



Lessons for the nascent regenerative medicine industry from the biotech sector

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As regenerative medicine has so many parallels with biotech directed to molecular biopharmaceuticals, the lessons of bioscience-based business are highly relevant, and it is interesting to examine them.

Recently, Gary Pisano, a respected Harvard Business School professor, who has long followed the biotech industry, published a new book, *Science Business: The Promise, the Reality, and the Future of Biotech* [1]. It contains evidence for some striking conclusions, most stark of which is that the industry in aggregate has never made a profit. This tends to be overlooked because a handful of companies, most notably Amgen, have been so brilliantly successful (Figure 1). A second conclusion is that biotech ventures in general have been consistently no better or worse than pharmaceutical companies over a 25-year period in terms of cumulative R&D costs incurred per new drug launched.

Pisano examines why the performance of the biotech sector as a whole evidently has not been better and concludes that the industry is quite different to the silicon-based information technology sector. There, too, the pattern of university spinouts, venture funding and investment by major companies is found. However, in information technology, the intellectual property situation is more straightforward and the activities can be separated into modular parts that are distinct and relatively easy to interface and trade between stakeholders. In biotech, the elements of drug R&D are not modular, but are heavily interdependent. There is also, in spite of the great advances in biosciences, still a considerable degree of art to the discovery process and the judgements that follow. The intellectual property situation is also complex, with greater uncertainty of outcome on poorly defined and overlapping patents versus the more concrete intellectual property of software code [MacKay G, Pers. Comm.]. Again, in contrast to semiconductors, the new biopharmaceutical proteins of the biotech sector

have not displaced what went before, namely chemical pharmaceuticals, in the way that occurred with thermionic valves after the introduction of silicon chips.

Most new biotech start-ups have had very little capacity to learn by experience. They either got it right very quickly or they ceased to exist in any useful sense. A few, including Amgen, Biogen, Genentech and Genzyme, have succeeded, but in most cases, new waves of companies have replaced those that fell by the wayside and have begun the learning process anew. The biotech revolution and the companies leading it have opened up huge new scientific territories and created a completely novel kind of medicine, but by Pisano's criteria they have not succeeded commercially as a whole. With classical pharmaceutical companies in difficulty, new science such as genomics failing yet to help deliver safe products, and investors more cautious, the picture is disturbing.

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Challenges to regenerative medicine start-ups

Some of the problems faced by biotech companies are just as immutable for the regenerative medicine ('regen' [Box 1]) industry, most of which are start-ups. Those putting forward recombinant protein-based therapies generally faced great scepticism from classical chemical pharmaceutical companies, who doubted the general value of drugs that demanded therapeutic administration by injection and were produced by inherently more complex processes. For regen start-ups, the

Box 1. 'Regen'.

The shorthand term 'regen' has been used in a similar way to the terms 'pharma' and 'biotech' as routinely used to describe companies in the pharmaceutical and biotechnology sectors, respectively. Thus, 'regen' is the industry that develops and sells regenerative medicine products.

doubts regarding a profit-making paradigm by much of pharma are probably greater. With proteins, a few major pharma companies such as Eli Lilly were already involved, in their case in insulin extraction, and so were more inclined to listen, and one on two, most notably Roche in its investment in Genentech, were visionary. The consequence of general indifference, at least in the early days of therapeutic proteins, was that if a start-up wanted to see a product they had no option but to establish the whole vertical integration needed. That is as true today for most regen start-ups. However, in areas closer to established uses of human cells of the bone marrow transplantation kind, there are some commonalities. There is also a gradation via tissue engineering, where the addition of somatic cells to advanced biomaterials represents a link to more established companies such as Smith & Nephew and Johnson & Johnson. However, as the failure of the Smith & Nephew – Advanced Tissue Sciences venture and the withdrawal of Novartis from its Organogenesis partnership indicate, the bridges are not robust. The obligation in regen start-ups, especially with more advanced materials, to proceed to vertically integrated companies was also one of the causes of vulnerability with biotech. It stretches them across a great number of skill sets and leaves little room for mistakes or even delays. It emphasizes the value of the strategy adopted by a number of regen companies of choosing therapeutic targets that will be implemented by a relatively small number of clinicians such that large marketing forces and expenditure are not needed.

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As noted, the products of biotech have not displaced earlier pharmaceuticals and therefore compete in the same market place. At present regen products, such as engineered skin, owing to their present level of efficacy, have to compete with classical medical treatments such as bandaging. As the efficacy of regen products gradually emerges [2], there does seem a better prospect in the longer term that they could displace older and unsatisfactory procedures altogether; however, given clinical conservatism and the common payment separation between hospital and social care, that is too far away at present to be a

help to start-ups. If full displacement does happen, it will greatly increase the chance of strong interest by major pharma and healthcare companies and will expand the business options open to start-ups. Even now, there are signs that contract manufacturers in the biotech sector are beginning to take a growing interest in processing human cells for direct therapies, and the purchase of the Cambrex Bio-Businesses in the field by Lonza is indicative.

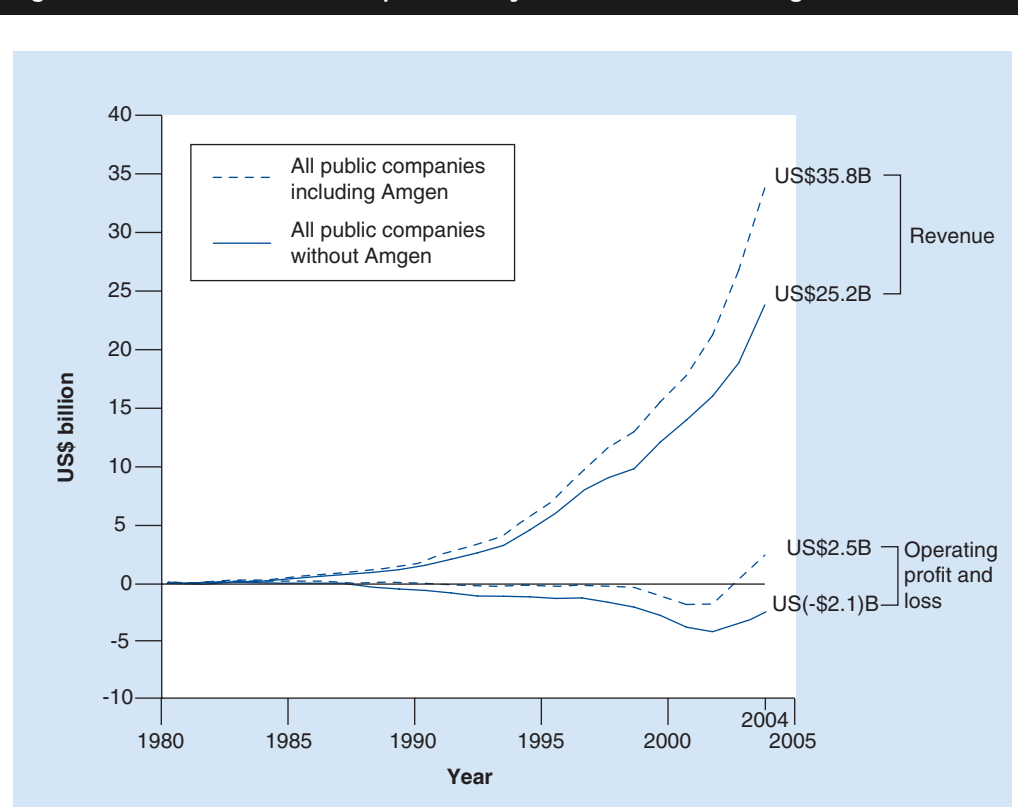
Regen may have one other characteristic that is generally harder for therapeutic proteins. This is that it can, with the same set of technologies, address a graded set of targets of progressive complexity and risk. This was also possible for the very early biotech companies, which explains their focus on producing, by recombinant methods, proteins already made from natural sources, such as recombinant growth hormone. However, these opportunities were very few, whereas in regen the gradations may be much more widespread.

Help from other quarters

One of the problems with both venture-capital money and pharma alliances is that the time spans of funding are very short in relation to the development times for medicines. There would be great virtue in more patient investment, albeit with the same need for rigorous regular evaluation [3]. Here, the value of venture philanthropy of the kind involved in charitable foundations such as the Bill & Melinda Gates and Cystic Fibrosis Foundations is clear. The California Proposition 71 research funding could be of this kind. Such funding might also address the concern that funding by individual universities often leads to an excess of spinouts, too many of which are so narrowly based as to lack a good chance of success, and indeed of a return to the investors. Equally intriguing is that there are already concerns that, if US government funds for human embryonic stem cell-based research on cell lines made later than August 2001 [101] are unfrozen at the end of the present US Presidency, entrepreneurs may prefer to use their academic links to access those funds with their lack of a requirement to repay in some form.

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Figure 1. Biotech revenues and profitability with and without Amgen, 1980–2004*.



*Values are inflation adjusted.

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In his book, Pisano makes a plea for biotech that universities should be less obsessed with spinouts and more concerned with establishing a 'scientific commons' [102]. As with the basic recombinant DNA concepts and patents, this need not mean seeking no return on investment in research, but it would where feasible and sensible mean more nonexclusive licensing so that the field can be opened up rather than closed off. One feature of regenerative medicine is that the bioprocesses by which products are made have a lot of common features that can be examined by university groups and then applied to specific systems by companies and embodied in their particular intellectual property. In the biopharmaceutical protein field, where a similar situation applies in downstream processing, we find it straightforward to have multicompany research consortia, even though a major proportion are US companies governed by strict antitrust laws. The use of this approach should reduce the cost to individual regen companies by laying a broad bioprocess foundation.

Start-ups do often represent islands of specialism, and universities could help with interdisciplinary research and training. This is not an easy role, in that universities and their peer-review process are themselves divided into narrow territories, but this need argues strongly for more breadth of vision within the regen sector. It should be helped by the fact that, unlike most early biotech companies, regen start-ups are much more aware of the importance of bioprocessing issues and the vital link between cell biology and engineering [MacKay G, Pers. Comm.].

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The issue of public-private partnership is being raised in government circles, and not only in relation to regenerative medicine (e.g.,

Recommendation 1 of the UK Stem Cell Initiative Report [103]). As the pharmaceutical industry spends ever more on R&D and discovers ever fewer significant new drugs, the question is raised regarding whether it may oblige the public sector to take their role in basic research further towards the clinic before passing over the action to industry. If it does so, it would need to receive some of any resulting profits.

One of the concerns in government regarding therapeutic proteins is that they are so costly as to limit use. This strain is set to increase and, unlike small molecules, the progression to generics is more difficult because of the problem of proving bioequivalence. While it is not the direct business of regen companies to be concerned with the burden of the costs of their products, the full development of the industry and its influence will be affected by its capacity to produce affordable goods. It will, of course, be greatly aided if they yield cures or long-term periods of health, rather than brief stays of disease remission of the kind provided by some biopharmaceutical proteins.

Learning from the pioneers

It would be good to believe that universities, venture-capital funds, pharma companies and regen start-ups would take note of biotech's experience. If all could be more receptive to the need for patient, longer, partnerships with a broader spread of concepts in harness together, the outcome could be better for all. It might reduce the chance of a huge payback for a few but, even for those with a gambling disposition, the odds are not good. Identifying the enablers of this is not easy. It could be visionary pharma companies such as Roche in biopharmaceuticals, who were supportive of Genentech by understanding their ideas and then patiently letting the start-up use its judgement. After many pharma companies

missed the boat with the early therapeutic proteins, perhaps a few may see virtue in patient support of regen activities. It might be angel investors or venture philanthropists, who corral activity in particular sectors, or it might be venture-capital companies, who, even now, do work to link together start-ups (to a limited degree). Finally, perhaps even private equity companies may become interested in the difficult middle stages of investment.

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For the present, the nascent regen industry has to live in the world as it finds it. However, it can hope to learn from the biotech sector, which is its closest relative in terms of being equally based on advanced life sciences. From that sector, it knows that early start-ups can do extremely well, that there are gains though some disadvantages in having a range of activities from simple money earners to more risky advanced targets, and that, as well as good efficacy, its products must be competitive with alternative, if less efficacious, treatments. Clearly, a key message is that every company must pay close attention to the models adopted by early regen start-ups, to their inevitable mistakes and to the solutions that the best of them adopt to correct these. The real success would be if regen could make the healthcare advances of therapeutic proteins and be highly profitable. That would be good for patients, companies and future government investment in regen research and innovation.

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