

Making money from microbes – case studies

Spinning out

■ Jeff Errington

The traditional approach to antibiotic discovery was to screen chemicals or natural products (e.g. microbial culture filtrates) for the ability to inhibit the growth of bacteria. This was spectacularly successful in the golden age of antibiotic discovery – the 1940s and 1950s. However, from the 1960s onwards, the discovery of new antibiotic classes began to dry up. Most new compounds that killed bacteria also killed mammalian cells or belonged to one of the known classes of antibiotic. In the mid-1990s the pharma industry hit on a new model for drug discovery, based on genomics; the so-called 'target-led' approach. Good targets are proteins that are essential for bacterial viability and are conserved across a broad range of bacteria, but with no counterpart in mammalian cells. Chemical inhibitors that work on such targets should be selectively toxic for bacteria and active across a broad range of pathogens. Genomics promised to provide a plethora of new targets and therefore rejuvenate the search for novel antibiotics.

Over the years, most pharmaceutical companies had accumulated large collections of chemicals – 'compound libraries' – that could be screened for specific kinds of activity. Active molecules would then be modified to optimize their potency and pharmacological properties, so as to produce new drugs. The challenge for the pharma industry was to develop good screening assays for compounds acting on the desired targets. A major bottleneck arose here because this usually required a deep understanding of the biological function of the target. This specialist basic knowledge is usually available only in academic labs that have focused their energy and intellect on the subject area over many years. I realized that the skills and expertise that my lab possessed in the molecular genetics of cell cycle processes in bacteria might be applicable to the new target-led screening.

On the advice of a friend, I drafted, and the university filed, several patents describing ideas that I had on various screening assay methods. We tried to interest a number of companies to take out licences on the patents. Unfortunately, this proved to be difficult. The main problem was that our assays were based on the use of live bacterial cells containing reporter genes, whereas the screening departments in industry were geared up to do assays on purified proteins, and so were run by biochemists rather than microbiologists. It soon became clear that we needed to demonstrate that the assay principle worked in a high-throughput format, rather than at lab scale. The challenges of developing robust high-throughput screening assays, and 'marketing' these to the pharma industry seemed achievable only through a spin-out company.

Aided by the University of Oxford's superb technology transfer resource, Isis Innovation Ltd, and after a huge amount of time and effort, Prolysis was finally launched in June 1998.

The early days were particularly difficult. For an academic with no knowledge of the commercial environment, I was on a very steep learning curve. We had to recruit

the right staff, including a mixture of scientific and commercial people. We had to find premises, and organize the refurbishment and equipping of them. Most problematic of all, the administrative tools and facilities needed for a proper business had to be set up, including health and safety, employment, a library and a minefield of legal and commercial documentation. Most academics have no concept of these issues because they are usually taken care of by central administration in a university department.

Prolysis currently employs 15 full-time staff, including 13 graduate or doctoral scientists, and we have now gone far beyond the proof of principle stage. We complement advanced compound screening approaches with a range of molecular genetic and digital imaging technologies, and have several ongoing compound development programmes running in parallel. We play to our strengths on the biological side and access top-class chemistry through a collaboration with an Oxford-based company, Evotech OAI, where we fund a team of seven full-time medicinal chemists. We have established our own library of >100,000 different chemical compounds, with drug-like characteristics. These are screened for potential antibiotic activities using the cell-based assays mentioned above. Promising active compounds are then put into a development pipeline. Although the costs escalate the further into the pipeline compounds go, the company could profit hugely from compounds that make it into the clinic and beyond.

The main difficulty Prolysis and most other biotech companies face is that huge costs are incurred before any financial return is possible, and the only way to raise funds in the early years of the company is through venture capital. Fund-raising can be a draining and demoralizing process. An investment round can take 9 months or more from start to cheque and can involve scores of presentations to potential investors. Even when the decision to fund has been taken, there are lengthy negotiations, incredible legal costs and huge legal documents to read. Nevertheless, Prolysis is now a vibrant, well established biotechnology company with a bright future. Provided that the economic outlook continues to improve, the prospects for further growth into a fully fledged drug development company look good. The last 5 years has been an exciting adventure into the world of commerce for me, and I look forward optimistically to the day when Prolysis announces its first drug!

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Starting up

■ Duncan Maskell

Founding a start-up company is the beginning of a long and arduous journey that encompasses many potential pitfalls along the way. It would be nice to think that having the innovative idea required to get a company off the ground was the hard bit, and that as long as the science was good enough, somehow, as if by magic, loads of money would come rolling in. If only life were that simple!

Most start-ups are specifically designed to do clever basic research and to bring it closer to an applied outcome. Inevitably therefore, the attrition rate is high, with many companies failing at an early stage. This may be because it becomes obvious that the original ideas are not going to work after all, or because the investors cannot see sufficient increased future value and will not put in the funds to support the company beyond the life of the initial (usually minimal) seed funding. Even if the company gets beyond this stage and starts to build a profile and pipeline, it is often at the expense of tension between the initial scientific ideas and the agenda that is set by investors in terms of where they see the best business opportunities coming from. Companies that walk this tightrope for any length of time and succeed in achieving an initial public offering (IPO) on the stock market, or in being bought out for a large sum of money in a trade sale, often look very different from when they were founded and indeed often end up working in areas that did not form part of the initial business plan.

When I founded Arrow Therapeutics Ltd. in 1998 with Ian Charles, Alastair Hawkins, David Stammers, Jeremy Stables and Ken Powell, I had the naïve belief that because our ideas for antimicrobial drug discovery were strong, then there was little or no reason why we should not succeed in bringing products to the market in the near future. To a large extent this confidence was justified, and we delivered some excellent research that led to the identification of several candidate chemical series and the development of at least one of these nearly into a pre-clinical programme. This level of success was enough to keep our initial 'investment angels' very happy and to ramp up the valuation of the company considerably when we landed our first really big chunk of investment. The company grew rapidly and was very successful. However, as is all too common in research, some of our programmes did not progress beyond certain checkpoints and the normal attrition rate set in to our research pipeline. This was disappointing and not entirely unexpected, but it

certainly made me grow up quickly and realize that being able to cash in my founder shares to make a significant profit in the short term was becoming somewhat unlikely.

This fantasy was further shattered on 11 September 2001, when the markets collapsed as a consequence of the terrorist attack on the USA. The market conditions in the aftermath of that kind of world event are inevitably very poor for flotation, or indeed any business transactions. Consequently, the company, which had by then grown to an appreciable size, employing about 70 or 80 people, had to make moves to go out for another large tranche of venture capital finance. Even this was going to be difficult in the market conditions, as the attitude to risk of the people with the money had hardened enormously. A requirement to have potential near-market projects was now the common message from all of the potential funders. Fortunately, Arrow Therapeutics had re-focused a little, bringing some of its projects forward to replace some of the earlier ones that had run their course. One of these was successful antiviral research that had identified lead compounds that could be moved quickly into a Phase 1 clinical trial. This is a clear example of how a company's research portfolio has to evolve and how projects that were not at the front of the queue when the company was founded can move up in the pecking order and rapidly become its central activity. This doesn't always please all the people involved from the start in a small company, but in the real, hard world out there, this is often simply what has to be done to survive. In our case, the team running the company was able to secure substantial funding, despite the hostile investment environment, that should see Arrow survive and prosper for quite some time, albeit with a scientific agenda that, though basically the same, is different in detail from that at foundation over 5 years ago.

In all of this roller-coaster ride, inevitably, my share in the company has diminished. It is unlikely that I will get rich in the short term, but longer term, if it does float successfully on the stock market, or goes through some similar kind of exit strategy, I may still be in for a handsome pay day. I have already made some money out of the exercise through being paid a consultancy fee, but it still doesn't bring my combined earnings up to even a fraction of those of the various other professionals with whom we have interacted during the life of the company!

Making money out of the start-up was only one aspect of why we did it. It has enabled us to do some fantastic science with much more resource and much less hassle (amazing but true!) than would have been the case if we had tried to do this work with public money. It has brought over 80 new jobs into existence and has engendered antimicrobial drug programmes that may soon result in completely novel therapeutic drugs for some serious medical conditions. I think that, all-in-all, I am happy with this outcome. Maybe we'll make even more money out of our next start-up!

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LEFT: One of the chemistry laboratories at the London headquarters of Arrow Therapeutics Ltd. COURTESY D. MASKELL