CAREER DEVELOPMENT : ARTICLES

Judes Poirier (Courtesy of McGill Centre for Studies in Aging)

Walking the Pharmacogenomic Tightrope

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More than 4 million people suffer from Alzheimer's disease (AD) in North America, and the numbers are growing quickly as the population ages. Unfortunately, today's drugs can only stabilize some of the symptoms, and not for very long. That's why some AD researchers are turning to pharmacogenomics: the study of how genes influence the way we respond to drugs. Tailoring drugs to the patients' genetic profiles, they believe, may be the key to developing novel drugs that will lead to earlier treatment and slow or even stop clinical advances of the degenerative brain disorder. Developing those drugs will require the resources of pharmaceutical companies as well as academia. As director of McGill University's Centre for Studies in Aging, Judes Poirier has been learning not only how to apply human genetics to AD drug development but also how to communicate and collaborate with companies.

"What most pharma look to me for is my 10 years of experience in pharmacogenomic clinical drug trial design and result interpretation," says Judes Poirier, director of McGill University's Centre for Studies in Aging.

Discovery

At age 45, Poirier has earned an international reputation and won awards for his pharmacogenomic approach to AD. In 1993, Poirier and his Montreal-based team co-discovered an important genetic risk factor involved in the most common form of the disease: a defective gene, called *Apolipoprotein E type 4* (*ApoE4*), that prevents the normal transport of cholesterol and phospholipids to the brain. Since then, he has shown that *ApoE4* interferes with drug responsiveness in AD sufferers. The cholesterol normally carried in the blood and central nervous system by the apolipoprotein is vital for regeneration of neural synapses in the brain. Without it, protein deposits spread and eat away at the brain, affecting mental capacity and behavior and eventually leading to death. "*ApoE4* has become *the* genetic factor in Alzheimer disease and is found in about 50% of all cases, so we're talking about a fairly large risk factor in large populations," says Poirier.

Now Poirier is collaborating with large pharmaceutical companies and small biotech firms that are developing and manufacturing memory-enhancing drugs. As a member of their scientific advisory boards, he helps the study directors design the pharmacogenomic portion of new clinical drug trials. He also analyzes the pharmacogenomic data and their potential impact on drug approval and commercial sales.

AD patients with different genotypes respond differently to those drugs, he has found. Poirier initially approached Parke Davis--the first company to sell an Alzheimer drug--and suggested to them that patients who don't respond to their drugs might carry the wrong genetic profile. After hearing about his work, several other companies, including Pfizer, Bayer, and Eli Lily, decided to examine the effects of different genetic variants on the efficacy and safety of drugs

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they had in development. Some companies noticed that the faulty *ApoE4* gene directly impacted the effectiveness of the drugs they studied.

Poirier hopes that with further funding and support, his studies will lead to the development of drugs targeted to specific genotypes, making them safer and more effective and reducing side effects. He envisions delaying the onset of the disease by as much as 5 years, cutting the number of cases by half.

A balancing act

For Poirier, keeping a foot in both university and industry has proven to be a tricky balancing act, but a necessary one. Academics need companies to supply the drugs, extensive patient populations, and their associated DNA samples--and sometimes funding--for a study. In exchange, companies get to draw on the unique experience and expertise of researchers such as Poirier.

However, he says, pharmaceutical giants often have their own agendas and sometimes offer less scientific freedom than do universities. From the very first collaborations with companies doing pharmacogenomic analyses on new drugs, he has had to abide by strict agreements of confidentiality. "I could not discuss my results anywhere, except internally," he says. Some of his most exciting work is still embargoed, but he feels that the chance to "move the field forward" has been worth the restrictions.

Such collaboration makes sense to Michael Phillips, scientific director of Genome Quebec Pharmacogenomics Centre and the Montreal Heart Institute, who has worked for both industry giants and universities. Academic researchers have to keep in mind that the goal of companies is to make money, he points out. "If I build a set of genotyping assays and it turns out that it doesn't work, I can probably still publish it in academia. But a company can't afford to do that. If a company invests in it and develops it, they will need to sell it."

"Usually when pharmaceutical companies reach outside their own quarters for science talent, there needs to be something unique about the individual: For example, they need to bring with them special techniques, expertise, or sometimes patient populations," Phillips adds.

In Poirier's case, his multidisciplinary approach to the understanding of the etiology of neurodegenerative diseases gives him an edge. Trained as a biochemist with a strong organic chemistry background, he has done a Ph.D. in neurotoxicology and a postdoctoral fellowship in genetics. He is comfortable discussing medicinal chemistry, toxicology, drug safety and response, and, of course, genetics.

"What most pharma look to me for is my 10 years of experience in pharmacogenomic clinical drug trial design and result interpretation," he explains. He knows a lot of confidential information about pharmacogenomic drug trials from a number of pharmaceutical companies, and although he cannot talk about it, it shapes his formal recommendations. For example, he understands the way several genetic risk factors affect how quickly dementia progresses in patients taking placebos in clinical trials. "Improper randomization of patients who are fast decliners because of their genetic background could literally compromise a $30 million Alzheimer trial," he says.

Although academia may not have the money and testing capabilities to bring ideas to market that a large company might, it does offer something priceless: scientific credibility. That's very attractive to industry. "Building up your own independent research program with full-blown funding at a university is the best way to build your credentials with the pharmaceutical companies that you will want to collaborate with," he says.

Being based out of university has been beneficial for Poirier. It means that companies don't consider him a threat, as they would if he worked for a single competitor. "I've been contacted by many pharmaceutical companies to do pharmacogenetic profiling--not only for *ApoE4* but for a whole series of genes that we have identified as potential candidates on the basis of their biology," he says. Those genes might influence how patients respond to drugs, or what side effects they experience. Studying how genes affect different drugs manufactured by different companies gives Poirier greater influence on future drug development, he feels, which would not be possible if he was employed at any one pharmaceutical research lab.

Working with the pharma and biotech industries, Poirier focuses on both performing the genetic tests in his laboratory and designing the clinical drug trials. A decade ago, he was testing only for the presence of the defective *ApoE4* gene. Now he looks at a whole range of possible genetic markers for the disease, in every patient taking part in every AD drug trial.

Guidance

Poirier credits much of his success to lessons learned from his Ph.D and postdoc supervisors in the late 1980s and early '90s. As a graduate student, he says, "I wrote to the 10 best guys in aging research, and I asked them where's the field going and what's going to be the science in 10 years." Much to his surprise, four of them replied. All four had the same advice: The baby boomer generation will likely make the health care system collapse, they told him, and unless science and society pay more attention to age-dependent diseases such as AD, they will bankrupt the health care system. That advice, and the advisers who gave it, helped shape his career.

He chose one of the scientists who replied, Caleb Finch at the University of Southern California in Los Angeles, as his postdoc supervisor. "The way I figured it, if this person took the time to reply, he would be a damn good supervisor, because he cared," Poirier says. He took the time to question Finch about the future directions of science and the ins and outs of working with companies. Finch explained to him the difference in mindsets between the research-and-development teams and the marketing groups at pharmaceutical companies. For Poirier, the key message was that R&D groups have a mandate of innovation and discovery, whereas the marketing division's mandate is to do what is necessary to sell the drug and provide profits for the company shareholders.

He considers these discussions invaluable to his career. "He later told me that I was the only one asking these kinds of questions. The others in the lab were more concerned with how much money they could make and what they could hope for in terms of teaching," says Poirier.

"I've been trained to think big, never quit, and make things happen--and that's what I've been striving to do my whole career," he says. Collaborating with industry is part of that. "There are always compromises that you'll have to make, but as long as you don't plan on being rich and famous, and you believe in what you're doing, then go for it."

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