



## A gift from the ancestors

Gene-based drug therapy has the potential to revolutionize health care. As researchers try to pinpoint the genes, pathways and biomarkers associated with common hereditary diseases, interest by pharmaceutical companies in their work is growing fast.

BY THE GAZETTE (MONTREAL) MARCH 29, 2008

Gene-based drug therapy has the potential to revolutionize health care. As researchers try to pinpoint the genes, pathways and biomarkers associated with common hereditary diseases, interest by pharmaceutical companies in their work is growing fast.

But for many companies and investors in this complex field, success has been hard to achieve.

Montreal-based Genizon BioSciences Inc. is trying to change that story and help usher in a new era in medicine.

On any given day at its St. Laurent labs, researchers hunt for genetic clues to a range of diseases including psoriasis, schizophrenia, Crohn's disease, rheumatoid arthritis, Alzheimer's disease, hyperactivity attention deficit disorder and coronary heart disease.

A mutation in a person's genetic code produces a susceptibility to a disease. The hope is that once those genetic triggers have been identified, drug treatments can be developed to target them.

Genizon is not in the drug development business itself. But its research findings could one day lay the groundwork for a blockbuster drug at a pharmaceutical company that purchases rights to its discoveries.

With 130 scientists and information technology specialists, including 26 with doctorates, the privately-held company has received more than \$130 million in funding since 1999, including \$100 million in venture capital.

Genizon's story is an exciting one for the company's investors, who believe it can succeed where others have failed.

"There have been quite a few companies like ours over the past 10 or 15 years," says chief executive officer Dr. John Hooper in an interview. "Most of those failed."

"The reason was that the technology to do what we're doing wasn't available to them," he says. "They were too early."

The result is that Genizon is virtually alone in the world, although Hooper notes that a company in Iceland does "something like we do."

Joe Nadeau, a genetics professor at Case Western Reserve University who has served on Genizon's scientific advisory board, says "there are only a handful (of companies or academic institutions) in the world that are doing anything like what Genizon is doing on the same scale."

What makes it unique is not just the proprietary technology and computer algorithms it uses to scan and analyze the human genome. More important is that the company is located in probably the world's best place for such detective work.

The Quebec founder population of 6 million people is descended from a group of just 2,300 French settlers who arrived in the

17th and early 18th centuries.

This relatively homogeneous population is a genetic researcher's dream, Hooper says.

sss

Genizon started up in 1999 after several scientists decided to leave Montreal's Algene Biotechnologies to form their own firm. They asked Hooper, then retired, to help them with a business plan.

"I got very excited by what they were doing, it seemed really novel. I was in retirement for about a week," he recalled, before agreeing to come on board as CEO.

Hooper's own track record is a highly successful one. He built Montreal's Phoenix International Life Sciences into a major player in contract research before it was sold to MDS Inc. for \$500 million in 2000.

He wasted little time in reorienting Genizon. At the time, the company was concentrating on research into two diseases, but Hooper worried that if one of those two research efforts were to fail, half the business would be gone.

"Let's target a lot of diseases," he decided, "and we'll figure out a way to do it."

The challenge was to collect DNA in a methodical and rational way, allowing researchers to compare those suffering from a given disease with a control group.

At the end of 2003, Genizon hooked up with a California company that had developed technology to scan all of the three billion letters in the human genetic code.

"We combined with those guys to do that kind of thing on Crohn's disease," Hooper said. "We found a very large number of genes for two reasons: one, we had access to the technology, and two, we were using a population that has special genetic characteristics."

Quebecers aren't any different from anyone else in the world in terms of the genes they carry, he explains. It's just that they carry fewer varieties of them.

"That really simplifies the process of identifying which of those varieties is involved in diseases." Clearer signals can be detected because there's less genetic "noise" in the Quebec population.

The company is collecting information on 27 diseases in some 48,000 DNA samples from French Quebecers who have agreed through their family doctors to co-operate with the research effort. It is the most extensive genetic sampling of its kind in the world, he says.

Although about 15,000 people from France originally settled in Quebec, two-thirds eventually went back home, either because they were homesick, couldn't adapt to the climate or were tired of battling Indians. The British conquest of New France in 1759 closed the door on new arrivals.

Of the 5,000 who were left, some didn't have children, and others had birth lines that died out later on, with the result that only about 2,300 are represented in today's population.

For example, Pierre and Anne Tremblay married in 1657. There are now 280,000 descendants from that couple in North America (including the mayor of Montreal).

"Since there's been a limited number of people coming in, there's not much variety in the genes," Hooper says.

"This is a very unusual population -- the only other population like this is in Iceland

"It's not that they are inbred - they are no more so than you or me. But there's much less variety in the number of mutations."

Nadeau of Case Western Reserve calls it the "Goldilocks" phenomenon. "Some populations are too young or too old, some are too big or too small. But, for researchers, Quebec's population is just right.

"You want this balance of size and age."

In common diseases, no one gene is the cause - there could be 20 or 30 genes involved, and a person doesn't have to have all of them to fall sick. There are also environmental and lifestyle issues which may affect whether one gets ill or not.

"It's a complicated situation," Hooper says, "and it makes it much more difficult to find genes." That makes the Quebec population all the more valuable.

sss

The business plan at Genizon is simple enough: find interactions between genes and then license the therapeutic or diagnostic rights to drug companies. Indeed, the company has concluded two such deals already, with Genentech and Pfizer.

But despite mounting excitement over what it's been discovering, Genizon is a long way from break-even and has not found it easy to raise financing.

One reason is that it came along at a tough time - just before the biotech bubble began to burst in 2000. Over the past few years, Hooper went cap in hand to many investors and venture capitalists in the U.S. and Canada, but all of them had been burned so badly by the biotech crash that they didn't want to give him the time of day.

Europe, however, has proved to be more fruitful. The European venture capital industry has a better understanding of biotechnology and is more patient than its American counterpart, he says.

Hooper convinced Swiss, Finnish and Swedish investors to come aboard. Genizon also hooked up with a Dutch venture capital firm, BTF B.V. of Haarlem.

The Netherlands fund, which focuses on late stage investment opportunities, made an initial \$5 million investment in 2001, then stepped up with a major commitment in January, acting as lead investor in a \$31 million financing.

Jan Mellegers, chief executive officer of BTF, says Genizon makes "a compelling investment case" because of an "outstanding DNA platform" that is applicable to many stages of drug development.

"We had a basic belief that the Quebec founder population was the only suitable one to do this kind of genetic research," Mellegers said in an interview.

Now that Genizon has developed several gene maps for different diseases, "all the development risk is over," he said.

The product has come at the right time, Mellegers believes, because "every pharma company is falling off a cliff. In general, they see half their revenues disappearing in the next four years" as drugs come off patent.

"They're in the worst R&D crisis ever. They can't possibly fill their pipeline with the amount of drugs they're losing."

One way to address the problem, he says, is to integrate genetics into the process. The U.S. Food and Drug Administration is now insisting on drug development that comes with a more accurate diagnostic picture of how patients will be affected.

"If you can't match your future drug with a suitable patient group, you'll have a very hard time getting those drugs approved."

sss

In the last few years, several academic institutions have begun to do the same kind of analysis as Genizon, using large numbers of DNA samples. They have found a number of genes associated with diseases.

But they haven't had much luck in discovering how those genes work together so that drugs and diagnostics can be developed. That's Genizon's advantage, says Hooper: its ability to use sophisticated computer software and algorithms to interpret the four billion DNA analyses it generates each month.

The impact will be substantial, he predicts. "If we detect the disease early, we can treat it much better than we do now."

On average, drugs affect only 60 per cent of the population; the other 40 per cent don't really benefit too much.

This adds a new challenge: finding out if people are genetically predisposed to certain drugs, and why.

It also sets the bar higher: to develop new treatments that respond to a larger proportion of the population.

This has to happen, he believes, because the cost of new drug development has begun to exceed the ability to get the money back.

The number of new drugs being approved in the U.S. has been dropping steadily, with little prospect for new drugs that are revolutionary. The main reason is that all the easy discoveries have been made.

"Now we need to know much more about the fundamentals of the disease to address it patient by patient," Hooper says. "If we give a breast-cancer drug tailored to a particular gene only to women who have that gene, the success rate will be very high."

This can allow for what is being called personalized medicine - a treatment tailored on an almost individual basis. "You genetically profile people and you choose the best drugs to operate on them."

Personalized medicine will produce a more assured market, he says, because "what drug companies really want is that they treat someone with a drug and the person stays on that drug, not that they go off it in 6 months."

All of this has the promise to dramatically alter the course of medicine.

But Nadeau of Case Western Reserve cautions that there are many obstacles to overcome. Just because research has identified

a gene doesn't necessarily mean that the gene is "druggable" or that the right molecule can be developed with efficacy and safety.

Some of Genizon's strategies will accelerate that process, Nadeau says, "but it's still a long road."

And while the ideal strategy for the investor group might be to take the company public, Mellegers of BTF isn't pushing that option.

Investors in public markets don't understand the science, he says, and don't have the patience to wait for the eventual payoff - something he believes will come one day.

phadekel@videotron.ca

Quebec has almost ideal founder population

Founder Estimated number Estimated number Current

population of generations of founders population

Ideal 10-20 200-5,000 > 1 million

Quebec 12-16 -2,600 > 6 million

Costa Rica -12 -4,000 2.5 million

Finland (northeast) 12-20 200-400 1 million

Ashkenazi Jews -30 -1,500 10 million

Sardinia -400 -500 1.6 million

Newfoundland -16 -25,000 500,000

Iceland 15-40 -20,000 280,000

Mormons 7 -43,000 1.6 million

A founder population is a group of people who are all descended from a limited number of common ancestors and who have been isolated from intermarriage with outside groups for several generations.

Such populations may have high levels of genetic homogeneity making it possible to detect the presence of specific disease genes. Because of its relatively young age, limited numbers of founders, and very large current size, the Quebec Founder Population is one of the best populations in the world for use in gene mapping.

source: Genizon

© (c) CanWest MediaWorks Publications Inc.