REPRINTED FROM
FEBRUARY 2007
VOL. 21 | NO. 2
WWW.THE-SCIENTIST.COM

TheScientist
MAGAZINE OF THE LIFE SCIENCES

BioBusiness

Trends in the pharma, biotech, and life sciences industries

PHOTOS © JOHN SOARES

Cracking the Biotech Code

Genzyme CSO Alan Smith discovered the initiation codon and mapped out SV40, then started himself on a career in biotech.

By Keith O'Brien

Alan Smith grew up in southern England thinking he wanted to go into astronomy. But once at Christ's College in Cambridge, Smith realized that the required physics courses bored him. He switched his focus to biochemistry, a rapidly evolving field, and earned his bachelor's degree in 1967. He then set out to earn his PhD at the prestigious MRC Laboratory of Molecular Biology (LMB).

"The structure of DNA had only been known for 12 years at that point," recalls Smith, now 61 and chief scientific officer at Cambridge, Mass.-based Genzyme. "Protein synthesis – how it happened – was only beginning to be sorted out. And the people who were doing it were right there."

Smith says he was more than a little star-struck to find himself at the LMB, at a place that "to this day, has won more Nobel prizes than any other square footage of the planet." Despite that, it wasn't a cutthroat environment. On the contrary, Smith says, it was there that he learned the importance of collaborating and of doing science for the sake of science. "I really didn't want to be the biggest professor in the world," he recalls.

Nonetheless, Smith was well on his way to making a name for himself, says Harvey Lodish, then a postdoctoral fellow at the LMB and now a professor of biology and bioengineering at Massachusetts Institute of Technology. "There was no question about that," says Lodish, who was impressed with Alan's good nature and intelligence, and his vision for the future of molecular biology. "You have to understand that 1966 is 40 years ago. We were just getting the first sequences of transfer RNA. That's what they were doing back then. The genetic code had just been discovered. Molecular biology was really beginning, and the notion of methionine-initiated proteins was brand new. This is all old-hat now, but this was a time when a lot of basic principles of molecular biology were being discovered, and Alan wanted to be part of it."

While studying the initiation of protein synthesis in eukaryotes in 1970, Smith showed that AUG is the initiating codon and methionine is the initiating amino acid. The finding not only bucked conventional wisdom at the time, it also ▶

TheScientist
MAGAZINE OF THE LIFE SCIENCES

served to work out one of the last pieces of the genetic code.

Smith went on to study DNA tumor viruses, specifically simian virus 40 (SV40), and he established SV40's genome structure. This work, according to Rich Gregory, the head of research at Genzyme, established Smith as an important figure in microbiology. "Nobels have been awarded for similar kinds of work," says Gregory.

It was fulfilling research, says Smith. And in 1984, a recruiter called him to see if he was interested in going to work for Integrated Genetics, a small biotech start-up company in Framingham, Mass. "I surprised everybody, including myself," recalls Smith, "by coming."

Moving on to Genzyme

As scientific director and vice president of Integrated Genetics, Smith was now working in the world of biotech start-ups, specifically focused on the mammalian expression of recombinant proteins. He wanted to know how to make recombinant proteins better and faster, and by 1987 he showed that scientists could make therapeutic proteins in the milk of transgenic animals. To Smith, it was a good example of biology, and not bioreactors, doing the work.

Just five years after Smith joined, Integrated Genetics merged with Genzyme. Integrated had the resources to better produce the enzyme Ceredase, a Genzyme drug candidate used to treat Gaucher disease, a rare genetic disorder. Lodish, one of Genzyme's scientific founders, says Smith's well-known talents also factored into the merger: "It was clear that, shall we say, Alan was one of the most valuable commodities that Integrated Genetics possessed."

Part of the reason was Smith's reputation as an intelligent, careful, hard-working scientist. "He's very rigorous," says David Livingston, a professor of genetics and medicine at Harvard Medical School. "There's not going to be any moss growing under his feet." And he isn't just rigorous, says Livingston; he's often right. "I know very few scientists you can say that about," he says. "Alan Smith is one of them."

According to his colleagues, Smith was such an asset both then and now not only for his mind, but also because of his hands-off, easygoing management style. He is a scientist's scientist, an administrator who will hear out another's argument even if he happens to disagree. He will listen to the ideas of both a research assistant and a vice president with the same interest, so long as the ideas are good. He started at Genzyme in 1989 as senior vice president of research, and seven years later was named chief scientific officer.

"Many of the scientists that I'd met that were well-known tended to be somewhat arrogant and egotistical, and that's not the way that Alan is at all. He was very down to earth, very humble, and very easy to work with."

—John McPherson

"When I met him, to tell you the truth, I was expecting something a little different," says John McPherson, Genzyme's head of biological products R&D. McPherson first hired Smith at Integrated in 1988. "Many of the scientists that I'd met that were well-known tended to be somewhat arrogant and egotistical, and that's not the way that Alan is at all. He was very down to earth, very humble, and very easy to work with."

Growing Pains

This created an open atmosphere at Genzyme that encouraged the exchange of ideas; people wanted to work for Smith. Shortly after the 1989 merger, the new parent company began to grow rapidly. Within five years, the company was no longer producing Ceredase by extracting enzymes from human placenta. On Smith's watch, they abandoned this cumbersome approach and began genetically engineering the cells needed to treat Gaucher disease. In 1994 the Federal Drug Administration approved the new drug, called Cerezyme. Sales were projected to peak at around $200 million, but those projections were way off. In 2005, Cerezyme generated nearly $1 billion in revenue for Genzyme.

"You can say that Genzyme pioneered the sort of commercialization of drugs for rare diseases, the orphan diseases," says Smith. "We pioneered that. And you have to give credit to Genzyme, and you have to give credit to the CEO, Henri Termeer, for seeing that."

Not everything, however, turned out so well. Heartened by the possibilities of gene therapy, Genzyme, led by Smith, next set its sights on developing a product to treat another genetic disease: cystic fibrosis (CF). As Smith recalls, the target made sense. Genzyme had identified the flawed gene that causes CF and had developed a way to place a normal copy of the gene into cells. The trick was delivering the protein to the human airways.

As scientists struggled with the delivery problem, they ran into a series of barriers, says Michael Welsh, a professor of medicine and physiology at the University of Iowa Medical School who collaborated with Smith on the project. Namely, Welsh says, they could not determine how to deliver the product to human airways that are built to resist foreign invaders. Despite the best efforts of Smith and others, the project failed.

"In the end, what you learn is humility," says Smith. But he walked away from the cystic fibrosis research with practical lessons as well. Recognizing just how difficult it can be to evade the human immune system, Genzyme is now working on delivering gene therapy directly to the brain, where it's less likely to be rejected. Meanwhile, overall, the CF failure reminded Smith just how difficult it is to move a product all the way from discovery to the marketplace, a realization that places a premium on reducing risk. "That's the conundrum," he says. "And so my ambition – and it may be an unachievable ambition – is to better understand what that means and how to deal with it in the context

of trying, sustainably, to discover new things."

Acquiring Companies and Knowledge

Genzyme posted $2.7 billion in revenue in 2005 and spent more than $500 million in research. In recent years, the company's quest for sustainability has led to the acquisitions of companies with late-stage products, including the 2006 purchase of AnorMed for $580 million. AnorMed's drug, Mozobil, has been shown to stimulate the release of stem cells from the bone marrow into the bloodstream; it could be a boon to patients undergoing stem-cell transplants. Smith says it's the classic example of what Genzyme is seeking when it grows: "There's an unmet medical need, there's a good business need, there's good clinical data, and there's interesting underlying science."

"Acquisition is an integral part of the business," says Smith. "Why? Because it's so darn hard to discover new things and take them all the way through. It takes so long, it's so risky, and it costs so much money." Smith isn't comfortable, however, relying on acquisitions alone to grow the business. He believes that the 750 people he oversees are responsible for knowing what's on the horizon, and he challenges them to be what he calls "the eyes, ears, and voice of Genzyme."

"What that means is, there's no good [being done by] sitting at your lab bench and looking at your test tubes all day," he says. "You've got to be out there, knowing what's going on. What are other people doing? What's new? What are the needs that physicians see, that patients need?"

To help answer these questions himself, Smith has begun holding annual dinner meetings with the top scientists working with Lodish at MIT. The goal is open discussion about what's happening, or not happening, and how Genzyme might be able to make a difference. At the meetings, Smith gives no big speeches. He's just another person at a dinner table talking about science, and that's the way he likes it.

Discovering and producing viable drug candidates may not be any easier than it was when he first started at Genzyme nearly two decades ago. Smith claims to have no secrets to success, but he does have a vision: Genzyme will continue to grow and diversify in the years ahead, both from within and through acquisitions. With these changes, Smith says Genzyme's goal remains the same – finding unmet medical needs for which its scientists can make a difference.

"I know Genzyme is one of the most successful biotechnology firms of its generation," says Livingston. "It's here to stay. Its science is first class. And that is no small measure, if not a large measure, the product of the actions of Alan Smith." ■