Three researchers developing therapies based on RNA interference talk about their experiences leaving academia for biotech companies.

Tales of Transition to Tech

By Laura Bonetta

In the late 1990s, Sam Reich grew frustrated with the obstacles that he encountered in trying to deliver therapeutic molecules using viral vectors. As a graduate student in a gene therapy lab at the University of Pennsylvania, Philadelphia, PA, he turned his attention to a budding area of science, RNA interference (RNAi).

At the time, most experiments using RNAi had been done in invertebrates, but Reich, who was working in the department of ophthalmology, showed that RNAi could effectively knockdown the expression genes in the mammalian eye. A chance meeting with colleague Michael Tolentino, also at Penn, presented a way to apply this technology to therapy. Tolentino had discovered that hyperactivation of a protein, vascular endothelial growth factor (VEGF), was involved in age-related macular degeneration (AMD), the leading cause of blindness among aging individuals. This protein contributes to the growth of abnormal blood vessels in the eye, which start to leak and dim central vision. Tolentino was looking for a way

to inhibit VEGF, and the RNAi technology developed by Reich provided an ideal candidate. Reich licensed the technology from the university, and Acuity Pharmaceuticals of Philadelphia was created in 2002. Now, only 5 years later, the company is poised to bring the first RNAi-based therapeutic to market.

Many diseases, like AMD and cancer, involve the increased expression of particular genes, and short interfering RNAs (siRNA) can specifically inhibit the expression of these harmful genes and provide a therapeutic benefit. "As a class of drugs, siRNAs are comparable to monoclonal antibodies, although they have a different effect," says Reich. Like Reich, Jeremy Heidel of Calando Pharmaceuticals in Pasadena, CA, and Jim McSwiggen of Nastech Pharmaceutical Company in Bothell, WA, left stellar research programs in academia to pursue the therapeutic potential of these molecules.

An Agonizing Decision

Reich's decision to move from academia to industry was a particularly difficult one. He had not yet completed his Ph.D. thesis, and joining Acuity would mean not getting his degree. "I spent a lot of sleepless nights agonizing over the decision," he recalls. But in the end, he decided to follow his research. "The VEGF program was moving so much faster than my Ph.D. would have. It had taken a life of its own, and I decided to stay with it to maintain the momentum," he explains. "The research was more important to me than a title."

Reich became Acuity's executive director for research and development and started to put together a team of "top-notch individuals" to deal with the various aspects of bringing a product to market. The new role did not come easily, but it was something he looked forward to doing from the start.

Sam Reich

"Taking really exciting basic research and then trying to figure out how to make a product based on it presented a whole new list of questions and problems that needed to be solved and that you never think about in the lab, such as applying for patents, fundraising, and human resources. It was exciting to me," he recalls. "I really enjoy being at junction of business and science."

To learn the business side of things, Reich relied on his own intuition as well as the expertise of others at Acuity, such as the chief executive, Dale Pfof, who had joined the company in its earliest days. "Dale replaced my Ph.D. advisor in a way," says Reich. According to Reich, obtaining and maintaining the necessary funds for the different programs in a changing market and economy makes up one of the more challenging aspects of managing a biotech start-up. "So far, we have been successful in staying on track and maintaining momentum," says Reich. "But it can also be a distraction."

The Team Approach

The diversity of roles and challenges faced by researchers working in start-up companies is what persuaded Jeremy Heidel to join Calando Pharmaceuticals in 2005. Having completed a successful Ph.D. thesis, he had several career options to pursue, but the idea of working for a start-up biotech company was particularly appealing to him. "Each of the professors I worked with had founded their own companies, and I had worked in one of them for a couple of summers as a student. The experience gave me a sense for what life might be like," he explains.

Heidel liked the excitement among the people working at these companies and the fact that the roles of employees were not precisely defined. “A lot of start-ups begin lean and mean; there is rarely an excess of manpower. As a consequence, every employee has to be able to adapt,” he says. “If we don’t have someone with a particular expertise, you have to step up to the plate and learn what needs to be done.”

Heidel was a graduate student at the California Institute of Technology, Pasadena, CA, in the lab of Mark Davis, when they developed a system for the systemic delivery of siRNAs and validated it in a mouse cancer model. In an earlier study, Heidel showed that synthetic RNA molecules alone don’t trigger an immune response. But the

Jeremy Heidel

scientists needed a delivery system to protect native RNA from degradation and to bring it to its target tissue or cell. Heidel’s work laid the foundation for Calando. The company is now preparing to bring its first therapeutic siRNA-containing formulation into phase I clinical trials by the end of 2007. This formulation aims at the M2 subunit of ribonucleotide reductase, a well-established cancer target.

In August 2006, Calando appointed Heidel as chief scientific officer and vice-president of research and development. “I have taken on a more managerial role. Instead of doing experiments myself, I help coordinate the work of our scientists,” says Heidel, adding that his role is probably similar to that of a principal investigator in an academic lab. But unlike an academic lab, his group has to stay focused on a particular end point, on meeting time lines and budgets, and the objectives that the company set out to meet. “Not that these goals are not important in an academic lab,” explains Heidel, “But they are perhaps more flexible in that environment.”

For Heidel, who joined the company straight out of graduate school, overseeing Calando’s scientific team presented a steep learning curve, but he welcomed the challenge. “I like the variety of tasks and the variety of people I get to interact with—other members of the management team, numerous consultants who give me valuable advice, people working for manufacturing and methods development, and scientists I meet at conferences or those working at other companies focused on RNAi,” he says. “No two days are the same for me.” But he admits missing bench work. “I enjoy working with my hands and generating data. But there are only so many hours in a day,” says Heidel.

A Start-Up in a Big Company

Jim McSwiggen found a way to continue doing bench work. As a bioinformatician, that translates to computer work. After completing his graduate studies at the University of Oregon, Eugene, OR, McSwiggen joined the laboratory of Nobel laureate Thomas Cech, then at the University of Colorado at Boulder, where he studied ribozymes, which are RNA molecules capable of catalyzing chemical reactions. In 1992, he took a job with Ribozyme Pharmaceuticals Inc. (RPI), Boulder, CO, a company that later became Sirna Therapeutics, San Francisco, CA. His decision to take a job in industry was “not a totally logical decision,” he says. “I had an offer from RPI, and what they were doing sounded interesting. I thought that I could always go back to academia if I did not like it.” The decision was not a particularly difficult one, but something that “I questioned many times after,” he recalls.

Jim McSwiggen

After spending 13 years at RPI and Sirna Therapeutics, McSwiggen needed a change. “It was starting to feel stale,” he says. That is when an interesting opportunity emerged. Natestch Pharmaceutical Company, Bothell, WA, an established biotechnology company that had a solid foundation in nasal drug delivery, decided to develop a new research group for RNAi-based therapeutics. McSwiggen was asked to lead one of the four teams in this group. “In a way, it gave me an opportunity to be in a small start-up within a large company,” says McSwiggen. “The company consists of 200 people and has been around for 30 years, but the research group is 35–40 people in size and only a couple of years old.” He joined Natestch in the spring of 2006.

McSwiggen’s in vitro testing program, which he started forming 9 months ago, now comprises more than half a dozen people, a mix of Ph.D. scientists and research associates. Having built his team, McSwiggen says he is eager to get his “hands dirty” and start doing science. As the only bioinformatics expert in the group, he will be responsible for analyzing sequence data. “I would not want it any other way. I would not enjoy just telling others how to get things done,” he explains. (continued to page 16)

Start-Up Drive

Welcome to
the Office Park

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When he is not at the computer writing documents or gathering data, McSwiggen is meeting other members of the company, from the CEO—to keep him informed about progress—to other scientists in his group—to hear about their work—to the legal team—to discuss patent applications. “The variety is definitely what I enjoy most. Although it is nice some days, if I come in on a weekend, to spend an entire day doing one thing,” he laughs.

Because the RNAi research group is new, McSwiggen says that they have to “run fast to get ahead of the competition. But the company already has a delivery technology that works for other purposes and experience in developing products.”

Blurring the Lines

While there is no denying that academic and industrial environments differ in many respects, scientists who have experienced both worlds say they are more similar than outsiders might think. “Research and discovery are very similar. They involve open-minded, smart people who are excited about science,” says Reich. “In industry, there is less pressure to publish, and there is probably a focus on answering slightly different questions. We also impose stricter quality control and quality assurance.”

Nonetheless, moving to a company might not be the right choice for everyone. “Academic research is more often focused on telling the whole story. Because a company has to develop a product or intellectual property, sometimes you have to move forward based on incomplete information. Sometimes that means having to set interesting question aside,” explains McSwiggen. “The compensation is that we get to work collaboratively with our colleagues and know that we are making a product that will improve human health.”

A recurring theme among researchers in biotech companies is that their work and achievements depend on a team effort. Entire research programs might be focused on the single goal of bringing a product to market. “Here, it is a more focused effort. So employees have to share materials and information,” says Heidel. “We definitely want to recruit people who are ambitious and motivated to do good science, but not necessarily seeking individual fame. If we are successful, it leads to the advancement of the company as a whole.”

In the past decade, RNAi has shot into superstardom. It is rare to pick up a scientific journal and not find among its pages a study that uses siRNAs to knockout a gene and measure its effects. Despite the popularity of siRNAs in basic research, only a handful of companies are trying to make drugs from these molecules. But those who saw the potential of this technology early on are now starting to reap the benefits. “I made the right decision,” says Reich. “I had to make a trade-off early, but now I will be involved in bringing the first siRNA to people and will see patients benefit from it. It is very satisfying.”

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