Practical experiences in starting up life science companies in the academic sector

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Abstract The authors discuss their experiences in Starting up life science companies in the academic sector as a means of identifying the key issues and highlighting ways of addressing these issues. Sheffield University Enterprises Ltd has led the formation of over 30 companies at Sheffield University in the past three years, many of which are in the biotechnology sector. Ithaka Life Sciences Ltd specialises in supporting the formation and growth of life science businesses by providing specialist expertise to assist the founders; it works with a number of universities and emerging companies around the UK. The paper focuses on the technical, commercial, intellectual property, financial and, above all, practical aspects of working with academic scientists to found biotechnology companies.

Keywords: life science, biotechnology, spin-out companies, academic sector, entrepreneurship, fund raising, venture capital

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Introduction

The UK has a world-class reputation in the biosciences and related subjects. It has earned over 20 Nobel prizes in the life sciences, and British researchers have made many breakthroughs, from the discovery of the structure of DNA, to more recent advances in antibody engineering and cloning. The UK leads Europe in biotechnology in terms of industry revenues for the year 2000 (UK, 2,066m; Germany, 786m; France, 757m).1 The UK has around 300 dedicated biotechnology companies and over 460 companies involved in bioscience-related activities.[2]

The results of the 2001 Research Assessment Exercise (RAE) indicate that the UK continues to have a world-class academic research base, spread across a wide variety of disciplines. They show that British research, ranked among the best in the world, has further improved since it was last examined. More than half of researchers are based in departments containing work of international excellence, compared with a third in 1996.[3] Britain now ranks first in the world in terms of the numbers of publications and citations it generates per £ spent on research. Six years ago, British-based researchers wrote 11 per cent of the most frequently cited papers; that figure has since risen to 18 per cent.

However, in contrast to the USA, the UK has been relatively slow to exploit its strong academic research base in the life sciences through the formation of start-up

companies. The position appears to be improving and a recent official survey showed that 199 enterprises were established in 1999—2000 to exploit knowledge from academic research, compared with an annual average of less than 70 over the previous five years[4] (we have been unable to obtain specific numbers of biotechnology start-ups). Some success stories can be quoted (see Table 1) but it is the authors' contention that there is much that can be done to enhance the UK's track record in spinning-out biotechnology companies from the academic sector.

Commercial exploitation of the university research base

Traditionally, the UK universities have regarded their key roles as being teaching and the creation of knowledge through informed research. However, in recent years, the universities have come under increasing political pressures to play a full role in developing a US-style enterprise economy, and the universities are expected to develop skills in fund raising, knowledge transfer and regional and local economic regeneration. In addition, the universities are expected to provide teaching for greatly increased numbers of students while facing static, or even declining, financial support from government.

These political and financial pressures are providing motivation for the universities to generate wealth through exploitation of their intellectual property (IP). Traditionally, the universities have exploited their IP, if they have done so at all, through licensing. More recently, increasing numbers of universities are seeking to capitalise on their IP through the creation of new commercial enterprises, but there are significant cultural and operational issues that need to be addressed if this new role of the universities is to be effective.

The universities create large amounts of IP, much of which may be in the form of patents, but it can also include know-how and similar skills. The academic scientists may create this IP, but the universities, their employers, generally own it by right of employment contract. Academics often find this hard to understand: they created it, so the IP must be theirs. This can lead to conflict between the academics and the university administrative office with responsibility for IP, resulting in many cases in the early death of a bright idea.

Universities find IP difficult to deal with because their main functions are teaching and research. Many universities would much prefer 'someone else' to handle IP and its exploitation for them. Consequently, with few exceptions, they invest very little in providing resources for the protection and exploitation of IP through licensing or company formation. Few universities provide adequate budgets for patent filing and prosecution, frequently leading to early abandonment of patent applications at the end of the priority year if a third party cannot be found to finance the filing of foreign applications.

The technology transfer offices of many universities are unable to attract professionals with relevant industry

Table 1 Selected examples of successful UK spin-out companies

Company	Year of formation and originating institution	Comments
Celltech	**1980, Medical Research Council (MRC)**	**Market capitalisation of £1,380m (January 2002)**
Oxford Glycosciences	**1988, Oxford University**	**Flotation on LSE in 2000 (£319m raised)**
Cambridge Antibody Technology	**1990, MRC Laboratory of Molecular Biology**	**Flotation on London Stock Exchange (LSE) in 2000 (£153m raised)**
Oxford Asymmetry International	**1992, Oxford University**	**Valued at £503m on acquisition by Evotec Biosystems in 2000**
Bradford Particle Design	**1995, Bradford University**	**Valued at £213m on acquisition by Inhale Therapeutic Systems in 2000**

experience due to budget constraints that prevent the universities offering attractive remuneration and incentive schemes. This leads to a situation where staff with inadequate experience and training are expected to deal with large caseloads. The end result is that opportunities are lost or short-term expediencies are followed ('let's license out quickly to get this case dealt with').

If the UK wants to retain its place at or close to the top of the IP generating league, we need to keep the best brains in universities doing world-class research. This means paying competitive salaries to researchers. The recent changes in student funding make it even more difficult for the best students to remain in academe and become researchers. The average student debt on graduation is £12,000. The research stipends (basic £7,000 p.a. although there are some top-ups to £20,000, but even this is not attractive compared with 'City' salaries) on offer to graduate students in many disciplines make it very difficult (economically at least) for anyone with even modest ambitions for a reasonable life-style to contemplate a career in academic research.

Unless and until the tertiary education sector can get much closer to affording the levels of salary available in industry, or the City, the only people likely to consider a research career are those:

- who are prepared to make a considerable material sacrifice in the belief that eventually they will find some way of enriching themselves; or
- who are motivated by a desire to enhance their knowledge of a particular subject and enjoy the freedom offered by universities to pursue their interests without undue pressures from the outside world.

Neither of these groups can be assumed to be ideal as a basis for IP exploitation via university spin-off companies. It is a common myth that universities are stacked full of frustrated entrepreneurial academics. In our opinion, this is not the case. But, on the other hand, research-rich universities
are full of academics who are very effective at obtaining research grants to pay for their research.

Starting up companies in academia: practical issues

A key issue that needs to be addressed up front when starting up a company in academia is IP ownership. An investigation of this issue often reveals a complex picture. Academic researchers fund their research from many different sources, each of which may have different provisions for ownership and exploitation of IP. Typical sources of funding for life science research are as follows:

- The Research Councils: the University typically owns the IP and the Research Councils encourage IP exploitation wherever possible.
- Charities (eg Wellcome Trust): the charity or university may own the IP. In some cases the charity may expect to be consulted on, and to share in the rewards of, IP exploitation. This can add a further layer of complexity to the exploitation process.
- Industry: companies seek to own the IP or to have exclusive exploitation rights.
- European Union R&D programmes: the university typically owns IP.

Academics are expert at finding 'soft' sources of funding, which may come from unspent grants, 'slush' funds and unallocated pots of money that may be hidden away within the Byzantine financial management procedures of many universities. The ownership of IP generated from these 'soft' funds may be not at all clear. Furthermore, the bedrock of academic research is collaboration. IP may have been generated using materials supplied by a collaborator from another organisation (academic or commercial) under the auspices of a material transfer agreement (MTA), which may or may not contain provisions for ownership and exploitation of IP.

Inventorship is also often an issue that

becomes important not only when filing patent applications but also when assigning IP to the start-up, and for determining which academics should share in the rewards stemming from exploitation of the IP. The academic tradition of naming everyone involved in a project as authors on the ensuing publications can cause complications when trying to identify inventors for patent filing purposes. Inadequate records of invention and failure to follow relevant guidelines for recording data in laboratory notebooks can further complicate the picture (and can also cause future problems with defending the IP against litigation). The end result is often a complex web of IP rights that will need to be unravelled before the new venture can start with a 'clean' IP portfolio.

Once the ownership of IP has been clarified, arrangements need to be made to grant commercial rights to the start-up company. This can take the form of assignment or licence (or a combination of both). Assignment offers the greatest value for the start-up because it provides full ownership rights and thus increases the asset base of the company. Additionally, European venture capital investors greatly prefer companies to own their IP wherever possible. In our experience, assignment can be an issue for some university technology transfer executives. This is difficult to understand, but it may reflect the familiarity of such executives with exploitation through licensing rather than through formation of a commercial enterprise. Some universities will press for assigned IP to revert back in the event that the company becomes insolvent. However, this proposal fails to recognise that the university is receiving a fair consideration for the assignment, and it ignores the commercial reality that the IP is probably the major asset of an insolvent company; such value as can be obtained should be shared by the company s creditors and shareholders (which probably include the university). In any event, under UK insolvency law any arrangement that attempts to put a company's assets beyond the reach of its creditors will probably be overturned by the liquidator. A common
solution is to insert into the assignment agreement provision for the IP to revert back to the university in the event that the new company fails to raise an agreed amount of finance within an agreed period of time after formation of the company.

The founders of, and investors in, university start-up companies are often keen to secure rights to future IP created by the university in the technology field of the new enterprise (so-called 'pipeline' agreements). Universities are understandably reluctant to sign away future rights at this early stage when it is extremely difficult at ascribe a value to the future IP. In addition, pipeline agreements create difficulties for the university in rewarding the inventors of future IP, some of whom may not even have been employees of the university at the time that the pipeline agreement was executed. A frequent solution is to grant the new company a right of first refusal to negotiate a licence to future university IP in the relevant field. This allows the IP to be valued at a point when it is wanted by the company and allows the university to share the value with the inventors.

Typically, the university assigns the IP to the start-up in return for equity, although we have seen examples where the university has agreed a mixture of equity and royalties. This raises potentially one of the most emotive issues of the start-up phase: what is the equity split between the university and the founding academics? Universities usually seek to obtain equity for two contributions to the new venture, the university IP and provision of the infrastructure (laboratory facilities, IT systems, library, salaries of tenured staff, etc.) that allowed the IP to be created. Although most academics will concede that the university IP has a value (assuming that they have accepted in the first place that the university, rather than the academics themselves, owns the IP), many are reluctant in the extreme to concede that the provision by the university of facilities and an administrative infrastructure merits any share of the equity at all. Indeed, many academics will argue that the university administration system is a handicap to

research! Universities will often seek to avoid a conflict by using a set formula (50:50 is not unusual) to set the equity split between the circumstances' prevailing in the case of his or her new venture. In any event, senior academics are usually in a much more powerful position within the university hierarchy than the executive charged with exploitation of the university IP.

Biotechnology start-ups will almost certainly require investment finance to support their development; however, investment finance for university start-ups has been difficult to find in the UK because such new ventures are considered to be too risky by most venture capital funds. There are a small number of life science venture capital funds active in the university spin-out sector, with Avlar Bioventures, Prelude Technology Investments, Abingworth Management and Quester Capital Management being examples. Business angels are the other source of investment finance for new companies, but most business angels are wary of biotechnology investments because of the difficult science and the long timescales. However, it is interesting to note that Isis Innovation, Oxford University's wholly owned subsidiary technology transfer company, has established the Isis Angels Network of investors offering a total of £19m for investment in university research.[5]

The Government addressed the funding gap for university start-ups through the launch of the University Challenge scheme, with backing from the Wellcome Trust and Gatsby Charitable Foundation, in a bid to increase the flow of seedcorn funding for university spin-out companies. Two sets of awards were made in 1999 and 2001, leading to the formation of the Challenge Funds listed in Table 2.

As can be seen from Table 2, the sizes of the individual Challenge Funds are rather modest. However, the scheme has been successful in promoting university spin-outs by investing in opportunities that, in general, are too high risk to be of interest to the mainstream venture capital funds. However, the effectiveness of the scheme is severely constrained by the government-imposed limit of a university and the founding academics. However, a determined academic may well find ways of persuading the powers that be of the 'special £250,000 investment in any one company. In the biotechnology sector such a sum is unlikely to enable a significant reduction in the risk profile of the investee company. In some cases the Challenge Funds have been successful in finding co-investors for particular start-ups and so increase the level of investment.

A perennial issue for the Challenge Funds is valuation of the start-up. Clearly the Challenge Fund will tend to seek a low valuation, as this will maximise its share of the start-up equity. In contrast, the university and the founders will be seeking a high valuation in order to retain a higher proportion of the equity. When resolving this potential conflict the parties must bear in mind the need to arrive at a valuation that will not cause difficulties at the next round of funding when investment from venture capital funds is likely to be sought.

Practical issues facing university start-ups include location, facilities and founders' commitment. These issues are often interlinked as the extent of the founders' commitment can be strongly influenced by the proximity of the new enterprise to the founders' academic laboratories. In any event, unless the initial investment in the new venture is significantly in excess of the Challenge Fund limit, the start-up is likely to have to make use of the research facilities in the founders' own laboratories in order to minimise costs. Such an arrangement can facilitate the day-to-day involvement of the founders in the new venture but it can also raise potential conflicts of interest between the academic's university responsibilities and his or her commitment to the company. A clear demarcation needs to be established between company-funded research and academic grant-funded research in order to avoid the perception that the company is benefiting indirectly from government (ie taxpayers) funding. At one level these issues can be managed through a service contract between the company and the university, but it also requires the academic to establish

Table 2 University Challenge Funds

Fund	Size (£m)	Comments
White Rose Technology Seedcorn Fund (Universities of Leeds, Sheffield and York)	6	1999 award. Managed by Aberdeen Murray Johnstone
Manchester Technology Fund (University of Manchester and UMIST)	6	1999 award. Internal fund manager
Sulis Seedcorn Fund (Universities of Bath and Bristol)	5	1999 award. Extended to include University of Southampton through a 2001 award. Managed by Quester Capital Management
Mercia Fund (Universities of Birmingham and Warwick)	4	1999 award. Managed by West Midlands Enterprises
University of Cambridge Challenge Fund (joint with Babraham Institute)	4	1999 award. Internal fund manager
The Cardiff Partnership Fund (University of Cardiff and University of Wales College of Medicine)	4	1999 award. Bio-medical focus
Imperial College, London	4	1999 award. Internal fund manager
KinetiQue (King's College London/Queen Mary and Westfield College London)	4	1999 award. External fund manager
London Business School/King's College London/Queen Mary and Westfield College/University College London	4	1999 award
University of Oxford	4	1999 award. Managed by Quester Capital Management
University of Strathclyde/University of Glasgow	4	1999 award. Internal fund manager
Bloomsbury Bioseed Fund (University College London/ Institute of Cancer Research/Cancer Research Campaign Technologies Ltd/School of Pharmacy London/Imperial Cancer Research Fund/Royal Veterinary College)	4	1999 award. Life science focus Internal fund manager
Edinburgh Technology Fund (University of Edinburgh/ The Moredun Foundation/The Roslin Biotechnology Centre/The UK Astronomy Technology Centre of PPARC/Edinburgh Station of the British Geological Survey)	4	1999 award, Internal fund manager
Queen's University Belfast/University of Ulster	2	1999 award. Internal fund manager
University of Aberystwyth/The Institute of Grassland and Environmental Research (IGER)	1	1999 award. Internal fund manager
Universities of Aberdeen, Dundee and St Andrews	3	2001 award
ICENI fund (Universities of East Anglia and Essex, John Innes Centre, The Sainsbury Laboratory, Plant Biosciences Ltd and the Institute of Food Research)	4	2001 award
Universities of Leicester, De Montfort, Loughborough, Nottingham and Nottingham Trent	4	2001 award. To be managed by Quester Capital Management
Universities of Surrey, Sussex, Brunel, Reading and Royal Holloway (University of London)	3	2001 award. To be managed by Generics Asset Management

a clear modus operandi with the departmental head.

Although a location in the founder's laboratory during the early stages of the new venture can have significant benefits, it does raise the issue of how to establish a clear business focus for a venture that is embedded in an academic environment. In our experience many academics need to be weaned off a 'grants mentality' and on to a commercial management focus if the new venture is to achieve its technical and financial goals. This process can be greatly facilitated by an early relocation of the company into an incubator facility (preferably located near to the university) and the use of a professional manager ('mentor') with relevant business and technical experience to work alongside the founders at all stages from development of the business concept through to the point where the company has the financial resources to be able to employ a full-time CEO. In the early stages of a new enterprise, full-time commercial management is not usually required, but the use of a mentor on a consultancy or part-time basis can significantly accelerate the development of a

commercial focus for the enterprise through the transfer of commercial experience to the founding scientists.

University start-ups: the next phase

In the biotechnology sector most new ventures are financed through a series of venture capital investments through to the point where the venture capitalists can exit and obtain a return on their investment by means of a trade sale or flotation of the company on a stock exchange where the shares can be publicly traded. For most university start-ups the first significant milestone after the initial investment from business angels or Challenge Funds is the first round of venture capital funding.

Venture capital investors typically are looking for the following attributes in life science companies:

- world-class management, proven track record;
- products that address major needs;
- access to range of technologies – product stream;
- proprietary position on technology or product;
- corporate alliances with market leaders;
- realistic valuations;
- clear and credible business strategy;
- strong near-term milestones.

This can be a daunting list of features to which a start-up must aspire. The business advisor or mentor can play a significant role in ensuring that the new venture meets the venture capitalist's list of desiderata, particularly if the mentor has founded companies previously and raised finance from the venture capital markets ('been there and done that!'). However, of the list above there are probably two issues that represent particularly significant challenges for university start-ups.

The first challenge is recruiting experienced management. It is unlikely that a venture capital fund will make a significant investment in a company without an experienced CEO. However, most start-ups cannot afford to recruit an experienced CEO until the venture capitalist has made the investment. One way out of this dilemma is to line up a CEO who commits to joining the company on completion of the investment round. An alternative solution that we have observed is for the venture capitalist to make the investment contingent on finding an acceptable CEO. In the UK biotechnology sector experienced management is not an abundant commodity and start-ups will face strong competition from more established companies which are also seeking to strengthen their management teams. Executive search firms are often used to identify a suitable CEO, but such recruitment services do not come cheaply so the new enterprise may need to find an executive search firm that is willing to work on a contingency basis.

The second key challenge is obtaining access to a range of technologies that can be used to generate a steady stream of product opportunities. Most university start-ups tend to have a narrow technology base because they have been founded around the work of only one or two scientists. Increasingly these days, biotechnology companies need to combine a broad technology base with a clear product focus. From an early stage the new enterprise should be seeking opportunities to access complementary technologies and products. The business advisor or mentor can play a major role in opening the founders' eyes to the opportunities in the wider world and leading the development of the company. There are many alternative strategies including company merger or acquisition, technology or product acquisition or licence, joint venture, R&D collaboration, etc. The company should be continually assessing potential opportunities. The venture capital funds also have a prominent role here as they seek opportunities to strengthen the existing companies in their portfolio. The prospect of being acquired or merged with another entity is often a major concern to company founders as they frequently are loath to cede control of their venture. However, at the end of the day they need to

remember that 100 per cent of nothing is nothing!

Conclusions

The purpose of technology transfer from our universities can be regarded as the generation of wealth for the institution concerned or for the greater good of 'UK PLC'. In either case, the transfer process needs to be efficient and effective if the purpose is to be achieved.

The results of the recent RAE indicate that the UK continues to have a world-class research base, and that the academic population is well occupied carrying out this research – plus teaching, administrative tasks, external examinations, developing new courseware, sitting on committees, etc. So, why change a winning combination? Let the academics concentrate on what they are good at (research!) and bring in business expertise to complement their skills. Some of the larger universities have invested significantly in building up relatively large technology transfer offices staffed by executives with some business experience. However, few of these managers have founded their own companies and therefore they tend to be more comfortable with technology licensing as the route for IP exploitation.

One effective way of promoting university spin-out companies that we have described in this paper is to bring in as mentors or advisors people with a company start-up background and relevant technical expertise. Another approach that can be effective is to use corporate commercial exploitation vehicles such as British Technology Group or Cancer Research
Ventures, which can facilitate 'technology bundling' to create companies with a broad technology base. A more radical option is to create university-owned technology transfer companies that operate on a commercial footing and can attract and retain executives with a high level of televant business expertise. One way to do this could be to set up a wholly owned university subsidiary company ('NewCo') that will hold, on behalf of the university, equity in the university spin-out companies. The value of NewCo will reflect the growth in value of the spin-out companies and could be used to reward the technology transfer staff through a NewCo share option scheme. Furthermore, the value in NewCo could be used to generate cash through monetisation or by issuing NewCo equity to investors. The funds raised could then be used to attract and retain experienced executives for NewCo.

Whatever the mechanism used to enhance technology transfer out of the universities, creating successful biotechnology companies is a major challenge that can only be met by ensuring that the start-up benefits from experienced management, whether it be from mentors, interim managers or full-time managers, from the earliest possible point in the process.

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