Efforts to commercialize structural genomics may be limited

Following on from the Human Genome Project, the UK's Wellcome Trust (London) and about 10 companies are planning a non-profit high-throughput analysis of human proteins (*Nature*, **406**, 923, 2000). Similarly, the US National Institutes of Health (Bethesda, MD) recently launched a Protein Structure Initiative, and the governments of Canada, Germany, and Japan reportedly are also planning major structural genomics initiatives. But in addition to these public efforts, at least nine private ventures are keen to cash in on the commercial potential of structural genomics. Although these companies do not currently consider the public efforts a threat to business, several are aware of the limitations of the different techniques for protein analysis. While some are trying to increase their individual chances of long-term success, others acknowledge that consolidation is inevitable.

Broadly speaking, structural genomics companies fall into three camps, based on the technology applied—X-ray crystallography, nuclear magnetic resonance (NMR) imaging, or *in silico* computer-based predictive modelling.

Start-ups offering high-throughput protein crystallization and structure analysis on a fee-per-structure basis include Structural GenomiX (San Diego, CA), Syrrx (San Diego, CA), and Astex Technologies (Cambridge, UK). Although X-ray crystallography is not new, the firms believe the speed resulting from automation and integration of each step will attract pharmaceutical customers looking for protein structures. For example, Nathaniel David, Syrrx's co-founder and director of business development, says that the cost per structure could drop to around a tenth of today's cost (around £200,000), while Structural GenomiX claims to be able to analyse around 2,000 proteins a year. For this reason, Tim Harris, Structural GenomiX's CEO, says that in the short term, public initiatives such as the UK's Structural Genomics Consortium and the NIH's PSI offer little threat to his business. "Public initiatives using academic centres are a logistic nightmare," he says. "We can offer companies a 'one-stop shop' for proteins structures—today." He points out there are no institutes dedicated to structural genomics currently in existence, which will make setting up a consortium time-consuming and costly.

More importantly, there is the issue of exclusive access to data, which will not be offered by the public initiatives. "SNPs and even genes are a long way from drugs," says Harris. "But it's a much simpler step from the protein structure [in essence a drug "template"] to a novel small molecule." Drug companies will pay a premium for this information, he says.

Although the NIH's initiative has encouraged research using both X-ray crystallography and NMR, for now the UK's international consortium plans to use only crystallography in its structure-solving initiative. However, X-ray studies alone—whether through public or private initiatives—may be limited because some people estimate that more than 20% of proteins (many of them key membrane-bound proteins) are not readily crystallized. And even if crystal structures are available, additional data would be needed to determine the potential biological function of the protein.

This is why companies such as Structure-Function Genomics (Princeton, NJ), Integrated Proteomics (Toronto, ON) and Triad Therapeutics (San Diego, CA), which are using NMR to study protein structure and function, expect to be successful. NMR can be used to monitor the "flexibility" of proteins and to carry out high throughput screens of their interactions with small molecules. Unsurprisingly, these startups are critical of the "high-throughput" crystallography approach. "It's distracting to the main goal, which is to understand protein function," says Stephen Andersen, a co-founder of Structure-Function Genomics. Indeed, some academic protein chemists see the crystallographic approach as no better than "stamp collecting," and with the added risk that there could be a rush to solve the "easy-to-crystallize" proteins simply to bump up numbers.

Meanwhile, companies aiming to reconstruct protein structures virtually are already attracting pharmaceutical partners that believe they can provide accurate structural and functional data by constructing a "photofit"-equivalent of a protein from its component motifs. Structural BioInformatics (San Diego, CA), for instance, has already signed up three pharmaceutical partners, which were attracted by claims that it could move from gene target to the identification of small molecules within 60 days. Ed Maggio, the company's CEO, says that it already has 60,000 unique protein structures in its database. And GeneFormatics (San Diego, CA), which was established only 6 months ago, has four pharmaceutical customers for its "Fuzzy Functional Form" modelling system.

A similar company, Prospect Genomics (Belmont, CA), is focused on "homology modelling"—creating 3-dimensional models of proteins from matches with related protein motifs. Although there are so far no clinical success stories of drugs identified in this manner, Chiplin says that critics should remember the scepticism that initially surrounded the advent of computer-based rational drug design.

Nevertheless, the protein structure "land grab"—by whatever means—cannot guarantee the long-term profitability of companies. John Chiplin, CEO of GeneFormatics points out that "There's a correlation between the market value of many companies and their intellectual property (IP) portfolio," and IP from proteins must come from "added-value" information.

In particular, the long-term viability of crystallography companies is questionable. Gaetano Montelione, an advisor to Structure-Function Genomics and to the NIH's Protein Structure Initiative, asks: "The key issue is how to extract long-term value. You can't patent the coordinates from a crystal structure unless you can use this information to say something valuable about biological functions…unless this is part of the package, I don't see where their future growth will come from."

Aware of this, some start-ups already have plans for the future. For example, Astex's founder and chief scientific officer Harren Jhoti says that Astex is aiming to derive novel drug leads from its protein structures, which will add "long-term value" to the company. And Maggio says Structural BioInformatics has already started using its protein models to generate lead molecules in specific therapeutic areas.

Syrrx's David suspects that the public initiatives will ultimately "dilute the value" of the commercial companies, and Geneformatic's Chiplin thinks this will be addressed by "the healthy integration of all three technologies [NMR, X-ray crystallography, and in silico studies]"—something that will most likely come through consolidation in the sector. In the meantime, says David, there is still a "window of opportunity of 5–10 years" that could prove very lucrative for the start-ups.

Liz Fletcher

Liz Fletcher is a freelance writer working in Cambridge, UK.