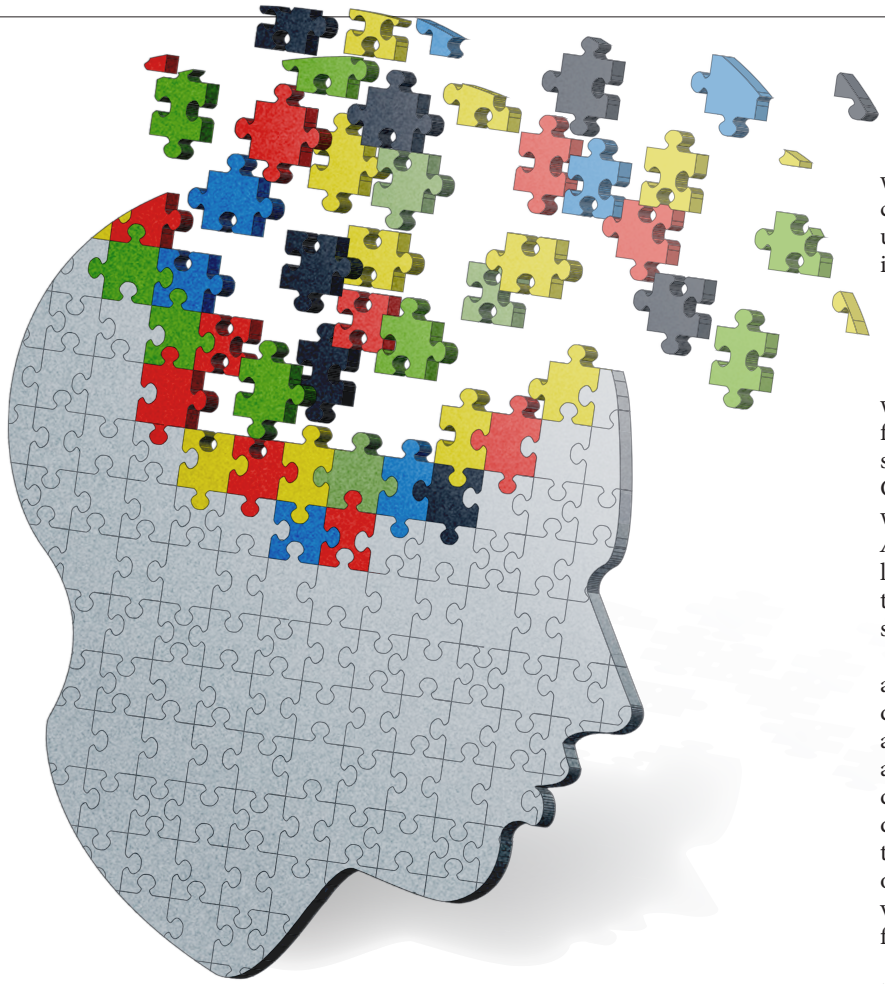
CAREERS

COLUMN Social media help researchers become science ambassadors **p.141**

EMPLOYMENT Better pay and hours lure graduates away from science **p.141**

NATUREJOBS For the latest career listings and advice **www.naturejobs.com**



D. GERASIMOSKI/SHUTTERSTOCK

LIFE SCIENCES

Biomarkers on the brain

Researchers hoping to have an impact in the clinic are searching for diagnostic tools for neurodegenerative disease.

BY ALLA KATSNELSON

Niklas Mattsson had always been interested in cognition and the biology of how it goes awry. Attending medical school to become a neurologist seemed a no-brainer. But after a year working in a neurology clinic, where many of his patients suffered from Alzheimer's disease, he found that medicine wasn't quite the right fit for him. "I enjoyed working with patients — it was very rewarding," he says. "But it did not give me the opportunity to really focus on basic disease mechanisms." Research on animal models or cellular processes also held little allure, because it would take him too far away from the clinic.

So in 2008, he embarked on a joint clinical and research residency in neurochemistry at Sahlgrenska University Hospital at the University of Gothenburg in Sweden, where he found his niche in biomarker discovery. "Biomarkers are really *in vivo* measurements of the pathology of the disease, so it's an opportunity to investigate the disease mechanisms on a patient level," he says. His dissertation research, which he hopes to defend in December, focuses on protein biomarkers in the cerebrospinal fluid (CSF). His work has moved quickly. In 2009, he was the first author on a multi-centre study of 1,500 subjects, which confirmed that levels of three CSF proteins could be used to identify people with Alzheimer's disease (N. Mattsson *et al. J. Am. Med. Assoc.* **302,** 385–393; 2009); it was the largest-ever study of such biomarkers. "I think the area is a very fruitful one for young scientists," says Mattsson.

In the past few years, interest in the discovery and validation of biomarkers for Alzheimer's disease has grown rapidly in both academia and industry. The surge is driven by a growing awareness that disease pathology takes root a decade or more before symptoms of cognitive decline become apparent. The most effective therapies will have to be administered early on, before symptoms are evident — and well validated biological measures will be needed for both diagnosis and prognosis.

A decade ago, grant applications proposing to look for such biomarkers were often rejected as mere fishing expeditions. "But I think the message that if you want to eat fish you'd better go fishing has been understood," says Simon Lovestone, a psychiatrist at King's College London and principal investigator at AddNeuroMed, a European public–private consortium aimed at identifying biomarkers for Alzheimer's. That change means that opportunities are growing for young researchers with training in a wide range of topics, including analytical chemistry, biochemistry, radiology, bioinformatics, epidemiology, clinical neurology and psychiatry.

PROJECTS AND POTENTIAL

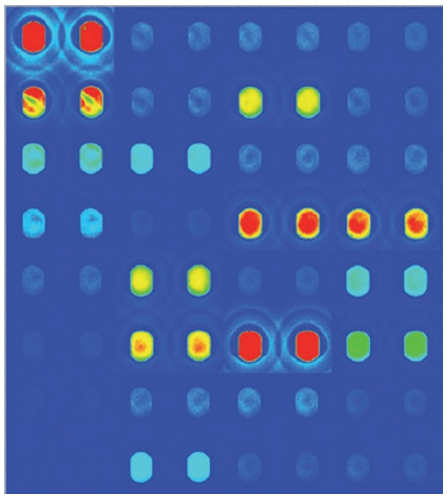
A biomarker can be anything that is reliably indicative of a biological state. This can include everything from a gene variant to a behaviour, but the term is generally used to refer to proteins or other molecules found in fluids such as blood or the CSF, or to physiological or anatomical changes that can be observed with techniques such as functional magnetic resonance ▶

imaging or positron-emission tomography. Much of the work on biomarker discovery has been done within large consortia. One of the biggest, the Alzheimer's Disease Neuroimaging Initiative (ADNI), is a public–private partnership with researchers at almost 60 institutions in the United States and Canada. It has core facilities at around ten institutions, each focusing on an aspect of defining the progression of Alzheimer's disease, such as radiological imaging, genetics or clinical assessment. In its first iteration, the ADNI ran from 2004 to 2010 with US$60 million in funding; it began its five-year second iteration this year, with the same amount of money. There are also ADNI projects in Europe and Japan, a related venture in Australia and others starting up around the world.

Such programmes hire early-career scientists and technicians. Leslie Shaw, co-director of the ADNI's biomarker core at the University of Pennsylvania in Philadelphia, says that his section needs staff to oversee the biofluid repository — labelling, identifying, storing and maintaining vast collections of samples and retrieving them for the many investigators who might use them. He is also looking for researchers to develop and run assays, work out conditions to confirm the assay results and standardize these with other ADNI labs. The people he hires don't have to be analytical chemists, "but they do have to be analytically focused", says Shaw. To capture changes that occur slowly over 10–20 years requires not only the most sensitive measurement tools, but also the ability to wield them wisely.

Data-analysis skills are in high demand across biomarker research. Increasingly, researchers are investigating panels of biomarkers rather than single proteins, and studies can involve hundreds or thousands of subjects, each with samples taken at several points over many years. Imaging work also produces massive amounts of data, and keeping track of all that information requires sophisticated programming and statistical skills. "We need more and more people who are able to handle large data sets," says Lovestone, noting that he is on the hunt for such people himself. "Bioinformatics, biostatistics, database handling — those are the most critical skills." David Holtzman, a neurologist at Washington University School of Medicine in St Louis, Missouri, who has been studying Alzheimer's disease biomarkers since the late 1990s, recalls a graduate student whose research compared several CSF proteins in patients with Alzheimer's and other dementias against those in healthy subjects. She needed to undertake a year's worth of statistics coursework to gain enough understanding to complete her dissertation. "She did not have — and nor did I — the background to do the analysis," says Holtzman. The experience convinced him that the next postdoc he hires should have such a background.

"It's an opportunity to investigate the disease mechanisms on a patient level."
Niklas Mattsson



There is a growing interest in assays such as this one of a biomarker for Alzheimer's disease.

L. YIN/S. O'BRYANT

Postdocs who want to launch their own labs in the Alzheimer's field would do well to include biomarkers in their scope. Neil Buckholtz, a neuroscientist at the US National Institute on Aging in Bethesda, Maryland, says that there isn't much dedicated funding for Alzheimer's disease biomarkers outside the multi-institutional projects, but he has seen more and more grant proposals that include them over the past five years. Shaw notes that if a scientist can find just one biomarker that accurately measures some aspect of the disease process, they could probably "make a career" out of understanding its molecular biology and how and why it is altered in the disease, and working out how, when and where to measure it.

INDUSTRIAL INTEREST

For industry, biomarkers are big business — large drug-makers hope to use them to get better clinical-trial results, and will pay smaller companies to design and run assays. According to BCC Research, a market-forecasting company in Wellesley, Massachusetts, the market for biomarkers of central-nervous-system diseases such as Alzheimer's is expected to grow to $3.2 billion in 2015 — up 17% from 2010. Biomarkers are gaining a crucial role in Alzheimer's drug development: although they were hardly on the radar six years ago, today the vast majority of the drug industry's Alzheimer's programmes use biomarkers to probe drug mechanisms or select patients for clinical trials, says Holly Soares, director of clinical neuroscience biomarkers at Bristol-Myers Squibb, a pharmaceutical company in Wallingford, Connecticut. But she adds that researchers shouldn't look to the drug industry for a job in biomarker discovery.

In today's climate of downsizing, "there are probably fewer opportunities than there were three or four years ago" — and Soares expects the decline to continue for a few more years yet. Pharmaceutical companies get much of their biomarker data through collaborations and licensing agreements with academic labs, core facilities or consortia such as ADNI and AddNeuroMed, or through contracts with smaller companies that specialize in identifying possible biomarkers and designing assays for detecting them. So far, there aren't many such companies, so opportunities are still slim, says Ralph McDade, strategic development officer at Myriad RBM in Austin, Texas, which designs and runs immunoassays for protein biomarkers of Alzheimer's and other diseases. But he thinks that will change as the regulatory climate for biomarker diagnostics becomes more accepting, and as researchers move beyond the few markers that are already well charted and start to explore molecules that require new assays. "Are new companies going to emerge? Absolutely, they will," says McDade.

FROM LAB TO THERAPY

One area of the industry that is hiring, notes Soares, is translational medicine, in which biomarkers are commonly used to help gauge the effectiveness and specificity of a drug candidate as it moves from bench to bedside. Vacancies exist at most pharmaceutical companies, and are generally open to people with MDs, PhDs and pharmacology doctorates, says Soares. Rather than generating biomarker data, these jobs are "more about strategy — how you use the biomarkers to make decisions".

A. HALLIN

Conducting translational-medicine research on biomarkers is a great way to stay in academia, says Sid O'Bryant, a neuropsychologist at the Texas Tech University Health Sciences Center in Lubbock, who runs the biomarker component of the Texas Alzheimer's Research Consortium. Funders are pouring significant money into translational projects, providing an opportunity for young scientists applying for grants.

"We think right now we're entering the golden age of biomarkers," says McDade. "Over the next 15–20 years, there's going to be some phenomenal things discovered in this area." But many researchers caution that the field is immature, and tools and methodologies are still being developed. Scientists must choose projects and labs carefully. "It's not a piece of cake — you don't just snap a couple of switches and turn on a couple of machines," says Shaw. "You have to know what you're doing, and you have to be in a highly experienced lab." ■

Alla Katsnelson *is a freelance writer based in Astoria, New York.*