Opinion

Is 'big biology' a commercial enterprise?

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Abstract

Big projects in biology - such as the human genome project and a number of related and ensuing enterprises - require big funding. A new tradition is growing in which some types of basic research take place within commercial organizations. This article reviews some of the reasons for this and some of the key players, in the USA, Europe and Japan, and highlights some issues to be considered when deciding whether particular research belongs in a company rather than an academic setting.

When I was asked by this journal to write about the role of commercial businesses in the field of 'genome biology', I found it a surprisingly difficult article to write, because on the one hand I find it amazing that there are not more companies in the field (particularly in Europe) while on the other I am surprised that any succeed at all.

History

Sequencing DNA reliably and reproducibly at extremely high throughput using commercial-quality machines was, for all of us life scientists, the first experience of scaling up an experiment to provide large numbers of biological results, rather than a large amount of a biological product. (I say this specifically to differentiate the present challenges from those faced by the original biotechnology companies, such as Genentech, who in the 1970s were deriving new ways to produce large amounts of a protein therapeutic using cloning techniques and large-scale fermenter technology.) From the point when DNA sequencing became industrial in scale - around the early 1990s - it became apparent that providing comprehensive, and ultimately complete, genome information would be possible. At that time, the main question was who would do the work. While many people were interested in the results of high-throughput methods, many felt uneasy with the introduction of production-like facilities into academic research departments. Firstly it was feared that hard-to-find grant money would become concentrated in supercenters, and secondly it was regarded, perhaps correctly, as an 'engineering problem' rather than basic research (see, for example, [1]).

While these debates were continuing, a company - Human Genome Sciences Inc. (HGS, of Rockville, USA) [2] - teamed up with a non-profit institution - The Institute for Genome Research (TIGR, also of Rockville, USA) [3] - in order to sequence and patent a large number of expressed sequence tags (ESTs), partial sequences from cDNAs that are sufficient to identify the encoded gene product. HGS had decided that there was commercial mileage in scaling up the sequencing 'experiment' and attempting to create a position of owning intellectual property around large swathes of the human genome. This initial idea gained commercial credibility when SmithKline Beecham (now part of Glaxo SmithKline, headquartered in Brentford, UK [4]) and Takeda Chemical Industries (of Osaka; Japan's largest pharmaceutical company) [5] decided to license the data. The response to this unprecedented development was itself unusual, with Merck & Company (Whitehouse Station, USA) [6] deciding to finance a public sequencing facility at Washington University in St Louis, USA to make EST data freely available to all. For completeness, it is worth noting that other companies were also embarking on a similar strategy. Incyte Genomics (Palo Alto, USA) [7], for example, also started around that time and is now arguably the best known company for generating and licensing EST and full-length cDNA databases.

The lessons that I gleaned from these examples were the following. Firstly, scaling up biological experiments can be extremely valuable, from both an academic and a commercial viewpoint. Secondly, the commercial value of a scaled-up experiment depends on three key factors: a subjective view of the value of the data - either from using it as a key platform for in-house research or out-licensing; the barrier to entry costs for anyone else (in particular not-for-profit institutes) trying to repeat the experiment; and finally a worry factor - which in the particular case described above was concern that a limited number of companies might control key genomic information if no other action were taken.

Commercialized experiments

So, how do some of the major genomic biology experiments fit in the commercial world? The best known is the sequencing of the human genome. Unlike EST sequencing, genome sequencing had already started when Celera Genomics (Rockville, USA) [8] came on the scene. Celera's idea was to sequence the human genome faster than the public-domain Human Genome Project could do it, to develop interfaces to facilitate interpretation of the genome sequence, and to back this up with other genome-sequence data, such as the mouse genome sequence and human single-nucleotide polymorphism (SNP) data, for which public funding is not as plentiful. Whether this turns out to be a good business model or not remains to be seen, but Celera is certainly acquiring a large number of licensees in both the commercial and the academic spheres, suggesting that many consider it worthwhile to pay for the added value it provides over the public-domain data.

Three other areas of biology that are being scaled up in academic and private spheres are proteomics (high-throughput protein identification by mass spectrometry), structural genomics (high-throughput three-dimensional protein structure determination by nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography) and bioinformatics - the sector I work in. Here, I consider each of these in order, highlighting the companies I consider to be the major player in each area.

Proteomics

There are three main commercial players in the proteomics field: Oxford Glycosciences (OGS, of Abingdon, UK) [9], MDS Proteomics (Toronto, Canada) [10] and Cellzome (Heidelberg, Germany) [11]; the latter two both recently published articles in *Nature* showing how their technology can be applied to the yeast proteome to provide valuable protein-interaction data [12,13]. These three companies appear to be in a relatively strong position, as there is little competition from the public sector and their methods can genuinely be thought of as high-throughput. OGS is by far the most advanced of the three, having been in existence since 1988 (as compared with 1999 and 2000 for MDS and Cellzome, respectively), and has a dual business model, with a licensing part (now a venture in its own right, joint with Marconi and called Confirmant [9]) and an apparent longer-term goal of becoming a pharmaceutical company. To fund its push for the latter, OGS last year raised approximately $200 million on the NASDAQ stock market.

Structural genomics

Structural genomics also has three big commercial players: Syrrx Inc. (San Diego, USA) [14], SGX Pharmaceuticals (previously Structural Genomix; also of San Diego, USA) [15] and Affinium Pharmaceuticals (formerly Integrative Proteomics, of Toronto, Canada) [16]. In contrast to the experience with genome sequencing and proteomics, there have not really been revolutionary changes in the ways we determine structures over the past twenty years. Of course, there have been tremendous incremental improvements, but these are essentially available to all. The determination of protein structures is still a relatively slow process, although it is more successful for some proteins (particularly bacterial proteins) than others. The main problem that these companies have to contend with, therefore, is the large number of competing academic consortia around the world (see [17]). These consortia include supercenters such as those involved in Japan's Structurome Project [18] - which dwarfs all the companies. Indeed, some key personnel in this sector maintain involvement in both academic and commercial camps. Perhaps the main points in favor of the companies are that the process is so slow, and human proteins (which are of most interest to pharmaceutical companies) receive less attention from the consortia because they are the most difficult to determine. As a result, companies have the opportunity to concentrate on proteins belonging to a small number of therapeutically relevant families, in contrast to the 'solve it and see' approach of the academic labs.

Bioinformatics

Companies with bioinformatics as a core competency probably face the fiercest competition from public-sector activity. For the 2002 financial year the US National Center for Biotechnology Information (NCBI) [19] alone will probably receive grants of around $50 million, and the European Bioinformatics Institute (EBI) [20] may receive around $19 million. Add to this the number of other national and academic websites worldwide and one's product has to have a clear benefit to stand a chance of success. DoubleTwist (a reincarnation of a company previously known as Pangea; based in Oakland, USA [21]) pinned its hopes on providing processed views of the publicly available genome data. This was a pretty neat idea when launched and seemed to fill key market niche - but the recent announcement that DoubleTwist is to stop operating suggests that it found it hard to become profitable [22]. It had to contend with the public-domain Ensembl project [23], which recently received £8.8 million (around $6.2 million) of funding from the Wellcome Trust to place similarly

processed genome information in the public domain free of charge. Ensembl almost certainly now has more money to inject into this field than any company; furthermore, Ensembl does not have to list 'return on investment' as one of its measures of success.

A more successful company in this area is Lion bioscience (Heidelberg, Germany) [24], which provides solutions for companies that wish to combine in-house data with that from the public domain but which also have a traditional paranoia about sending their own data over the internet to insecure websites. The vast majority of pharmaceutical companies now have at least one Lion product, producing a solid business opportunity (although how much further growth is possible may be more debatable).

Moving closer to drug discovery, Inpharmatica (where I work; London, UK [25]) specializes in areas of bio- and chemoinformatics that use protein three-dimensional structures as key components. This is currently a fairly specialized sub-area of the informatics field but is believed to have comparatively high commercial value as a result of its direct relevance to pharmaceutical target selection and drug design.

Securing funding

How did the companies mentioned above start out? In most cases they began with an academic scientist with an idea of how to commercialize and scale up a key area of research. As described previously, securing funding for a new company will ultimately depend on how investors view the scientific proposal, management team and the market opportunity. Naturally all of these rely on a bit of luck. A combination of my own experience and anecdote suggests the following as key elements.

Strong science

In a crowded field, a major challenge for young companies is how to make their technology stand out from the crowd. The scientific credibility of the scientific founders is of course important, but an interesting development recently is the number of companies that, once set up, continue to publish high-profile research in peer-reviewed publications, at least during their early years. In general, the approach has been to publish work in prominent journals, in some cases concentrating on model organisms to provide proof of principle. Rosetta Inpharmatics (of Kirkland, USA [26]; see [27], for example), MDS proteomics [10,12] and Cellzome [11,13] have all had papers in *Nature* or *Science,* and this has undoubtedly attracted attention to their techniques. This 'shop-windowing' of technology is quite different from the behavior of traditional companies, which normally wish to keep their abilities under wraps. Of course it does not mean that the approach will ultimately be commercially viable, but it does provide a concrete answer when asked to differentiate your company's technologies from those already available.

Management

The availability of strong management is also a key element, as good ideas usually require a hard slog to become reality. From what I have observed, this seems to operate better in the US than in Europe, as there is a stronger pool of managers and financiers who are prepared to work in start-up companies. Europe has traditionally found it difficult to tease senior management out of big companies to apply their valuable knowledge to start-ups, although this is changing as Europe starts to have its own success stories. Japan is dramatically behind both the US and Europe in this area, with few people prepared to exchange their 'job for life' for a sea of uncertainty. To combat this, Japan does have limited-lifetime research institutes that operate in new areas of science; as this is rather unusual, the following provides some background for readers.

Japan has an unusual set of research institutes that are funded by a combination of big companies and a government department (see [28] for further discussion). The technologies are usually in areas that companies are not prepared to fund themselves but have sufficient interest in to participate with others. Each institute has a fixed time span after which the project is closed (although many arise, like a phoenix from the ashes, with similar personnel and a different name). The names of the institutes are usually descriptive of their aims - for instance, Protein Engineering and Computational Biology. These are currently the closest Japan has to a venture-capital-funded company, and these institutes may be relatively good targets for conversion into real companies at the end of their guaranteed period. Presumably, some investors would be interested in the data and intellectual property generated during five years of generous public funding, but, more importantly, those seconded to the 'start-up' might be keen to continue working in such an environment rather than moving back to their old company. Certainly during my time working in such places, many people viewed their return to the 'mother ship' with as much relish as attending a funeral.

A touch of reality

With many difficulties to overcome, it is hardly surprising that securing venture capital is difficult. Even when you have convinced yourself that there is an opportunity, it is quite another matter to convince those who do not have your own specialist knowledge (and bias) but have more experience of funding such ventures. The number of companies that receive funding in the US is far larger than the number in Europe, which is probably a good reason to reside in the US for the set-up phase. This does not mean that US companies are ultimately more likely to be successful, but it may be easier to get off the starting blocks.

Those thinking of setting up a company should also be aware that the number of very successful companies in the biotech area is extremely small, yet it is these successes that drive

further interest. Rosetta Inpharmatics [26] is the most recent example of a major success, having been sold to Merck [6] for over $600 million. There was certainly a flurry of interest in all start-up companies after that announcement was made, and 'platform companies' - those with a proprietary technology base - are now in vogue once more.

The US invests the most in biotech and has the largest number of success stories. Europe invests less and its major success stories are correspondingly fewer. Japan invests hardly anything and consequently has almost no biotech industry whatsoever. I once asked a well known Japanese financier why this should be, and he replied that most Japanese venture capitalists considered the funding of a new pizza chain to be fraught with risk, so biotech was not even on the menu.

In conclusion, the implementation of large-scale genetics and biology is unique in appealing to both commercial and academic spheres simultaneously. This can create both competition and opportunity (depending on one's viewpoint). Although a great deal of attention has been paid to the overlap between the public [29] and private [30] genome-sequencing initiatives, most of the polarized viewpoints on this subject in fact arise not from the private sequencing initiative itself but rather from Celera having published its results with only limited data release [30]. I would argue that the commercialization of some areas of biology has been an exciting journey to reach as far as the current situation, and seems bound to continue both to contribute to basic understanding of biology and to test the boundaries between academic and commercial sensibilities. The successful entries into the marketplace will always be those companies that identify areas where they can provide key utility and overcome the barriers to entry into the field for other players trying to achieve the same ends. I look forward to discovering which areas feel the effects next.

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