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Exploitation of biotechnology in a smaller company

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The establishment of a research-orientated biotechnology company was one of the recommendations of the Spinks Committee. How the National Enterprise Board, the Medical Research Council and private sector financial institutions responded to this recommendation, leading to the formation of Celltech in November 1980, is described. The paper then outlines Celltech's current position (it is no longer a small company) and future plans and describes the two areas of technology in which the company has achieved a leading position: mammalian cell culture and the engineering of the genes coding for monoclonal antibodies.

Celltech's methods of working with academia and the benefits to both are then described, and finally the paper tries to reach some conclusions about the part smaller companies play in technological innovation.

Introduction

In the late 1970s the world woke up to the potential impact on medicine, agriculture and industry of the new biotechnology.

In the U.K., as in other countries, numerous organizations took stock of the situation and decided what (if anything) they should do about it. The initiative of the Advisory Council for Applied Research and Development, the Advisory Board for the Research Councils and the Royal Society led to formation of the Spinks Working Party. This converged with initiatives of the Medical Research Council (MRC) and of the National Enterprise Board (NEB) towards the formation of a new research-orientated biotechnology company: Celltech.

What happened in 1980

The influence of the Spinks Working Party, with its very senior membership, was certainly not confined to their report and recommendations. Throughout 1979 the Working Party and its sponsoring bodies provided a focus for the U.K.'s activities in biotechnology. They encouraged numerous contacts, including those which led to the formation of Celltech. The report itself extended this influence. Recommendation 4.14 in the report was 'that the NEB, in conjunction with the NRDC, should investigate the possibility of establishing in the United Kingdom, and with some public funds, a research-oriented biotechnology company of the kind now taking shape elsewhere.'

In fact the NEB had started on this task in the middle of 1979. A small team led by myself worked part time on the idea and by the autumn of that year had convinced the Board of the NEB that the idea was well worth pursuing. Unfortunately a political row led to the resignation of the whole NEB Board and we had to start again. This turmoil lost us at least six months. But by the spring of 1980 things were on track again and Sir Arthur Knight, then the NEB Chairman, became an enthusiastic supporter.

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The National Research Development Corporation (NRDC) was then an independent body (although much later it and the NEB were merged into the British Technology Group (BTG)). NRDC were much less happy with the idea. At that time the NRDC had a monopoly in the exploitation of discoveries made in the course of work supported by the Research Councils and they viewed Celltech as the thin edge of a wedge that might break it up. Whether or not this was so, the fact is that the NRDC monopoly position no longer exists, much to the benefit of U.K. science and industry. But in 1980 we had a battle on our hands, which I'm glad to say was won by the NEB and the MRC. Although the NRDC opposed Celltech's special links with the MRC I should like to record that once his battle was lost Jim Cain, the Chief Executive of the NRDC, became a generous supporter of Celltech.

What was the role of the MRC? In the late 1970s the MRC had reached the conclusion that the mechanisms it had for the exploitation of its discoveries were too stereotyped and limited; especially in the field of biotechnology U.K. companies seemed unresponsive to opportunities for the exploitation of the recent discoveries. The Spinks report stressed that British industry should respond faster to these opportunities. The MRC's response was experimental, as might perhaps be expected from an organization that has made possible some of the most important biological discoveries of this century. It decided to back the as yet unformed biotechnology company on which the NEB was working. The MRC felt that by giving this new company exclusive access to its discoveries in the areas of recombinant DNA and cell fusion for a limited period they would help it greatly in getting going and also help it to develop a strong orientation towards collaboration with academia. The company in turn would actively develop MRC discoveries and pay royalties to the MRC.

Having gained the backing of the NEB and, particularly importantly, that of the MRC, we approached a number of private-sector institutions for venture capital and got the support of four of them. Representatives from these four joined with my team at the NEB to set up an organizing committee whose efforts led to the formation of Celltech on 6 November 1980. Celltech's initial Collaboration agreement with the MRC was signed on the same day.

Our shareholders have mostly taken a very long-term view, the kind of view that is reputed only to be found in Japan. In particular, British and Commonwealth Holdings and the Prudential Corporation were shareholders at the start and today hold very sizable stakes in the Company. They each nominated senior executives to Celltech's Board who have, over the years, played a key part in the direction of the company.

It took a lot of effort to get Celltech started but of course that was just the beginning. We have had eight years of very hard work which sadly I must skip over. Dr Norman Carey who, as Director of Research and Development (R&D), was responsible for gathering together and organizing our scientific team, plans to report elsewhere on how we set up our science. However, I shall now give a quick overall picture of where Celltech is today.

Celltech today

Celltech's financial year runs from 1 October to 30 September which is unfortunate timing for this symposium, as it means that the only figures for a full year that I can disclose are 12 months out of date. However, for our seventh year, i.e. that ending 30 September 1987, Celltech's results were as follows.

Our Products and Sponsored Development Business, which supplies products, undertakes

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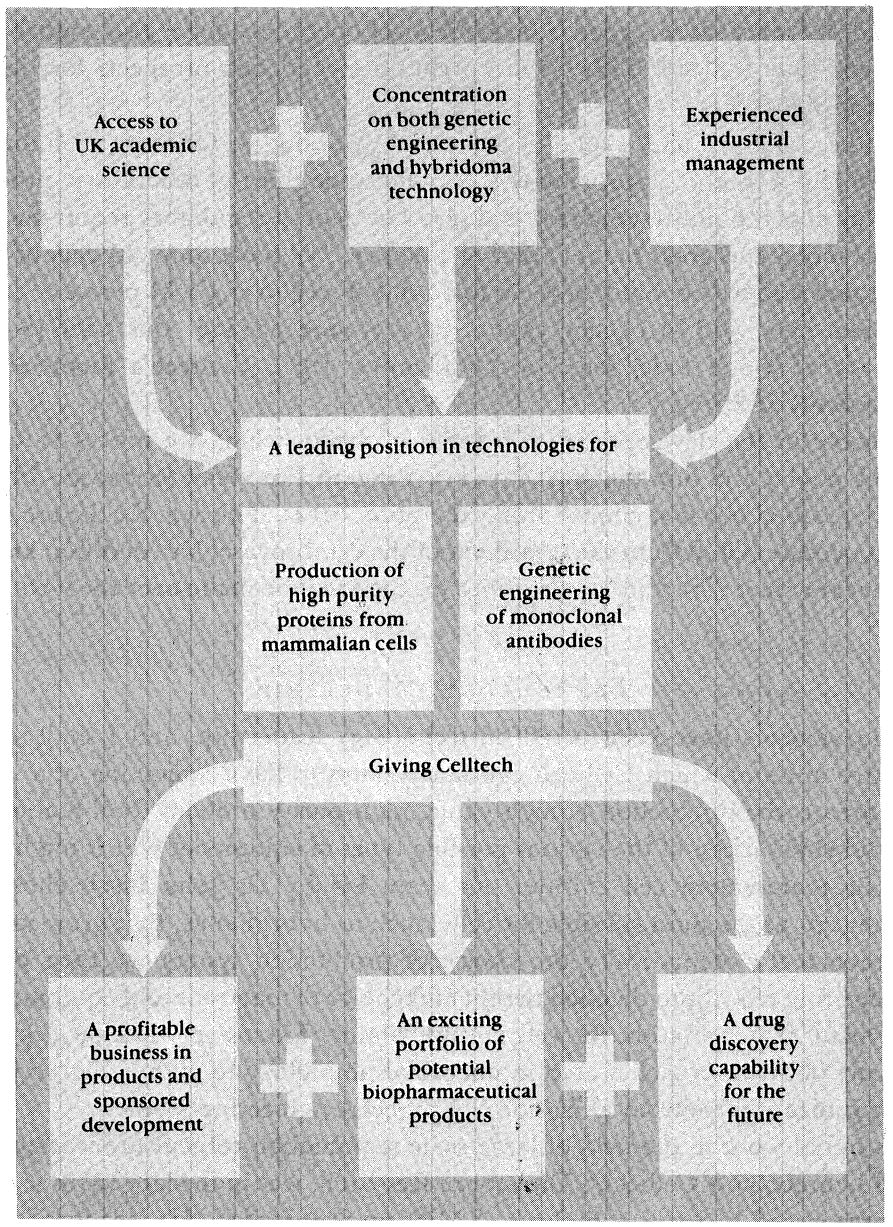

FIGURE 1. Celltech's current and future business position.

contract manufacturing and does research and development for other companies, and a sales turnover of £11.4 M.

This business made a profit of £4.1 M.

Our biopharmaceutical business, which is developing Celltech's own drugs for future marketing, has no sales turnover at present. It reported a loss of £3.4 M, which represents our investment during this one year in developing this new business area.

Celltech's R&D expenditure on its own account (i.e. not sponsored by other companies) was £2.7 M, mainly in the biopharmaceutical business.

Overall, Celltech's profit was £0.23 M.

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The heart of our business is our leading position in key technologies, but sound strategic decisions and, if I may say so, good management of operations have also contributed greatly to our success. Our well established current business and our prospects for the future are summarized in figure 1.

In September 1988 we had a total of 329 people working at Celltech, including 79 Ph.D. scientists. We had a total of approximately 150000 square feet of laboratory, production and office space, most of it built to standards that allow us to meet regulatory requirements for good laboratory practice and good manufacturing practice. We have some 40 collaborations with academic groups and we are funding them to a total of well over £1 M per year. In December 1987 we raised over £42 M of new capital in a private placing; this after the collapse of financial markets which took place on 19 October 1987. Celltech's financial position is therefore particularly strong.

We are active in the development of a series of drugs, which we intend to take through clinical development and into the market in key Western European territories. In June of this year we were granted our first clinical trial exemption (CTX). This was for the use of calcitonin gene-related peptide (CGRP) in the treatment of the cerebrovascular condition known as subarachnoid haemorrhage. Further applications for CTXs will be made over the next few months.

Technology leadership

These achievements have been based on technology leadership, and I shall now describe briefly the two areas in which Celltech can fairly claim to have something of a world lead.

The first area is the production of high-value, high-purity proteins from mammalian cells. After a careful comparison of the various possible types of equipment which might be suitable for large-scale mammalian cell culture, our team led by Dr John Birch chose the airlift fermenter concept as the most suitable for cells, such as hybridomas, that grow in suspension. Having approached systematically the choice of production system we then put a sizable process engineering effort into detailed design and choice of materials and equipment, and into the development of automation for cell culture plants. Extensive work on cell physiology, applying many of the approaches used in microbial physiology to mammalian cells, and then in process optimization went on alongside the process-engineering studies.

Celltech's initial work in the field of large-scale mammalian cell culture was also driven by need. Dr Ed Lennox, now Celltech's Director of Research, was in the late 1970s working in the MRC Laboratory of Molecular Biology (LMB) at Cambridge. He produced monoclonal antibodies to the determinants of A and B blood types and Celltech undertook the development of these in collaboration with Dr Lennox and his group. Because blood typing involves a visual end point, the amount of antibody required is much larger than for most other *in vitro* procedures, for example than most radioimmuno assays. To bring these products to market as replacements for the blood typing reagents then in use, which were based on human sera, therefore required us to manufacture kilograms of monoclonal antibody. In 1981 this was a formidable task, especially as there was an upper limit for production cost set by the fact that the aim was to replace an existing product in the market. But the big advantage was that we knew exactly what we had to achieve in quantity, specification and cost. And we did achieve this. Today, well over half the world's blood-typing reagents are based on monoclonal antibodies produced by Celltech.

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Experience in producing blood-typing reagents led us into making a large variety of monoclonal antibodies in bulk. To date over 100 cell lines have been grown in quantities over 100 g and a total of over 6 kg of antibodies has been produced.

I should add that the development of economical methods for purification of antibodies in bulk has been of great importance. Market need drove us here, too, as safe and economic production of monoclonal antibodies for human therapeutic use depended on this. Again we achieved our aim.

Now Celltech has two 1000 l and one 2000 l airlift fermenters in operation, as well as many smaller-sized vessels. As well as producing monoclonal antibodies we also make a number of other therapeutic proteins in cell culture. For Serono Laboratories we make human growth hormone from mammalian cells and we are assisting Johnson and Johnson in the production of erythropoietin.

I shall now turn to the second field of technology of great importance to Celltech: the engineering of the genes coding for monoclonal antibodies.

Quite early in Celltech's history we decided that a company involved in both recombinant DNA and monoclonal antibody technology ought to be able to combine the two. A research team directed by Dr Spencer Emtage set out to learn how to clone antibody genes and express them in various cell types. Papers published in 1984 and 1985 reported this work and at that time Celltech filed patent applications, the earliest filing in the world on work of this type (Boss *et al.* 1984*a*, *b*; Wood *et al.* 1985).

Of course, we were not the only place where work of this kind was being done and probably the strongest group was in the MRC Laboratory of Molecular Biology in Cambridge.

Dr Terry Rabbitts, Dr Mike Neuberger, Dr Greg Winter and their co-workers at the LMB made a remarkable series of discoveries that laid the foundations for the genetic engineering of antibody molecules. These include size reduction, incorporation of specific attachment sites, the making of chimeric molecules (e.g. human constant regions with mouse variable regions) and the grafting of complementarity-determining regions (CDRs) from one antibody to another. The CDRs are of course the part of the molecule that gives it its specificity, and to be able to retain the antigen specificity of a mouse antibody in a molecule that otherwise is a human antibody has enormous potential. These discoveries were made at a time when MRC had no patents budget, as it now has. Celltech assisted in the filing of patent applications and has acquired rights to their use, for some applications exclusively.

With the aid of these two key technologies (for large-scale manufacture of proteins in cell culture and antibody engineering), Celltech has been able to commence a number of programmes for the discovery of antibody-based drugs. The most advanced are aimed at treatment of cancer, endotoxic shock and similar conditions, and thrombosis.

In the anti-cancer field Celltech is working with the Lederle division of American Cyanamid, and the partnership was formally initiated in March 1986. This is a good example of a strategic partnership between a large international organization and a rapidly developing company, a point to which I shall return later.

Our alliance with American Cyanamid is progressing well and I believe that both partners are confident that it will lead to important advances in the treatment of cancer. For obvious reasons I cannot say very much about the results of our R&D work, but recently two scientific papers have been published that lift the lid on two parts of the programme.

The first paper concerns antibody engineering (Whittle *et al.* 1987). A crucial feature of the

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use of monoclonal antibodies in the diagnosis and treatment of cancer is the appearance of cell-surface antigens on tumour cells that can be recognized immunologically. Many monoclonal antibodies directed against tumour-specific antigens have been described, including B72.3, a mouse IgG_1 that recognizes a large glycoprotein called TAG.72. Over 85% of colorectal, breast and ovarian cancers are recognized by B72.3 but it has no significant cross reactivity with normal human tissues. The antibody has been used clinically in diagnosis, in a radioiodinated form.

An important reason for making chimeric antibodies is that the pharmaceutical potential of the antibody is increased because the incorporation of human elements reduces its antigenicity. This should allow repeated dosing of a radiolabelled antibody, improving the eventual prospect for successful therapy.

Chimeric immunoglobulin genes with the B72.3 specificity were constructed by a team at Celltech led by Dr Mark Bodmer, which collaborated with Dr Jeffrey Schlom and his colleagues at the National Cancer Institute in Bethesda, Maryland. Dr Schlom's group originally discovered the B72.3 antibody. The work benefited from Celltech's collaborations with scientists at the LMB and the Celltech team was able to make chimeric genes joining the mouse combining regions with human constant regions. They made separate clones for the heavy and light chains of the antibody molecule. These genes were expressed in mammalian cells and the heavy and light chains then associated in the correct manner to form stable antibody molecules. The chimeric antibody retains its ability to recognize and bind antigen *in vivo* and from the binding point of view is virtually identical to the mouse antibody.

Animal model data on the *in vivo* localization of chimeric B72.3 to human tumours have been reported recently (Colcher *et al.* 1989).

We are now in the process of scaling up our production of the chimeric antibody for use in clinical trials for tumour imaging and therapy. Commercially viable yields of this antibody, over 30 mg l^{-1}, are now being obtained in fermenters of 1000 l size. We expect clinical trials in both the U.K. and the U.S.A. to start early in 1989.

The second paper concerns the chemistry part of the programme. For imaging and for radiotherapy of cancer, radionuclides have to be attached to the antibody molecules. This is a considerable challenge, as the useful radionuclides usually have very short half-lives so that the antibody–nuclide conjugate has to be prepared immediately before the imaging or therapeutic procedure. This means that the coupling has to take place quickly and simply. But once coupled the conjugate has to be very stable. It would vitiate the whole purpose of using antibody-directed therapy or imaging if nuclide were to be shed from the complex and dispersed in the body rather than remaining in the tumour.

Among the approaches Celltech has followed in seeking a solution to this problem is the use of macrocyclic molecules called cyclams. These readily take up metal ions and bind them tightly. This approach necessitates the linking of the cyclam to the antibody and finding ways to do this without impairing the specific binding capacity of the antibody, reducing its stability, or impairing the uptake of metal ions by the cyclam. A Celltech group led by Dr Mike Eaton has worked with Dr Parker's group in the Department of Chemistry at Durham University and with the MRC Radiobiology Unit at Harwell to solve these problems (Morphy *et al.* 1988). A linker molecule carrying a vinyl pyridine group was attached to the cyclam molecule. Free thiol groups were generated on an antibody (B72.3 was also used in this part of the work) and

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the vinyl pyridine group reacted selectively with them. There was no diminution of immunoreactivity, i.e. the antibody retained its ability to bind with the antigen and radionuclides used in imaging were taken up by the complex.

Three principles for a specialist biotechnology company

To be in the forefront of technical fields such as these has not happened by accident. Such leadership comes from careful choice of the scientific fields on which to concentrate and by the application of enough skill and resources to make a real impact. Early in Celltech's thinking we identified three principles for a specialist biotechnology company. These were

to have enough financial resources to take a reasonably long term view;

to aim nevertheless for some early commercial successes;

to achieve synergy between in-house scientific excellence and external scientific collaboration.

I believe that we have followed these principles consistently and to good effect. The long-term view taken in the areas of large scale mammalian cell culture and antibody engineering show we have followed the first of these principles. We have been able to take a long-term view in Celltech because our two major shareholders have had a similarly long-term perspective. As to the second principle, the launch of the monoclonal-antibody-based products such as the blood-typing reagents, which I have already discussed, is an example of an early commercial success.

The best example of the synergy between in-house science and external collaborations is Celltech's relation with the MRC. During the initial three-year period up to the end of 1983, Celltech had exclusive rights to MRC discoveries in certain fields, which the MRC granted to help in the establishment of Celltech and to ensure the fast flow of inventions into development and commercial use. I have spoken about the most important of these, but there are many other examples. The relation with the MRC remains strong and continues to be of benefit to both parties. Where Celltech and the MRC see opportunities to serve each other's interests we will continue to be an obvious and rational route for the exploitation of MRC inventions. But we derive advantages from the MRC link not from legal obligations but from Celltech's skills and from the close mutual understanding that we have developed with the MRC over the years. We have benefited the MRC, partly with money; a total of nearly £650000 over $7\frac{1}{2}$ years in grants and royalties. The MRC now has a good deal of experience in the application of basic science, much of it derived from working with Celltech.

I think we have repaid the MRC in scientific terms as well. The flow of ideas has not been all one way. And most important of all, we have achieved rapid exploitation of MRC discoveries here in the U.K.

Celltech takes academia very seriously. We have a continuing high level of senior management involvement in our academic links, and often such involvement is the key factor in ensuring effective action. For example, Dr Gwyn Humphreys is our Director of Academic Liaison. We have appointed him, a senior and experienced scientist, to this post because we believe it is a vital area for Celltech.

I hope it will not be thought out of place if, in passing, I ask the U.K. Government to take academia equally seriously. Industry depends heavily on academia for trained people, for

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continuing high-quality basic research and for collaboration in the field of strategic and applied research. U.K. industry and academia are learning to work well together and I hope the Government will help by restoring morale and confidence within the universities and Research Councils and by offering them the resources needed to do their job.

So Celltech was founded with some clear principles in mind and our success has shown that they were sound ones. Perhaps I should have added a further principle to this list, one that applies to any business, indeed to any organized human activity, and that is excellent communication. We put a great effort within Celltech into continuous good communication between all who work in the business. We are willing to share confidential information about the progress of the business and about technical development with anyone inside the company and this trust has been repaid by a high level of commitment to the Company's objectives. We work on our communications skills. In a rapidly changing and quite complex business we need to be able to explain clearly what we're up to; and this doesn't only apply inside the Company.

The role of smaller companies in high technology

I have given something about Celltech's history, current status, technologies and business principles and I shall now draw out some general points about the role of smaller companies in high-technology fields.

A feature of advanced economies in the late 20th century is the emergence of small technology-orientated companies staffed by highly knowledgeable people. The interaction between knowledgeable people within a tightly knit organization can result in very high levels of creativity and productivity. New technological opportunities are taken up energetically and in innovative ways. So it is not surprising that in the first couple of decades following the basic discoveries that made possible such fields as semiconductors and biotechnology, much of the running has been made by smaller companies.

In this paper I have concentrated on Celltech, for obvious personal reasons and because of the link to Spinks. But it would be wrong not to acknowledge the contributions of similar biotechnological companies in the U.S.A. Genentech's scientific and business success has been outstanding, and other companies such as Amgen, Genetics Institute and Chiron have also done very well.

There is no consensus on which of the characteristics of small new companies are most important in making this contribution. Some or all of the following might, among others, be involved:

smallness, leading to good internal communications and plenty of cross fertilization of ideas;

newness, meaning that there is no commitment to old technologies to inhibit the development of new ones;

incentives, because directors and employees generally have a much bigger stake in these businesses than in larger, established organizations;

openness, because new companies have few settled ways of doing things and because in a climate of scarcity of internal resources there is a greater readiness to accept other people's ideas, e.g. from academic science – in other words, there is less of a not-invented-here problem.

As a field matures the creativity, flexibility and speed of small companies becomes somewhat less critical and large companies start to show their advantages. Big firms can mobilize large resources of money, materials, less skilled manpower, market access, transportation and so on. They can benefit from economies of scale and accumulated experience.

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There is also a great opportunity for partnerships between large and small organizations and in biotechnology these have been an important feature from the late 1970s onwards. Celltech has had several highly beneficial partnerships; two important examples that I have already mentioned are that with Johnson and Johnson, for whom we manufacture a number of products including erythropoietin, and that with American Cyanamid, with whom we are collaborating on monoclonal-antibody-based treatment for cancer. I am sure this pattern will continue.

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