# 1 Introduction

Biotechnology is one of the most significant industries developed in the 20th century, and it now has an impact across all sectors of the economy. It not only offers new products such as new drugs and medical procedures, but it also affects traditional industries such as agriculture and animal husbandry. Because biotechnology is an enabling technology, it has the potential to destroy traditional businesses and industries. Australia is no exception to these general trends.

## 1.1 Development of the biotechnology industry

Although molecular biology is not new, the biotechnology industry began to make a serious economic impact in the mid-1970s, especially in the USA, where incumbents in pharmaceuticals, chemicals and agri-business found that their existing knowledge base, such as organic chemistry, was challenged by new and revolutionary ideas, products and processes. The first-generation biotech firms both revolutionised how drugs were made and created a new kind of company environment. Large scale bureaucratic structures with prohibitive barriers to entry gave way to small firms that had been established to commercialise revolutionary technologies discovered in university laboratories. With the assistance of scientifically-aware venture capitalists who had built their skills in the computer industry, the scientists built pharmaceutical companies that were able to compete in markets previously the domain of multinational firms. Thus the initial biotech entrepreneurs were able to create a new industry based on new science with an innovative approach to management.

Multinational pharmaceutical, chemical and agri-business companies found it difficult to respond quickly to the change in direction, given the relative rigidity of the large firms. They were also facing the imminent loss of patent protection with little in the product pipelines to fill looming revenue gaps. The combination of these two factors established a pattern of small firm growth for the industry, where scientists made the discoveries in the university, established a small company to develop the research and

then sold the products at a big profit to large pharmaceutical companies such as Eli Lilly and Schering Plough.

This bifurcation of the industry created a new paradigm in drug development. The huge profits earned by the original scientists promoted a surge of other entrepreneurial scientists aiming to repeat the processes in clusters around US university campuses, such as in San Francisco and San Diego in the west, and Boston and Route 128 in the north-east. The role of entrepreneurial perception was critical to the readiness of academic scientists to establish firms to commercialise their research discoveries. The US culture and institutional settings encouraged such activity. Whether this pattern of growth and its eventual success can be replicated in other countries, specifically Australia, was the focus of the current study.

## 1.2 The research problem

Australia is recognised for its strong scientific research output in health and medicine, with many cutting-edge research centres and world ranking in molecular science and clinical research. However, the historical experience indicates that Australia has always lacked an ability to turn the research and development (R&D) in its research institutions into viable, profitable and exportable products. There appears to be a major divide between Australia's high level of research output and the capability of the biotechnology industry to put this output into practice as products. The objective of this study has been to identify problems encountered by Australian Biotechnology (ABT) firms as they progress through the growth pattern described above. Such an objective has been pursued in an effort to provide an insight into contradictory outcomes of scientific excellence compared with commercialisation efforts in Australia. This study has demonstrated that, although Australian scientists encounter similar obstacles to their growth aspirations as those outlined in overseas studies, they experience additional problems that seriously impede potential commercial success.

The spatial patterns of interactions in the industry have been described as an important factor in the establishment of the industry in Australia. This has been considered by researchers (Thorburn, 1999; West, 2001) as particularly important because Australia's population is concentrated in a relatively small number of cities. This spatial

distribution has meant a lack of critical mass for the industry in Australia compared with other industrial countries such as the USA, UK and European countries such as Germany. This study has not concentrated on concepts like industrial clustering that dominate other countries' biotechnology industries; instead, it has focused on patterns of linkages within the biotech supply chain for each of the firms studied. In addition, commercialisation difficulties have been exacerbated by the distance of Australia from large pharmaceutical companies that form the third link in the pattern of growth for the industry. Understanding such linkages is critical for the ABT industry and hence it was a major focus of this research.

The size of the biotech market is enormous. Biotechnology is not a single product but a collection of technologies that may be applied as platforms across different sectors and, as a result, any industry processing or using organic matter of any sort is potentially affected by its innovations. Biotech's potential ability to decouple economic growth from environmental degradation, and its ability to significantly improve human health through early diagnosis and cure, have led it to be widely seen as the major driver of sustainable economic growth in the 21st century. Given the importance of the industry to the national interest, a number of studies have been conducted on ABT firms in recent years (Ernst & Young, 2001a, 2004; Hopper & Thorburn, 2003; eGcapital, 2004; PwC, 2004; Biotechnology Australian, 2005). However, much of the research has taken an industrial, quantitative approach, using survey methodology that takes averages of measures that have been removed from their context. This research, on the other hand, has taken a historical perspective that demonstrates the issues facing a sample of ABT firms through their first three critical phases of growth as they begin to build competencies to take their discoveries to global markets. It is argued that such rich data assists in providing some understanding as to why Australia's outstanding medical research is not being converted to the commercial success realised by other countries with similar research capabilities.

## 1.3 The research approach

The growth pattern of the industry dictated the research approach, which was to examine small science-based entrepreneurial firms progressing from a public research

institution to commercial success. In 1934 Schumpeter described the entrepreneur as visionary, battling against accepted trends with limited resources to combine production factors in novel ways so as to produce either new products or old products more efficiently, and in the process create new economic space. These characteristics are demonstrated within the industry with its visible movement of inventions out of academic institutions into industry through the establishment of small enterprises. Within this process the role of the entrepreneur is critical. However, new scientific discoveries, although full of potential, do not necessarily develop into commercially viable products. What works in the laboratory does not automatically translate into commercial success. Furthermore, an emerging industry presents particular problems to new firms that do not yet have the skills or resources to sustain them through long gestation periods (Garnsey & Heffernan, 2004). This study has also investigated why some firms are able to overcome obstacles to reach global markets while others fail early in their progress, and whether there are unique patterns of obstacles that constrain growth in Australia.

Determining a structure from which to analyse the ABT market and identify critical problems for firm growth has been difficult for several reasons. Small firm entrepreneurial activity gave way to large bureaucratic structures throughout the 1960s. Within this trend, business schools for the last 50 years have devoted considerable resources to studying the entrepreneurial activities of large companies, devoting little effort to systematic research about starting and growing new businesses. Bhide (2000:xiii) laments that "the conceptual problem has become serious; long neglect has left the small business field with few well-framed hypotheses that researchers can confirm or modify".

Garnsey's (1998) small firm growth model offers a suitable framework for the current research. Her conceptual growth model provides "an invitation to compare other firm's experience with the composite account...in order to find common patterns and to use evidence to challenge, refine and extend the model" (p. 531). Her first three phases – resource access, resource mobilisation and resource generation – are sequential and provide the units of analysis. The problems within each phase constitute the variables that are sources of comparison. The resource access phase is also a good fit with the biotechnology firm that begins as a research project within a public research institution before it becomes established as a firm, providing a further reason for the choice of

model. This study has taken the transition of the research project to the establishment of a firm as the shift from resource access to resource mobilisation phase, although it recognises that resources continue to be accessed in later phases. The ability to reach breakeven point and generate profits has been viewed as the transition from resource mobilisation to resource generation phase.

This research has adopted a qualitative approach to examine the patterns of growth of a sample of five firms in the ABT industry, and has sought to identify and examine the critical problems encountered by the five firms as they progressed through three early growth phases. It focused on the building of competence by firms to address the sequence of critical obstacles to their growth, comparing these problems and competence building activities within each phase across five firms to develop an empirical framework from which to answer the research question.

A small number of other studies (Sparling & Vitale, 2003; Vitale, 2004) have also sought to address similar concerns with qualitative research in the Australian context and have combined a qualitative approach with a quantitative perspective. Vitale (2004) noted that each of the nineteen companies he investigated would be worthy of an individual case study. However, the findings were presented in summary form without the historical detail included in this study to demonstrate lessons learnt and best practice. The work by Sparling & Vitale (2003) focused on the second phase of development, represented by the central circle in Figure 1.1.

The three circles in Figure 1.1 are very much aligned with the three phases of the Garnsey (1998) model. However, this research focused on a longer historical perspective incorporating all three phases of growth demonstrated in Figure 1.1. Such an approach highlights path-dependent activities of entrepreneurial problem-solving as the firm progresses through these three phases.

As an example of the benefits of a qualitative, historical approach, Sparling & Vitale (2003) found that in the middle circle entrepreneurs considered that "being born public" ensured that their IPO was less stressful than those companies that had adopted alternative strategies. This study was able to extend the data to see beyond the one phase providing valuable information on problem solving and corporate learning that had led to this decision, adding another layer of information from a micro-level perspective on

small firm growth in the ABT industry. Furthermore, by identifying the processes of change within the small entrepreneurial science based firm, this study is able to contribute to a body of knowledge to assist in appropriate policy setting and further enhance the chances of success in commercialising outstanding Australian medical research.

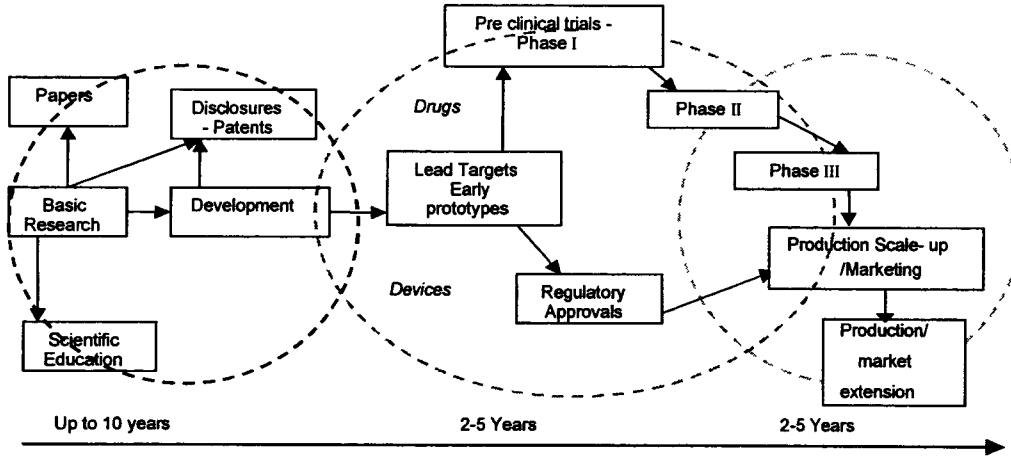


**Figure 1.1:** Biotechnology development process (Sparling & Vitale, 2003:6)

## 1.4 Thesis structure

The thesis comprises seven chapters. Chapter 2 provides an overview of the biotechnology industry by focusing on its origins in the USA. Within this context the emergence and growth of the first two biotechnology firms, Genentech and Hybritech, are discussed to provide a background for comparison with the Australian industry and a comparison of problems for the companies in the different national settings. The chapter then describes the Australian industry and highlights the institutional disadvantages that are encountered by Australian firms compared with their US counterparts.

Chapter 3 discusses the literature on new venture growth, examining the emergence and evolution of firms from an economic point of view. Economic theory does not, however, provide the basic frame of reference and the chapter explores a number of 'life-cycle' growth models from the strategic management literature on the theory of new firm growth. It is argued that these models fail to adequately account for the great

variety of ways firms grow, and the pioneering perspective of evolutionary theory is then discussed. The critical role of the entrepreneur in this industry is described, with particular focus on the theories of the Austrian economist, Joseph Schumpeter. The discussion of the Schumpeterian (1942) entrepreneurial model leads to the Penrose (1959) resource based view (RBV). However, Penrose discussed firms that had already been established and, although this makes the RBV an appropriate underpinning to the current study, it is Garnsey's (1998) small firm growth model, which originated with reference to engineering firms with in-house production, that provides a more appropriate framework for this research. This model is summarised and discussed in the context of exploring the emergence and growth of enterprises in the ABT industry. Garnsey's (2003) model of the UK biotechnology industry is introduced to demonstrate specific differences between the engineering and biotechnology industries. It is argued that the three-phase growth pattern is maintained, although there is considerable difference in the business models pursued throughout the mobilisation phase in the biotech industry compared with the engineering model.

The five firms differ in their trajectories but face similar constraints in attempting to survive the Australian environment on their way to global markets. Their appropriate selection is discussed in Chapter 4, which describes the research methodology. The main data for this research were collected in a series of interviews with executives of small ABT firms. Details of the methodologies adopted for these interviews are provided.

Chapter 5 presents a summary of the results of the empirical study of the five sample firms. The case studies combine the research data to describe the technology, founders and growth paths of the five sample firms. The firms are Cochlear Ltd, an implant device company; Novogen Limited, a drug discovery company; Cotton Seed Distributors, a cotton seed developer; BTF, a diagnostic company; and Proteome Systems, a hybrid protein technology, drug discovery and diagnostics company. Each case is summarised in the chapter, with full details of each case provided in the appendices.

Chapter 6 presents the results of the data analysis. This chapter follows Garnsey's narrative and compares the growth of the five firms with her model. The chapter is divided into three sections which reflect the first three phases of the model: resource

access or early prospecting phase, resources mobilisation phase and resource generation phase. The sections are further divided into the variables driving each phase, as outlined by the Garnsey (1998) model.

Chapter 7 presents the conclusions, identifies gaps in the literature on small firm growth in the ABT industry and areas of further research, and discusses the limitations of the study. The chapter concludes with the observation that the critical problems identified within each phase seriously impede the growth of ABT firms, and their identification goes some way in explaining why Australian medical researchers have difficulty in commercialising their science.

# 2 The biotechnology industry

This chapter examines the nature, characteristics and dynamics of the Australian biotechnology industry, with a particular focus on the position and role of small companies within the industry. The first section describes the industry on a global scale, outlining its significance to world health and the rationale for substantial government funding. The second section outlines the origins of the industry and highlights the significance of the small firm and the importance of context to the emergence, growth and success of firms. Case studies of the first two biotechnology firms, Genentech and Hybritech, illustrate the importance of context in shaping serendipitous encounters and entrepreneurial behaviours in the industry and highlight the lack of contextual awareness typically associated with small firm growth. The final section provides an overview of the Australian biotechnology market, in particular the problems faced by Australian firms in their efforts to reach global markets.

## 2.1 Defining the industry

The OECD defines biotechnology as the application of science and technology to living organisms and the parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services. Biotechnology, commonly referred to as 'biotech', is not a single product but a collection of technologies that may be applied as platforms across different sectors (Hopper & Thorburn, 2003). The industry ranges from low commodity to high value products and services, and is characterised by its diversity:

- human therapeutics, including development of biotech-derived drugs to treat or prevent disease, and in-vitro fertilisation

- diagnostic products and services, aimed at identifying and diagnosing human disease

- Agbiotech, using biotech for developing and delivering products and services for the agricultural sector, such as promoting plant and animal growth, identifying and preventing disease, or breeding programs

- food and beverages, encompassing the use of biotechnology for the development of new foods, including functional foods and food additives

- suppliers of molecular biologicals, such as monoclonal antibodies, diagnostic reagents and gene chips (Hopper & Thorburn, 2003).

The term 'biotechnology' is being used increasingly loosely so that many processes (and firms) are often counted as biotech when they do not meet the criteria outlined above (Hopper & Thorburn, 2003). Medical device companies, for example, do not fit into the OECD definition, yet Cochlear and ResMed are considered among the top biotechnology companies listed on the Australian Securities Exchange (ASX) (eGcapital, 2004). Medical device companies are included in most Australian reports on the biotechnology industry and therefore they are included in this study.

### 2.1.1 Characteristics of biotechnology development

Characteristics that distinguish the development of biotechnology from technological development in other sectors are its diversity of use, its high dependence on basic research in molecular biology, and the controversy surrounding its commercialisation (Bartholomew, 1997).

Biotechnology is the use of microbial, animal or plant cells and enzymes to synthesise, break down or transform materials and, as such, potentially has commercial application across a wide variety of industrial sectors. Other areas of technological innovation, such as computer engineering, for example, are not confined to industrial segments but are spread across the economy. The different structure of the biotechnology industry affects the way it permeates the economy, and makes it difficult to compare the biotechnology industry with other 'high-tech' companies, even though they are both within the knowledge economy.

Biotechnology has a high dependence on basic research in molecular biology. Recombinant DNA and genetic engineering techniques "represent radical scientific breakthroughs that are being transferred to industry and reduced to practice" (Mowery & Rosenberg 1993:70). Sigurdson (2000:304) proposed that "basic research is very important in a science-driven industry (such as biotech) while the research on generic technologies is the key to success in an engineering-driven industry". Basic research in molecular biology is concentrated primarily in institutions such as universities and government laboratories (Kenney 1986; Nelsen 1991). Consequently, the sources of research funding for biotechnology are more likely to be governments or foundations, compared with the industry funding of engineering-driven research.

Furthermore, scientists are increasingly required to show commercial skills, such as the 'know-how' to market innovative products and the ability to negotiate funding in an industry that faces considerable lag times between conception and distribution to market. A close connection thus clearly exists between basic scientific research and commercial biotechnology activities (Bartholomew 1997). The scientist, therefore, must gain entrepreneurial skills and collaborate with other professionals to enhance the potential success of their discovery. In contrast, in engineering and other high-tech industries the genesis of the industry and important information flows have been between engineers in companies (Prevezer, 2001).

There is substantial uncertainty and controversy around the commercialisation of genetic engineering research. Regulations on the patenting of life forms and the testing of new biopharmaceutical products, for example, are important factors in the speed with which new scientific discoveries come onto the market. Once tested, engineering products can go straight to market. Biopharmaceutical products, on the other hand, require many years of expensive trials and regulatory approval before they can provide a return to the investor. In addition, community disapproval of genetically modified products can bring research to a quick halt after many years of investment. An example is the Monsanto Soy gene which is currently experiencing moratoriums in many countries, including Australia.

These peculiar characteristics of the biotechnology industry are "particularly important in understanding how different national institutional environments (including Australia) will shape different approaches to biotech innovation" (Bartholomew 1997:242). They

also highlight the importance of understanding the difficulty of commercialising scientific innovations and the process of knowledge transfer from research institutions to commercial environments.

### 2.1.2 Biotechnology – a disruptive technology

Since the mid-1990s, biotechnology has been highly disruptive of industries such as pharmaceuticals, chemicals and agri-business (Madhok & Osegowitsch, 2000). The existing knowledge base, such as organic chemistry, was no longer adequate as the first generation biotechnology firms revolutionised how drugs were made. Multinationals who were largely protected against new start-ups through high entry barriers found it difficult to change direction, enabling new firms to develop a niche in a previously impenetrable market.

The disruptive effects of biotechnology, however, have been limited to the upstream stage. The capabilities required downstream in clinical testing, regulatory approval, marketing and manufacturing remain largely unchanged. As a result these incumbents have survived the technological upheaval relatively unscathed and few of the new biotech firms have acquired significant downstream competencies to become fully-fledged competitors in their respective industries.

Madhok and Osegowitsch (2000) suggested that the bifurcation of the biotech industry into the relatively small, science-driven firms on one hand and the large incumbent corporations on the other has been driven by their different but complementary capabilities, as well as the high incidence of alliances, both within and across national borders. The experience of firms learning how to manage their alliance partners has led to a new organisational paradigm (Madhok & Osegowitsch 2000). Such alliances become additional relational resources, but can create some critical problems as both groups attempt to manage routines and expectations within their own interests.

Kogut (1991:199) agreed that industrial innovation depends upon "the complex interweaving of basic research and market-induced applied R&D". Similarly, Porter (1990:80) noted that "investments in basic research, while important in seeding possibilities for commercial innovation, will not lead to competitive advantage unless

transmitted to and further developed by industry." Robins-Roth (2001) on the other hand proposes that the initial biotech entrepreneurs not only created new science, they also built new pharmaceutical companies and created an entire industry based on the new science, an innovative approach to management and some incredibly creative financing ideas" (Robbins-Roth, 2000:13). This author proposes that small firms in the biotechnology industry were able to undermine big pharmaceutical companies' stronghold on the drug industry in two ways. Firstly the breakthroughs in scientific discovery for this industry were in biology not chemistry requiring a total change in focus that was not easily managed in large corporate structures. Secondly the research had been conducted in public research institutions funded by the National Institute of Health (NIH) not in-house R&D programs, creating the advantage of breaking through the previously high entry barriers. The perceptions of entrepreneurial scientists backed by science-aware venture capitalists emanating from the high tech computing era in the US spawned a series of new small businesses that challenged the big pharmaceutical companies' powerful position in drug development. In the process, the spinning off of small business ventures from public research institutions provided the structure for the biotechnology industry, creating a new paradigm in drug development.

> *"These new companies have managed to outdo the practitioners of the art at their own game. Biotechnology develops new products to sell into markets dominated by multinational companies that are better financed. These young companies walked into a mature market and succeeded...That is the allure of biotechnology" (Robbins-Roth, 2000:8).*

A subsequent wave of successful commercialisation processes and intensified research and development (R&D) throughout the 1980s resulted in a differentiation of the industry into varied technologies and applications. New pharmaceutical products that resulted from the discovery of new active substances and new technologies such as genomics, proteomics and gene therapy have provided the major opportunities for R&D and the emergence and growth of new companies. The new biotech drugs resulting from this R&D have become the new standards of treatment for diabetes, heart disease, stroke, hepatitis, anaemia, breast cancer, multiple sclerosis, and rheumatoid arthritis, changing health care delivery strategies on a global scale (Zeller, 2001).

### 2.1.3 Biotechnology – defining 21st century progress

Don Szaro, Global Health Sciences Director for Ernst & Young, suggested in his 2004 report that biotechnological innovations are defining 21st century progress in health care, agriculture, industrial production and environmental management. Michael Hsu, CEO, Endpoint Merchant Group, New York, agreed:

> *"Biotechnology is an enabling technology for countries in attaining global competitiveness with its ability in solving problems of food production and human health...it now has the potential to replace information technology as the engine of economic development for the 21st Century" (E&Y, 2004:23).*

These products can deliver on two vital goals: improved health and sustainable growth and development:

> *"Innovative biotech products and services if delivered successfully, have the potential to help decouple industrial growth from environmental degradation and deliver a more resilient, more bio-based economy, less susceptible to uncontrollable global events and less dependent on large-scale distribution systems" (OECD, 2004:5).*

The impact of the industry is extensive. In 2003, global revenue for core biotechnology products and services for 2003 was US$46,553 million, growing by 17% from 2002, with the US acquiring US$35,854 million of the total (E&Y, 2004). The heavy spending by the US on public R&D has paid off. Since 1998, US revenues have increased by 115%, keeping the US well ahead of other countries in revenue-earning capacity in this industry despite substantial public investment into the sector by successive governments in Europe and the Asia-Pacific region. For example, the Singapore government invested US$2 billion in biotechnology during 2000–2004, and provides tax incentives for multinational pharmaceutical companies and home grown biotechnology start-ups (E&Y, 2004). In 2002, an announcement by the Korean government that it had budgeted about US$90 million to promote the biotech industry spurred the chaebols (large conglomerates) to raise funds with the intention of investing an additional $450 million over the next several years. In 2004 in Japan a handful of biotech Initial Public Offerings (IPOs) created a new industry with a market value of more than $4 billion. Strong government support for biotechnology throughout the region and the strengthening of intellectual property regulations have accelerated development of this sector (E&Y, 2004).

Governments around the world have adopted various proactive policies to focus on capturing the economic, environmental, health and social benefits of biotechnology:

> *"[A] better understanding of the underlying biology of disease, gleaned through the human and other genome projects and elsewhere, is providing researchers and health professionals with the opportunity to employ safer, more effective interventions based on biotechnological products and processes that promise a better match between the supply of effective health interventions and increasing societal expectations for good health and better quality of life in OECD countries and beyond"(OECD, 2004:9).*

However, delivery of innovative health-related products and processes often depends heavily on a range of supporting public policies. There is growing recognition of the difficulty in determining the most appropriate measures for effective public policy. For example, traditional Asian values sometimes sit uneasily with the concept of profiting from health care, as demonstrated by Japanese physicians' resistance to market-oriented reform (E&Y, 2004). European suspicion of genetically modified (GM) crops limits the development of agricultural biotechnology in that region. In Australia, governments provide incentives for investment into R&D but the incentive is to commercialise, not just to invest (Hine & Griffiths, 2004), and large taxes on capital gains are an inhibiting factor (PwC, 2004).

The magnitude of the required investment, and the efficiencies that private sector disciplines can provide, make it inevitable that private capital will underpin the public sector in keeping the industry viable (E&Y, 2004). The continued combination of substantial private and public investment has enabled the commercially oriented culture of the US to maintain its lead in terms of patents, products, and cultural and institutional support systems; the two US case studies in the next section of this chapter highlight this issue. It is generally agreed that "finding the most cost-effective strategies for commercialising this revolutionary technology is in everybody's interest" (E&Y, 2004:2). How to determine such strategies from a national perspective within cultural boundaries has been an objective of this study.

### 2.1.4 Biotechnology – creating a changing focus

Technological advances are particularly apparent in health. Diagnostic techniques for susceptibility and early detection of illnesses, vaccines for infectious diseases, and

effective treatments for chronic conditions such as cancer and Alzheimer's disease, have altered the architecture of hospitals and delivery of health care as radically as they changed the pharmaceutical industry in the 1970s and 1980s. With the genomics revolution, potential health problems can now be detected before they become chronic conditions. In addition drug makers have transformed horizontal care, or hospital treatment, into vertical care, or outpatient and home treatment. Strong government support for the industry is driven by the enormous demand of hospitals on the public purse. Changes have included reduced demands on long-term hospitalisation, adjustment of personnel needs and re-evaluation of equipment and treatment procedures (Hopper & Thorburn, 2003; E&Y, 2004). By working together in an integrated system, drug and medical device manufacturers and hospitals can package and promote products and services that constitute a responsible, cost-efficient course of treatment (E&Y, 2004).

### 2.1.5 Biotechnology – a chain of networks

This convergence of drug and medical device makers with health care providers is creating a global health sciences network that operates in what can be described as a new health economy (see Appendix 3):

> *"Today, rather than a segregated supply chain of innovation in which biotech discovers, big pharma develops and sells, and hospitals deliver, alliances exist along all points of this chain, enabling the interdependent players to influence product development, share risk, and adapt to disruptive technologies" (E&Y, 2004:1).*

The niche opportunities for scientific entrepreneurs are considerable in such a complex web of high-tech alliances. Because size is not necessarily important, the global economy is available to smaller companies, who pursue the global niche market by exploiting new technologies and distribution systems to reach previously inaccessible international consumers (James, 2005).

The convergence of stakeholder interests along this biotech value chain is most visible in academic medical centres that conduct clinical trials and pursue some of the most advanced research. Indeed, the undisputed source of biotechnology innovations is academic medical centres that yield the technology on which start-up biotech companies

are founded. Drug makers rely on hospitals for access to patients to test new medicines. Genomics advances have created collaborations between health care providers who share collections of diseased tissues and drug makers who identify genetic targets for therapeutic interventions (E&Y, 2004). Any new biotechnology incentive with any hope of success must manoeuvre through this co-dependent chain with many important global links. The case studies in the current research indicate that the best chance of survival for biotechnology companies is to stay within their core area of expertise and use existing distribution chains. These issues are further reinforced by the short term of the patent, usually around 20 years.

## 2.2 Origins of the science

In the late 1970s and early 1980s departments of microbiology, human genetics and biochemistry grappled with the question of how the human immune system protects people from cancer and serious infections. The research was based on a relatively new area of immunotherapy that tried to isolate the specific proteins used by the immune system cells to communicate with each other and to signal attacks on tumours or viral infection of cells. The aim was to purify these proteins, study how they work and then apply that knowledge to treatments. Unfortunately the relevant proteins were present in only very small amounts, and identification and isolation from surrounding material were extremely difficult and time consuming. Despite evidence from early experiments that proteins play key roles in major human diseases, making enough of the important proteins to provide widespread treatments was impracticable (Robbins-Roth, 2000).

Two scientific breakthroughs provided the answer: the discovery of the recombinant DNA technique by Cohen and Boyer in 1973 at Stanford and UCSF universities in the US, and the discovery of monoclonal antibodies by Kohler and Milstein in 1975 at Cambridge University in the UK (Prevezer, 2001). These two discoveries became the building blocks of biotechnology research and industry growth. They were initially developed by two separate US companies, Genentech and Hybritech, respectively. The unique institutional context of the US at that time included strong government support for the newly emerging biotechnology industry from agencies such as the US National Institute of Health (NIH) (Bartholomew, 1997). It also forged a strong tradition of interaction between industry and

academia, and an abundant availability of risk capital. The entrepreneurial orientation of such traditions resulted in the willingness and preparedness of academics and other researchers to start their own companies. The following sections discuss these contextual characteristics and provide a base for comparison with the Australian biotechnology experience, discussed later in this chapter.

### 2.2.1 Government support

Much of the molecular biology research that formed the backbone of genetic engineering in the US was funded by the US National Cancer Institute (NCI) and the US Government, which allocated enormous sums to fund cancer research (Kenney, 1986; Orsenigo, 1989; Prevezer, 1997, 2001; Robbins-Roth, 2000). It is estimated that 11% of all federal R&D dollars was allocated to basic biomedical research, and the NCI dominated the NIH's budget with US$989 million annually on cancer research by 1981 (Robbins-Roth, 2000). Funding for cancer-related areas of research and the NIH's Viral Oncology Program increased substantially during the 1970s, underpinning the eventual commercialisation of the research:

> *"The campaigns undertaken by NIH to find cures for diseases such as cancer have turned out to be projects that prepared commodities to the point at which they were ready for commercialisation by industry" (Kenney, 1986:241).*

US public financial support for the research continued to grow. By 1983, 64% of university R&D funding came from the federal government (US$5,387 million) and another 8% from state and local government (US$653 million) (Prevezer, 2001), providing strong impetus for the US development of this industry:

> *"The all pervasive federal research monies that are the baseline of support for university research continues to be of primary importance (to the industry). The American research system has been and is, quite simply, based on federal (that is, public) funding. NIH and NSF (National Science Funding) funding allowed the development of an enormous medical research base in the United States and made possible the construction of numerous laboratories and even entire research complexes" (Kenney, 1986:18).*

In contrast, Australia has suffered from funding cutbacks to tertiary institutions:

> *"Policies often appear to be driven much more by ideology than by economic reality, and the consequences have not been totally positive for the Australian biotechnology sector" (Vitale, 2004:7).*

The Australian context is discussed later in this chapter.

### 2.2.2 US academia–industry environment

The Bayh-Dole Act in the US in 1980 gave incentives to universities to commercialise their research. It was possible for US academics to found companies whilst retaining their positions as scientists. This is in marked contrast to the much starker divisions between the academic and industrial environments in continental Europe or the UK, where there are few incentives for academics to commercialise their research. (Prevezer, 2001). The tacit nature of knowledge means that it cannot be codified and transferred with blueprints and instructions (Zeller, 2001); rather, it needs to be acquired by concrete practice (learning by doing) and direct social contacts (learning by using) (Howells, 1998). The fluidity and density of professional and social networks in the US scientific community is thought to have played a key role in the diffusion of ideas, technical expertise and commercial opportunities related to biotechnology areas (Prevezer, 2001).

The growth of the industry and a supportive entrepreneurial culture made biotechnology an appealing alternative career for biological scientists in the US. Until the 1980s, biological researchers had few opportunities outside academia. Biochemists and cell biologists working for the big drug companies had been required to conform to onerous company standards. New biotech companies such as Genentech offered attractive salaries and allowed postdoctoral researchers to do innovative research without having to waste time writing grant proposals or changing their 'science nerd wardrobe'(Robbins-Roth, 2000:12). Although academic colleagues decried the abandonment of campus for an industrial setting, the migration soon grew in momentum. The ethos of the early biotechnology firms such as Genentech, imitating in part the early computing firms, was one of openness and informality, aimed at attracting high calibre research scientists and encouraging them to maintain their scientific links and their status as academics (Prevezer, 2001). Informal dress codes and flexible working hours were designed to imitate academic laboratories and be attractive to top research scientists. Dense social networks also facilitated the emergence of geographical clusters of biotech activity.

Attempts elsewhere, including Australia, to artificially build such clusters can be productive in an industrial sense although these orchestrated clusters cannot provide the normal professional networks that develop gradually over time (Martin & Sunley, 2002).

However, technological change is not only a reaction to changes in market conditions, it is also influenced by technologies already used (Zeller, 2001). Technological progress is only possible from the basis of the technological level already achieved. In this sense technological change is cumulative, and the networks and expertise gained throughout the growth and development of the US IT industry had created an infrastructure for the nascent biotechnology industry. The lack of such conditions within a locality has hindered attempts by various public bodies to artificially imitate this process (Audretsch, 2001; Prevezer, 2001). Cortright (2002) noted, for instance, that there remain only five major centres in the US, despite much US government spending at the local level.

### 2.2.3 Abundant availability of risk capital

As noted, the US biotechnology industry benefited from the earlier development of computing in California. Several of the ingredients for successfully developing technology companies were already established, including a pool of scientifically aware capitalists, a pool of highly skilled mobile labour, and the entrepreneurial culture and good communications networks to facilitate the spread of ideas (Prevezer, 2001). The examples of US technology ventures, with the comparative ease for young technology companies to raise capital and find backing, raise the question of whether similar new enterprises are possible in other countries lacking the same infrastructure, such as Australia.

The experiences of Genentech and Hybritech, as the models of small firm emergence and growth for the biotech industry, are presented in the next two sections of this chapter as a benchmark against which to compare the Australian experience. Both of these firms were based on novel science developed in public research institutions supported by NIH funding. They began with fortuitous meeting of scientists with entrepreneurial perspectives and entrepreneurs with scientific awareness. They both encountered similar structural and managerial problems, although their technical problems differed. Both companies enjoyed the interest of multinational pharmaceutical companies and public

investment, enabling them to access financial assets to progress their growth patterns to extraordinary heights. Similar problems are faced by contemporary Australian biotechnology firms, although the lack of similar opportunities has constrained their opportunities for growth.

### 2.2.4 Genentech – the leader of the pack

Cynthia Robbins-Roth has documented the growth of the company as the blueprint for small firm growth in the new industry, in her book, *From Alchemy to IPO*. In 1980 she left her postdoctoral fellowship position at the University of Texas Medical Branch in Galveston and joined Genentech, attracted by the high salary and the opportunity to work in a creative environment for a company she now appropriately calls "the leader of the pack":

> *"To do innovative science without the trappings of the big pharma environment, and away from the crazed politics of government-sponsored academic research" (Robbins-Roth, 2001:12).*

Genentech was the first biotechnology company to use deliberate genetic engineering to successfully increase protein manufacturing from the small quantities used for research to the much larger quantities needed for clinical trials and marketing. The research that provided the company with its breakthrough technology was conducted over many years in various publicly funded research institutions, including by Dr Herb Boyer at UCSF and Dr Stan Cohen at Stanford. These two scientists had joined forces in 1972 to use an enzyme that could cut and paste a gene from one organism into another in order to read the gene and make a needed protein. By mid-1973, the collaborators had created a recombinant strain of *E. coli*, a common bacterium, that kept dividing and reading out a gene that originally came from toads. Niels Reimers, head of Stanford's technology licensing group, convinced them to apply for patents covering this recombinant technology.

Bob Swanson from venture capital company Kleiner & Perkins (K&P, later to become Kleiner, Perkins, Caufield & Byers), read of Cohen and Boyer's work and recognised an opportunity to build an exciting new company by joining forces with the two scientists:

> *"Swanson picked up the phone and called Boyer, and they met for a beer at Churchill's, a Bay area bar on Masonic at Geary Street. Based on that conversation, Boyer and Swanson formed a partnership with the two scientists in January 1976 to create a business plan for Genentech (short for genetic engineering technology)" (Robbins-Roth, 2001:15).*

Swanson became CEO and K&P invested US$100,000 in the company. Boyer also invested US$500 as half interest in their partnership. The company began as a virtual company out of the K&P offices. Swanson and Tom Kiley, a partner in intellectual property firm Lyon & Lyon, put together the first contract research deal with an academic group operating from UCSF and City of Hope National Medical Centre. The deal gave Genentech product rights and used the venture funding to develop proof of concept.

Despite technical problems, the team was able to produce the first product in nine months. Ironically, two contract scientists from City of Hope had failed to attract federal funding for the work because the reviewers doubted the scientific merit of the research and thought it was unachievable within the 3-year timeframe of the grant (Robbins-Roth, 2001). Had the funding been granted a very different story may have emerged, highlighting the serendipity that underpins the industry and many scholars allude to when discussing its characteristics. The example also highlights the difficulty of planning research commercialisation and company growth when so much depends on unforeseen circumstances.

Once the project had demonstrated proof of concept, Swanson acquired a warehouse for use as a laboratory in South San Francisco through his friend Brook Byers, who eventually joined the company as a full partner. Kleiner, Perkins, Caufield & Byers went on to become one of the leading venture capital (VC) firms in the emerging biotech industry. This association illustrates a tight social network that grew from chance meetings into strong social ties in California during the late 1970s and early 1980s. Byers noted that:

> *"At the time there were only about a dozen young associates working with the venture funds in the area. We all knew each other" (Robbins-Roth, 2001:15).*

Such chance associations were the embryos of future clusters of biotech firms that brought about much of the theorising on cluster development.

Robbins-Roth recalls that working in Genentech in those early days was like working in an academic lab, with everyone knowing what the others were doing and little need for formal documentation except for the technical aspects of the research:

> *"Swanson had set up a company that focused on results. He allowed huge freedom for researchers to set their own hours and encouraged the staff to play as hard as it worked" (Robbins-Roth, 2001:17).*

Long working hours were common, driven by the commitment of the scientists:

> *"We were driven by the science and the sense that what we did could make a profound difference to patients...the message came through loud and clear – Genentech's research was keeping people alive, people who otherwise might have died. That was an incredible impetus" (Robbins-Roth, 2001:17).*

Genentech employed workers with a range of skills. As well as the strong core of molecular biologists and organic chemists were scientists in the entire range of disciplines needed to encompass drug discovery and development, and a nucleus of executives focused on making it a financial as well as a scientific winner. Gower, former Senior Vice President at Genentech, remembers the chaos of early business meetings:

> *"We had lots of ideas of where the company could go, but it was hard to make cohesive plans at first...The key was that Bob hired very strong people. There was nobody who was uncomfortable expressing opinions and arguing with Bob. Swanson hired people who were strong and he listened to them...Genentech in the early days was all academics and corporate mavericks - people who succeeded in spite of themselves" (Robbins-Roth, 2001:23).*

Robbins-Roth considers the environment within any entrepreneurial company is best understood by looking at the leader.

> *"The leader's attitude is what shapes the corporate culture. Bob Swanson single-handedly drove Genentech into existence, coupling strong business instincts with a love of the science and a willingness to step off the usual CEO pedestal to do whatever it took to keep the company moving forward" (Robbins-Roth, 2001:19).*

Senior managers who were recruited from big pharmaceutical companies in an effort to fast track biotech start-up management teams were not always suited to the position in a new and growing company. They often lacked the skills to raise money, work with the press, negotiate with bigger and stronger corporate partners, or handle concerned shareholders, as they had previously delegated these tasks to others. On the other hand, as

the company grew and jobs became more specialised, the ability of pharmaceutical managers to move into downstream networks became critically important.

This demonstrates one of the leadership problems of new companies in the industry. Finding a successful focus for business strategy is difficult. Many firms are so excited about potential applications of their new technology that they try to pursue every opportunity at once. Between the risk of the new technology and concerns about how the FDA (Food and Drug Administration) would react to these new drugs, many company executives and investors in the 1980s looked for a quicker, less risky path to product revenues. Agriculture and industrial applications were seen as faster, cheaper routes because of the perceived lack of regulatory agency interference and the avoidance of the time- and dollar-consuming clinical trial process, but human health promised the big payoffs. Genentech's initial report reflects Swanson's interest in building three businesses: industrial chemicals, animal health and human health care. Eventually it was decided to aim for those with the best potential of return potential. In 1983 the company changed its strategy to focus exclusively on human health.

Genentech was the first company to use the tools of the new biology exclusively to create products (Robbins-Roth, 2001). Press coverage focused on its cancer fighting properties, declaring it to be the "hottest thing going on in cancer research" (Robbins-Roth, 2001:19). Very positive and often emotive press coverage set the scene for a successful Initial Public Offering (IPO), a necessary source of funding to take the research to the next stage of development. Within a highly emotional media environment, Kleiner took two bankers on a tour of Genentech in 1978 in an effort to begin discussions about an IPO for the company. The bankers and the company eventually settled on a market valuation for this new company of 1 million shares at $35 per share, a huge amount for a company with no products on the horizon until 1984 (insulin), a brand-new technology and so many potential pitfalls that the front cover of the offering memorandum is emblazoned with "HIGH DEGREE OF RISK" (Robbins-Roth, 2001:20). Despite such risks, enthusiastic investors increased the stock to $89 per share within 20 minutes of free trading. This record for an IPO doubled Genentech's market capitalisation in 24 hours as a publicly traded company, and gave a clear indication that the market was willing to place a high value on this totally untried company.

This IPO opened the floodgates, convincing other biotech start-ups that big money was available. Stelios Papadopoulos, now one of the top bankers in biotech, commented:

> *"It really started for me in 1980 with the Genentech IPO. I was a physicist doing structural biology. When I came into the lab and saw the article about the Genentech IPO, I got a feeling it was a big thing. If I wanted to get out of the lab and do something more business-like, maybe this was the way to do it! That IPO may be the second most important event for biotech, following the Cohen-Boyer invention of genetic engineering. It showed that you could actually finance this business in the public markets" (Robbins-Roth, 2001:22).*

It is obvious the firm attracted much hype, and the question remains whether the same results could have been achieved without it:

> *"Ironically, the more actual data there were, the harder it was to partner a project...everyone thought that it (gamma interferon) would be a miracle cure for cancer and there were no data to refute that because there was not much data" (Robbins-Roth, 2001:27).*

Such comments add weight to Bartholomew's (1997) argument that without the appropriate institutional and cultural environment, replication of the successful results of US biotechnology experience is unlikely.

One of the clear advantages that Genentech was able to achieve as the leader in the market was to enlist the interest of pharmaceutical companies such as Eli Lilly & Co:

> *"In 1978, Genentech sold worldwide rights to its recombinant human insulin to Eli Lilly & Co. and had sold all rights to its human growth hormone to AB Kabi, then the world's largest supplier of cadaver-derived growth hormone. Hoffmann-La Roche bought the marketing rights to Genentech's interferons in 1980" (Robbins-Roth, 2001:25).*

These deals were important to the young biotech company in two key ways (Robbins-Roth, 2001). First, having respected big pharmaceutical players pay for marketing rights to Genentech products gave potential investors the message that the technology was real and valuable. Second, the deals gave Genentech cash to support its growth, although making these deals was not necessarily simple. In the 1980s most of the big pharmaceutical companies didn't accept that biotech could deliver marketable products. However, Papadopoulos reflects that, in many ways, the most important thing for biotech in the 1980s was that big pharmaceutical companies didn't realise its importance. Denials of technology's value gave the biotechnology industry time to mature. Eli Lilly, Roche

and Schering-Plough were the only big pharmaceutical companies to place any major value on biotech products, partnering with Genentech for insulin (Lilly) and interferon (Roche) and with Biogen for alpha interferon (Schering-Plough).

At first big pharma argued that the science just wouldn't work. When insulin was approved in 1982, they argued it was impossible to manufacture these protein drugs in a commercially feasible manner, but the biotech firms subsequently solved those problems. Next they argued about patentability of recombinant versions of naturally occurring proteins, but the US Patent Office resolved that issue. Then they argued that injectable drugs couldn't be the basis of a big business because the market was limited, but Amgen's huge market capitalisation is based on two injectable drugs, Epogen and Neupogen. The final argument was that biotech companies could not market drugs as well as big pharma. By October 1985, Genentech was marketing the human growth hormone (HGH). Big pharma assumed that once the biotech companies got into small-molecule drugs, big pharma's powerful in-house medicinal chemistry programs would allow it to take over. But again, biotech hired top talent and set up its own in-house groups. According to Papadopoulos:

> *"Basically, the denials of big pharma throughout the 1980s allowed the biotech evolution to happen. If big pharma had had half a brain, there never would have been a biotech industry" (Robbins-Roth, 2001:28).*

Genentech's science lead was expected to last a few years but it lasted throughout the 1980s (Robbins-Roth, 2001). The lead allowed the company to build the industry and recruit leading scientists from academia, lured by the chance to do academic-style research in an entrepreneurial biotech setting. It was much harder for big pharmaceutical companies to build the right group in-house, given their less flexible structures. Genentech switched from being a boutique R&D company to a pharmaceutical company by retrieving the US marketing rights to human growth hormone in 1983 and obtaining FDA approval in 1985. This strategy saw revenues reach US$214 million by 1998, with a stream of new products ensuring a strong revenue position (Robbins-Roth, 2001).

Today, many US biotech companies follow a similar path of evolution: beginning as an R&D house, using partners for late-stage clinical development and marketing, retaining more rights with the next product, and finally retaining all manufacturing and marketing

rights. In the US, public markets have provided a huge boost in market cap to biotech companies that are able to progress to selling their own products (Robbins-Roth, 2001). However the Australian context, discussed briefly in Section 2.3 and in greater detail in Chapter 5, is different.

### 2.2.5 Hybritech – the biotech based on monoclonal antibodies

The second scientific breakthrough in the biotech industry was the discovery of monoclonal antibodies:

> *"Monoclonal antibody technology allowed scientists to grow large vats of pure antibodies aimed at selected targets. This technique in turn let them use target recognition and tight target binding of monoclonal antibodies to design new diagnostic tests and therapeutics. The therapeutics became known as magic bullets because they were injected into the bloodstream and then headed straight for their disease target, carrying a deadly payload. It was revolutionary" (Robbins-Roth, 2001:49).*

Although the technical discovery that fuelled monoclonal antibody development came from the UK, the first company created to exploit this groundbreaking technology was based in the US. Hybritech was founded in 1978 by venture capitalist Brook Byers (of Kleiner, Perkins, Caufield & Byers), Dr. Ivor Royston, a professor at the UCSD and Howard Birndorf, one of Royston's researchers.

Serendipity also played a part in the formation of this company (Robbins-Roth, 2001). During sabbatical leave in the Milstein laboratory in the UK, Dr. Leonard Herzenberg, a genetics professor at Stanford, had learned how to make hybridomas, the cell lines that pump out monoclonal antibodies. Back at Stanford the technique was eventually taught to Birndorf, who worked for Royston. Birndorf and Royston began to discuss how this technique might be applied to myeloma, a cancer of the antibody-producing immune cells, where a single B cell uncontrollably multiplies a single type of antibody. Classic cancer treatments would wipe out the entire immune system, leaving the patient vulnerable to infection. Birndorf and Royston, however, discovered that a monoclonal antibody aimed only at the multiplying B cell would have a better chance of slowing the cancer without killing the patient. They also discussed the possibility of commercialising their research, although neither scientist knew how to bring this about. Birndorf is quoted as saying:

> *"I bought a book on how to start your own business and wrote a five-page business plan. I figured we needed about US$178,000 to buy equipment, rent lab space, hire some people, and start making antibodies but I had no idea where you go for something like this" (cited in Robbins-Roth, 2001:50).*

The social networks at that time in the Californian region made a big difference to the formation of Hybritech. Royston had made several unsuccessful attempts to raise capital. Then through social contacts he met Byers, now with experience in the highly successful venture Genentech, who convinced K&P to invest $300,000, subject to a due diligence review. Byers spent three months completing the due diligence, and then flew to England to negotiate a deal for the Milstein hybridoma research with the UK Medical Research Council. However, Milstein had not filed patents for making hybridomas, because he considered it pure science that should be available to everyone. This episode highlights the insulation of academic researchers from changing commercial circumstances in failing to recognise a commercial opportunity. Indeed, the UK government berated itself for years for the failure of UK institutions to patent the method of making monoclonal antibodies and the consequent loss of competitive advantage and earning potential (Prevezer, 2001). The entrepreneurial cultural perspective of the Americans is in stark contrast to the status given by the British to pure research and the failure to recognise the benefits of applied research.

As soon as the rights to the patent were acquired, the company went into operation. Birndorf remembers:

> *"We closed the deal in October 18, 1978. The next day was my last day at University of California, San Diego (UCSD). Monday, October 23, I became Vice President of everything. The plan was that Ivor (Royston) would stay at UCSD and be a consultant to the company. I opened a bank account, had lined up a lab to lease, and found myself sitting in an empty office next to a bare lab with a desk, chair, telephone, and scientific catalogs" (Robbins-Roth, 2001:51).*

By December, Birndorf had hired five people and worked with the mice himself to complete the first proof of principal experiments making monoclonals to the hepatitis B antigen. Byers had given the team six months to do the work; Birndorf completed it in two months (Robbins-Roth, 2001).

In January 1979, the partners heard a rumour that another group, led by Ted Greene, had recognised the value of monoclonal antibodies. Byers convinced Greene to join

Hybritech. Greene was a crucial addition of experienced management for the young company. He spearheaded the creation of an updated business plan, raised several millions of dollars to fund the development work, and began recruiting from established firms the management team that would later create many of the key San Diego biotech firms.

The company went public in 1981 in an environment excited with the prospect of biotech possibilities. The IPO raised around US$12 million, followed by a US$33 million secondary offering in 1982. Its first product, a detection kit, was soon in production and the company went on to commercialise many other diagnostic tests, all based on monoclonal technology. This technology revolutionised clinical lab medicine, moving it away from enzyme-based tests to rapid antibody formats. The team pulled together to create and grow Hybritech to the level that Eli Lilly & Co bought the company in 1985 for an unprecedented US$375 million. This was the first lucrative biotech buyout and only the third buyout of any size for this industry. The management team, often with financial backing from Byers, subsequently became involved with second and third generation companies in San Diego.

The biotechnology industry benefited a great deal from the informal networks developed through these initial associations. The networks linked the science base and commercial community of small firms with venture capital and large user companies. The ability to build informal networks through trade associations, personal ties, scientific conferences and venture capital was state-of-the-art in California. The process was also self-reinforcing. Job mobility was high because it was relatively easy to find a new job in an area densely populated by different types of firms in the industry. The region's culture encouraged risk and accepted failure. Those who attempted to start a firm were held in high regard. UCSD created the CONNECT network in 1985 as a university private sector partnership to encourage local high technology entrepreneurs and put them in touch with relevant scientific, technical and managerial expertise (Prevezer, 2001).

The Australian experience was not as glowing. Although commentators such as eGcapital (2004) note that the industry is maturing in this country, approximately 66% of firms still have a market capitalisation of less than $50 million and most have still not developed past Phase I trials. The next section provides an overview of the Australian biotechnology

market and discusses the difference between the US and Australian biotechnology environment.

## 2.3 The Australian biotechnology context

### 2.3.1 Background

Australia has a history of eminent medical scientists. Of the country's seven Nobel prize winners, six have been within the bioscience sector. Australia's outstanding record as an innovator in medical technology started with Howard Florey and the discovery of penicillin. More recent outstanding scientists include Peter Doherty, the Nobel prize-winning immunologist, Sir Gustav Nossal, a leader in immunology research at the Walter and Eliza Hall Institute, Graeme Clark, leader of the team that developed the bionic ear and Barry Marshall and Robin Warren who together revolutionised the treatment of gastro-duodenal ulcers.

But even with such leading edge science, Australia has been struggling to produce an FDA-approved blockbuster drug. Australia has not achieved much business success in this area and few Australian listed life sciences companies are making profits, particularly in the drug sector. One of Australia's best known biotechnology companies, Biota, which introduced a generation of investors to biotechnology, was able to obtain FDA approval only in March 2006 for its influenza-preventing drug Relenza.

In June 2005 there were 70 publicly listed biotechnology companies on the ASX, mostly engaged in drug discovery and development, medical devices and diagnostics. The three most successful stocks are diversified medical device companies: CSL (a medical products company selling blood as a commodity), Cochlear (a hearing device company) and ResMed (producer of sleeping devices). The human drug sector offers little future for this country because the costs of approval by regulatory authorities and distribution in global markets are prohibitive for small, early stage companies with little ability to attract capital for production and marketing.

The figures support this analysis. In November 2005, Australia had around 400 biotechnology companies and 560 medical devices companies (Biotechnology

Australia, 2005). Fifty per cent of new firms had emerged from public research organisations and employed 6100 people, averaging a mere 6.35 people per company. Furthermore, only 70 biotechnology companies were listed on the Australian Stock Exchange on 30 June 2005, and most had listed only in the previous 5–8 years. Their combined market capitalisation was A$14.6 billion. However, without the three major players, CSL, Cochlear and ResMed, the combined market capitalisation was only A$5.3 billion (eGcapital, 2004), demonstrating that most of Australian biotechnology companies are SMEs with an average company stock market valuation of A$55.1 million, and median of only A$26.9 million. These are very small companies compared with the same sector in other parts of the world. Table 2.1 lists the market capitalisation of the ASX-listed biotech companies in September 2004.

| Market Cap Band ($ million) | Number of companies |
|---|---|
| >300 | 4 |
| 100–300 | 12 |
| 50–100 | 11 |
| <50 | 54 |

Source: eGcapital (2004:4)

**Table 2.1:** Number of companies per market cap band

As further illustration the infancy of the Australian biotechnology sector, only 10 of the 37 trials that reported results in the second quarter of 2005 had been conducted on humans; all other data reported came from laboratory or animal tests. Only two of those 10 were in Phase II trials, the remaining eight were in Phase I. The need for capital by Australian biotech firms causes some to list on the ASX before they have a reasonable prospect of commercial success and, although IPO numbers looked positive for the year, almost all companies under-performed post-listing and the sector continues to be volatile (PwC, 2004).

A shortage of appropriate funding in the industry is causing biotechnology companies to be formed too early in the research project in order to access grant funds and later to seek venture capital (Hopper & Thorburn, 2003; PwC, 2004; Vitale, 2004). The number

of early stage, pre-clinical trial, biotech listings in the Australian market is higher than elsewhere in the world. This is partly explained by private biotech companies and their stakeholders realising that they can generate more money through IPOs than from venture capital funds. However, a consequence is that for secondary funding, small listed companies rely on market conditions and momentum creating investor demand, rather than having access to the capital associated with third and fourth round private funding in other markets. This is not an ideal situation for Australian biotech companies attempting to become competitively commercial. Premature and early listing has translated into volatile share price movements and investor disappointment (Hopper & Thorburn, 2003: PwC, 2004).

Despite the difficulties faced by smaller biotech companies, some of the most heavily traded local life sciences companies are from the drug sector. Of the three main product subtypes, drug discovery, devices and diagnostics, in 2004 the drug discovery sub-sector performed best, achieving average returns of 47% (eGcapital, 2004). Sir Gustav Nossal, one of Australia's best-known scientists and a principal of the Foursight Associates consultancy group, considers that Australia has strengths in devices and veterinarian medicine, but the biggest potential market is human medicine. He agrees that the market is very competitive, but rejects the notion that Australia cannot commercialise the science:

> *"It can be done but it requires skills and links with the big pharmaceutical companies. Investors just have to remember this is a long-term investment" (Kirby, 2003:54).*

Although patient capital has been invested in the sector, many investors consider the long term risk too great, as evident in the volatility of the market. Furthermore, access to pharmaceutical companies is not easily achieved in this country and this is an additional constraint for companies attempting to succeed in Australia.

Most Australian companies that do not fall into the category of drug discovery companies are device makers. They are perceived to engage in more predictable work than drug discovery. The device industry follows the principles of the manufacturing industry and avoids the "blue sky" of drug discovery and development. Achieving approval for a medical device as seen as easier, based on the philosophy that a hearing aid or breathing device is much less likely than a drug to kill or seriously injure, a

perceptions "reflected in the higher success rate of local companies such as ResMed and Cochlear" (Saville, 2004:38).

It is true that two of Australia's most successful life sciences companies, Cochlear and ResMed, are device makers. However, there are clear differences between the requirements of market access for these two firms, although they are usually both classed as manufacturers. Cochlear produces a product that has to be surgically connected to the hearing nerves in the brain, and hence it required FDA approval before it could be deemed safe. This company therefore was constrained in its growth in a very similar manner to a drug discovery company. The case study (Chapter 5) suggests that its success is more a reflection of its 20-year history and some very entrepreneurial early strategies rather than its manufacturing focus. The problems of this sector can be summarised as:

> *"Far too many companies, many went to the market too early and therefore don't have the range and depth of products or skills to succeed" (Quinlivan, 2005:24).*

Alex Waislitz from Thorney Holdings, a private-equity company with holdings in several life sciences companies including the drug researcher Amrad, the medical testing company Kinacia and the medical device manufacturer Ambri, says:

> *"Right now in life sciences you are getting a convergence of computer power and emerging technologies like nanotechnology. When you get this combination there is bound to be a tremendous amount of opportunity and as an investor you want to be in there. Of course there are problems with management and with loose discipline in capital expenditure".*

He suggests, however, that there are solutions to such problems:

> *"The bigger issues for the sector right now are to do with management. First we have to get life sciences out of the university environment. Then we have to get professional management into the life sciences companies. If these companies are still run by scientists who founded them get problems when it comes to making priorities with science projects" (Kirby, 2003:54).*

These sentiments highlight the main problem of this sector of Australian industry: many companies are really still only research projects, and they are listing too early without the skills to survive once their initial offering has been spent.

Other studies (E&Y, 2001; Hopper & Thorburn, 2003; Vitale, 2004) have found that Australian firms have difficulty in recruiting skilled managers with expertise in commercialisation, deal structuring and business development. The US entrepreneurs, discussed above, emerged from three sources: venture capital firms with experience in the high tech boom, business leaders from previously successful biotech firms that had been sold to large pharmaceutical firms, or from the pharmaceutical companies themselves. In Australia these sources have not generally been available. The pharmaceutical industry is small, acting more as distribution chains for head office rather than R&D centres. Therefore it is "unlikely to produce the flow of expert personnel so desperately required. The alternative of recruitment from overseas under current tax policies remains difficult and expensive" (Vitale, 2004:26). Furthermore, although there are some venture capitalists with commercial experience in the northern hemisphere, anecdotal evidence suggests that this sector is immature in its understanding of the biotech industry and unlikely to provide a great source of business acumen.

### 2.3.2 The problem of money

There are several sources of funding available to potential scientific entrepreneurs. These include the public research organisation in which the research was conducted, business angels, immediate associates, professional equity investors, government funds and venture capital. In 2003–2004, biotech and healthcare was the leading sector in attracting venture capital funding (Biotechnology Australia, 2005). However, Vitale (2004) painted a different picture for 1996–2003:

> *"Australian venture capitalists have invested approximately A$130 million in core biotechnology companies" (Vitale, 2004:12).*

As a comparison he states:

> *"On a single day, 6 February 2004, six American biotechs announced a total of US$114 million in venture capital funding" (Vitale, 2004:12).*

Furthermore:

> *"Australian biotechs are trying to compete in a global industry from a country in which the amount of venture capital funding is orders of*

*magnitude less than that available to their overseas rivals." (Vitale, 2004:12).*

Finally, he notes:

> *"The general view of Australian venture capitalists was that they tend to be conservative and risk-averse compared to their counterparts overseas. Some interviewees felt that the small number of venture capital companies in Australia has led to a less than fully competitive and transparent marketplace for funding" (Vitale, 2004:15).*

Further difficulties for the biotechnology entrepreneurs are created by R&D cycles and product lead times of 20–30 years. Hine and Griffiths (2004), for instance, noted the consequences when long gestation periods are juxtaposed against the shorter-term perspective of venture capitalists, financiers, managers, government industry analysts and other investors:

- Problems of a mismatch are created between industry viability and stakeholder expectations.

- For many investors reference to the new economy has created associations between high-technology industries, firms and stocks with expected high rates of market returns.

- Little consideration is given to the structural characteristics of the industries that drive the wealth creation process, R&D life cycles and marketable outcomes.

- The biotechnology sector is a case of a sector that requires the reconsideration of expectations.

Such expectations lead to volatility in the availability of funds from venture capital and stock market sources:

> *"Market driven policies and practices impact on the sustainability of firms operating in the industry" (Hine & Griffiths, 2004:138).*

Estimated public sector spending on biotech R&D was A$1.29 billion in 2002–2003, an increase of 33% from A$968 million in 2001–2002 (Biotechnology Australia, 2005). Most state governments, in particular Queensland and Victoria, are competing to be biotech centres of excellence providing additional support. Two rounds of Biotechnology Innovation Fund (BIF) have contributed A$15.8 million, mostly

supporting human therapeutics products. While business spending on R&D in biology and medical/health sciences in 2002–2003 was A$659 million, an increase of 27% from 2001–2002, how these funds are allocated has been questioned and is discussed in Section 2.3.6.

Superannuation funds and other institutional investors could provide substantial funding for the sector. Citigroup's global corporate and investment banking group in Australia and New Zealand estimates that every year, about A$70 billion of new investment capital is created. Rob Thomas, chairman of Heartware and formerly chairman of Citigroup, has estimated that new issues take about A$34 billion of that amount, leaving A$36–40 billion unallocated.

> *"The pressure of investment funds and super is well documented and super fund flows are not expected to peak until 2009-11" (James, 2005:52).*

Superannuation funds have been concerned about the mixed record of Australian life sciences and have been slow to enter the sector. One exception was the Queensland Government's Investment Corporation (QIC), with a portfolio of A$260 million. However, in late 2005 QIC announced that it had relinquished its holdings in more than a dozen biotech companies. Concerned with the falling value of its portfolio, the fund is now concentrating on a smaller number of bigger capitalised stocks. ING and AMP superannuation funds have also supported the industry, but only on a small scale.

A major source of Australian finance for biotech companies are so-called Business Angels. Two wealthy Australians, the late Kerry Packer and Richard Pratt, invested in the life sciences. Kerry Packer was associated with a string of companies, including Circadian Technologies Limited, a life science portfolio investor, and his name remains as a shareholder in Syngene Limited, a genomics company within the Circadian group, and on the share register of the drug delivery company Acrux Limited. Other investors associated with Acrux include Maurice Newman (ASX chairman), Nunzio D'Aquino (CEO of Carlton and United Breweries), Bruce Mathieson (Melbourne poker-machine entrepreneur) and Ross Dobinson (once head of the corporate advisory division at Dresdner Australia Pty Ltd).

The industry has attracted several other significant investors. Harold Clough is

chairman of listed engineering company Clough Limited. In 2003 the Smorgon family became investors in the peptide manufacturer Peptech through the private equity company Escor Limited. Bryan Frost, executive chairman of investment company Peregrine Corporate Pty Ltd, has invested right across the life sciences sector, notably with the biotechnology commercialisation company Prima Biomed Limited and alongside the Liberman family in the Alzheimer's drug company Prana Biotechnology. The Liberman family, through Jagen Investments, is also an investor in the drug delivery researcher Eiffel Technologies. Frost says:

> *"There has been a lot of money going into the life sciences. Private investors and institutions understand the market and we understand management, the science is understood by the scientists. But, the big companies will not take the risks in life sciences that smaller companies are willing to take. So there is a process where the smaller companies make the discoveries and then sell those discoveries at a big profit." (Kirby, 2003:54).*

The examples of Genentech and Hybritech, discussed in the previous section, may be the ideal strategy for small biotechnology firms, but the Australian market is different, with a lack of Australian 'big companies' to buy out small firms making such a strategy infeasible in this country. Perhaps the cultural gaps between science and commerce contribute to the reason why Australia is still not reaching global commercial success despite its global scientific success. Frost's descriptions highlight the cultural gaps, with concepts of "goal-oriented" versus "blue sky" research and "publish or perish" versus "commercially sensitive publications" not easily reconciled. In some cases, as the case studies described later, the conflict between saving lives and making profits is difficult to resolve. Yet to take an invention from the lab to the global market, such cultural changes in perceptions are critical.

Furthermore making the discovery is not enough in this industry. Proof of concept or successful Phase I trials, although exciting, mean very little for the final product. Phase II, where humans are tested, is much more expensive and could negate positive results in animals.

| Phase | Activity | Duration (years) |
|---|---|---|
| I | proof of concept testing with animals | 5–10 |
| II | proof of suitability and benefit for humans | 5–10 |
| III | many humans in several countries with extensive documentation | 2–10 |

**Table 2.2:** Phase duration of biotech development

A company that uses all available funds in proving the concept will have little chance of taking the concept to Phase II trials. However, even success at this stage is insufficient, because there may still be side effects experienced by the wider community. The Phase III trials that involve many human participants in several countries can take many years to collect reliable data (Table 2.2) and cost up to A$500 million to get FDA approval for a drug. Vitale (2004:17) noted "in this environment, the wisdom of encouraging early company formation may be questionable". Furthermore, unlike large pharmaceutical companies who have undertaken FDA approvals before and know the system, it is often a first time experience for the Australian company, limiting their chances of a successful outcomes even further.

### 2.3.3 The problem of language

A crucial stumbling block for most investors is the language of science, which isolates the business from non-specialist investors. To alleviate this problem some investors hire in-house scientists to review and filter life sciences investments in their private investment operations. For example, Kerry Packer used Alistair Galloway as scientific adviser at CPH Investments, and Dick Pratt has used Silviu Itescu at Thorney Holdings. Some investors use specialist scientific consultants: stockbroker JBWere, for example, has used Foursight Associates, the boutique life sciences consultancy associated with Sir Gustav Nossal, and groups such as eGcapital also provide investor information. However, few retail investors can afford private advisers. Anecdotal evidence suggests that fund managers even bring in geologists to assess biotech proposals when biologists are not available, highlighting the lack of understanding of the industry. Scientists, on

the other hand, often do not understand the language of commerce, and find that writing business plans is not a skill that comes easily.

### 2.3.4 Business models

The immediate lessons for survival and adaptation from the executives of the biotechnology companies studied by Vitale (2004), and confirmed by the companies interviewed as part of this research, are that Australian biotech companies should adopt a hybrid model that includes some sort of short term cash-generating activities to fund the long term discovery process. Cochlear, for instance, charged $10,000 for its prototype to be implanted, even though it had not yet received FDA approval for the technology. Novogen, on the other hand, sold its herbal products to generate cash flow and develop its global brand and experience. In both cases the companies concentrated on niche markets and products to maximise returns from limited capital. Also, with the US representing 40–50% of the market for most biotech companies, and stringent US Food and Drug Administration (FDA) regulatory requirements, companies pursue overseas and US markets because they are a large and very attractive option compared with the local market.

### 2.3.5 Creating entrepreneurial cultures

The emergence of the biotech industry in the US has been facilitated by the country's unique institutional context (Bartholomew, 1997). The context includes strong government support for the newly emerging industry from agencies such as the National Institute of Health, a strong tradition of interaction between industry and academia, and an abundant availability of risk capital. The entrepreneurial orientation of such traditions, Bartholomew proposes, results in the willingness and preparedness of academics and other researchers to start their own companies. Yet many of these institutional aspects are either missing or only beginning to emerge in the Australian context. Why this is so can perhaps be explained from a historical perspective. Penrose (1995:xiii) emphasised that "history matters" in the theory of the growth of the firm; this section describes several events that contributed to the current institutional settings.

Despite Australia's outstanding record as an innovator in medical technology dating from Howard Florey and the discovery of penicillin, narrow institutional perspectives have allowed an unfortunate set of industrial dynamics to emerge during the origins of the Australian biotech experience (Mathews, 2001). In his case study "*The Birth of the biotechnology era: Penicillin in Australia, 1943-1980*", Mathews (2001) described the notable achievement of Australian science, technology and industry in the development of penicillin as a wartime project in which Australia made major contributions. During that period Australians contributed a great deal to a possible future pharmaceutical industry:

> *"...scientific identification and purification of penicillin, and to the industrial scaling up in its production at the Commonwealth Serum Laboratories (CSL) in Melbourne. And yet the nascent antibiotic industry was allowed to run down and eventually disappeared by the end of the 1970s" (Mathews, 2001:iii).*

The case study provides an insight into the historic perceptions of commercialisation of Australian scientific research:

> *"Contrast in aspirations between the highest levels of scientific and technical achievement in bringing penicillin into widespread use (Australia being the first country in the world to provide penicillin to the civilian population in 1944) and shockingly poor performance in sustaining and developing a national industry"(Mathews, 2001:18).*

Despite CSL's remarkable achievements, the penicillin industry did not provide the infrastructure that could have underpinned the current focus on the commercialisation of Australian biotechnology research. Mathews (2001:2) described why:

- The penicillin industry never became a vital national industry seeding new companies, exports or related activities in antibiotics.

- CSL was never allowed to spin off new, dynamic companies involved in antibiotics or vaccines.

- There was no effort made to diffuse the industrial processes of antibiotic production to the private sector in order to build up a national antibiotic industry.

- Foreign multinational pharmaceutical companies were allowed to set up plants in Australia to produce cheap penicillin and other antibiotics, without any requirement

being imposed on these companies to localise their supplies or in any other way contribute to the creation of a national industry in Australia.

- CSL itself continued to produce the highest grade, safe and reliable product, but in increasingly difficult competitive conditions and with process technology that was falling behind the world best, certainly in terms of scale of production.

The Industries Assistance Commission (IAC), established by the 1972–1975 Whitlam Government to take over from the former Tariff Board, took a consumer standpoint rather than a national industrial development perspective, and recommended that penicillin production at CSL be wound down, in favour of a single foreign pharmaceutical corporation, Abbott Laboratories. Indeed the efforts of one Australian producer, F H Faulding in Adelaide, were actually rebuffed, with the Department of Health refusing to allow Fauldings access to any government data, thus reducing its efforts to a less advanced level of technology.

Paths not taken in the Australian penicillin industry and policies that led to its "dismemberment" produced what Mathews (2001) referred to as a sorry end to a brilliant beginning. He notes the very important seed that had been planted in Australia during the war years, which was capable of growing into many diversified industries involving different forms of antibiotic production and export, as well as associated entities such as vaccines. Moreover, a revitalised penicillin industry would have stimulated related industries such as biological fermenters, specialised glassware and a host of other areas. But instead, the industry was shut down because it was judged to be 'uneconomic' by the narrowest criteria of current costs and market size. All possibilities of other diversified industry developments disappeared with it (Mathews, 2001).

Penicillin was and still is a wonder drug. In describing the long history of a strong cultural divide between scientific research and its commercialisation in Australia, Mathews (2001) referred to the cultural cringe that allowed the nascent industry to run down and be handed over to foreign interests. Such a cultural perspective that is indifferent to the industry's fate is unlikely to spawn a philosophy of entrepreneurial orientation resulting in the willingness and preparedness of academics and other researchers to start their own companies.

Thorburn (2000) confirmed this view in her study of spin-offs arising from research of the Commonwealth Scientific and Industrial Organisation (CSIRO). She found that 75% of these new technologically based firms (NTBFs) failed before their fifth year, which she attributed to the lack of such essentials as company resources, including technology and finance, and post-founding activities such as marketing and management. She noted that (Australian) research institutions have often lacked the strong entrepreneurial culture that is needed to encourage researchers to try a career in industry rather than research. The CSIRO study demonstrated that in the majority of cases, spin-off activity was permitted rather than chosen as the preferred commercialisation path, and levels of support for these firms were low:

> *"Business training was available to only one spin-off, but identified by many respondents as a key need" (Thorburn, 2000:267).*

Thorburn (2000) also suggested that research institutions licensing to spin-offs have not provided business training or finance (or broker finance from others) to maximise the chances of success from a commercial sense.

More recent studies (Hopper & Thorburn, 2003; Vitale, 2004; PwC, 2004) have continued to highlight the need for universities and research institutions to re-examine their policies on intellectual property and commercialisation processes. In surveying the commercialisation policies and processes of public research institutions, Vitale (2004) found that Australian universities had not changed their policies very much since the Thorburn (2000) CSIRO study:

> *"Australian universities are devoting comparatively little effort, and in some cases no effort at all, to commercialisation. One consequence of this lack of investment in commercialisation may be that Australian academics are relatively poorly informed about the steps required to commercialise their research, and about the realities of the global biotechnology marketplace" (Vitale, 2004:23).*

The rate of company formation increased by 8% in 2004, but how many will still be in operation in five years' time is debateable.

### 2.3.6 Public policies set the scene

Studies on the state of the industry confirm the need for consistent and realistic government policies to narrow the gaps between applied research and market development. Many researchers have noted the need for government reform of Australian tax regulation and company laws to improve incentives for VC investments in Australia. As outlined above, Australian biotechs receive much less funding than their overseas counterparts. However, Vitale (2004) noted that it is not clear if such improvement would actually lead to additional investment, as "perhaps it would just raise the threshold for venture capital funding" (Vitale, 2004:17). This sentiment comes from the proposition that government policies continue to encourage the formation of biotechs, many of which have been accurately described as being "less like companies and more like research projects with ABNs" (Vitale, 2004:6). It is perhaps more difficult to know how to develop the company once it has been established, but staying within a public research environment would contribute substantially to the longevity of the company.

In an effort to improve some of the shortcomings of the Australian biotechnology environment, on 29 January 2001, Prime Minister John Howard launched the federal government's Innovation Action Plan *"Backing Australia's Ability"*. The innovation statement outlined the government's strategy to encourage and support innovation in Australia by investing $2.9 billion over five years. The statement was an acknowledgment by the federal government that its biotechnology sector is under-developed compared with its world and regional competitors, despite evidence that Australia is well placed to be a leader in the knowledge-based economies with its world class universities and research institutions, a developing information technology sector and a modern communications infrastructure. Government assistance to these knowledge industries was also recognised as being comparatively low.

Vitale's (2004) findings have clearly demonstrated that government policies on biotechnology are sometimes inconsistent and even conflicting. He noted that the Commonwealth Department of Industry, Tourism and Resources uses the Biotechnology Investment Fund grant program to encourage company formation, while the Australian Taxation Office treats share options in a way that makes it difficult for new companies to recruit the staff that they need in order to grow. Furthermore, the

Department of Education, Science and Training gives universities money for research, but does not require them to devote any effort to the commercialisation, or even to the protection of the intellectual property that the research generates (Vitale, 2004).

The Vitale (2004) findings support others (E&Y, 2001b) that challenge many government taxation policies on such issues as options, capital gains tax and employee share acquisition scheme.

Vitale (2004) summarised the position by saying that Australia cannot win just by playing the same game as the USA. Rather, it must focus its efforts and scarce funds on areas of particular competitive advantage in order to gain highest returns for effort. To succeed, Australian biotechnology must concentrate on doing what it is good at, and capture maximum value from its intellectual property, its world class R&D and science, or its superior ability to serve niche markets and critical segments of international production chains.

As promising as the life sciences are, public debate on the ethics of these new technologies also inhibits the growth of would-be scientific entrepreneurial firms. Such questions as whether genetically modified crops should be grown, and whether funding should be allocated to stem cell science can halt the progress of much research. In Europe the growing of genetically modified crops was almost frozen for many years while in the US no such impediments exist. Which avenue Australia takes is yet to be decided. However, despite recent moratoriums on the growth of GM crops, there appears to be no slowing of the industry's growth, and company formations and listing continue to expand. In addition, with the recent formation of industry bodies such as The Australian Business Limited (ABL) and BioMelbourne Network, and with new support from established industry bodies such as the Australian Institute of Company Directors and Australian Venture Capital Association Limited, knowledge of the dynamics of the industry is bound to improve.

Geoff Brooke, a former investment banker with Rothschild Bioscience Managers and now a director of a specialist life sciences fund, GBS Venture Partners, also projects hope for the industry:

> *"All the main banks and broking companies are putting people into the sector. We are still a small sector and we are never going to replace mining*

*or agriculture, but it could give us a whole new level of enterprise that might represent 5% or more of GDP. What I am saying is, if we can get it right, we can have a new global industry" (Kirby, 2003:54).*

This research describes how a sample of five case studies have recognised the Australian contextual geographic and economic realities and acted in a way that maximised their individual commercial benefit, subsequently improving the chances of taking their unique technology to commercial success and fulfilling Geoff Brook's vision of a new global industry in this country.

# 3 Literature review

Many theories abound on what causes the growth of a firm. This chapter reviews the dominant approaches to explaining the dynamics of the growth of small firms. It discusses alternative paradigms employed to describe and explain business growth processes, it describes one particular growth model and finally evaluates whether, in the light of contemporary scholarship, this model appears to overcome key failings of its predecessors.

## 3.1 Economic focus on small firms' growth

Stochastic models of firm growth developed in the field of economic literature suggest that firms operate within conditions of perfect competition. The focus of economic theory is on perfect competition among homogeneous firms with given technologies and the underlying concepts of perfect knowledge and freedom to make choices between alternatives. Traditional economics concentrates upon explaining movement from one size to another in terms of the net advantages of different sizes (O'Farrell & Hitchens, 1988). The economic focus has largely been on how well an economy allocates resources with given preferences and technologies. Economic theory of firm behaviour posits that firms face given and known sets of choices and have no difficulty in choosing the action within those sets that is the best for them, given their objectives (generally assumed to be as much profit as possible). Thus the 'economic problem' is about getting private incentives right, not about identifying the best things to be doing.

Such a perspective does not allow for understanding of the micro level processes that propel some business ideas into large firms. Focusing on understanding the nature of economic activity and what constitutes good economic performance militates against paying attention to firm differences as an important variable affecting economic performance. The overall result of seeing firms as 'black boxes' is a view that what firms do is determined by the conditions they face and by certain unique attributes they possess, such as location or proprietary technology (Nelson, 1991). Nelson (1991)

proposed that where the theory admits product differentiation, different firms will produce different products but, in the theoretical literature, any firm can choose any niche. Thus there are firm differences but there is no essential autonomous quality to them.

One subfield of economic theory that does consider individual firms is Industrial Organisation (IO). IO studies oligopolistic rather than perfect competition. In industry studies, economists often have been forced to recognise firm differences such as size, performance and growth. Growth is perceived as attainment of economies of scale and minimisation of long-run costs. These theories are considered to over-emphasise the large firm as the ultimate stable outcome of growth, there being no perceived limit to the size that a business might achieve (O'Farrell & Hitchens, 1988).

A structural analysis that relies on economies of scale will explain why the number of long-run competitors in the pharmaceutical industry would be smaller than the number of chemical consulting firms. These studies provide interesting information on how the pharmaceutical industry works and its performance in various dimensions. The interest in the individual firm lies in how the particularities of these firms influence the industry more broadly. Such a broad overview cannot assist in understanding how the individual firm in a technologically innovative industry develops its competitive advantage and what drives its growth at the micro level.

Nelson (1991) noted that economic models do not effectively come to grips with what lies behind the firm differences or the implications of those differences. Therefore, although surveyed work purports to be concerned with the introduction of something new to the economy, such as new technology or a new way of organising a firm, the models in question do not address the processes of firm evolution and growth. Bhide (2000) also argued that mainstream economic theories tell us very little about how and why only some firms emerge, survive and grow. Variations in the size and longevity of firms have no influence on outcomes of the industry, and thus the evolution of a specific firm is irrelevant in industrial economics. The unrealistic nature of this research means that structural variables cannot explain why GM and Ford, for example, came to dominate the US automobile market when scores of other start-ups folded (Bhide, 2000). Detailed answers to such questions seem unnecessary for economists who are

more interested in the degree of concentration in an industry and its consequences for economic efficiency.

Yet this study requires that kind of information to answer the research question. Why do only some firms implement the key principles that are generally available to all? Is it, for instance, because only some decision-makers have more foresight, willingness to risk new technology, access to capital, or the ability to build organisational structures needed to effectively implement the new inventions? And is there anything unique about the decision makers that gives them such foresight (Bhide, 2000)?

Yet "through all this, the neoclassical synthesis remains as strong as ever, impervious it seems to these or any other attacks" (Mathews, 2002:2). Penrose (1995) suggested that the usefulness of traditional micro-economics is to concentrate on its function as "the theoretical foundation of the theory of the macroeconomic behaviour of the economy" (Penrose, 1995:*x*). Its significance is an overview of the economy in which the industry sits but since the firm as an organisation within this view "is thought to be irrelevant" (Penrose, 1995:forward), research into the emergence and growth of small firms requires additional perspectives.

Within the last quarter of the 20th century a body of new literature on the behaviour, management, and policies of business firms as organisations developed alongside the neoclassical perspective (Penrose, 1995; Garnsey, 1998; Bhide, 2000; Mathews, 2002; Rouse and Daellenbach, 2002; Lockett, 2005, among others). Penrose (1995) argued that there are several reasons for the interest in a different focus on the firm, including the growing dominance of smaller, flexible Japanese firms over their large, bureaucratic US rivals. One outcome of the change in dominance was an increase in applied economic studies of firms and a clear need for new ways of thinking about the emerging nature of a different type of industrial society, including the development of new forms of firm organisation. The biotechnology industry that evolved in the late 1970s and early 1980s was among the new industries and subsequent organisational structures that emerged during that time.

The underlying assumptions of economic theory regarding firm growth are difficult to reconcile with the biotechnology industry, where differences between firms matter and where new knowledge is carefully guarded with patents and other measures. Also, the

very long gestation periods for development of biotechnology discoveries and the astronomical costs of taking the product through regulatory approvals, clearly make freedom of choice a very unrealistic assumption. However an economic perspective to the theory of the firm "continues to hold the field despite vigorous attacks" (Penrose, 1995:10) and therefore provides a valuable basis from which to examine the mechanisms of firm growth.

## 3.2 Penrose's Theory of the Growth of the Firm

Penrose (1959) analysed the growth of a firm as a phenomenon separate from the advantage of size. This pioneering work argued that there is no optimum size of a firm. Penrose suggested that firms have a natural reason to grow: the economies of growth. The size of a firm is only a by-product of the process of growth.

Despite her insights, Penrose made little impact on contemporary economics of her day. She was writing in a period when neo-classical equilibrium economic theory was dominant. The quantitative objective of neo-classical economics, outlined above, offered obvious possibilities for the generation and testing of hypotheses. Other managerial models of contemporaries such as Baumol (1959), Williamson (1964) and Marris (1964), achieved a much more immediate impact (Thompson & Wright, 2005). Best and Garnsey (1999) proposed three reasons why it took several decades for Penrose's theory of firm growth to be accepted:

> *"Part of the explanation lies in the departure from the classical concerns of the economics discipline to integrate order and progress to the focus of modern economics on order alone; part lies in the radical departure in method, including the purpose and role of theory that informed Penrose's orientation; and part lies in Penrose herself" (Best & Garnsey, 1999:193)*

Penrose broke from the neo-classical tradition in both conceptual terms and methodology. She concerned herself with the growth of firms as institutions using case study methodology. She argued that internal inducements on expansion arise when some specialised service required for the operations of the firm demands a resource that will generally be available only in discrete amounts; that is, a 'bundle' of services must be acquired even if only a 'single' service is wanted. The incentive to use as profitably as possible the service obtained propels growth.

Her insights into firm growth provide propositions that include the notion that firms are fundamentally collections of heterogeneous productive resources, organised in an administrative framework that has been historically determined. For Penrose, every firm was unique and the uniqueness derived from a distinction between resources and the services that those resources provide through the unique experience, teamwork and purposes of each firm.

Firm heterogeneity and path dependency were given intermittent recognition by economists from the 1960s through to the 1990s. For instance, Richardson (1972) showed how heterogeneous firms derive different benefits from the adoption of the same new technology; Teece (1980) demonstrated that the transactions costs associated with asset specificity encouraged multi-product development by making the sale of underused factor services uneconomic (Thompson & Wright, 2005); and Nelson and Winter (1982) deployed a path-dependent approach. But it was in the 1990s, when the importance of a firm's history shifted from industry back to the firm level, that Penrose's work saw a renewal of interest among economists (Mathews, 2002; Thompson & Wright, 2005).

Penrose's view of the firm as a collection of resources organised in an administrative framework focused her concern on the way entrepreneurial firms with an eye for opportunity can use their resources to realise the shifting market opportunities that shape the firm's growth prospects:

> *"To explain growth of the firm, Penrose elaborates a process view of production and competition. This enables her to draw distinctions between first, resources and productive services and second, productive services and productive opportunities. With these conceptual distinctions, knowledge and technology are incorporated into a dynamic theory of enterprise growth" (Best & Garnsey, 1999:F188).*

For Penrose, the entrepreneurial activity of matching of resources and opportunities was a dynamic process and a key source of firm variation. She brought the significance of individual firms' resources, the relationship between these resources and the perceptions of the entrepreneurs to the centre of the analysis (Best & Garnsey, 1999):

> *"What an entrepreneur sees in his environment, and his ability to take advantage of what he sees, are conditioned by the types and amounts of productive services existing in the firm and with which it is accustomed to operate" (Penrose, 1959:215).*

Penrose's concern with internal dynamics was supported with an awareness that opportunities stem from external markets. Internal and external causes of growth cannot in reality be separated and the interplay between external and internal influences stimulates firm growth (Hugo & Garnsey, 2005:142):

> *"For a general theory of the growth of firms this procedure is legitimate if we can assume that opportunities for expansion do exist in some sense, and that some firms will always see them reasonably correctly and take advantage of them" (Penrose, 1959:215).*

Her focus demonstrated that learning within the firm is a complex and contingent process (Garnsey, 1998). Learning drives the accumulation of routines and skills that become the key resources. Managers influence firm growth by making decisions about the firm's activities while learning through their own participation in the process. Thus the concept of path dependency stems from management's input as it develops over time, and it will be constrained by the firm's resources and past activities (Lockett, 2005):

> *"The division of labour within and between firms leads to the development of skills and the perception of possibilities. Enterprise grows out of management...and is driven by human purpose, seeking to discover and exploit causal relationships by producing new goods for new markets" (Penrose, 1959:51).*

The central idea here is that:

> *"continual change in the productive services and knowledge within a firm along with the continual change in external circumstances present the firm with a continually changing productive opportunity" (Penrose, 1995:150).*

As management seeks to expand its activity, it takes on additional resources. As the firm generates productive knowledge through its management over time, excess managerial resources will develop. Expanding operations to take advantage of excess capacity and learning lead to a dynamic process of growth.

Penrose (1959) suggested the firm's managerial ability is the main limit on growth. The rate of growth and the effectiveness in the use of a large enterprise's resources has been found to rest upon the ability and ingenuity of its administrators to build, adjust and apply its personnel and facilities to broad population, technological and income changes (Chandler, 1962). A firm cannot take advantage of all expansion opportunities if managerial ability and expertise is limited. For Penrose, the small firm's size restricts it

to certain types of opportunity where the prospects of continued expansion are extremely limited (Penrose, 1959:215).

A weakness in Penrose's theory, which she herself admitted, was that she analysed growth only in firms that are able to grow. She did not analyse why some firms grew and some did not. As multiple studies during the late 1980s and 1990s have shown, the differences in growth rates between firms are immense (Storey et al., 1987; Storey, 1994).

Penrose's expectation that managers would behave rationally and always be motivated to use company resources as efficiently as possible has also been questioned. Cyert and March (1963) noted the Carnegie school's findings that factors such as changing environment, conflicting informational clues, complexity of the decision-making process, and competing goals and expectations tax the cognitive limitations of strategic decision makers. Strategic decisions are the result of behavioural factors rather than the result of techno-economic, rational optimisation.

The theory also does not explain why the differences in empirically detected growth rates of small companies can be so varied. For instance, a study of small firms in Northern England found that out of every 100 small firms, the fastest growing four firms would create half the jobs in the group over a decade (Storey et al., 1989). A study of new firms founded during 1979–1984 in Minnesota found that by 1986, 9% of surviving firms provided in excess of 50% of the employment (Reynolds & Miller, 1988). In analysing these studies and five other long-term employment studies, Storey (1994a) concluded that, in the long term, job creation among a small group of fast growing flyer firms substantially exceeded that of the failing and trundling firms (Storey, 1994b).

## 3.3 Life-cycle models of growth

Since the work of Penrose, numerous studies have concentrated on different factors that affect growth. A common model of small firm growth is of a series of phases or stages of development through which the business may pass in an enterprise life-cycle (Greiner, 1972; Churchill & Lewis, 1983; Kazanjian, 1984; McMahon, 1998; Kazanjian

& Drazin, 1990; Autio & Garnsey, 1997; Bhide, 2000). Greiner (1972), for instance, drew on the legacies of European psychologists:

> *"Their thesis being that individual behaviour is determined primarily by previous events and experience, not by what lies ahead" (Greiner, 1972:38).*

Greiner (1972) extended the analogy of individual development to the problems of organisational development through a series of developmental phases through which growing companies tend to pass. Greiner's (1972) model identifies five stages of 'evolutionary' growth that have 'revolutionary' periods requiring organisational reconfiguration (Autio & Garnsey, 1997) at each stage. The reaction to each revolutionary period determines whether the company will move into its next stage in the model, with external factors such as industry growth rate and profitability determining the rapidity of growth transitions. Life cycle models, therefore, set predetermined behaviour patterns on how firms develop, as well as advising entrepreneurs on nurturing their business at each stage (Bhide, 2000). Limits of such a perspective have been questioned by several authors (Garnsey, 1998; Bhide, 2000) suggesting that there are additional factors at play.

Churchill and Lewis (1983) built on the Greiner model. In this model growth is not considered the only alternative available for the firm. This version of the life cycle model also recognises stages of non-growth or stability. However, these stages are presented as a kind of disengagement or failure (Autio & Garnsey, 1997). The model proposes that situations of non-growth can be caused by either the small size of the industry segment or the entrepreneur's lack of motivation to grow. The authors proposed that a "company's development stage determines the managerial factors that must be dealt with" (Churchill & Lewis, 1983:50) and suggested that as the business matures, the entrepreneur's job is to progressively "let go". As the company grows, the owner must spend less time doing and more time managing. He or she must increase the amount of delegation and the inability of many founders to delegate explains the demise of many businesses in substages III-G (the success-growth stage) and stage 1V (the take-off stage) (Churchill & Lewis, 1983). However, the model does not explicate what it is that must be let go and what must be managed.

Scott and Bruce (1987) took a broader look at each growth stage by considering managerial and industry issues in addition to the organisational issues considered by Churchill and Lewis. However there are no major departures from the more general growth models. This model conceptualises growth largely as production intensive, with the problems in the main growth phase arising from scaling up production and sales capacity to build up market share (Autio & Garnsey, 1997). In later work, Kazanjian & Drazin (1990) linked the dominant set of management issues that the firm faces at any time to the life cycle stage of the venture and the critical contingencies that must be solved. The central thrust of this discussion was the fit between the growth stage of the firm and the design of the organisation focusing on the centralisation and formalisation of decision-making at each growth stage (Autio & Garnsey, 1997).

There are several common features in the models discussed above. While they have different numbers of stages and different dimensions to describe specific stages, most models of the organisation life-cycle suggest a fairly common pattern of organisation growth, comprising stages of start-up, growth and maturity. Studies centring on high technology firms have tended to divide start-up into two distinct stages: a period of R&D and prototype development activities, followed by an early commercialisation stage. Life cycle models centred on high-technology firms have suggested a four-stage growth typology, comprising conception and development, commercialisation, growth and maturity (Kazanjian, 1988; Dodge & Robbins, 1992; Kapeleris et al., 2004).

It is argued that early growth models are linear in the sense that all firms are expected to go through the same sequence of stages (Nelson, 1991; Autio & Garnsey, 1997; Bhide, 2000; Shane, 2000). In doing so these models emphasise the fit between the design of the organisation and the growth stage, and propose that the task of management is to restore the balance (Autio & Garnsey, 1997). Bhide (2000) argued that life-cycle models overextend the biological metaphor by asserting that businesses progress through predictable phases. His observation suggests that ventures evolve in unpredictable, idiosyncratic ways that do not conform to one-size-fits-all models of development. Thus "life cycle models fail to adequately account for the great variety in the manner in which firms grow" (Bhide, 2000:245), although there are some common development paths and features in the growth of companies:

> *"We have to distinguish between the identification and explanation of historical patterns and propositions with predictive value" (Bhide, 2000:245).*

Furthermore, these diagnostic models cannot provide an understanding of the interlinked causal processes involved in small firm growth, which are not addressed by the description of variations in growth stages (Autio & Garnsey, 1997). Criticism of the above models also refers to their growth orientation. Not all small firm owner-managers have the desire, or indeed the capability in terms of resources and expertise, to grow their business (O'Farrell & Hitchens, 1988; Storey et al., 1988). The overriding strategic objective is often the comfortable survival at the present enterprise size, rather than growth. The reasons for this are many, and range from personal wishes regarding life-style to a disinclination to surrender control and/or be accountable to others within and without the business in order that it may grow (O'Farrell & Hitchens, 1988). While developing their five stages of growth model, Churchill and Lewis (1983) studied 83 small companies and found that the 'grow or fail' hypothesis implicit in most simple growth-stage models is invalid. Some of the ventures had passed through the survival period and had reached a plateau, remaining essentially the same size with some marginally profitable and others very profitable, over a period of 5–80 years.

Although life cycle models acknowledge the importance of external conditions they do not incorporate these as theoretical components of the conceptual scheme (Autio & Garnsey, 1997:4). These models refer to the external environment:

> *"External conditions to which the firm must adapt; the rate of growth of the industry is one such parameter influencing the speed of growth; however, the descriptive focus of the models is what goes on within the firm" (Autio & Garnsey, 1997:4).*

Another noteworthy limitation of life cycle models lies in the over-simplification of the entrepreneur's role. In criticising the Churchill & Lewis (1983) model, Bhide (2000) argued that as businesses grow, entrepreneurs must do less of certain tasks and delegate more, thus making a smaller proportion of the overall decisions. The simple injunction to "let go" does not, however, reflect the complex nature of the tasks that entrepreneurs perform over several decades (Bhide, 2000). Building a long-lived firm entails radical changes in the entrepreneur's role. But these changes involve a broadening and expansion of responsibilities rather than the narrowing implied in letting go (Bhide, 2000).

## 3.4 Evolutionary economics

An evolutionary approach to firm growth has produced a dynamic and evolutionary perspective of the firm that addresses issues of innovation, where path dependence and trajectories are paramount. The pioneering work of Nelson & Winter (1982) has "almost become synonymous with evolutionary theory" (Bhide, 2000:249). Evolutionary theories, like life-cycle models, are based on a biological analogy but with an important difference. Life-cycle models implicitly compare the development of firms with the predetermined aspects of biological maturation that are programmed into the genetic code of a species. Evolutionary theories are inspired by models of how the inherited traits of a species change through chance variation and natural selection. But evolutionary models incorporate nothing predestined about firm development; different firms grow at different rates. History matters – firm development is "path-dependent" (Bhide, 2000).

As an example, Shane (2000) argued that technologists can change the world through their actions but at the same time they are severely constrained by their own and others' past choices, which determine the range of options open to them. The interpretations and purposeful actions of participants mediate and bring about what appears retrospectively as the inexorable advance of technology. To those engaged in technical innovation, opportunity and constraints are always mediated by perception and interpretation. The meanings participants attach to their experience provide the basis for their motivation, setting the process of technological innovation apart from natural selection. Thus innovations can develop in parallel under different conditions; similar technological outcomes can result from varied chains of action variously motivated.

Nelson & Winter (1982) used multi-period computer simulations to address problems such as explaining rates of technical change, how industry structures influence and are influenced by the R&D activities of firms, and the interaction of innovation and imitation. They typically started with a population of firms (or an 'industry') that followed specified rules of new techniques or investments in research and development. A stochastic process followed; the model assigned random probabilities to the success of each firm's efforts. The cumulative effects of these random draws over many rounds led some firms to grow faster than others and helped determine the structure of the industry.

Besides using different modelling techniques, Nelson & Winter (1982) also departed from basic assumptions of mainstream economics in the decision making processes they assumed their firms followed. In the conventional microeconomic theory, the perfectly informed, perfectly rational decision maker finds optimal solutions to problems. In the Nelson & Winter models the search by firms for new techniques – assumed to be an important precursor for their growth – saw firms retaining their existing techniques if their profitability exceeded a certain threshold; otherwise they searched for new techniques or imitated those of other firms.

Evolutionary theories have, however, been criticised for underplaying the role of entrepreneurs in fledgling companies (Bhide, 2000) and displacing attention on individuals as agents of change (Garnsey, 1998). Although all of the above theories assist in understanding aspects of the firm's growth, the importance of entrepreneurial behaviour in the biotechnology industry is also significant.

## 3.5 Entrepreneurship

Entrepreneurs are initiators of activities that may become systemic (Garnsey, 1998). The importance of the role of the entrepreneur in the market system has long been recognised in economic theory. Jean-Baptiste Say, in the early 19$^{th}$ century, described the role of the entrepreneur as hiring and combining factors of production (such as land, capital and labour) and serving as "the link of communication" between the "various classes of producers" and between the "producer and the consumer". The recognition of the entrepreneurial function was incorporated to some degree in the development of microeconomic theory in the early neoclassical era (1870–1914). For instance, Leon Walras incorporated functions of coordination and arbitrage in his theories. Alfred Marshall's entrepreneurs were coordinators, arbitrageurs, innovators and uncertainty bearers, depending on the matter at hand (Bhide, 2000).

With the emergence of microeconomic theory in the 1930s, academic study of the entrepreneur became marginal, arousing little interest even among those working in the tradition of Schumpeter (Nelson, 1991). Because an equilibrium framework does not allow people to recognise opportunities that others do not see, equilibrium theories explain entrepreneurship by identifying individuals who prefer to become entrepreneurs.

Shane (2000) argued that most research on entrepreneurship investigates the entrepreneurial process after opportunities have been discovered, because researchers typically draw on neoclassical economic or psychological theories. These theories assume that people will discover the same opportunities in a given technological change (Shane, 2000). Shane (2000) referred to the Austrian school of economics that challenges the validity of neoclassical assumptions, arguing that different people will discover different opportunities in a given technological change because they possess different prior knowledge. The possession of idiosyncratic information allows people to see particular opportunities that others cannot see, even if they are not actively searching for such opportunities. Differences in information lead people to see different value in the given goods or service and offer different prices to obtain it. This approach is similar to Penrose's view of the entrepreneur "seeing the market as an image in his mind" (Penrose, 1995:5).

Schumpeter (1961) argued that technological change provides the basis for the creation of new processes, new products, new markets and new ways of organising, and entrepreneurship is central to this process. Before technological change leads to new processes, products, markets, or ways of organising, entrepreneurs must discover opportunities in which to exploit the new technology. The more fundamental and sweeping kind of competition that drives capitalist dynamics was captured by Schumpeter's conception of the "creative gales of destruction" that regularly sweep through the capitalist system, initiated by entrepreneurs who break with existing arrangements in order to try out new combinations.

Kenney (1986) took up Schumpeter's microanalysis of the role of the entrepreneur and argued that a case study of the biotechnology industry yielded a nearly perfect fit with the observations and hypotheses that Joseph Schumpeter formulated in 1934. He questioned Schumpeter's 1942 hypothesis, which proposed that large corporations had developed such a strong position that they would be able to stifle small entrepreneurial companies, especially in light of the development of the biotechnology industry.

Schumpeter's most extensive discussions of the role of innovation in the growth of capitalist economies are found in his Theory of Economic Development (1934), in which he was careful to separate the two concepts of invention and innovation:

*"The social processes involved with producing inventions and innovations belong to different spheres with complex interrelationships and do not stand in any invariant relationship to each other" (Schumpeter, 1961:11).*

Important inventions or scientific breakthroughs can occur without being incorporated into innovations affecting industry:

*"The innovation is the outcome of a process of combining production factors in novel ways to produce old products more efficiently or to create entirely new products. For example tissue culture was transformed from being an invention to being an innovation by enterprising application of the technique to production" (Kenney, 1986:22).*

In the biotechnology industry the process of innovation can be problematic. The innovator whom Schumpeter terms the 'entrepreneur' is the central actor in transforming inventions to innovations (Kenney, 1986). Kenney identified the entrepreneur's motivation as falling into two categories: to be successful financially and secure large capital gains or entrepreneurial profits, and an overwhelming desire to succeed and 'conquer'. The joy of creating a company is vital to the entrepreneur (Schumpeter, 1961). Garnsey (1992), on the other hand, has researched the motives of participants in the processes of technological innovation of early academic firms that conduct technology transfer from the university to industry. Her findings showed that initially the prospect of financial reward tends not to be a primary consideration for the entrepreneur:

*"The entrepreneur/scientist is initially motivated by commitment to a project which interests them intellectually and for which they see exciting and practical applications if they are prepared to act as champion" (Garnsey, 1992:90).*

She stated:

*"The sources of motivation are diverse, but all academic entrepreneurs have a 'founding idea' or vision of doing or making something new for which founding a company is necessary" (Garnsey, 1992:90).*

Schumpeter (1961) noted that the entrepreneur need not necessarily be the inventor or an investor in the new company. Rather, he is a visionary who has had to struggle heroically against obstacles including a lack of interest and scepticism among potential capitalists, prohibitions upon the use of new machinery, a dearth of customers and inadequately trained labour. The vast majority of entrepreneurs, according to Schumpeter, are not capitalists (holders of large amounts of investable funds) and,

therefore, they must convince capitalists to provide sufficient capital to purchase the resources necessary to establish the company. Garnsey (1992) added that the single most important characteristic of a successful founder of a high technology venture would appear to be the capacity to project and share their vision of the future with those needed to bring it about. Kenney (1986) had suggested a similar view, describing how founders must convince potential co-workers, potential funders and customers by drawing on a substantial knowledge base and members of a network of expertise. Successful entrepreneurs in a knowledge-based enterprise can seldom undertake such an activity alone. It is in the nature of the activity that it requires considerable dependence on the expertise of others.

The market potential created by new technologies and possible new products encourages a rush of entrepreneurs into what Schumpeter termed a 'new economic space'. In biotechnology this new space is not limited to new firms. Older firms that have more far-sighted management and have provided internal entrepreneurial space will also expand into this growing new area. Others have argued that Schumpeter's later (1942) work:

> *"suggested that large firms have advantages because they have an established infrastructure in production, marketing, distribution as well as financial resources to exploit new technologies" (Van Moorsel et al., 2005:8).*

This reality was the basis for Schumpeter's later conclusion that smaller companies had little opportunity to be successful. However, the very long lead times in the biotech industry, often dependent on publicly funded research before serious development can take place, have led to an industry structure where both small and large firms exist side by side.

A distinctive feature of many innovative science-based ventures is their role in the process of technology transfer from university to industry; this role also accounts for their diversity, which follows from the variety of trajectories of technology transfer. Thus an effective working team is the hallmark of the initial innovative success. This structure calls for an unusual combination of characteristics in the founders: the ability to identify and draw in technical ability among others, leadership which is facilitative rather than dominating, fixity of purpose and adaptability to circumstance.

Schumpeter's analysis of capitalism provided a powerful tool for analysing the innovation process in genetic engineering (Kenney, 1986). Though many aspects of the innovation process have changed, the broad outlines of the process of innovation remain almost identical to his observations. The concept of creating a new economic space suggests not only research directions for social scientists interested in innovation, but also public policy initiatives. Kenney (1986) noted that the lack of historical perspective in much discussion regarding the formation of new companies to exploit genetic engineering could be remedied by consulting Schumpeter's approach to the entrepreneurial process.

## 3.6 Resource-Based View

The Resource-Based View (RBV) has risen to prominence in the strategic management literature over the last 15 years. Lockett (2005) argued that the central theories developed within the RBV can be traced back to Penrose's work. He shows that many of its key features such as the nature of productive resources, the importance of path dependency and firm heterogeneity, and the role of core capabilities in sustaining competitive advantage are present in Penrose's work.

Hugo and Garnsey (2005) noted that more recent resource based studies have taken divergent positions to Penrose's regarding processes of growth. Debate on the term 'resource', for instance, has divided its definition into 'capabilities' and 'resources'. Lockett (2005) argued that the term 'resource' is rather crude and it is much more useful to distinguish more fully appropriable assets, such as physical capital or brand names, from less tangible resources such as competences/capabilities.

> *"A capability has been defined as the know-how (or ability) which is created when firm-specific resources are deployed enabling a distinctive (productive) activity to be performed" (Lockett, 2005:85).*

Teece et al. (1997) highlighted the need to differentiate between capabilities and dynamic capabilities. These authors consider competition for the future depends on a firm's dynamic capabilities, which are a firms ability to integrate, build and reconfigure internal and external competences/capabilities in the face of a rapidly changing environment. Winter (2003, in Lockett, 2005) extended this discussion to explain the

difference between capabilities and dynamic capabilities as being the difference between zero-level and higher order capabilities, defining zero-level capabilities as those that permit a firm to make a living in the short term whereas higher order dynamic capabilities are those that operate to extend, modify or create zero level capabilities. Similarly it is necessary to distinguish static (Rumelt, 1984; Barney, 1986; Peteraf, 1993) from dynamic resources (Teece et al., 1997). The former consist of stocks of particular resources that may be utilised, as appropriate, over some finite life. The latter typically reside in capabilities such as the capacity for organisational learning or for innovation which allows the firm to develop additional opportunities over time.

Grant (1996) extended the resources theory with a knowledge-based perspective:

> *"Underpinning the knowledge-based view is an assumption that knowledge is the key resource of the firm and thus firm-level strategy should be concerned with the development, protection and transfer of knowledge" (Lockett, 2005:84).*

The basic insight of the perspective, however, is that resources are seen as lending distinctiveness to firms, i.e. generating heterogeneity. Resources are historically determined fundamental units of value generation that are path dependent. They do not exist independently, but are contained within firms and can be built by firms internally, enabling the firm to trade in markets. That is:

> *"Resources are the productive assets of firms, the means through which activities are accomplished" (Mathews, 2002:3).*

In summary, the RBV is a perspective on organisations that seeks to identify the characteristics of firms with superior performance. The framework essentially incorporates:

1 resources (tangible and intangible) which are bundled, linked, incorporated, converted and *organised* into

2 socio-technical *processes* (knowledge, routines, structures of relationships, cultures etc.) some of which are *rare, inimitable* (or costly to duplicate), and *non-substitutable* that form

3 *capabilities* and *core competencies*. These then become sources of *competitive advantage* which when leveraged into products and services generate

4 *value* and *competitive advantage* which are indicated by their performance.

Critics argue that the RBV of the firm sees firms developing their resources internally, ignoring the wider aspects of resource exchange. They also see the model as appearing to be "wedded to an incumbent's view of competitive dynamics, ignoring the challenger's perspective and the strategies that challengers use to acquire or leverage resources externally" (Mathews, 2002:3). The RBV literature, especially the dynamic capabilities literature, does, however, align with Penrose's approach (Locket, 2005). The following section examines Garnsey's (1998) firm growth model that draws on Penrose's concept of entrepreneurial matching of resources and opportunities to create value that incorporates path dependent aspects of firm growth before it becomes established.

## 3.7 Garnsey's (1998) Model of Firm Growth

Garnsey's (1998) *Theory of the Early Growth of the Firm* explores the growth process in a systems model inspired by Penrose. A sequence of phases in the early life of the firm reflects growth processes and problems, with solutions giving rise to new problems. Firms must access, mobilise and deploy resources before they can generate resources for growth. Subsequent phases – in which growth reinforcement and growth reversal forces contend – are not universal, but are set in motion in an important minority of firms, the major job creators. Beyond the early phases, critical problems facing the firm are more diverse. The growth of the firm is related to the building of the competence needed to respond to changing industrial opportunities (Garnsey, 1998).

The model identifies growth phases as symptoms of the dominant problems to which growth processes give rise, and consequently phases vary in duration and extent of overlap (Figure 3.1).

It is the problems and processes that are universal, not their phase manifestations. Resources must be accessed and mobilised in order to generate further resources if a firm is to become a system of activity with growth potential.

Growth of the firm, especially in the biotechnology industry, does not conform to any simple sequential model. Problems such as funding, for example, may not provide the full solution and recurrent efforts are usually required before the firm can move onto the next phase of problem solving.

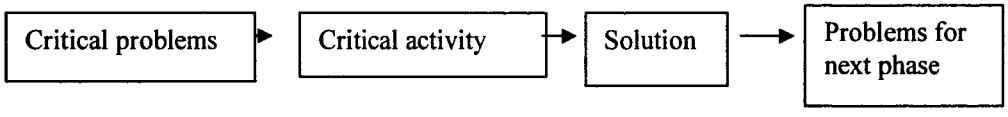


**Figure 3.1:** Firm Growth Process

Initially founders go through a preparatory search phase of identifying and matching resources and opportunities. This activity identifies the first resource access phase. Once the founders embark on a viable course of action they must gain use of the required resources and set up a resource conversion process with revenue potential; this set of problems dominates the resource mobilisation phase. Sometimes it is necessary to return to pre-preparatory work when resource mobilisation is unsuccessful. The problem-solving undertaken in the first two phases is put to the test as the resource conversion (production) process reaches operational stage which begins the resource-generation phase. Here the problems centre around ensuring that the process of generating revenue on the basis of the firm's output is both operational and sustainable. Incubated firms spin out of another organisation with a resource-generating process in place if, as a previous unit, they were already producing output or services for customers. Either way, when these early problems are solved, the firm reaches a minimum level of self sufficiency.

The challenges of sustaining resource generation overwhelm many firms, leading to closure or to a struggle for existence. Other firms move onto a plateau, either because entrepreneurs have limited growth ambitions or because they are locked in by unfavourable market relations. A diagrammatic representation of Garnsey's (1998) growth model is reproduced in Figure 3.2.

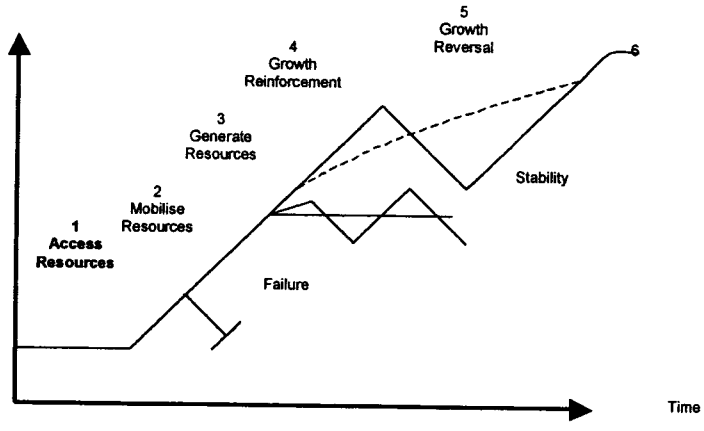


**Figure 3.2:** Garnsey's Small Firm Growth Model (Garnsey, 1998:530)

Structural factors and chance are at work, but both leave scope for initiative. Attributes of successful firms are likely to include foundation by a team rather than an individual, by founders who aim for growth and have qualifications and relevant business experience. These attributes increase the networking capacity of founders and their ability to match opportunities and resources and to develop production competence. The successful firm is likely to be innovative and secure market position by offering significant benefits to a growing set of customers. Its members build partnerships and alliances to secure complementary assets and achieve market repositioning. In these ways they increase exposure to favourable demand and investment conditions.

Initial conditions and resource endowments incline the system in a certain direction, but the actual path taken is unpredictable because it is subject to contingent occurrences and the initiative of agents. Not all chance events are significant; only those subject to reinforcing or feedback effects which result from the internal dynamics of the firm and its external interactions are important. In growing firms, chance occurrences are significant when they bring about a change in perceptions that affect the firm's ability to address and solve problems, when they make available or close off resources and when they initiate or alter key interactions and relationships.

In extending the Penrose analysis, the Garnsey (1998) model also uses the concept of the firm as an open system interacting with others in its environment to identify incentives and constraints which originate from the environment, as well as those which form through the internal dynamics of growth. Industrial structure sets the bounds of opportunity, but among the factors which make it possible to realise opportunities the most important, as Penrose emphasised, are the perceptions of entrepreneurs and managers. Market aspirations and attitudes to finance are influenced by interaction with others in a common business culture and by incentives linked to the institutional framework. The perception by others of the firm's prospects is no less important. How many new ventures will seek funding on the stock market, and at what stage of development, is a function of institutional structures and economic conjunctures, together with the entrepreneurs' assessment of the risk-reward trade-off.

Those entrepreneurs who aim for growth are likely to encounter problems caused by the very processes of growth. These factors include the increasing complexity of the firm as it grows. The mix of resources required for growth is very precise, and shortages of any one resource can create bottlenecks with knock-on effects. People with the right combination of skills and experience are the most difficult of resources to ensure for the growing firm, and the assimilation and motivation of staff can create serious difficulties. These are exacerbated if labour markets cannot provide qualified recruits, another institutional effect. As the firm grows there is increasing complexity in the information relevant to running the growing firm. The difficulty for decision-makers of assimilating and making considered judgments increases under conditions of rapid growth. Where reserves have been run down, delays and ill-judged decisions can bring growth to a halt. These problems cannot easily be remedied for decision makers in authority who have built up knowledge, and experience of the firm cannot be obtained on the external market.

Factors stimulating and facilitating growth are the obverse of these inhibitors, and again internal developments are linked to factors in the wider environment. The drive and ambition of entrepreneurs is in no small part influenced by their cultural setting and the example and help of others. Sponsorship can provide forms of accreditation which can reduce the "liability of newness". Access to key staff and financial resources depends in part on training and labour market conditions; funding is shaped by wider selection processes in the economy. Within these structures there is scope to obtain leverage from

resources and to pursue external opportunities. As early problems are resolved, there is pressure to exploit the unused capacity associated with resource discontinuities for further growth, allowing members of the firm to build on past experience to enhance their competence and career opportunities. These internal pressures will be reinforced by external pressures in the growing firm, as funders, customers and distributors call for expansion. Growth reinforcement processes propel further expansion. However, here growth may run into difficulties. Unless the firm is developing the capacity to integrate its new resources, respond to market discontinuities and synchronise expanding activities, the firm that earlier experienced successful growth is likely to encounter serious setbacks.

The Garnsey (1998) model originated with reference to engineering firms with in-house production. The model allows for regress and iterations between phases, which distinguishes it from the stage approach found elsewhere in the literature on small firm growth. In addition, the structure of the industry dictated the need to view the firm before it became established. This model was chosen as the guide for the present study because of its emphasis on the entrepreneur and the problems encountered by entrepreneurial scientists as they move from academia into the commercial world, even though other small growth models were available.

However, as described in Chapter 2, the engineering and biotechnology industries have some differences. In engineering, research is generally carried out in house, whereas biotech depends on basic research. The resultant structure of the biotech industry complicates the above model on several levels. Basic research is championed by the skills and energy of leading scientists; however, the commercialisation of the research requires commercial skills that most scientists have not previously experienced. Biotech also faces numerous variations of the common developmental process, and different sectors of the industry face very different problems regarding product development and marketing. The uncertainty that surrounds biotech products in terms of public acceptance and regulatory requirements results in long and expensive time lags drawing out the growth dynamic and funding perspectives. Taking these differences into account, Garnsey modified her model in 2003 (Figure 3.3).

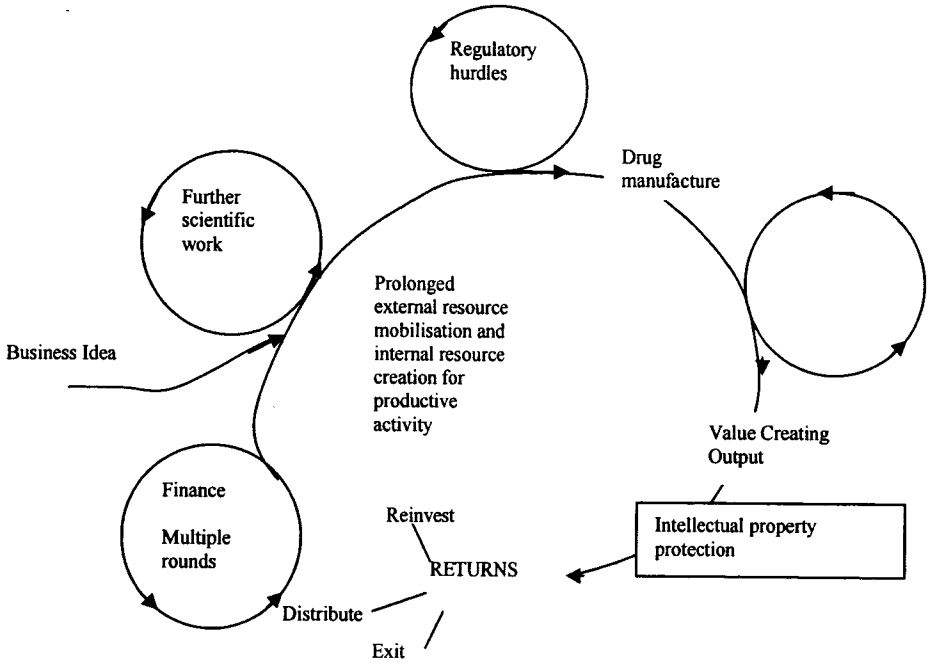


**Figure 3.3:** Delays in the achievement of returns from drug design for production (Garnsey, 2003:107)

The Garnsey (2003) model, however, begins at the foundation stage of the firm and therefore does not represent the early resource access phase carried out in research institutions by scientists before the idea takes on a business perspective. Garnsey's more recent high-tech growth models (Lim et al., 2006; Maine & Garnsey, 2006) focus on development cycles and process innovation that also do not lead to a better understanding of the entrepreneurial process illustrated by first three phases in the Garnsey (1998) model. Therefore this thesis proposes that the earlier model still holds for the biotech industry although, once past the initial resource access phase, modifications to the model are needed given the specific problems of the biotech industry just described. Garnsey's later research on problem-solving and competence creation in the early development of new firms (Hugo & Garnsey, 2005) builds on the 1998 composite account of typical growth phases outlined above in terms of resource leverage and creation, and has been incorporated into the analysis of the case studies. The discussion in Chapter 6 refers to both Garnsey models (1998 and 2003) models in its analysis of the findings.

The Sparling & Vitale (2003) model of the biotechnology development process, referred to in Chapter 1, represents the resource access phase as having a focus on the academic processes of doing basic research, presenting papers, contributing to scientific education and developing the initial idea to where lead targets or early prototypes are achieved. This thesis proposes that it is when this stage of the firm's growth has been accomplished, as indicated by its increased value and competence, that the scientific entrepreneur/team in the Australian context becomes frustrated with the academic environment and seeks to relocate in a commercial landscape. The transfer of knowledge from the public research institution to commercial markets constitutes the beginning of the second phase. During this phase resources of conceptually proven intellectual property (IP) and knowledge-building capabilities gained throughout the process of developing the IP can be extended to build capabilities where additional value can be added through the commercialisation process.

The argument advanced earlier in this chapter proposes that, from a RBV, resources are historically determined fundamental units of value generation that are path dependent. They are the productive or value-adding assets of firms, the means through which activities are accomplished. The initial idea and the expertise of the scientist are the original assets of the firm. The idea has some value in that it is generated by a scientist who is well known in their field. The knowledge asset has been developed over many years and generally the idea is the outcome of and contingent to such a capacity-building activity. In other words, the idea is the path-dependent outcome of the capability-building activity that in this instance is the scientific learning of the scientist/s. Additional assets are the scientist's ability to leverage resources such as unpaid labour (students), physical resources (laboratory space and equipment) and scientific networks that become available through the participation in a public research institution. Another critical resource is the scientist's entrepreneurial outlook and market awareness. Not all highly respected scientists will be willing or even interested in taking their idea to markets. In some cultural settings such as Australia the entrepreneurial scientist following market aspirations has, until recently, faced very hostile academic condemnation (Thorburn, 1999). The notion has been that pure research is more valuable than applied research and a scientist pursuing the latter is somehow tainted. What other obstacles the scientist encounters during the commercialisation of the scientific idea, is a question this study sought to identify.

In Garnsey's (1998) model, the resource access phase is represented by a horizontal line. That is, there is no additional value to the firm until it begins the process of resource mobilisation. Kapeleris et al. (2004) developed a value chain diagram of the biotechnology firm, reproduced in Figure 3.4.

| Discovery | | Development | | | Commercialisation | | |
|---|---|---|---|---|---|---|---|
| Basic Research | Applied research | Develop-ment | Veri-fication and valid-ation | Proto-type Develop-ment | Clinical trials | Manu-facturing | Marketing |

**Figure 3.4:** The value chain of the biotechnology firm (Kapeleris et al., 2004:89)

Value is the difference between what customers are willing to pay and the cost of producing the value (Porter, 1990). Kapeleris et al. (2004) described the biotechnology value chain as the set of interconnected value-adding activities in an organisation that together deliver value to customers in the form of a product or service. The growth line in Garnsey's (1998) model "can be interpreted as an approximate indicator of the value of the firm" (Garnsey, 1998:530). As the firm moves from resource access phase to resource mobilisation phase to resource generation, the growth line extends upwards over time indicating both growth of asset-building capabilities or competence and the ability to add value to a greater numbers of customers.

In biotechnology, different organisations will focus on different value-producing activities based on their core competency and the target customer group. Some enterprises will focus only on a specific set of activities across the value chain, which they then deliver to another firm where further value is added before the product or service is delivered to the end-user customer (Kapeleris et al., 2004). In general, the closer to marketing a new firm can reach, the greater the value created but the higher the cost of investment capital required (Garnsey, 2003).

Data collection for this study commenced in 2000, before the results of Garnsey's (2003) research were available. Garnsey (2003) identified various business models available to would-be scientific entrepreneurs in this industry. They include licensing

the use of patented IP; collaborative agreements with partners in other small business or various corporate giants to gain access to complementary technologies and skills; early launching on the stock market (IPO); directing skills to undertake research under contract for other companies; buying into the resource base of another company through acquisition; developing platform technologies that will spread risk over several potential applications as well as supplying process innovations. Some firms will cover the full spectrum of the value chain and deliver the final product to the end-user. Garnsey (2003) found that this route was difficult in the UK, with lower funds available to British biotech ventures than their US counterparts. The firms in this study have sought to fulfil activities across the value chain with some success.

The first of the three stages in Figure 3.4 represents the discovery component of the chain where activities centre around idea generation, idea evaluation, feasibility of concepts and proof of principle. This set of activities is described as the Resource Access Phase in this thesis. Once proof of concept has been established the firm moves into the development phase, where activities centre around testing for commercial manufacturing possibilities, quality control, clinical trials and regulatory approval processes, described here as the Resource Mobilisation Phase.

Extended external resource mobilisation and internal resource creation for productive activity have been viewed as multiple feedback loops in recurrent efforts to mobilise resources (Garnsey, 2003) and biotech ventures are required to review original business models in an effort to reduce development time from scientific discovery to manufactured product, often with the assistance of global partners (Garnsey, 2003). The biotech firm will generally go through portions of the circuit many times before it can reach breakeven point and begin to generate revenues, at which point the entrepreneur/s can choose to reinvest, distribute the gains to the shareholders or exit the firm (as do most venture capitalists). Garnsey (2003:114) noted that the realigning of original business models "is not unique to this sector; it is through encountering and solving problems in new ways that entrepreneurs innovate".

When sufficient resources have been mobilised to breakeven point, the firm has grown in value-adding competency to generate resources through commercialisation activities of manufacturing and marketing. In biotech terms the venture has obtained all regulatory approvals for marketing to customers. However, as outlined in Chapter 2,

customers are not generally the final users. Doctors, hospitals and clinics are the customers and, until recently, it has been considered unethical to market a biotech product direct to the patient, adding to marketing constraints of small new ventures. However, this is changing with patient access to medical information. Further difficulties for firms at this stage emerge from growth pressures to launch new products when there is a lack of innovative capability to do so.

Given the importance of understanding the commercialisation process, empirical evidence that demonstrates the growth processes of a sample of small firms in the Australian biotechnology industry has identified important issues in the industry within the Australian context. Using Garnsey's (1998) framework, based on Penrose's (1959) perceptions of the firm as a bundle of resources to produce value, this study focused on the individual firm and what it does at the micro level. Such an approach provided the basis for the case study methodology outlined in the next chapter.

# 4 Methodology

This research adopted a qualitative, rather than quantitative, approach for several reasons. Most significantly, the nature of the research question, 'how' rather than 'what', suggests a qualitative study. How do Australian biotechnology firms' growth processes compare with the Garnsey (1998) model of small firm growth? More specifically, how have Australian biotechnology firms overcome obstacles in their growth paths? Such broad questions call for exploration and description, highlighting a qualitative approach.

The qualitative tradition includes phenomenology, grounded theory, ethnography and case studies. The nature of the research aims shaped the choice of methods. Case studies offered an effective way to examine patterns of problem solving or competence building across settings. Moreover, case studies have the advantage of allowing a phenomenon to be investigated within its real-life context while permitting the use of multiple sources of evidence by the researcher (Yin, 2003). Finally, case studies suited the conditions set by participating companies – the provision of access to a number of key managerial resources for a short period of time.

## 4.1 Case study research design

Yin (2003:13) defines the case study as "an empirical inquiry that investigates a contemporary phenomenon within its real-life context, especially when the boundaries between phenomenon and context are not clearly evident". A recent phenomenon in this country is the commercialisation of scientific research by highly skilled scientists who has worked in an academic setting for much of their life. Understanding that commercialisation process and how successful growth of the emerging enterprise is achieved in the Australian biotechnology context lends itself to a case study analysis. However, case studies describing business histories can be told in many different ways, ranging from the austerely statistical to the richly romantic and dramatic. Both extremes have been rejected in this thesis. A purely quantitative study would not have touched the

problems of "how" and "why" in the stories of growth. Figures have been provided in the following chapter to illuminate and support descriptions, but they themselves required explanation in terms of real life:

> *"There is more to a business than figures but it is equally true that business life is not continuously romantic or dramatic" (Mason, 1954:ix).*

This study has aimed to be narrative and analytical, although combining these two contrasting characteristics has added to the difficulties of a task already made complex by the very nature of the businesses themselves. The approach, therefore, has been to primarily write a biography conceived in terms of a particular kind of concrete achievement – the business itself. The function then changed to an analysis of a comparison of the growth strategies undertaken by the five firms, guided by the Garnsey (1998) model. The yardstick for measuring the evidence has been whether a particular event or person contributed something indispensable to the growing business. Such contributions were both negative and positive: a failure can determine the future course of growth as much as a success.

Yin (2003:19) defined a research design as "the logic that links the data to be collected (and conclusions to be drawn) to the initial questions of study". In line with the definition, a number of methodological choices were made, based on the research objective. These included identifying an appropriate unit of analysis – be it the entrepreneur, the resources or the technology – that provided the firm's impetus for growth, and selecting appropriate firms for applying such methods. Each of these aspects is dealt with in turn in this section.

### 4.1.1 Unit of analysis

Garnsey's (1998) growth model of the small firm provided the conceptual framework and unit of analysis for the research. Garnsey referred to Edith Penrose's (1959) definition of the firm as an administrative unit with boundaries. The growth process from the Resource Based View, as proposed by Penrose, is conceived as:

> *"the growing experience of management, its knowledge of the resources of the firm and of the potential for using them in different ways to create*

*incentives for further expansion as the firm searches for ways of using the services of its own resources more profitably" (Penrose, 1995:xii).*

Using Penrose's approach, Garnsey (1998) provided an account of typical growth processes which can then be compared with and contrasted to others using a similar set of concepts. As outline in the previous chapter, the model identifies phases of growth of a firm as a sequence of problems that have to be solved in order for the firm to take form and generate revenue. The activities that are critical for overcoming these problems define the earliest phases (although they can overlap, make false starts and sometimes regress). Critical problems facing the firm beyond the early phases are variable and not sequential. The objective of this study, therefore, was to analyse the five firms through their first three stages of growth and compare them with the Garnsey (1998) account of typical growth processes. The units of analysis are the three initial phases of growth: access, mobilisation and generation of resources. Embedded in these units are sub-units of critical problems and activities that provide solutions to the problems within each phase.

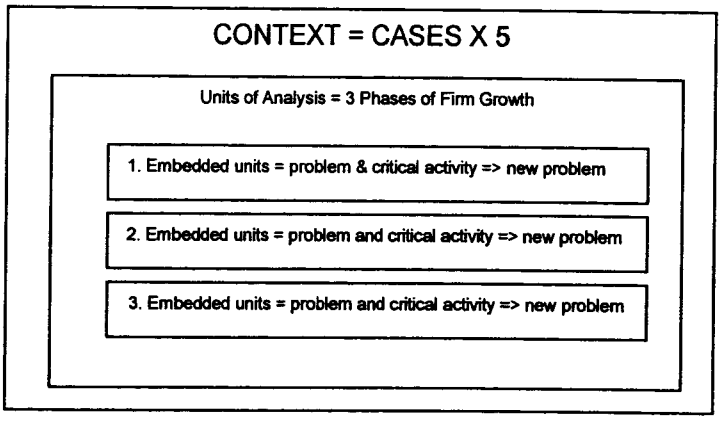


**Figure 4.1:** Case study design (from Yin, 2003:40)

The model also suggests seeds of other ideas, in particular:

*"(the) concept of path dependence implicit in Penrose's insistence that 'history matters' and the concept of the firm as an open system, consistent with her emphasis on the continual interaction between the firm's resources and its markets ... The firm's position depends on the nature of its interactions with key players in its environment" (Garnsey, 1998:526).*

The research design therefore followed the historical path of five firms in the Australian biotechnology industry, taking into consideration the impact of the external environment on these firms.

### 4.1.2 Sample selection

The number and nature of industry sectors in biotechnology have determined the selection of cases for study. A biotechnology firm is defined as a company that is established primarily to engage in the development, production and marketing of biotechnology products. Hopper and Thorburn (2003), drawing on OECD (2000) definitions, identified five sectors relevant to this study (listed in Chapter 2, pp 9–10). eGcapital (2004) also noted that most ABT firms fall into three main subtypes: drug discovery, diagnostics and devices. These three subtypes were included in the representative firms chosen for case studies. Agriculture is one of the original industries to use genetic modification and hence a representative firm was included in the study. Food Processing and Mining sectors were omitted from the study because they are not representative of small firms. A fifth firm was included because it had demonstrated a hybrid business model to provide some contrast to the other firms, although it soon became evident that all five firms were engaged in some hybrid of activity to survive the growth process. The cases were used to identify generic problem-solving processes and provide generalisability. To show that the problem solving that turns obstacles to advantage is not time specific, cases were chosen from ventures that had their origins in the late 1960s, early 1980s, late 1980s and late 1990s in the five sectors.

Choosing companies to represent these sectors proved to be difficult in some instances. Two companies manufacture medical devices, Cochlear and ResMed. Cochlear was chosen because of its longer history and availability of data. The agriculture sector, where biotechnology has been improving product yield and growing conditions, encompasses several types of industry, such as cotton, wheat and beef. The cotton industry had a clear starting date that was more easily compared with the emergence of the other firms. Other agricultural industries were difficult to place within age and development boundaries and were discarded. Another criterion for choosing the cotton sub-sector was that it lacked the public debate that has pursued other genetically

modified agricultural sectors and which muddies the evidence of their growth patterns. It appears that very similar problems face these agricultural areas with respect to environmental issues and global competition. However, a limit of the study was the ability to generalise the agricultural data to other products in this sector and further research will be needed to answer this question.

The selection of the five sample firms was based ultimately on three criteria. First, the firm had to have been established for at least five years. With high failure rates in high-tech industries, this was to ensure that the companies have 'come through' the early turbulent years (McDougall et al., 1994). Second, it had to employ at least 10 people, to ensure the firms are not deemed to be 'self-employed' enterprises (Carson & Gilmore, 2000). Third, only independent firms were considered, as opposed to corporate-sponsored counterparts, since research has revealed substantial differences between the two (Zahara & George, 2000). Firm growth was determined through comparing employee numbers and value of the firm over a 5-year period, although these figures were difficult to obtain; only estimates were available for older firms while the younger firms often saw quantitative information as commercially confidential. Value of the firm was difficult to confirm in companies without publicly available data. Growth was measured in terms of value-adding as the firm moved down the biotechnology value chain.

The final choice of the five firms was based on a pilot study of similar firms. Twenty companies meeting the above criteria were gathered from a database provided by BioMed North and E&Y's industry annual report. Short interviews with pilot firms were conducted throughout 2001 to confirm age of firm, evidence of growth in terms of assets and employees, sectors, access and cooperation potential of each firm. From this group, five firms that met the criteria were chosen to form the representative group of firms within the industry that would provide 'maximum variation'. The choice of this sample aimed to provide an examination of a diverse range of biotechnology sectors to provide general insights into competency building, as well as to explore variations within the Australian biotechnology industry.

## 4.2 Research methods

The actual research methodology included developing methods and tools, arranging access to case sites and conducting the fieldwork, and to the analysis and verification of the findings. These steps are described in the following sections, giving particular attention to measures aimed at minimising problems of research bias, internal validity and reliability.

### 4.2.1 Design, access and fieldwork

The case study design allowed for investigation of how commercial opportunities were identified by entrepreneurial scientists operating within universities to progress their discoveries through various stages of firm growth to global operation. The design incorporated a variety of different sources of evidence, including both archival documents and interviews (Yin, 2003).

The in-depth field study of the sample of five biotechnology firms was conducted between 2001 and 2003, and involved field interviews with the entrepreneurs and, where possible, their management teams. Interviews were semi-structured to ensure coverage of central concerns (e.g. transfer of knowledge from academic institution and access to finance to enable such transfer), while allowing broader issues to emerge and be explored. The interviews were 1–1.5 hours long. They typically began with an invitation to describe how the entrepreneur scientist initially perceived the commercialisation opportunity. Follow-up interviews and phone calls were conducted with many respondents to clarify issues.

Management's key concerns related to commercial confidentiality and the value and relevance of research findings. In each instance, in line with MGSM ethics requirements, management was offered, and accepted, a signed confidentiality agreement and a formal feedback report. In the pilot study it had become evident that taking precise notes of the interviews was not feasible, and so interviews for the five cases were recorded. Recordings, like field notebooks, were transcribed, rewritten and checked for accuracy by the interviewees and company representatives prior to coding. Altogether, 35 hours of interviews were conducted with 22 individuals, carefully

selected as being appropriate interviewees, and on average it took 3–6 months to complete a case study.

In qualitative case study research, corroboration of interviews through the use of archival records is important to validate information (Yin, 2003). Therefore the interview data were supplemented with information from other sources, such as annual reports and copies of business plans, press releases, contracts and product information. Many of these were available on the web. Venture capital and other financing records on the companies from database providers were included where possible. In each case at least two members of the management team were interviewed to corroborate information across the firm and these interviews were included in the case study presented to the firm for verification.

Following the procedure of Yin (1984), separate case studies on each of the five firms were developed from the interviews, database information, and archival records. Reliability was established through the development of a case study protocol and a case study database (Yin, 1984). The case study protocol included the use of 'table shells' to record data (Miles and Huberman, 1994). These outlines ensured that the data collection was focused on the process of firm growth, verified that the same information was being collected for all cases, and aided in the data analysis. Construct validity was established by using multiple sources of evidence, the creation of a chain of evidence, and by having key informants review drafts of the case study report (Yin, 1984).

### 4.2.2 Data analysis and verification

Data analysis consists of examining, categorising, tabulating, testing, or otherwise recombining qualitative evidence to address the initial propositions of a study. Analysing case study evidence is especially difficult because the strategies and techniques have not been well defined (Yin, 2003). Several strategies were implemented to guide the analysis of the data.

The first strategy was to follow Garnsey's (1998) theoretical propositions that led to undertaking a case study in the first instance. The second analytical strategy developed a descriptive framework based on the Garnsey (1998) model for organising each case

study. The reports of each case covered the range of topics and causal links identified by the model. The chapters were organised so as to describe the multiplicity of decisions that had to occur for survival and growth of each firm to succeed as per the model. This descriptive organisation led to the enumeration, tabulation and quantification of the various decisions. The approach was useful in identifying the embedded units of analysis and an overall pattern of complexity that ultimately was used in the causal sense to 'explain' why firm growth was able to occur (Yin, 2003).

Miles and Huberman (1994) described such strategies as pattern coding that identifies emergent themes, configuration or explanation. The main function of coding is to combine disparate material into more meaningful and parsimonious units of analysis. Such organisation also provides the researcher with analytical ideas during the data collection so that later field work can be more focused:

> *"For multicase studies, it lays the groundwork for cross-case analysis by surfacing common themes and directional processes" (Miles & Huberman, 1994:69).*

Initially the case studies were individually coded and analysed. Effort was made to match the variables identified in Garnsey's (1998) typical growth account; however, on occasion it was necessary to include additional variables that were identified through the interview and recording processes. In each instance, data were marked up within notebooks, transcripts and other relevant documents by the researcher before being transcribed into a case template built around the main issues or themes as they appeared from the individual case studies.

### 4.2.3 Explanation building

This analytical technique was used to analyse the cases by building an explanation about the companies' growth. The empirical evidence from the five case studies was compared against Garnsey's (1998) account of typical growth processes in one firm against the case evidence. The findings of an initial case, Cochlear Ltd, were then compared against this typical account. Where case evidence differed from the typical account, the differences were noted for comparison with the other cases. For example, Garnsey discussed the benefits of "clustering" firms to improve tacit knowledge transfer

from university to commercial firm. In the Cochlear case, although initial research was developed in Melbourne University and the firm was established in Sydney, the issue of knowledge transfer was addressed in other ways.

Yin (2003:122) warned that this approach to case study analysis "is fraught with dangers", with the researcher slowly beginning to drift from the original topic of interest. Consequently, the study made constant reference to the original purpose of the inquiry and looked for possible alternative explanations to help reduce this potential problem. In addition, other safeguards such as case study protocol and case study database were used.

## 4.3 Limits of case study methodology

Case studies are commonly criticised on the grounds that the scope of the study is relative only to that case and hence can be considered as microscopic. From this viewpoint, the case study permits the understanding of only the single facet that is intrinsic to the case under investigation. However, it is microscopic for want of a sufficient number of cases (Giddens, 1984). What is unclear is how many cases are required to allow generalisability of findings. Rouse and Daellenbach (2002:966) proposed that in terms of generalisability, it is "questionable whether sustainable growth through competitive advantage based on unique resources can be generalised at all". What is perhaps more important is that the chosen method seeks to provide an explanation through understanding competitive advantage resources in a particular context, which also suggests a degree of utility in assessing similar phenomena in similar contexts (Yin, 1984). Furthermore, evidence from multiple cases is often considered more compelling, and the overall study is therefore regarded as being more robust (Miles & Huberman, 1994). While the nature of the research aims meant that no well-constructed single case would suffice, significant care was exercised in sampling to maximise insights and generalisability from a small number of case studies.

A second reason for cross-case analysis is to deepen understanding and explanation. Multiple cases help the researcher find negative cases to strengthen a theory, built through examination of similarities and differences across cases. Glaser and Strauss

(1967, 1970) suggested that this process is much quicker and easier with multiple cases than with a single case:

> *"Multiple cases not only pin down the specific conditions under which a finding will occur but also help form the more general categories of how those conditions may be related" (Miles & Huberman, 1994:173).*

Thus multiple cases enhance the generalisability of each case and deepen the possibility of understanding and explanation.

However, using multiple case studies can create a tension between the particular and the universal. There is a need to reconcile the uniqueness of the individual case with the need for more general understanding of generic processes that occur across cases (Silverstein, 1988). Silverstein (1988) argued that the uniqueness resides in the individual's developmental history over time, but is encapsulated within the general principles that influence its development. Noblit and Hare (1983, cited by Miles & Huberman, 1994:173) also emphasised that "cross-case work must have a theory of social explanation that preserves uniqueness and entails comparison" because aggregating or averaging results across cases is bound to lead to misinterpretation and superficiality. Thus care was taken to preserve the unique historical development of each of the five cases and to use general variables as dictated by the Garnsey (1998) model to compare across cases but within the same context for generalisability.

Care was also taken to ensure that each of the five cases was unique in that it represented a different sector within the industry. Furthermore, to ensure that the uniqueness of the growth patterns were not time specific, the 'birth dates' of cases varied from 1969 to 1999. However, given the long lead times to product development in this industry, each firm was selected only if it had a history of at least five years. This time span had been demonstrated by other researchers to provide data spread across at least two phases (Sparling & Vitale, 2003).

Following Yin (1984), the data from the separate case studies detailing growth of each of the five firms were developed from interviews with senior management and scientists, data base information and archival records.

## 4.4 Chapter summary

A qualitative case study methodology was chosen to investigate how Australian biotechnology firms' growth processes compare with the Garnsey (1998) model of small firm growth, and how Australian biotechnology firms have overcome obstacles in their growth paths. The nature of the question provided the rational for the choice of methodology.

The research design followed the historical path of five firms in the Australian biotechnology industry selected in accordance with industry sectors as outlined by eGcaptial (2004). Garnsey's (1998) growth model of the small firm provided the conceptual framework and unit of analysis for the research. The design incorporated a variety of difference sources of evidence, including semi-structured interviews, archival documents, minutes of meetings and publicly available information such as annual reports, press releases and company web-sites.

Limitations to the research were addressed where ever possible although this contributed to some difficulties such as choice between available firms. Reliability was established through the development of a case study protocol and a case study database (Yin 2003). Construct validity was established by using such multiple sources of evidence (asking similar questions of a number of interviewees from the same company), the creation of a chain of evidence, and by having a number of key informants review drafts of the case study report (Yin 2003). Corroboration of interviews through the use of various sources of evidence as outline above was used to validate information.

The multiple case study methodology provided the opportunity to investigate the phenomenon of small firm growth in the Australian biotech industry within its real life context and to contribute an additional perspective to the currently available body of knowledge in this industry.