OBITUARY

Willem 'Pim' Stemmer 1957–2013

A truly original thinker and pioneering entrepreneur.

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On 2 April, the biomedical research community lost Willem P.C. 'Pim' Stemmer. Stemmer was an innovative protein engineer, a brutally honest colleague and a true biotech pioneer. His innovations provided the foundations on which several successful companies (and numerous products) have been built. Stemmer is perhaps best known for the invention of DNA shuffling, a breakthrough methodology that not only dramatically accelerated directed protein engineering but also enabled the directed evolution of metabolic pathways, viruses and whole organisms[1–4]. The method has been widely used by scientists around the world to create novel proteins and cells that have unique properties, with applications in biopharmaceuticals, vaccinology, agricultural products and biofuels, not to mention basic research.

A Dutchman by birth, Stemmer's formative education was at the Institute Montana, a boarding school in Zugerberg, Switzerland, from which he graduated in 1975, followed by an undergraduate biology degree from the University of Amsterdam in 1980. He then left for America, where he completed a PhD in molecular biology at the University of Wisconsin–Madison (UW–Madison) studying host-pathogen interactions and the bacterial pili and fimbriae in particular. Postdoctoral research at UW–Madison followed, in the laboratory of Fred Blattner, on phage display of random peptide libraries and antibody fragment expression in *Escherichia coli*. This research provided the basis for his work at San Diego–based Hybritech, an early biotech company focused on monoclonal antibody technology that was purchased by Indianapolis-based Eli Lilly for more than $400 million.

In the early 1990s, Stemmer moved to the Affymax Research Institute in Palo Alto, California. There, he invented the protein engineering technique called DNA shuffling[1–4]. His seminal paper from that period states: "Computer simulations of the evolution of linear sequences have demonstrated the importance of recombination of blocks of sequence rather than point mutagenesis alone. Repeated cycles of point mutagenesis, recombination, and selection should allow *in vitro molecular evolution* of complex sequences, such as proteins"[2]. The method mimics natural DNA recombination, rapidly accelerating engineering of therapeutic proteins, vaccines and industrial enzymes. The intellectual property surrounding DNA shuffling, often referred to as 'molecular breeding' or 'sexual PCR', provided the basis for the spin-off of Maxygen in 1997, a successful initial public offering in 2000, and the founding of Verdia (sold in 2004 to DuPont, based in Wilmington, Delaware) and Codexis, both based in Redwood City, California.

Stemmer left Maxygen in 2003 to start Avidia, a company based on avimer technology, which produced ultrahigh-affinity binders by cleverly joining multiple nonantibody scaffold domains[5]. Avidia was acquired in 2006 by Amgen, based in Thousand Oaks, California. In the same year, Stemmer cofounded Amunix (with V.S.). He was CEO of the company, based in Mountain View, California, until shortly before his death. Amunix's core technology is XTENylation, or "protein PEG"[6], as Stemmer often referred to it. XTENs are long, unstructured, hydrophilic protein chains that can be fused to biologics to improve their half-life in circulation. According to Versartis, the biotech company that licensed VRS-317, growth hormone fused to XTEN, VRS-317 is currently the only long-acting recombinant human growth hormone compound with a future for once-monthly dosing.

In addition to being a highly creative scientist, Stemmer also explored innovative business structures. He recognized the limitations of the typical small-biotech model with its aim for an early buyout by a large pharmaceutical company. It frustrated him greatly that such sales made technologies inaccessible to the broader scientific community (including the inventors) and thus profoundly limited their potential. For Amunix he envisioned a different fate. Two daughter companies in Mountain View—Versartis and Diartis—were created early, with the sole focus of product development, while Amunix retained its ability to further broaden and explore the full potential of its core technology platform. As a result, XTEN is now being evaluated by a large number of researchers for a wide range of indications, and Diartis and Versartis have continued clinical validation of XTEN leads.

For his work on DNA shuffling, Stemmer shared (with Francis Arnold of the California Institute of Technology) the 2011 Charles Stark Draper Prize, the US's top engineering honor (commonly called the Nobel Prize of engineering). He was no stranger to scientific accolades, receiving the Doisy Award from the University of Illinois at Urbana-Champaign in 2000 and the David Perlman Award in 2001. Stemmer also authored more than 100 patents. His portfolio from Maxygen was ranked as the top in pharma/biotech for 2003 by the *MIT Technology Review* and number 2 among the 150 largest pharma and biotech companies by the *Wall Street Journal* in 2006 (http://en.wikipedia.org/wiki/Willem_P.C._Stemmer).

Stemmer was only 56 years old when he lost his battle with metastatic melanoma. He will be remembered for his vision and for his outside-the-box thinking combined with a forthright, stubborn personality. If there was ever a scientist passionate about his work, it was Stemmer. He was tireless, enthusiastic and boundlessly creative; biotech has lost a giant in more ways than one.

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