Julian Davies

An icon of the European biotech industry and a pioneer of metagenomics, Julian Davies continues to pursue his lifelong love affair with microbiology.

Julian Davies is a biotech vanguardist. His studies on recombinant DNA technology in the early 1970s helped shape modern biotech; in the 1980s, he nurtured and led the outstanding scientific output from Cambridge, Massachusetts–based Biogen's European operation. His latest venture—a firm called TerraGen, located in Vancouver, British Columbia—was an early proponent of what is now known as meta genomic-based novel antibiotic discovery. For all his business acumen, however, Davies is happiest growing 'bugs' in the laboratory.

The Welsh-born Davies initially trained as a chemist in the UK, but it was at Boston's Harvard Medical School that he made the seminal finding in 1973 that antibiotic resistance in pathogens is evolutionarily related to antibiotic production in actinomycetes. Davies speculated that antibiotic resistance genes originated in actinomycetes and transferred horizontally through a chain of closely related organisms to pathogens. "Now with genomic sequencing, we could say yes, that's probably true," says Davies' friend Richard Baltz of Cubist Pharmaceuticals in Lexington, Massachusetts.

Antibiotic resistance genes were central to recombinant DNA technology, some of which Davies also pioneered. This may have been one reason Biogen, now Biogen-Idec, wanted him to join the barely two-year-old company in 1980 as director of research at its Geneva laboratories. A meteoric rise to president of the entire Swiss operation followed. "When Julian walks into a room, he lights up the place," says Baltz. "He's enthusiastic and optimistic, and he's always looking for a new way to think about things." Biogen cofounder, Nobel laureate and Massachusetts Institute of Technology professor Phillip Sharp agrees: "He recruited a remarkable group of young scientists and created an excellent lab in Geneva, and he made sure they worked as a team." At Biogen, Davies was glad to try his hand at something new. There were only 12 people in the Geneva laboratory at the time, and it felt like academia. "It was all research," he says. "This was really my chance to see if I could do something, and it seemed just like Nirvana for me at the time."

By 1985, Biogen was no longer a research boutique but a budding biotech company where clinical trials were being conducted and regulatory and management issues permeated work life. Pining to get back to research, Davies left the company for the Institut Pasteur in Paris, where he set up a new research group with his long-time friend, Nobel laureate François Jacob. Seven years later, he made another move: this time to Vancouver, where he became head of the microbiology department at University of British Columbia (UBC). He also got another shot at business as the founder of his own startup company. "They wanted to start something at UBC, and we thought it would be very nice to start a center of microbial diversity." This gave rise to TerraGen Diversity, with the idea of cloning genetic material from unculturable soil microbes to search for novel antibiotics.

In 1994, when TerraGen was starting, the concept of cloning directly from DNA isolated from natural sources was just emerging. Today, the concept is known as metagenomics, a term coined in 1996 by microbiologist Jo Handelsman of the University of Wisconsin–Madison. Davies' team sought to isolate large and complex biosynthetic pathways directly from the soil and then express the genes in surrogate hosts. But the technology hinged on the ability to separate high-molecular-weight, good-quality DNA from a decidedly mixed environment—just a teaspoon of dirt could contain up to 10 billion organisms representing a thousand or more different species. Because 99% of these species could not be grown in the laboratory, extracting good-quality DNA was an uphill struggle.

Ultimately, TerraGen was able to show it could clone complete biosynthetic pathways from almost any antibiotic-producing strain, thereby enabling the genetic manipulation of pathways and the production of new compounds. In the late summer of 2000, this got the attention of antimicrobial company Cubist, resulting in a collaboration to clone the entire biosynthetic gene cluster for Cubicin (daptomycin), a cyclic lipopeptide derived from the fermentation of *Streptomyces roseosporus* that is used to treat Gram-positive pathogens, such as *Staphylococcus aureus*, including methicillin-resistant isolates.

Cubist had run a program for a few years in which the daptomycin cluster was modified in various ways, but none of the novel compounds turned out to be therapeutically superior to the parent compound. Frustrated, the Cubist management dropped metagenomics in favor of engineering existing lipopeptide biosynthetic pathways to make analogs of daptomycin. "I think they gave up too soon," says Davies. "The technology was established but not fully exploited."

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Indeed, Davies laments the business of antibiotic drug discovery today. "They are making them and selling them," he says, "but they're not doing any research on them. I think it's creating a very serious problem in the infectious diseases world." Part of the problem is the conservative approach of regulators that seek to limit new antibiotics to use in last-line indications, rather than in larger markets, making it difficult for companies to recoup their investment. "Companies are no longer willing to take this big step," he argues. "You discover a great compound and develop it, and before you know it, you can't sell it."

Now at age 76, Davies spends nearly every day in his laboratory at UBC, where he has been professor emeritus since 1997. "I'm doing everything that I wanted to do, and I'm doing more lab work than I've been doing in a long time." As Richard Baltz puts it: "I don't think he's ever happier than when he's in a laboratory looking at a Petri dish with bacteria growing on it and talking with some student."

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