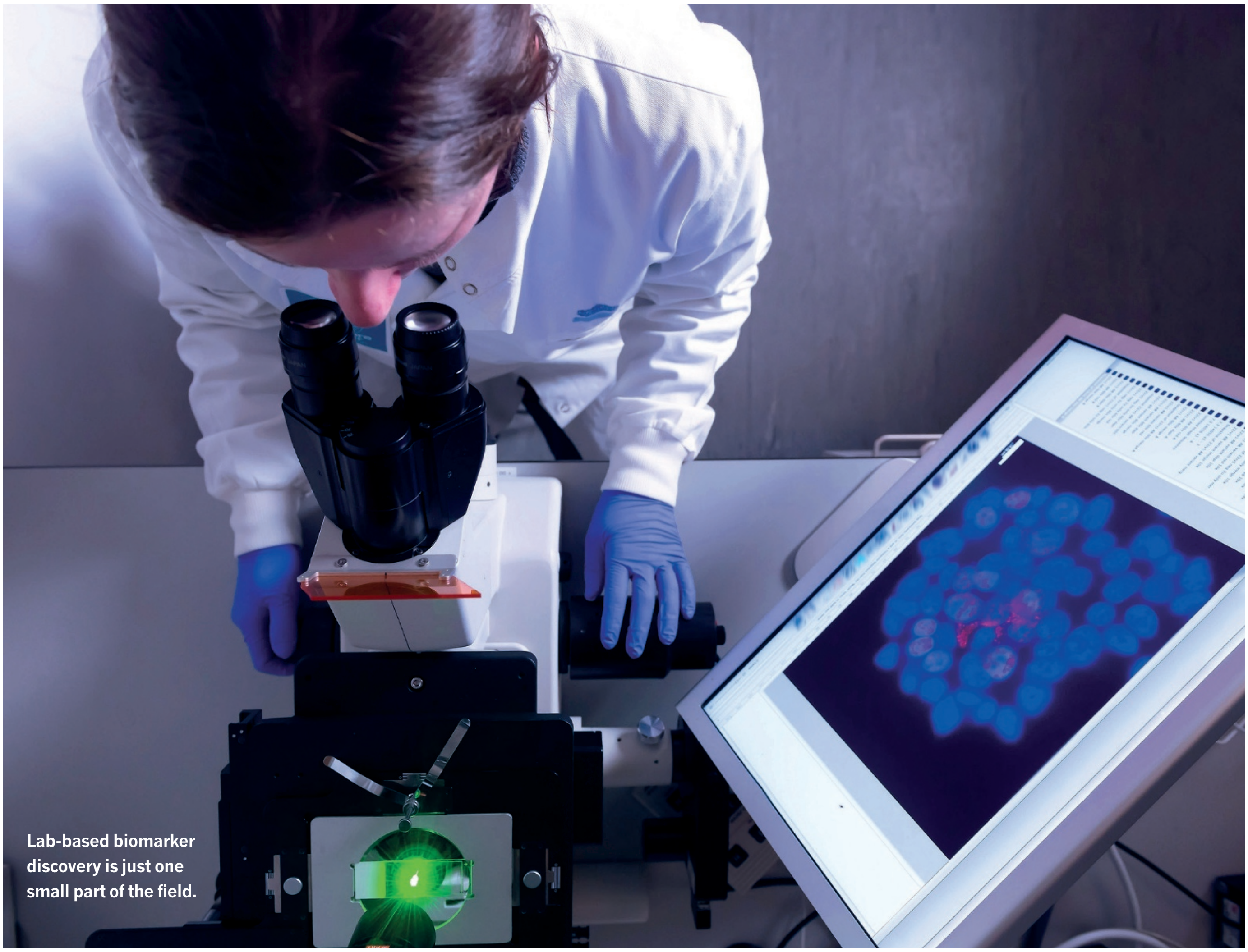
JONATHAN POW/GETTY



Lab-based biomarker discovery is just one small part of the field.

Join the hunt for biomarkers

As oncologists turn to targeted medicine, cancer biomarkers are emerging as a potent and much-needed tool.

BY PAUL SMAGLIK

Daniel Hayes has watched the identification of biological markers of disease go from a "sleepy niche" to an increasingly important aspect of personalized care. "When I started, there was little funding for tumour biomarkers in any way, shape or form in the clinic, and there was little if any academic credit given for doing so," says the cancer researcher at the University of Michigan in Ann Arbor.

Hayes didn't like the field when he started in it 35 years ago. His workplace, then known as the Sidney Farber Cancer Institute (now the Dana-Farber Cancer Institute) in Boston, Massachusetts, had moved him from his preferred discipline, protein biochemistry, to molecular and clinical pharmacology. "I was not happy," Hayes says. "I had a bad attitude. I found it boring."

That changed in 1985, when Hayes found that many people with breast cancer had a distinctive protein in their blood. The antibody he used to detect that protein, combined with another, became an early test for breast cancer — and launched his career.

Personalized medicine refers to tailoring treatment to a patient's biological repertoire. Biomarkers, an umbrella term for any physiological indication of a disease's presence, progression or state, can facilitate that by helping researchers to identify treatments that might be especially effective for patients with a particular genetic profile. They can also be used to monitor treatment and track the development of resistance.

There are many different types of biomarker around. People with breast cancer who express specific mutations of the *HER2* gene are known to respond particularly well to the drug Herceptin (trastuzumab). Clinicians keep tabs on levels of prostate-specific antigen (PSA) to track the progress of prostate cancer. Others exist for colorectal, pancreatic, ovarian and breast cancers. But those working on the front line of medicine ▶

need more. “There are not nearly as many as there should be,” says Hayes. “There are hundreds of publications on putative cancer biomarkers and biomarker tests every year. Only a few have analytical validity and clinical utility.”

There are other problems: many of the known biomarkers can be found only by taking biopsies, using surgical equipment to obtain tumour samples. And — like any surgery — the procedures are invasive, expensive, uncomfortable and potentially dangerous for patients. Furthermore, clinicians need regular access to biomarkers — patients may initially respond to targeted treatment, but develop resistance over time. And some cancers, in the lung and pancreas, for example, are almost impossible to get at more than once. Doctors are taking aim at a moving clinical target — but they have brought knives to a shooting range.

DRIVE FOR DIVERSITY

So the hunt for more blood-based biomarkers is gathering steam. Matthew Garnett, a molecular biologist at the Wellcome Trust Sanger Institute in Cambridge, UK, is helping to lead the movement away from biopsies. “We need less-invasive methods. Moving forward we really want to use a simple blood test,” he says.

The surge has been spearheaded by generous grants from the US National Cancer Institute (NCI), Cancer Research UK (CRUK) and the European Commission, among others. The field is attractive to scientists in both industry and academia: basic biologists can study disease processes and help to identify biomarkers; scientists interested in working in industry can focus on developing, optimizing and validating tests.

Developing tests that can track when tumour DNA or cancer cells reappear in blood after chemotherapy can help to identify disease resistance, Garnett says. He

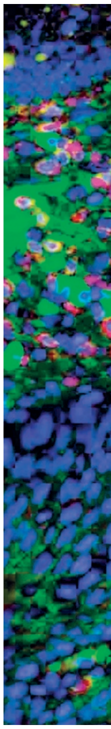
YOU NEED A LOT OF DIFFERENT PEOPLE WITH A LOT OF DIFFERENT SKILLS TO PULL THIS OFF.

points to instances in which biomarkers have directed therapy, with ‘dramatic’ clinical responses in breast, lung and skin cancers. Garnett suspects that more are out there, and wants to use them earlier in the clinical process, to guide both diagnosis and treatment.

The width and breadth of the teams involved in biomarker discovery means there is plenty of room for scientists of all stripes to enter the field. For instance, as in other modern biological and biomedical research fields, teams require a wide range of mathematical expertise, from data managers to biostatisticians. Good statistical analysis can point physicians to causation and help them to tailor drugs to individual patients.

And the huge amount of public cancer data makes the field ripe for computational biologists, says Florian Markowetz, a cancer researcher at the University of Cambridge, UK. They can mine existing data to find putative biomarkers, or ones relevant to one type of cancer that might also help to detect or track another kind. “I am a huge supporter of having open access and transparent science,” Markowetz says. And the more data are shared, the more there are for computationalists to chew on, which could speed up discovery. “This is one example of where it’s really important,” he says.

Because of the wide variety of disciplines in the cancer-biomarker mix, knowing how to work with teams of scientists from varied backgrounds is essential. “We need biostatisticians who can communicate statistics to people who aren’t as familiar with the area,” says Lucinda Billingham, director of statistics at the CRUK Clinical Trials Unit in Birmingham. “We also need people who can contribute to a research question on a broader level and add value to the project.”



WIDE FIELD OF VIEW

Caroline Dive runs a group of 80 researchers at the CRUK Manchester Institute. She and her team focus on developing blood tests for lung cancer that could not just detect the disease, but also track how it responds to treatment. “You need a lot of different people with a lot of different skills to pull this off,” Dive says.

She divides her team into two broad groups — one to work on disease mechanisms, the other to develop, refine and validate the tests. She puts postdocs interested in academic research in the first group, because that kind of work generates the publications essential for an academic career.

Industry-minded scientists tend to work in the other group, because those skills align more closely to the expertise that pharmaceutical and biotechnology firms need. Off-the-bench skills, such as broad knowledge of regulatory affairs and the ability to communicate complex clinical information to patients, also come into play. Those skills have helped several of her scientists to find jobs outside academia. “Many of my staff have ended up in pharma,” Dive says.

Fortunately, training grants are helping her to build up these skills in her group. She recommends that scientists interested in developing expertise in biomarkers get on programmes covered by training grants, so group leaders don’t need to write applications for funds every year. Such core funding “is paramount to success”, she says.

SIGNS OF SUCCESS

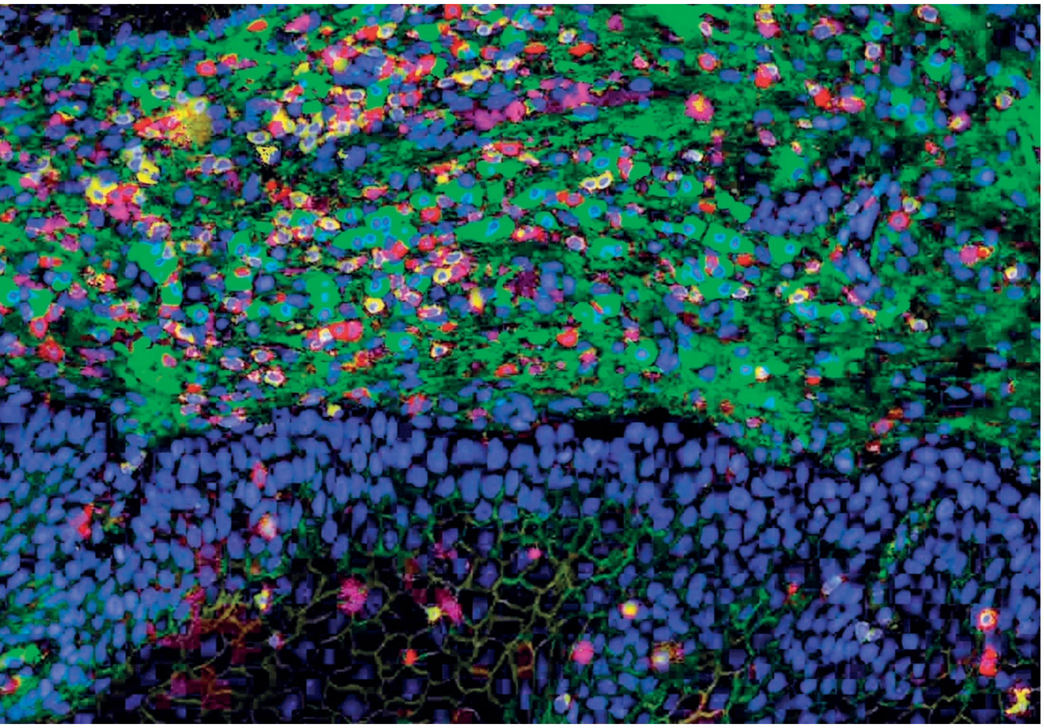
Big data turns to cancer

A new company with Silicon Valley pedigree is devoting itself to catching cancer biomarkers early. GRAIL, of Menlo Park, California, has raised a US$900-million war chest from various technology and life-science investors since last January, including Johnson & Johnson Innovation, Amazon and ARCH Venture Partners. Early investors included Google, Amazon founder Jeff Bezos and Microsoft founder Bill Gates.

The company aims to find signs of cancer at its earliest stages, says Vik Bajaj, GRAIL’s chief scientific officer. “Our mission is to detect cancer early where it can be cured. By moving the point of detection — when the disease is less advanced and less complex — we hope to treat it more effectively.”

GRAIL has already grown to 150 employees, and is looking for more. On the basic side, it is seeking scientists with backgrounds in computational biology, assay development, cancer biology, genomics and immunology. On the technical side, it is recruiting data-collection specialists, data-science and machine-learning scientists, software engineers, clinicians and those with skills in designing and running clinical trials.

The company’s first major scientific goal is to discover the set of measurements that most sensitively and specifically detect cancer in its earliest stages. It plans to monitor potential biomarkers in the blood of 10,000 people — 7,000 with cancer — over time. GRAIL is busy building infrastructure to accommodate the huge amount of data it expects to generate. “It requires clinical experiments with unprecedented scale,” says Bajaj, who stepped down as chief scientific officer of Verily Life Sciences (formerly Google Life Sciences) to join GRAIL after losing his father to cancer. **P.S.**



Various biomarker signals (yellow, red, pink and green) indicate presence of cervical cancer cells.

TISCH CANCER INSTITUTE AT THE MOUNT SINAI SCHOOL OF MEDICINE/NATL CANCER INST./SPL

Klaus Pantel, chair of tumour biology at Germany's Medical Center Hamburg-Eppendorf, and the lead on a European Commission cancer-biomarker programme with 36 other centres, thinks that the field is attractive to students because it offers clear career paths into both academia and industry, as well as the clinic and the lab. "Because of the close interaction of laboratory and clinical research groups, you can create really nice PhD and postdoc programmes," Pantel says. "For the student, it's really attractive because they can interact with people in each world."

GOOD CONNECTIONS

For students and postdocs looking to break into the field, Pantel suggests looking for an institution that already has well-established connections. A link to an academic medical centre is important, because researchers often need access to patient samples. Finally, look for places that have robust industrial partnerships, so that young scientists can collaborate with researchers in academia and industry.

For Pantel, this overlap has brought him renewed vigour. "It's nice for me," he says. "I go to clinical meetings, I go to basic metastasis meetings, clinical chemistry meetings."

But, he says, the best feeling comes when he has an opportunity to change a course of treatment for the better. "I can steer colleagues to different ways of doing things because I am surveying treatment options more broadly and in more tumour types. Sometimes I can see how it can help cancer patients."

There is one hurdle in clinical biomarker study that will be familiar to many researchers: funding, especially for early tests, says Sudhir Srivastava, head of the NCI's Cancer Biomarkers Research Group. Standard academic government and charity support is often hard to come by, but could soon be supplemented, as drugmakers consider including biomarker tests to accompany new treatments to increase efficacy. Investments by Bill Gates, Jeff Bezos and other big tech names should further shake up the biotech biomarker field and attract young talent (see 'Big data turns to cancer').

Meanwhile, many scientists have been lobbying for the adoption of biomarkers into front-line primary care, to identify risk factors and catch cancer early. Currently, the majority of biomarker research focuses on studying how a disease responds to treatment, rather than on early identification of disease.

The obstacles to wider, earlier biomarker use are daunting, says Srivastava. Getting to a point at which risk factors can be found in an individual patient involves testing a massive population of people — only a handful of whom will develop cancer. The financial costs and logistical challenges of recruiting and monitoring such a group are formidable, he says. But the pay-off in terms of health outcomes may be well worth it.

So is entering into a career focusing on biomarker research a good move? "I am biased," Srivastava says, "but I would love to see more young people come in to this field." ■

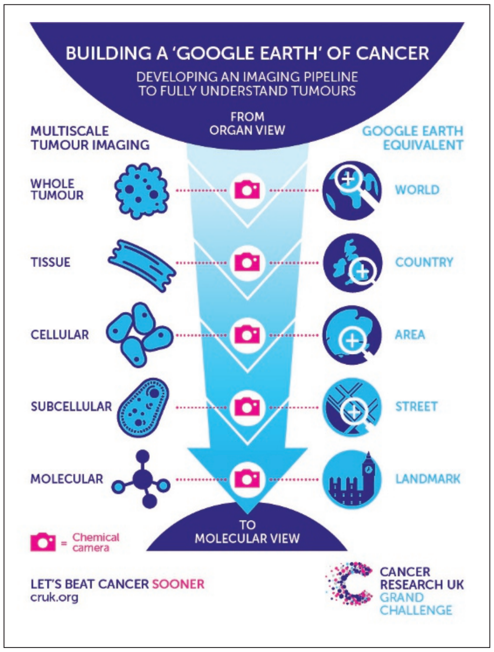
Paul Smaglik *is a freelance writer in Milwaukee, Wisconsin.*

CANCER RESEARCH UK | BEATSON INSTITUTE

Are you ready for the Challenge?

Would you like to develop your scientific career in a research institute that is founded on the quality of its people and designed to promote the development of the most outstanding and dedicated scientists? Many early career researchers have already made that decision and at present over 100 of them are now benefiting from our excellent training programme and all that our cutting-edge services and advanced technologies can offer.

Add to this the support we receive from Cancer Research UK, the recent Grand Challenge award and other major funding, and you quickly understand why the Beatson Institute is an internationally recognised centre of excellence for cancer research.

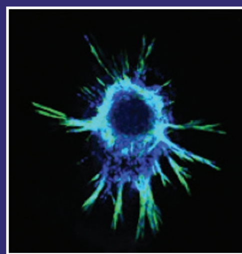


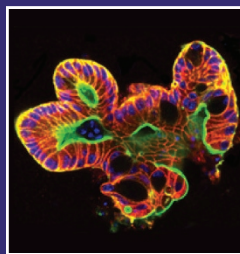
The Institute supports world-class research into the molecular mechanisms of cancer development with a particular focus on the regulation of tumour microenvironment and cancer metabolism. Our ultimate goal is to develop better treatments to improve the quality of life for cancer patients.

The Beatson also benefits from close interactions with the University of Glasgow – it has strong links with the Institute of Cancer Sciences and is a key partner in the Cancer Research UK Glasgow Centre (**www.glasgowcancer.org**). Details of the research programmes at the Institute can be found on our website **www.beatson.gla.ac.uk**.

The Institute is located on the edge of the cosmopolitan and vibrant city of Glasgow, close to the west coast of Scotland and at the gateway to the spectacular Highlands and Islands, making it an excellent place to live and work.

The Beatson prides itself on its collaborations and is a participant in a number of important national and international research projects, including the recently launched **Grand Challenge** (**www.npl.co.uk/grandchallenge**) led by Dr Josephine Bunch (National Physical Laboratory) to map cancer in unprecedented detail. Our Interim Director Prof Owen Sansom has been instrumental in determining the molecular hallmarks and cell of origin of epithelial cancers. Using this experience the Sansom laboratory will provide the Grand Challenge team with the in vivo models that will be mapped in 3D.





Current Scientific Research Opportunities

Prof Sansom is looking for two outstanding postdoctoral research scientists and a PhD student to join his laboratory and be part of this exciting collaboration.

In addition we are currently inviting applications to the following research groups:

Prof Robert Insall, Cell Migration and Chemotaxis

Dr Alexei Vazquez, Quantitative Cancer Metabolism

Dr David Lewis, Molecular Imaging

Please see our website (**www.beatson.gla.ac.uk/careers**) for more details on the vacancies and how to apply.

U288571RL