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PROFILE

Choosing Industry: Biotech Makes Its Mark

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Image courtesy of Ulrich Stilz

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It's a question that almost all young chemists and biologists ask themselves as they embark on their careers: what kind of job should I pursue? With few academic positions open each year, many scientists are widening their options and seeing decided benefits in industry. A natural fit for both chemists and biologists is the biotechnology field. In this Profile, we meet three scientists from different backgrounds who have forged successful careers in biotech: Ulrich Stilz, a chemist who has spent more than a decade with pharmaceutical giant Sanofi-Aventis; Mary Katherine Raymond Johansson, a chemist who has worked for the small biotechnology firm Biosearch Technologies since 2000; and her husband, Hans Johansson, a molecular biologist who has worked in parallel with Raymond Johansson at Biosearch Technologies since 2004. Each of these researchers took different paths to choosing careers in industry. However, each has found that industry indeed has its rewards.

Following Big Pharma. Ulrich Stilz was born in the southwest German city of Mannheim in 1963; his father is a chemist, and his mother was an interpreter. He acknowledges that his father played a pivotal role in shaping his interest in science—it was an undeniable part of his childhood. However, he notes that his parents never pushed him toward any particular career path. Rather, he says, they encouraged him to follow whatever interests he enjoyed.

When he was 10 years old, Stilz received a microscope from his aunt and uncle. Though the gift initially sparked his interest in biology, allowing him to delve into the world of cells, he developed his own fascination with chemistry as he learned to mix dyes for stains. "Over time, I discovered that chemicals are quite interesting," he remembers.

By the time he finished high school, Stilz knew that he was interested in pursuing a scientific career. He enrolled in the University of Freiburg in Germany in 1982, choosing chemistry as his major. He remembers initially being bored by introductory general chemistry classes. As his education deepened into more specialized areas, he found a passion for organic and physical chemistry.

After two and a half years at Freiburg, Stilz felt ready for a change. "I thought, I'm young—I want to see the world," he recalls. Bringing his newfound interest in organic and physical chemistry with him to another country, he enrolled in Eidgenössische Technische Hochschule (ETH), a university in Zurich, Switzerland. The school had an excellent reputation for its chemistry program.

There, Stilz found camaraderie in a smaller, more intimate environment. Unlike at Freiburg, where he often had to arrive early to class just to find a seat, he remembers that classes at the Swiss school were empty until just before lectures started. Students from around the world attended the school, and this allowed him to work with many new international colleagues—an experience that influenced his career to come.

Stilz continued on at ETH to work toward his master's degree. For a final project, under the guidance of Dieter Seebach, he studied stereoelectronic effects in activated ketone complexes. Through the determination and study of the complexes' crystal structures, he found that hyperconjugation plays a role in influencing π-electron distributions on the two faces of a carbonyl group. The work became the focus of his first scientific paper, published in 1987 (*1*).

As he finished his master's degree in April of that year, Stilz contemplated what direction his career would ultimately take. After witnessing firsthand how different diseases devastated friends and members of his family, he decided to pursue biomedical research. However, his course of study hadn't placed much emphasis on biology, an important prerequisite for most types of drug development. To gain that missing knowledge and experience, Stilz decided to focus on biochemistry for his doctoral studies. After applying for and receiving a grant aimed at students interested in switching universities, he began a Ph.D. program in biochemistry at the Max Planck Institute in Martinsried, Germany.

Stilz soon joined the lab of Dieter Oesterhelt, whose work focused on membrane biochemistry. There, he studied the photosynthetic reaction center in *Pseudomonas*, a membrane-bound pigment protein complex that uses the energy from light to mediate a charge separation across photosynthetic membranes. Though the crystal structure of this protein had been characterized (*2*), little was known about which parts of the protein were important for its function. Stilz and his colleagues performed mutagenesis and spectroscopic studies to probe the role of various amino acid residues on quinine binding and electron transfer (*3*). One of the important learning experiences from the project was working with other research teams across Germany. "It was a good learning experience in how to collaborate in an interdisciplinary way," he says.

Stilz spent three and a half "very intense" years on this project, which culminated in his doctoral thesis being published in 1990. He also maximized this time by attending as many biochemistry lectures as he could fit in. By the time he graduated, he felt prepared to continue pursuing the interface between biology and chemistry in his postdoctoral fellowship. He found the ideal position at the California Institute of Technology (Pasadena, CA; Caltech) in the lab of Peter Dervan. Much of Dervan's work focused on studying triple-helix complexes of DNA. For the next two years, Stilz synthesized novel nucleoside analogues with modified bases, then incorporated these analogues into small DNA stretches to try to expand sequence-specific recognition. His discoveries were published in 1993, highlighting his work on sequence-specific recognition of CG pairs (*4*).

When his work with Dervan ended in 1992, Stilz made the leap to pharmaceutical research. Although drug discovery had been his ultimate goal, he remembers that leaving academia was a "tough decision", but one he felt driven to pursue. "I just was inspired by trying to find new medicines, and my feeling was this can be best done in industry, where all different disciplines are available to work together," he says.

In November of 1992, Stilz accepted a position as a research scientist with Hoechst AG, a large chemical and pharmaceutical company based in Frankfurt, Germany. The first project he worked on focused on developing an antithrombotic drug that acted on a fibrinogen receptor known as GP2B3A (*5*). Within nine months, the compound Stilz was working on had become a clinical candidate—an unusual occurrence, with a lot of luck involved. "It was great because I got picked as the chemist to go with this compound, to bring it into preclinical and early clinical development," says Stilz. "I got to learn about drug discovery by following this compound through the pipeline—it was tremendous training for the first two years of my employment."

The compound ultimately didn't make it to the market as the mechanism of action didn't hold its promise in the clinic. However, the training gave Stilz experience to bring to his next few compounds, candidates aimed at treating osteoporosis, asthma, and rheumatoid arthritis. After participating in several overseas collaborations and coordinating different research teams, Stilz was promoted into a management role overseeing a group of 60 people. The company changed as well over time—first acquiring Marion Merrell Dow, then merging with Rhone-Poulenc Rorer, and finally becoming Sanofi-Aventis in 2004.

Today, Stilz oversees a diverse group of scientists as head of chemical sciences. Though he no longer works at the bench, he has found new challenges in directing the work of others and developing new ideas to speed drug discovery. He participates in a mentoring program to help researchers move into management, and he has implemented numerous changes at Sanofi-Aventis, such as putting more focus on the integration of new technologies into the drug discovery value chain.

Stilz cautions that applied research is not for the impatient. "The success rate is low—most projects fail, so you have to be really persistent not to get easily frustrated." However, he notes that joining a big pharmaceutical company is a great experience. "It offers a chance to work with colleagues in many types of disciplines across the globe and to share the enthusiasm of moving projects forward." The benefits of making a useful product continue to keep him interested in his work every day. "To make an impact by discovering new medicines still motivates me—that hasn't changed."

Small Biotech Benefits. Also a chemist, Mary Katherine Raymond Johansson's path guided her to the small biotechnology company where she works today. Born in Oakland, CA, in 1969, Raymond Johansson's parents are both Ph.D. chemists. Her mother and father each encouraged her love of science in different ways: while her father took Raymond Johansson and her siblings camping and hiking to pique their interest in nature and the outdoors, her mother encouraged the children to focus on their schoolwork, including their science classes.

When Raymond Johansson was in the eighth grade, a single event brought science to the forefront of her studies. After using her mother's lab at Caltech to study pollutants in local waterways, Raymond Johansson won her school's science fair.

"I just wanted to continue doing lab work and research—it was so much fun that I couldn't imagine doing anything else," she recalls.

Image courtesy of Mary Katherine Raymond Johansson

She notes that her good lab protocol may have won over the judges. "I kept very careful entries in a lab notebook and followed the scientific method," she says. Other than providing lab space, her mother gave her little assistance with the experiment. Being able to take control of her research was empowering, she recalls.

Though she spent little time performing laboratory studies in high school, her middle school experience gave Raymond Johansson an impetus to continue her science studies. After enrolling in Reed College in Portland, OR, in 1987, she decided to follow her parents' path and major in chemistry. Each summer, she received a fellowship to work with Prof. John Roberts, an emeritus chemist at Caltech. "The Caltech SURF program allowed us to pretend like we were grad students," recalls Raymond Johansson. "And at the end, you usually end up with a publication." The summer research focused on the rotational C(O)–N bonds' strengths in urea and resulted in a publication (*6*). Raymond Johansson collaborated with Dr. Roberts on another NMR project investigating the nuclear Overhauser effects and T_1 enhancement in histidine for her senior thesis. She finished her bachelor's degree at Reed in 1991, and her research results were later incorporated into a publication (*7*).

As Raymond Johansson neared the end of her undergraduate years, she knew that she wanted to keep studying science. "I just wanted to continue doing lab work and research—it was so much fun that I couldn't imagine doing anything else," she recalls. For her graduate work, she was interested in pursuing a project that combined physical and synthetic chemistry. She found the perfect combination at the lab of Josef Michl at the University of Colorado at Boulder. There, Raymond Johansson joined a group studying the photophysics of silicon chains. She fondly recalls her time working with her graduate student and postdoctoral colleagues. "Michl's group was very interesting. They were mostly immigrants from Eastern Europe. There were lots of cultures in the lab—it was a very rich experience."

Raymond Johansson's graduate work involved many different facets: making silicon compounds, then purifying them, formulating theories and developing models, writing computer code to calculate the compounds' different properties, and performing measurements, among other tasks. She had a hand in building much of the equipment needed for the experiments. "I even went to the machine shop and used a lathe," she says. Using these tools, the team discovered a type of dual fluorescence from a permethylated silicon chain (*8*).

By the time she finished her graduate studies in 1997, she had not only gained a doctoral degree but a fiancé. She and Hans Johansson worked in the same building—he worked as a postdoctoral fellow several floors above her. But ultimately, the couple met at a beer festival in nearby Denver.

Raymond Johansson notes that Hans, originally from Sweden, was homesick by the end of his fellowship. After receiving a repatriation grant, the couple moved to Sweden, where Raymond Johansson found a postdoctoral fellowship of her own. "I was inspired by working with mostly Europeans during my Ph.D.," she says. "I was ready to try living in a different country."

For her fellowship, Raymond Johansson joined a team at Uppsala University studying artificial photosynthesis. Under Leif Hammarström, her work focused on examining the mechanism behind electron transfer from ruthenium to manganese. "We were trying to come up with this artificial model for photosynthesis and trying to get a long-lived charge-separated state," she says.

She notes that the way of doing research in Sweden differed from the American model. Rather than each group working independently, she explains that the Swedish groups formed complex collaborations with researchers all over Europe. This research style had its advantages, such as not needing an expertise in the many areas on which her team relied. However, she adds that she came to prefer the American style of research in the end. "I admired the Swedish way of doing things, but I like the American way. If you want to do something, you do it yourself," she says. "I think that's why I ended up at a small biotech company—I have a very entrepreneurial spirit."

As Raymond Johansson's postdoctoral fellowship continued, her husband's career at the same university flourished. However, she saw few opportunities for advancing her own career. She was also feeling homesick. After three years in Sweden, the couple made a decision to look for work in the U.S.

Searching the Internet, Raymond Johansson found a promising job that was located close to her childhood home. She traveled to interview at the company, Biosearch Technologies. After meeting with the CEO, Dr. Ron Cook, she recalls feeling an instant connection. The warm California weather also won her over. "It was the dead of winter in Sweden, and when I came to California, I thought: this is it," she says.

One of the company's main interests was developing fluorophores and quenchers for real-time polymerase chain reaction (PCR), a focus that remains today. When Raymond Johansson arrived, the company had recently developed a new line of products that they named Black Hole Quenchers. Although the products worked well, the company had few clues about their mechanism. "An obvious first task was to understand how they worked," says Raymond Johansson. She showed that the Black Hole dyes operated by static quenching, forming a ground-state complex between the reporter and quencher.

The finding quickly led to two prominent publications that affirmed Raymond Johansson's choice to join industry (*9, 10*). "I did much better my first couple of years in terms of publishing than I would have at an academic job, and I had the freedom to do it myself. That's what I wanted," she says.

Since she joined the company seven years ago, she continues to direct other projects, including developing her own product—an organometallofluorophore geared specifically for a particular brand of real-time PCR instruments. She notes that the freedom to pursue her own projects and dabble in other areas of business, such as quality control and manufacturing, continues to drive her interest in biotech. She adds that working for a small company has other advantages as well: when she gave birth to her son two years ago, the company allowed her to work part-time, a benefit not usually granted in the academic world.

Raymond Johansson explains that working in industry can be somewhat isolating—it doesn't come with the same ability to reach out to new colleagues as an academic job does. However, she adds that being able to work more independently is empowering in its own right. "I feel like I'm on an island sometimes, but it's exciting because it's my own island," she says.

Culture Change, Culture Gains. Though he works at the same company as his wife, Hans Johansson came from a different discipline. A molecular biologist, Johansson was born in 1964 in a town just outside Stockholm. His mother is a nurse practitioner and his father was a civil engineer. "I ended up right between their career paths and kept on walking" he says.

Johansson grew up exploring nature, hiking, and investigating his small town and nearby parks. When he was 17, he joined the Rotary student exchange program, leaving Sweden for a high school in Elkhart, IN, for his senior year. There, he took an aerospace class taught by Mr. Lutey. As an incentive to spark his students' interest in the physical sciences, the teacher took some of the students in his class up in an airplane. Johansson recalls his awe in seeing the small town from another perspective.

After graduating from his American high school, Johansson returned to Sweden to finish high school, then spend compulsory time in the Swedish Navy before attending college in Stockholm. He became fascinated with molecular biology and biochemistry, largely because of his professors, he says. As his undergraduate years drew to a close, he pursued graduate school to continue his studies. "We kept asking questions in class, and we didn't get answers. Pretty soon, I realized that there would always be something more out there to figure out," he says.

The same year that Johansson completed his bachelor's degree, Tom Cech and Sidney Altman shared the Nobel Prize for the discovery of catalytic RNA. Fascinated by RNA, Johansson became interested in focusing his studies on the molecule in graduate school. After seeing a flyer advertising graduate studies at the European Molecular Biology Laboratory in Heidelberg, Germany, he applied to and joined the lab of Matthias Hentze. Hentze was focusing on basic molecular biology and protein synthesis as it relates to iron metabolism and anemia. "Although it was fundamental molecular biology, you could see future applications for disease treatments," Johansson says.

Image courtesy of Hans Johansson

He took on a project to investigate a small cytoplasmic RNA (scRNA) that shut off protein synthesis when added to cell extracts. He and his colleagues discovered that the RNA itself wasn't responsible for blocking synthesis. Rather, heparin used in purifying the RNA was pivotal, with implications for dozens of other scRNAs (*11*).

For his thesis, Johansson investigated messenger RNAs that appear to be regulated by iron. Using novel antisense oligonucleotides, he and his colleagues were able to arrest different intermediates along the translation initiation pathway (*12, 13*).

Seeking to further his RNA studies, Johansson began a postdoctoral fellowship at the lab of RNA researcher Olke Uhlenbeck at the University of Colorado at Boulder, whose work centered on RNA–protein interactions. There, his work focused on these interactions in the MS2 bacteriophage. This virus's four genes are translated individually over time, making it a good model for studying translational regulation in bacteria.

Johansson and his colleagues sought to further their understanding of how coat protein dimers bind to the virus's RNA to both turn off replicate synthesis and initiate capsid assembly. The team synthesized small RNAs, incorporating unnatural nucleotides. They found the reason why changing one particular base significantly increased the RNA's affinity to the coat protein, speeding capsid assembly (*14, 15*). "You might assume that high affinity would be advantageous for the phage," notes Johansson, "but if assembly initiates too early, few phages are made."

As Johansson's research progressed, so did his relationship with Mary Katherine Raymond, now his wife. After Johansson was offered a grant that included repatriation money, the couple decided to move to Sweden together. There, Mary Katherine began her postdoctoral fellowship as Johansson began his assistant professorship.

Johansson became interested in a translation initiation factor called 5A, which uniquely carries the polyamine hypusine. His lab verified the function of hypusine in archaeal growth (*16*), performed phylogenetic and mutagenesis studies that led to the discovery of a second vertebrate isoform of eIF5A (*17*).

"It's been a change for me to have to think more about a product rather than a paper," he says "but it puts a better focus on the research."

In 2000, they began looking carefully at returning to the U.S. Mary Katherine received a job offer from biotechnology firm Biosearch Technologies in California, and Johansson received an offer from Children's Hospital Oakland Research Institute to continue his research on eIF5A. He brought postdoctoral fellow, Zandra Jenkins, with him to his new lab in California. The lab also renewed its interest in iron metabolism in disease in collaboration with Dr. Elisabeth Theil (*18, 19*).

However, when donations to the hospital slowed, funding for Johansson's research position was cut. Johansson instead continued to study eIF5A in collaboration with John Hershey at U.C., Davis and Dr. Myung-Hee Park at NIH (*20, 21*). While looking for a more permanent job, one coincidentally opened up at Biosearch Technologies. "They were looking for someone to take over a project on gene expression," says Johansson. "It's one of my passions, so I applied. It was and still is a very good match."

Johansson's primary focus has been developing a new gene-azoreductase-based expression reporter system that releases fluorophores from quenchers. "We think this will be a potent complement to other reporters because of the signal to noise ratio," he says. The NIH has just awarded a phase II SBIR grant for the project. He hopes the NIH will look favorably at the next SBIR application that aims to adapt Biosearch's dyes for RNA labeling.

At Biosearch, Johansson is one of two molecular biologists. He notes that he is surrounded by chemists who often don't understand the details of his work. "Biology and chemistry are two different realms, especially when it comes to living things." He adds that his focus on biology rather than chemistry keeps his work mostly separate from Mary Katherine's.

However, this cultural difference is a small price to pay for the benefits he enjoys at a small biotech company, he notes. Like his wife, Johansson emphasizes that he enjoys the freedom of pursuing a variety of different projects. "I get to do what I like to do—it's the best part of the job," he says.

Johansson notes that he's had a lot to learn about the culture of working in industry. Along with keeping up with the literature, for example, he explains that he and his colleagues must keep up with other companies' patents and protect Biosearch's intellectual property. He adds that focusing on the profitability of his research is another new twist. "It's been a change for me to have to think more about a product rather than a paper," he says "but it puts a better focus on the research."

However, he explains that industry has allowed him to do the parts of science that he enjoys, while leaving behind the parts of academia that he was less fond of. "I get to pursue good science, I don't have an administration to deal with, I don't have to attend many meetings, and I don't have to set up teaching schedules or worry about finding money every day," he says. "I see myself doing this type of work for the forseeable future."

—Christen Brownlee, Science Writer

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