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By Karen Hopkin

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**BIOBUSINESS**

## From Buckets of Banana Mash

Genizon CSO Tim Keith's cautious but rigorous approach has made it possible for companies to separate real data from noise.

In the late 1990s, Tim Keith was the leader of a team at a company called Genome Therapeutics that discovered *ADAM33*, the first gene to be associated with asthma. The milestone paper, published in *Nature* in 2002, "is probably one of the most widely cited papers in the asthma field," says Stephen Holgate of the University of Southampton, who supplied DNA samples collected from families in the United Kingdom. Although no drugs have yet emerged from the pipeline, Schering Plough (Genome Therapeutics' corporate partner in the *ADAM33* discovery) has been working on turning the findings into novel therapies for the treatment and prevention of the disease.

Keith's career commenced far afield from human genetics, however: It started with flies. And not just any flies; she used *Drosophila pseudoobscura*. As a graduate student in Richard Lewontin's lab at Harvard in the early 1980's, Keith wanted to study how evolutionary forces contribute to genetic variation in fruit fly populations. "Clearly you can't do that if you're using laboratory populations," she says. "So I went out into the field and collected my own flies." But New England dumpsters were home to the more common *D. melanogaster*. Keith was looking for populations that were more isolated, more natural, and more wild. "So I went out to California and collected two different populations of fruit flies," says Keith. "One from the San Jacinto Mountains, way up in elevation in the middle of nowhere. The other from a small vineyard called Gundlach Bundschu. It was a wonderful place, with wonderful wine, too," she recalls.

She collected the flies "by going out at dusk and putting out buckets full of fermenting banana mash," says Keith. "It's actually quite phenomenal. You're there in the middle of the woods, in the middle of nowhere, and there's not a fly to be seen." Bring out the fermenting banana mash and - *viola* - instant doctoral thesis fodder. Back at Harvard, Keith examined the frequency and number of variants in two enzymes, esterase-5 and xanthine dehydrogenase, in each population. Comparing the distribution of variations within and between the two populations, she concluded that both enzymes had been subject to purifying selection.



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**Keith is a great facilitator, which Robert Spadafora considers**

unique.

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## From Flies to Humans

Although she "learned a tremendous amount" from her work with flies, Keith says the project was "a bit esoteric. So I was struggling to decide whether to continue working in strict population genetics in *Drosophila*, or whether to branch out into something that could have, well, more practical relevance." Then in 1986 she found Collaborative Research, a small biotech company in Waltham, Mass., that had been established to produce and sell oligos to the academic community. But its scientific advisory board - which included David Botstein, Ron Davis, Gerald Fink, and David Baltimore - pushed to "bring the company into the modern age," recalls Helen Donis-Keller of the Franklin W. Olin College of Engineering, who became Collaborative's director of human genetics. In particular, the group was keen on developing a genetic linkage map of the human genome, and using that map to identify disease genes.

"For me the choice was clear," says Keith. "Here was a wonderful opportunity to translate everything I loved about genetics into something that could have an impact on human health." And for Keith, the transition to industry was almost seamless. At Collaborative, many of her projects received National Institutes of Health funding, she continued to work with academics, and the environment was a familiar one. "Our little laboratory was separate from what we called 'world headquarters' where all the administrators and corporate types worked," says Donis-Keller. "We had a little picnic table in the back and a basketball court. The atmosphere was pretty academic."

The large-scale mapping project, which was backed by \$20 million from venture capitalists, "took a lot of time and a huge amount of effort," says Donis-Keller. "We had 400-some odd markers. We had to establish their order and then tie them back to their chromosomes by physical hybridization." But the efforts paid off, and by 1987 the team had produced the first genetic linkage map of the entire human genome, a result that garnered Collaborative a *Cell* paper, a front page story in the *New York Times*, and "the ire of the academic community, who thought that they, and only they, should be doing things like this," laughs Donis-Keller, "and Tim was a really vital part of that effort." Collaborative eventually sold its RFLP probes to academics and other companies interested in using them to locate their own favorite genes.

In addition to her intelligence and her analytical mind, says Donis-Keller, Keith contributed a buoyancy that helped the team stay afloat through "the ups and downs at Collaborative, of which there were many." Financial difficulties and "a revolving door of CEOs and CFOs," she says, "meant we were always in danger of being shut down. We just tried to keep our heads down and do our scientific work. But there was always this threat hanging over our heads that we weren't going to be able to finish this project or that one." Keith "always maintained her equilibrium," Donis-Keller says. "She remained upbeat and would reassure everyone that whatever happened, we'd just deal with it. She was someone you could count on."

"I remember her being day in, day out, the most reliable experimenter in that group, except maybe for Helen," says David Botstein, now at Princeton.

## Listening to Academic Allies

In 1994, Collaborative Research morphed into Genome Therapeutics as the company became more commercial, forming alliances with pharmaceutical companies to translate its

discoveries into potential therapeutics and also developing and marketing diagnostics, such as genetic tests for cystic fibrosis and polycystic kidney disease. At the time, the company had about 80 employees, 70 of whom were scientists, and most of its revenue came from government grants.

Keith took on more responsibilities, heading up projects designed to deconstruct the genetic underpinnings of a handful of heritable conditions, such as bipolar affective disorder, asthma, and a rare condition resulting in high bone mass (essentially the opposite of osteoporosis). For each of these projects, Keith and her team established the platforms that covered everything from "how to get DNA from the patients to pumping the resulting information through the 'machine' to ultimately get the gene," says Robert Spadafora of Oscient Pharmaceuticals, the company that Genome Therapeutics became when it merged with GeneSoft Pharmaceuticals three years ago. Keith also helped form the alliances with the pharma companies - Schering Plough for asthma and Wyeth for osteoporosis - that would bring the findings closer to the clinic.



Tim Keith with H el ene Fournier, Director, Genotyping Laboratory at Genizon.

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Holgate recalls that Keith's penchant for really listening and engaging in scientific debate helped them put together a protocol that has stood the test of time. Asthma is a highly heterogeneous condition that often includes a smorgasbord of symptoms, from bronchial hypersensitivity to allergy-induced wheezing. So the group had to "filter out some robust subphenotypes that captured the aspects of asthma you could use in genetic analyses."

The careful definition of the disorder allowed the researchers to capture and present their data in a format that could be fed into the databases and run through the statistical analyses that would then finger the polymorphism that would lead them to the gene.

As part of her duties at Genome Therapeutics, Keith helped to establish and maintain key alliances with academic researchers, such as Holgate, who provided pedigrees and DNA samples collected from families affected by the condition in question, and also with the drug companies interested in turning the discoveries into marketable therapeutics. Keith performed that balancing act with grace and with ease.

"With the academic groups, you have to say, 'This is your baby. I know you've raised him 'til he's one. Now we've got him. But don't worry, we'll take good care of him'," Spadafora says. "It can be difficult for academics to let go. But Tim had a way of dealing with those issues, and with letting her academic collaborators know that she would convince the pharmaceutical company to publish when the time is right. And on the pharmaceutical side, they're results-driven. They have milestones. And Tim always hit her milestones. Not to mention, Tim had great respect," within her lab and in the larger community, he adds.

"When Tim spoke, people listened," says Bob Egan of Millennium Pharmaceuticals, who was with Schering Plough when Keith and her team partnered with that company in their search for asthma genes.

### The Move to Genizon

All those strengths made Keith a great recruit for **Genizon BioSciences**, the Montreal-based company for which she is now chief scientific officer. Established in 1999, the company's mission is to use genome-wide association studies to

search for the genes involved in complex common diseases. Since then, Genizon has raised more than CDN \$83 million and signed two licensing agreements, with Genentech and Pfizer, covering discoveries in four disease programs.

In 2004, Oscient shifted its business strategy to commercializing its first product, a drug called gemifloxacin, which the company now markets in addition to another compound called fenofibrate to the tune of \$46 million in revenues in 2006. With its focus on sales, Oscient phased out its genomics R&D program, and Keith moved to Genizon along with three other members of her team.

"For us Genizon was a very exciting home," she says. "People had been wanting to do genome-wide association studies for years, but the resources just weren't there to do it." Over the past five years, says Keith, the completion of the human genome sequence, the identification of large numbers of polymorphisms by the SNP consortium, and the generation of a comprehensive map of these SNPs by the International HapMap project have made such association studies technically feasible from the standpoint of analyzing the DNA.

The only hurdle left was to find the raw material: a population that's genetically homogenous enough to allow disease-associated variations to rise above the background noise of neutral genetic change. The company has access to the French-Canadian population of Quebec, founded by some 2,600 hardy individuals who first settled along the St. Lawrence River in 1608. These Catholic settlers had large families (an average of 36 children and grandchildren per household), and the population expanded 80-fold in 300 years.

To date the Genizon team has completed eight genome-wide association studies for conditions ranging from asthma to Attention Deficit Hyperactive Disorder (ADHD). At an average of 350,000 SNPs per patient, and more than 1,000 patients and controls per study, that's a lot of data to crunch, but looking at data and thinking through the implications are among Keith's strengths. "She doesn't jump to conclusions," says Genizon CEO John Hooper.

In one study, he says, "When the data for the first chromosome came rolling off, we found a large number of hits, an abnormally large number of hits. It didn't make sense. We know that common diseases are complex, but they can't be that complex, otherwise everybody would have them." Keith pored over the possibilities and discovered that in a population where everyone's related, some people are more related than others. It turned out that among the controls was a surplus of people whose grandparents all hailed from the same small region of Quebec. When the researchers eliminated this imbalance, says Hooper, "we got meaningful data, and most of the hits we got are indeed signals for disease genes," a result he attributes to Keith's scientific rigor.

Although the identity of these genes is not yet public, Genizon last year formed a partnership with Genentech to develop therapeutics based on its whole-genome association study of Crohn disease, and in January announced a partnership with Pfizer to develop diagnostics based on its studies of ADHD, Alzheimer disease, and endometriosis.

Caution can be key when dealing with potential pharma partners, says Caroline Fortier, Genizon's vice president of corporate development. "They know we only present data that we know are valid," she says. "That for us is very, very important because it can mean the difference between them doing the deal with us or not." Keith adds strength to that hand. "She's a scientist who's got a business sense, so that's very good," says Fortier.

As for Keith, she just loves the science. "While I do a lot of things that promote the business, and I enjoy doing them, the driving force for me is the science," she says. "It's finding new disease genes that will hopefully make a difference in human health."