

Willem 'Pim' Stemmer

One of the most pioneering protein engineers of his generation is also a serial entrepreneur with a flair for spotting new business opportunities.

The same year that Pim Stemmer, a native of Holland, obtained his PhD from the University of Wisconsin, Madison, he founded his first company, Genetic Designs. It was 1985, and his firm was pioneering three key protein engineering technologies: peptide phage display, codon-based synthesis and antibody expression in *Escherichia coli*. Eight years later, working as a research scientist at Affymax, Stemmer invented and developed 'gene shuffling', a process that has since transformed protein engineering. Rather than mutagenize sets of single residues in existing proteins or design new proteins from scratch, Stemmer's technique mimicked natural DNA recombination, producing modified proteins with enhanced or new activities over time frames suitable for commercial development.

The gene shuffling approach proved exceptionally powerful, and the resulting intellectual property formed the basis for Redwood City, California-based biotech Maxygen in 1997. Paradoxically, however, Stemmer is today barred from using it himself. "The perspective that Maxygen took on the portfolio was to control very tightly close to 100 patents," Stemmer says. When he left Maxygen in 2003 to spin off a new company, Avidia, no license was made available. "What I think is too bad is that Maxygen has never widely out-licensed the technology and it is still widely underutilized, or utilized and called something else," he notes rather wistfully.

There seem to be no hard feelings, however. Russell Howard, Maxygen's CEO, has known Stemmer since 1992, when the two worked together at the Affymax Research Institute. "My first impression of him—excited about science; born optimist; creative and always prepared to think differently to provoke debate," Howard recalls. "He is the ideal person to have in the ferment of discovering technologies for a specific purpose when the precise technology path is not clear but the goal is clear and the path seems feasible, if only remotely."

It is not just Stemmer's approach to scientific conundrums that impresses Howard. "He is an entrepreneur prepared to place his money, reputation and bets on ideas that he has for new ways to create biotechnology products."

Stemmer admits to being excited by the intellectual challenges of both business and research. "I really enjoy science concepts, but the entrepreneurial part is especially exciting because I am still learning at a rapid pace. The concepts are newer to me and I have to prove myself more."

Indeed, Stemmer has just launched Versartis, his sixth biotech company, based on the 'versabody' technology held by his current company Amunix, based in Mountain View, California. "Our business model is to spin off additional product development companies for different disease areas," explains Stemmer. "Amunix creates the technologies and products. The spin-off gets a basket of specific compounds to take into the clinic, but the technology stays with Amunix."

The versabody format is inspired by the toxins produced by poisonous snakes, spiders, scorpions and leeches, which are disulfide dense and non-immunogenic. In a versabody, the hydrophobic amino acids that typically form the protein's hydrophobic core are replaced by a disulfide scaffold, resulting in a disulfide-rich 'microprotein' that is smaller, more resistant to proteases and heat, and not recognized by the immune system. Amunix was the brain child of Stemmer and cofounder Volker Schellenberger.

Amunix has also developed what it terms 'recombinant PEG' or 'rPEG'. The rPEG technology is a long (at least 40 residue) unstructured poly amino acid chain (with glycine, aspartate, alanine, serine, threonine, glutamate and proline comprising ~80% of the chain) that, when genetically fused to a therapeutic protein, extends serum half life in a similar manner to polyethylene glycol. Unlike polyethylene glycol, however, rPEG requires no chemical conjugation or repurification, greatly simplifying the manufacturing process. Versartis' first products will be to create rPEG versions of existing biologics (for example, extending a daily injectable therapeutic to a weekly product).

Stemmer has high hopes for his product-driven business model. "The typical biotech scenario starts out with a couple years of research, and as soon as [you have] a product candidate, [you] go out and hire a development group and then lay off most of the research group. Then you sell the whole company in phase 1 or phase 2a," says Stemmer. "For VCs [venture capitalists], this is fine. For scientists, this is not ideal."

Instead, Stemmer thinks that discovery and development should plug and play quite differently. "Amunix is a stable group of about 30 people who invent new, practical technologies and create new products based on them. A set of products then serves as the basis for a spin-off company that is led by an experienced development

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team of five or six people who outsource everything else," he explains. "It's designed to be a bite-sized piece that a pharmaceutical company can easily acquire."

Stemmer's capacity to make difficult seem easy has always set him apart. Stephen Del Cardayre, vice president of research for the South San Francisco-based biofuels company LS9, met Stemmer in 1996. "Aside from being one of the most insightful evolutionary technologists around, he is a fire hose of ideas and is unique in his ability to get them implemented," states Del Cardayre.

The power and breadth of gene shuffling means that Stemmer also worries about its use, or more specifically its misuse: "Arguably, it's the most dangerous thing you can do in biology," he says. What's more, he is worried about the potential for "many blue-sky projects to be misunderstood." Indeed, Stemmer is no stranger to controversy, having been criticized by both environmentalists and agrochemical companies when he came up with a scheme to produce non-transgenic seeds from transgenic crops (*Nat. Biotechnol.* **20**, 215–216, 2002).

For that reason, he is happy for others to wrestle with the ethical and societal problems associated with breeding new life forms. But snake venom? No problem.

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