”

### PERSONALIZED MEDICINE USING INFORMATICS

One sort of clever biologist, the bioinformatics specialist, will be indispensable in cancer research centers, be they academic-, hospital-, or industry-based. Although **Simon Vincent**, head of personal awards funding at Cancer Research UK in London, says he is reluctant to name any one area as “hot.” He explains that he “would not



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have predicted 10 years ago that today it would be metabolism and the Warburg effect.” Though he does point to one area with the promise of staying power: stratified medicine.

“Taking all of the information about the biology of [specific] tumors and using that to decide the best treatment course for patients and getting them into the right trial—that will have longer term impact,” says Vincent.

Cancer Research UK, Europe’s largest private funder of disease-specific research, has funneled a significant portion, about US\$26 million (£16 million), of their approximate US\$530 million (£333 million) budget toward patient-stratification research. Vincent’s organization will act as a coordination center to bring together its funding mechanisms and five core research institutes and use the benefits of the United Kingdom’s centralized healthcare system and records.

“One of the challenges for scientists highly skilled in data manipulation and informatics is to pull all [these data sets] together, be they genetic, patient, or hospital data sets, to inform research,” says Vincent. In addition, he says, the long history of centralized records makes the United Kingdom a leader in both classical epidemiology and genetic epidemiology of cancer. He notes an early example of the power of bioinformatics in cancer research was the identification of the BRAF gene as a driver in melanomas through the Cancer Genome Project.

Salem agrees that informaticists will be the gatekeepers of personalized medicine. He points to the WIN Consortium, or Worldwide Innovative Networking in personalized cancer medicine, a group of 22 cancer centers worldwide that will be implementing a common system for gathering microarray data from all their patients, which should enable them to track patients over time and divide data into subpopulations. One of the founding centers, the Institut de cancérologie Gustave-Roussy in Villejuif, France has been collecting patient tumor samples, whisked from the operating room to the hospital’s laboratory in pneumatic tubes, for the last eight years.

“More and more centers are becoming interested in getting [multiple] ‘omics data sets from patients,” says Salem. And this trend, which started with cancer research, is rapidly moving towards other fields, such as neurology, cardiology, and metabolism. “There will be a significant increase in the number of people needed to understand the scientific output from clinical labs,” he explains.

Given the complex nature of the changing landscape in cancer research, the researchers who are likely to be in high demand and get the jobs are “the most curious people, who have changed their projects frequently and are not locked into any particular field,” says Maher. “And, those who have deliberately cross-trained.”

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