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Buying big into biotech: scale, financing, and the industrial dynamics of UK biotech, 1980–2009

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This article explores how the UK's biotech firms have evolved in response to their financial environment. As investors' expectations about the potential of biotech have changed, funding options have opened up and closed down, leading firms to develop new business models and routes of technology development. After a favorable period, new constraints on stock market funding have forced UK biotech firms to compress their life cycles, constraining their ability to generate the late-stage drug candidates sought by large pharmaceutical firms. These changes are analyzed within a neo-Chandlerian framework in the context of a selection environment where rather than firms of varying inefficiencies being selected by an efficient market, we find entrepreneurs submitting themselves to an inefficient investment-selection process at the intersection of industries attempting to achieve their own scale economies. The article highlights the importance of the scale of investment at the firm and industry level, and suggests that decline in the size of the industry can have adverse consequences for investment and firm performance in this setting.

JEL classification: L23, L25, L65, N23.

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1. Introduction

Pharmaceutical innovation is particularly challenging (Fernandez *et al.*, 2012), with the failure rates of R&D projects escalating, the costs of R&D expanding, and the time taken to move from drug patent to market launch increasing (Pammolli *et al.*, 2011). Recently, the withdrawal of high-profile products because of safety concerns (e.g. Vioxx, Avandia) and questions over the efficacy of blockbuster drugs have led to calls for increased regulation and scrutiny (Kirsch, 2009, Goldacre, 2012). Moreover, pharmaceutical firms have struggled to improve their stagnant levels of novel drug approvals while investment in R&D has increased, leading to a prominent debate in recent years about how to address the industry's productivity crisis (Munos, 2009, Pammolli *et al.*, 2011). As performance has declined, investors have become dissatisfied and stock prices have fallen (Fernandez *et al.*, 2012). However, even in this climate, investment in "biotech firms"[1] has boomed (Huggett *et al.*, 2011) as established pharmaceutical firms continue to sign large numbers of deals to access promising drugs from these younger, smaller firms (Munos, 2009).

While some have cautioned that biotech investors are being rewarded for activities that generate limited benefits to society (Lazonic and Tulum, 2011), in recent years, new market entrants have been contributing an increasing proportion of new drugs reaching approval (Kneller, 2010). As a result, a view has emerged (albeit controversially—see Pisano, 2006, 2011; DiMasi and Grabowski, 2007; Lex, 2010) that small and medium sized enterprises (SMEs) can outperform large firms because of their specialization, flexibility, and creativity. Corporate advisors have even begun to suggest that the large pharmaceutical firms that have dominated the industry in the past should leave early-stage drug R&D to more "cost effective" SMEs (Baum *et al.*, 2010).

How the increasing amounts of capital flowing into the biotech sector during an ongoing change in the division of innovative labor will affect productivity is far from certain, given the complex web of organizational interactions at work. Yet it is clear that where populations of SMEs have emerged in different countries, they have maintained investor interest to different extents, despite their common exposure to the major challenges facing the global drug discovery endeavor. In particular, the UK sector has traditionally had lower investments in each firm than has been the case in the USA (Bains, 2006), and more recently, the UK firms also faced comparatively more reticent investors (Smith *et al.*, 2009). However, as the article

[1]As we explain further in Section 3, this article is concerned with therapeutics firms founded in the UK since 1980. Many of these firms are not focused on modern biotechnologies, for example, as classified by OECD 2005. We observe that "biotech" has become established as a colloquial term for small loss-making life science firms (e.g. Anon (1998) who in the *Financial Times* notes "investors tend to brand any smaller loss-making business that develops drugs or medical devices a biotech company"). These may be focused on a variety of application areas (drugs, diagnostics, industrial processing); however, this article will focus on therapeutics and uses the term "biotech" in this colloquial sense.

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will show, this weakening of investor support follows an initial period when a number of institutional innovations in the finance sector favored the growth of the UK biotech SMEs.

Using the UK sector as our reference site, this article explores the following questions: How have the UK's biotech firms been financed, and how have changes in R&D and finance influenced the structure of the UK sector? Finally, how have biotech firms performed in drug R&D during these changes?

Using empirical evidence over three decades, we will advance the argument that scale effects, related to the amount of money invested in firms and the number of firms in the sector, are important not only for emerging drug development firms but also for the viability of firms specializing in SME investment, as the size of the sector allows costs and risks to be spread and shared. Drawing on Chandler's Scale and Scope framework (1990) we interpret the rise and relative decline of the UK biotech sector in terms of scale imperatives interacting across sectors.

Using Chandler to understand the financing of networks of small scientific firms may seem surprising, given his focus on large manufacturing firms. Indeed some have argued that the shift in industrial organization from large firms to networks of organizations challenges his framework (e.g. Langlois, 2004 and Lamoreaux *et al.*, 2003), and may amount to a falsification sufficient to displace it (see the insightful discussion in Langlois, 2003). However, while one implication of Chandler's explanation is that under certain circumstances industrial organizations move from small firms to large firms, when those circumstances change, industrial organizations can move from large to small. Moreover, we suggest those changes in circumstances can be driven by the dynamics of scale in another sector, in ways that are entirely consistent with Chandler's theory. The article highlights these scale imperatives and their interactions among the key actors in funding and undertaking drug discovery: the biotech SMEs, the large pharmaceutical firms, venture capital (VC) funds and institutional investors.

These systemic inter-sectoral or even inter-industry effects are important because the type of financing a firm receives influences its strategic behavior and performance. A financialization process that encourages short-term investment and short-term strategies may distract firms from developing innovative products (Lazonick and Tulum, 2011; Andersson *et al.*, 2010) and even inhibit the emergence of new industries (Mazzucato, 2011, Bains, 2009).[2] Until now it has been difficult to explore the long-term impacts of changes in funding because of the lack of comprehensive long-term data. Previous analysis in biotech, for example, has focused on subsamples such as stock market–listed companies, or samples that blend national figures,

[2]Indeed, Bains notes in his book on the European Venture Capital industry and its influence on biotech firms that "The requirement for VC cash and the demands of the VC business model shape everything in the modern biotechnology industry. It is a principal contention of this book this is a bad thing" (Bains 2009:12).

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overlook private firms, merge boundaries (e.g. between therapeutics with research tools and diagnostics), or cover short periods (Smith *et al.*, 2009; Editorial, 2010; Kneller, 2010; Huggett *et al.*, 2011). In this article, we use a new comprehensive data set to show changing patterns of interaction between investors and investees, which allows us to explore how the selection environment influences the generation of capabilities and hence the evolution of firms and sectors (Zollo and Winter, 2002).

The coevolution between firms, industries, and adjacent institutions has been explored before in other sectors (Dijksterhuis *et al.*, 1999; Djelic and Ainamo, 1999; Helfat and Raubitschek, 2000 and Henderson and Ithai, 2004) and by Murmann (2003) in the pharmaceutical sector. Our work provides an alternative analysis, exploring some of the dynamics of development, that is complementary to formal coevolutionary analysis.

The article proceeds as follows. Section 2 outlines our framework (Chandler, 1990; as iteratively advanced in Nightingale 2000a, b, and Nightingale *et al.*, 2011), and the key characteristics of the four actors listed above. Section 3 discusses the methods used to undertake the study. Section 4 describes key trends in the financing of the UK biotech SMEs across three decades, the 1980s, 1990s, and 2000s. Section 5 then compares the performance of SMEs founded in each of these decades, using the key metrics of the number of SMEs supporting development of one or more products passed P.II trials, and the time taken to achieve this. Section 6 discusses the results and their implications for both theory and policy, while Section 7 draws conclusions.

2. Direct and indirect Chandlerian influences on biotech R&D

In the literature on the theory of the firm, firms can either be seen to indicate the existence of market failures, where transaction costs prevent markets from working efficiently, or as organizational successes that outperform markets (Lazonick, 1991). A key stream in this later work, going back to Babbage (1835), Lardner (1850), and J. M. Clark (1923), focuses on how firm-based coordination can outperform markets by better utilizing specialized resources to avoid wasteful idleness.

Chandler (1990) highlighted how the potential economies of scale and scope in production and distribution that come from increased size or sharing of processes only generate actual cost advantages if the flows of materials were managed to maintain high levels of capacity utilization. When utilization levels fell, diseconomies rapidly set in as fixed costs were much higher (Chandler, 1990: 24). As a result, profits and costs are closely related to "the actual amount processed within a specific time," which is dependent on "both size-rated capacity—and speed—the intensity at which capacity is used" (ibid), i.e. the throughput of work done.

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As well as improvements in efficiency, managerial coordination improved firms' effectiveness by giving them the Schumpeterian dynamic capabilities needed to move in and out of expanding and declining markets (Chandler, 1990:36). Chandler's theory has been discussed in detail elsewhere (Teece, 1993) and modified versions of it have been applied to investment banks (Nightingale, 2000a), pharmaceutical firms (Nightingale, 2000b), retailing, telecoms, elevators, and financial services (Nightingale *et al.*, 2003), as well as project-based organizations in general (Nightingale *et al.*, 2011). In its modified form, relative economic performance is explained by static efficiency and dynamic effectiveness. Static efficiency relates to the extent to which high fixed cost investments, improved capacity utilization and speed of processing influence the actual amount processed within a specific time, and hence the final balance between fixed and variable costs. Dynamic effectiveness relates to a firms' ability to move in and out of markets that provide higher value and allow these higher fixed costs to be spread.

Put in these terms, the theory does not imply that industrial dynamics inevitably moves from small firms to large firms, even if Chandler himself sometimes suggested that it did. Indeed, large firms are not mentioned in the synthesis above. Instead, the theory has a more general application, as it implies that if the conditions that allow scale and scope economies to develop then change, so to will the balance between large and small firms. Moreover, it implies that the economic imperatives toward improved capacity utilization can influence firms in other sectors by changing these conditions. We explore this process in more detail below, focusing on the cross-sectoral interactions involved in the financing of the UK biotech sector, beginning with an introduction to each of the major sectors that interact in the financing of drug development: VC, institutional investors, pharmaceutical firms, and biotech firms.

2.1 VC funds as scale intensive Chandlerian firms

VC is "the process of external equity finance provision by professional investors in a new or young (i.e. early stage) company to create new assets for the primary purpose of reaping substantial economic gain through a market flotation [initial public offering (IPO)] or trade sale" (BVCA-NESTA, 2009). From a Chandlerian perspective, VC funds can be seen as a pipeline operating over a fixed period of time (typically 10 years during the period studied), containing a portfolio of investee firms, that are chosen from a stream of high potential investment opportunities by selective investment managers. The managers then transform these opportunities into high-value firms, by providing staged equity investments and managerial support (Sapienza *et al.*, 1996). As the investee firms grow, new rounds of funding are typically required, which can be syndicated to diversify portfolio risks. Investee firms eventually "exit" through a trade sale (acquisition), or an IPOs, which allows the VC partnership to realize the value it has created.

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The returns from this style of investing are highly skewed (Booth and Salehizadeh, 2011) with the majority of profits coming from the top quartile of VC funds. Within funds most investments either fail, or make poor returns, with a small number generating large enough returns to cover the rest of the portfolio and (ideally) satisfy investors (Murray and Marriott, 1998, Murray, 1999).

The fixed costs of the organizational infrastructure needed to find, support, and sell a portfolio of investee firms make VC a scale sensitive sector. Typically ~2% of the fund goes toward covering these managerial costs each year, which accumulates over the life of a fund. For a small fund, of say £25 million, 2% will not pay for a viable investment team. Small funds therefore generally generate lower returns because they either spend too little to attract strong management or spend a disproportionate amount of the fund on management, which can have a damaging effect on final returns (Murray, 1999; Murray and Marriott, 1998; Jääskeläinen *et al.,* 2007). Larger scale also allows funds to diversify their risk more efficiently across a larger portfolio, and crucially allows them to make follow-on investments when new shares are issued in investee firms. This allows them to maintain their ownership share, and ensure their returns do not get diluted by deeper pocketed coinvestors. Finally, scale may also provide a signaling effect for syndication deals, help to attract and retain key staff, and attract high-quality firms to the portfolio, as time-constrained fund managers may see small size as a signal of low quality.

The viability of a VC sector therefore depends on a sizable "deal flow" of high potential opportunities worth investing in, which allow VCs to specialize in a particular business area, investors willing to take on the high risks involved, skilled managers and external advisors able to add value to investee firms, and exit markets capable of generating the high returns needed and cover the high fixed costs this involves. To generate the sorts of returns investors seek, this system has to generate substantial increases in the value of the equity stake taken in the successful investee firms in a portfolio. If these levels of returns cannot be captured, funds will be unable to attract new investors and raise additional funds. Hence, VC is an extremely expensive source of risk capital for the investee firm, only suitable for a tiny minority of firms, and VCs are demanding investors (BVCA-NESTA, 2009; Bains, 2009) who can only operate when exit routes are available and place intense pressure on their investee firms to increase in value during a short period (Bains, 2009; Lazonick and Tulum, 2011, Fernandez *et al.*, 2012).

2.2 Institutional investors and economies of scale

Institutional investors manage diverse portfolios of investments on behalf of clients. Examples include pension funds and investment trusts. Institutional investors are important for the SME biotech sector as they invest in VC funds, indirectly supporting early-stage firms, and more directly, they provide funding for IPOs and subsequent stock market financing events (among a wide range of other investments).

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By investing in stocks as they come to the stock markets, generalist or specialist investors who cannot hold their investments over the full duration that therapeutic products take to pass through the R&D process are able to take ownership from VC funds and then pass ownership on to other investors, as they require (Andersson *et al.*, 2010). As we will explore in Section 4, the emergence of a VC sector and new stock markets in the UK created a "funding escalator" with finance accessible for firms at different stages of development (BIGT, 2009). Finance in the UK is centred on the City of London, which is an international market (Kynaston, 2011) that, in common with the USA, but unlike much of Europe, has a funded pension system (i.e. pensions are not paid from firms' current earnings). This has generated a large pool of investment capital and a large number of specialized institutional investors to manage it. As a result, institutional ownership of equities is more significant than elsewhere, and can reach 80% for large firms (Golding, 2001:23).

In Chandlerian terms, institutional investors can be seen as pipelines that process financial contracts rather than physical materials (Nightingale, 2000b). The profitability of these investments is determined by their size, margin, risk, and liquidity. The organizational and technical systems that draw in financial resources, transform them, market them to customers, evaluate their risks and performance, and ensure regulatory compliance are expensive. The costs are fixed in the sense of a fixed cost of production (i.e. not being a variable cost), but not in the sense of being stable or unchanging over time. Indeed funds' costs are compounded over the life of a contract, and can accumulate to have a substantial impact on the final performance of a long-term product such as a pension.

As a consequence, the relative economic performance of institutional investors depends on spreading these accumulating fixed costs, typically achieved by increasing funds under management, which drives fee income, and increases capacity utilization and throughput over a fixed period. Thus, institutional investors have become large: by 1999 the top five asset managers had funds under management larger than the combined Gross Domestic Product of France and the UK (Golding, 2001). The flow of capital into and out of these large funds reflects their relative performance compared with other funds (and indices), which, given their overlapping holdings, can be disproportionately influenced by seemingly marginal investments. This creates herd behavior, short termism, risk aversion (Haldane, 2011), and an emphasis on the predictable profitability and liquidity of easy-to-understand investments. Liquidity is particularly important given the scale of the funds, with a £500 million fund typically divided into a portfolio of 80–90 investments.[3] Individual investments are therefore large enough that it becomes prohibitively costly to hold and eventually

[3]These will typically be divided between bonds, equities, real estate, and short-term money market securities, with a small proportion in alternative investments, such as private equity, hedge funds, property, and VC.

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move out of illiquid positions, which is one reason why institutional investors are less interested in investing in medium-sized and small firms.

2.3 Pharmaceutical firms as Chandlerian firms

Large incumbent pharmaceutical firms are classic Chandlerian firms that can exploit the scale and scope economies emerging through the coordinated integration of high fixed cost R&D and global marketing and sales operations (Nightingale, 2000a). These high fixed costs are spread over a pipeline of potentially high-value drug discovery projects that need to succeed in sufficient numbers to generate enough profits to reinvest in future innovation and satisfy institutional investors. While economies of scale and scope are seen (to a point) in parts of drug development (Danzon *et al.*, 2005), overall productivity is declining as the output of new drugs has not kept up with increasing R&D spending (Pammolli *et al.*, 2011).

A novel drug takes an average of 14 years to progress through this pipeline from patent to regulatory approval with estimated costs (including paying for failures) somewhere between several hundred million and several billion dollars (Munos and Chin, 2011, Pammolli *et al.*, 2011). Only a fraction of drug R&D projects reach the clinic, with success rates of 1.3–19.7% depending on therapeutic field. As a result, large firms build high-fixed cost capabilities to effectively find, evaluate, and exploit innovative drug targets, avoid late-stage clinical failures, and direct projects toward profitable markets (Hopkins *et al.*, 2007; Martin *et al.*, 2009; O'Neill and Hopkins, 2012). The capacity utilization of the drug development pipeline is maintained with internal R&D projects, in-licensing of projects from other therapeutics developers, and increasingly by accessing projects through mergers and acquisitions (Munos, 2009). Large pharmaceutical firms make substantial bets of £1–7 billion annually per firm (Rafols *et al.*, 2012) in large numbers of new drug candidates to hedge against high failure rates. Throughput is increased (in theory) by speeding up development using automation, information and communication technologies, miniaturization, and new biotechnologies to gain scale and scope economies in R&D, which allows firms to learn to avoid time-consuming experimental dead ends (Nightingale, 2000). The speed of development (throughput) is important because patent lives are fixed, and each day of delay might cost £2–5 million for a blockbuster drug in lost revenues (O'Neill, 2012; Pammolli *et al.*, 2011).

Hence, some pharmaceutical firms seek economies by increasing the efficiency of their internal "R&D engines" (Garnier, 2008) by acting as systems integrators, spending hundreds of millions of dollars a year sourcing subsystems through corporate alliances, and integrating them to generate technology platforms in areas such as genomics and combinatorial chemistry that they hope will improve performance (Hopkins *et al.*, 2007). However, these investments (particularly prominent from the 1990s onward) have not yet yielded significant productivity improvements (Pammolli *et al.*, 2011) and may have negatively impacted productivity by

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encouraging reductionist, scalable research at the expense of lower throughput, more tacit-knowledge–based approaches (Scannell *et al.*, 2012). These disappointing results have led firms to rely more on projects from SMEs (Kneller, 2010)[4] to maintain capacity, and in recent years, externally sourced molecules have had higher success rates than internally originated molecules (Danzon *et al.*, 2005). As a result, large pharmaceutical firms have faced pressure from their investors to "exit early-stage R&D and create value" for shareholders (Baum *et al.*, 2010) as mentioned in Section 1.

2.4 Biotech SMEs and the time cost of capital as a Chandlerian imperative

Early biotech firms such as Genentech exploited recombinant DNA technology and antibody technology to produce novel drugs or make established treatments (e.g. insulin) in new ways. While some of these early biotechs built themselves into fully integrated firms that could compete directly with incumbent large pharmaceutical firms, most have found this difficult (Pisano, 2006; Sharp and Senker, 1999; Orsenigo, 1989; Kaplan and Murray, 2008). Instead, waves of biotech start-ups continue to emerge to exploit new biotechnologies, often creating dense networks of alliances with pharmaceutical firms and other biotech SMEs (Pammolli and Riccaboni, 2002; Powell *et al.*, 1996). Biotech firms' drugs are more successful when developed in alliances with more experienced firms (Danzon *et al.*, 2005), and projects in firms with fewer alliances seem more likely to fail (Powell *et al.*, 1996). Rather than growing into integrated pharmaceutical firms, biotech SMEs now often specialize in particular stages of development, therapeutic areas, or on emerging technological approaches, with many building technical capabilities that they exploit over multiple projects, both internally and/or externally with partners (Hopkins *et al.*, forthcoming; Nightingale *et al.*, 2011).

The drugs in biotech firms' pipelines often originate in upstream public sector research. Biotech firms access research, evaluate and filter opportunities before developing viable projects to the next stage. In doing so, they act as "middlemen" between the science base and downstream incumbent firms with global market access (Owen, 2001; Stuart *et al.*, 2007). They out-license their products in exchange for payments and/or royalty streams (Rothaermel, 2001). The resulting networked mode of innovation has become a defining feature of the biotech sector (Powell *et al.*, 1996; Powell *et al.*, 2005).

For a research-intensive biotech firm that does not have any products, access to external finance is essential. Drug development is unsuited to debt finance because of the high risks and lack of collateral, particularly as the book value of the firm will reduce as funds are spent developing projects that do not increase the value of the

[4]Pharmaceutical firms have of course followed a range of strategies to maintain their profitability from focusing on emerging markets (Sanofi) to counter-balancing high-risk R&D with lower-risk consumer products (Glaxosmithkline); however, our focus here is on economies of scale and scope related to therapeutic R&D.

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firm until regulatory milestones in clinical trials are passed (Andersson *et al.*, 2010; Hopkins, 2012). As a consequence, biotech firms often rely on professional equity investors, such as VC funds.

As highlighted earlier, this equity investment amounts to an extremely high fixed cost of production because of the high time cost of capital for VC investors, for example, who expect annual returns of 20–70% (Hopkins, 2012; Bains, 2009). While this is a fixed cost of production in the sense it is needed to undertake production, it is not fixed in the sense that it remains the same over time. Instead, the cost of capital increases through time, creating a Chandlerian imperative toward improving throughput and getting projects completed as quickly as possible.

The force of this imperative can be seen in Figure 1, which is based on amalgamated data from three UK VC-backed biotechs founded in the 1990s. It shows how and when these firms accessed VC funding (totalling ~£45 million each) over a series of funding rounds, and the expected returns at different stages implied by a 50% compound annual growth rate—demanded by some VCs. At this rate, firms with 6 years of VC investment totalling £23 million would have to return over £80 million to investors at exit to generate the required returns, while retaining VC support for a further 2 years (for example, to undertake another phase of clinical trials) would require another round of investment (£11.5 million) and raise expected returns to more than £200 million. Another round of similar size and another 2 years might raise expectations of a return greater than £470 million. With these sorts of requirements, even technically successful firms that IPO for large amounts of money relative to cash invested can be poor investments. As a result, exits that may seem premature from a firm's perspective might be rational for a VC fund.

Given these costs biotech firms need to increase the throughput of their R&D pipeline to develop at least one high-value therapeutic project within the timeframe required by investors. In theory, this involves exploiting their nimble organizational structures and advantages in fast decision making to effectively (a) find target drug candidates for valuable markets and (b) efficiently reduce the number of experimental dead ends that need to be explored to advance these drug candidates through clinical trials. However this is only an advantage if this swiftness offsets biotech firms' much higher cost of capital (established pharmaceutical firms can issue corporate bonds with coupon rates of <5% at present).

In summary, three sectors interact closely with biotech SMEs in the UK and each is influenced by Chandlerian imperatives, which shape their investment behavior and interactions: VC funds need high returns to satisfy their investors, and use expensive staff and demanding investment plans to achieve these, generating high fixed costs; institutional investors benefit from scale efficiencies but to do so must avoid investing in small, low liquidity, hard-to-understand firms; while, pharmaceutical firms need to access external drug candidates to feed their pipelines amidst declining R&D productivity, but nonetheless have strategic preferences regarding which externally sourced drugs they wish to fund and develop. After setting out our methods, in

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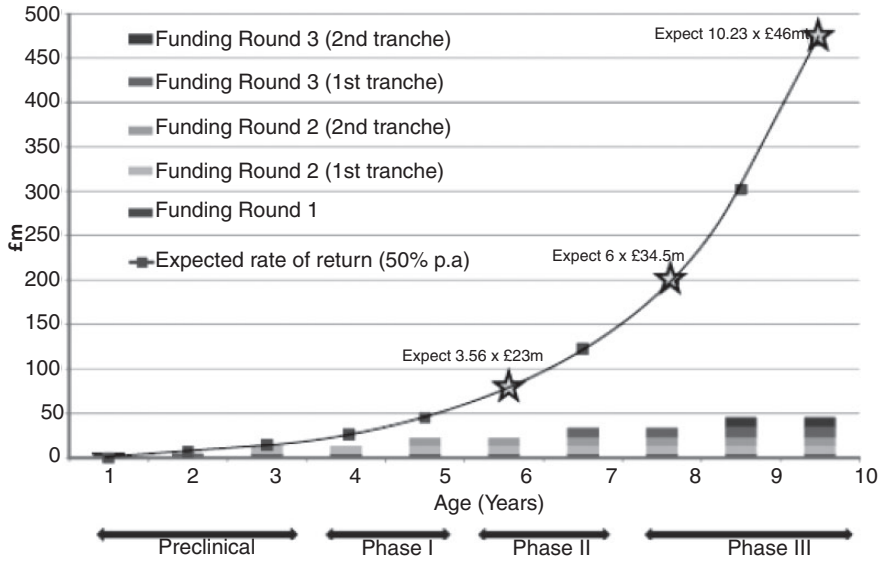

Figure 1 VC investment and expected returns based on the time cost of capital. *Source*: Hopkins (2012) based on author's own data.

Section 3 and Section 4 we will show how interactions between these investors have influenced the growth and development of the UK biotech industry. A key focus of the account is the consequence of firms from these different sectors not achieving Chandlerian economies from exploiting emerging biotech opportunities.

3. Research setting, data, and limitations of the method

To address our research questions, we have identified as fully as possible the population of firms in the UK SME biotech sector and followed their financings and research performance over the 30-year history of the sector. We identified 247 firms, including both public (i.e. stock market listed) and private (i.e. unquoted) firms, as well as those firms that have and have not successfully advanced their therapeutic assets. The data set was built from a range of historical sources that name SMEs, to avoid survivor bias (Cassar, 2004), and then cross checked with the Pharmaprojects database (see www.pharmaprojects.com), which was used to screen these for all current and historically active UK firms owning one or more projects. This is necessary because Pharmaprojects does not retain the country of origin of acquired firms or projects that have changed hands. Pharmaprojects is an industry standard database that is widely used for large scale longitudinal studies (see Munos, 2009; Pammolli *et al.*, 2011). Only including firms contained in pharmaprojects excludes a small number of recently founded firms that have not yet

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acquired or developed projects or are new. No firms founded in 2009 and proclaiming to be engaged in drug discovery qualified, for example, and we find few for 2008. Hence, there is likely to be some "right censoring" in the data set and so conclusions are drawn with caution about population trends in the period 2005–2009.[5]

New entrants are defined as SMEs founded in the UK between 1980 and 2009, actively engaged in drug discovery and development activities related to at least one proprietary therapeutics project of which they own rights to (either wholly or in part). Firms involved only in fee-for-service work are excluded. Activity at any stage of drug discovery/development qualifies but firms active only in sales and marketing, distribution or manufacture are excluded. While most firms included in the data set are independently founded, the study has not excluded spin-outs from larger entities. Not-for-profit entities such as medical charities are excluded, although their spin-out firms are not.

The definition of therapeutics includes biopharmaceuticals, synthetic chemical drugs, including novel reformulations, as well as drug delivery methods, and products based on whole cells (e.g. stem cell therapies) vaccines or other biologics, but excludes firms developing diagnostics and medical devices who do not develop therapeutics (or reformulations thereof). Figure 2 shows the sources used to build the sample and the numbers of new firms founded each year. Data sources are indicated by year of publication (where these are one-offs, although they may themselves rely on a host of prior sources) or by their period of service provision (for databases/ directories).

3.1 Classification of funding routes

Throughout the period studied, biotech firms have predominantly adopted a "forward integrator" strategy (Hopkins, 2012) whereby firms are founded to develop drugs, and are built up from early-stage R&D toward the market.[6] Such firms require external equity investment over extended periods (1–2 decades is common) and for each firm we have identified their funding route. The choice of funding sources available to firms has expanded over time but can initially be categorized as deriving from revenue, equity or debt (Patel *et al.*, 2008; Hopkins, 2012). We are principally concerned with sources of external investment for equity, particularly VC funds, institutional investors, and pharmaceutical firms, who are the main sources of capital for the sector (Ernst &Young, 2011; Huggett *et al.*, 2011). All 247 UK firms were tracked through funding route-maps (see Figures 4, 5, 9 in Section 4) from

[5]In fact, other data sources suggest relatively few biotech firms (qualifying or otherwise) have been founded recently due to poor economic conditions in the UK (BIS 2011) or more widely (Ernst and Young 2010).

[6]One notable exception being Shire Pharmaceuticals Plc that started with a sales operation and eventually integrated backwards by acquiring discovery stage firms.

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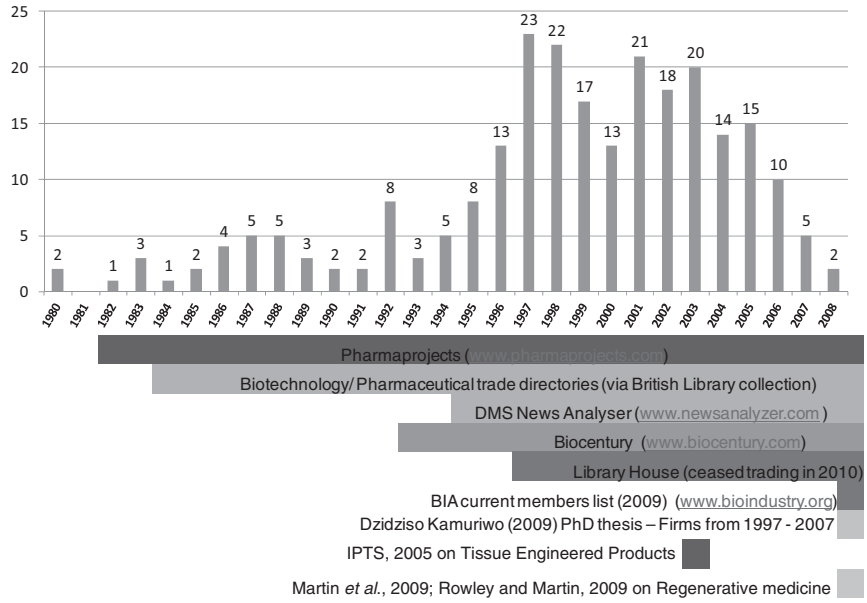

Figure 2 Number of firms detected by founding year vs. publication years of data sources used.

foundation to the point the firms (rather than the investors) exit the industry (i.e. cease to be independent entities).The route-maps capture the following events:

3.1.1 Foundation

Firms may be created with financial resource from a range of seed funders (e.g. universities, charities, parent firms, business angels). Given the small amounts involved at this stage, compared with the tens or even hundreds of millions invested subsequently, we do not distinguish between these different kinds of early-stage funders.

3.1.2 VC funds

SMEs receiving one or more rounds of funding from one or more formal VC funds, as defined in Section 2, are counted as taking the VC route, regardless of the mix of other investors that are present. Where the age at VC is taken, this refers to the age of the firm on its first VC investment round. We do not classify funds created under the UK Venture Capital Trust investment scheme Trusts as VC investors, despite their name, as they distinct investment vehicles that are stock-market listed, open-ended investment trusts which have more limited capital to invest in individual firms (Siepel, 2009).

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3.1.3 Stock markets

A range of stock markets have supported the UK biotech firms. These are varied in their funding capacity and stringency, but crucially unlike VC funds, stock markets provide open access to a wide pool of potential investors, and are not time limited. A firm that joins a stock market by any route (e.g. IPO event, or reverse merger with a listed firm), and obtains funds from one or more public placing(s) is classified as taking the stock market route.[7]

3.1.4 Alternative finance

Firms that have never had a VC funding round or offered shares through a public placing on a stock market are categorized as taking the alternative funding route. This broad category includes many types of equity investors such as business angels, Pharma Venture Funds, and Venture Capital Trusts.

3.1.5 Pharmaceutical firms

Support often comes in terms of staged funding for specific drug projects in return for licensing rights, rather than equity investment in a biotech firm per se (although such investments are captured in "alternative investments" if no VC or stock market investment occurs). Because such support is project specific, we track the contribution of pharmaceutical firms to individual projects (Table 1); however, we find equity investment in biotech firms is relatively rare and is not shown in the funding route maps.

3.1.6 Exit

The analysis tracks SMEs through their life cycles to the end of their time as independent entities in the sector. We distinguish between mergers and acquisitions (M&A), divestment from the UK sector, and failure. Where M&A occurs, junior partners in mergers (<49% of the resulting entity) are treated as ending their independent existence. Contributions they make to continuing companies, such as drug projects, are recorded using "family trees" (analogous to the approach of Hoang and Rothaermel, 2010). Where firms leave the sector for other reasons, these are coded as emigration or divestment.[8] Few firms have taken this route and these are not

[7]This includes instances of firms (e.g. Senetek) moving from 'public' bulletin boards where buyers and sellers are matched graduating to more formal markets such as NASDAQ or LSE or those buying other listed firms to gain access to their stock market listing (e.g. Skyepharma). These events may not initially raise funds, hence their stock market debut is not an 'IPO' and the number of IPOs (events where new investors show their support for a firm) we show in the following sections differs from the number of firms actually listed on stock markets substantially for this reason.

[8]A notable example is BioVex Ltd., which moved its operations to the USA before being acquired by Amgen—a lucrative deal for investors.

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Table 1 Firms achieving at least one P.II trial success and related project details

Company	Founding decade	Alternative investors?	Which sources of funding were accessed before advance of first therapeutic passed P.II				Therapeutic project	Type of project	First indication	Years to advance passed P.II (to nearest 3 months—E denotes estimate)	Notes
			VC?	Stock market?	Corporate alliance?	Acquirer/new parent company?					
Senetek	1980s	No	No	Yes	No	No	VIP (aviptadil + phentolamine mesylate)	Reformulation/DDS	Erectile dysfunction	11.5	
Medeva	1980s	No	No	Yes	No	No	Hepagene (HepB immunotherapy)	Biologic (immunotherapy)	Infection (viral)	8.5	
Antisoma	1980s	No	No	Yes	No	No	Theragyn/Pemtumomab, Murine IgG1 MAb (HMFG-1) specific for PEM-10	Biologic (MAb)	Cancer	10.5 (E)	
Innovata	1980s	No	No	Yes	No	No	Icodextrin, CAPD	Small molecule drug	Urological/renal	3.5	
Celltech	1980s	No	Yes	No	Yes (Bayer)	No	BAYX 1351	Biologic (MAb)	Anti-TNF (septic shock)	13.75	
Shire	1980s	No	Yes	No	Yes (Warner Lambert)	No	Tacrine (tetrahydroaminoacridine)	Small molecule drug (established strategy)	CNS (Alzheimers disease)	3.5 (E)	
British Biotech (subsequently Vernalis)	1980s	No	Yes	Yes	No	No	Lexipapant (acute PAF antagonist)	Small molecule drug (novel)	Acute pancreatisis	6	
Oxford GlycoSciences	1980s	No	Yes	Yes	No	No	Zavesca/Vevesca (miglustat)	Small molecule drug (novel)	Gauchers disease	11	Orphan

(continued)

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Table 1 Continued

Company	Founding decade	Alternative investors?	Which sources of funding were accessed before advance of first therapeutic passed P.II				Therapeutic project	Type of project	First indication	Years to advance passed P.II (to nearest 3 months—E denotes estimate)	Notes
			VC?	Stock market?	Corporate alliance?	Acquirer/new parent company?					
Amarin	1980s	No	Yes	Yes	Unknown	No	Estradiol + norethisterone transdermal patch	Reformulation/DDS	HRT	Unknown	
CAT	1980s	No	Yes	Yes	Yes (Knoll and others)	No	Humira (adalimumab)	Biologic (MAb)	Rheumatoid Arthritis	11.25	
Porton International	1980s	Yes	No	No	No	Yes (Ipsen biopharma)	Genital Herpes vaccine	Biologic (vaccine)	Infection (viral)	Unknown	
Fermentech	1980s	Yes	No	No	No	Yes (Skanditek)	Vitrolife (hyaluronic acid)	Biologic (Recombinant protein)	Ophthalmology	11	
Enact Pharma	1990s	No	No	Yes	No	No	Voraxaze (recombinant glucarpidase)	Biologic (recombinant protein)	Chemotherapy-induced injury	Unknown	Orphan
Alizyme	1990s	No	No	Yes	No	No	COLAL-PRED (prednisolone sodium metasulphobenzoate)	Reformulation/DDS	Inflamation (IBD)	6	
Skye Pharma	1990s	No	No	Yes	No	No	DepoDur (sustained release morphine)	Reformulation/DDS	Pain (postoperative)	5	
GW pharma	1990s	No	No	Yes	No	No	Nabiximols (Sativex) (tetrahydrocannabinol + cannabidiol)	Small molecule drug	Multiple sclerosis	3	

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Table 1 Continued

Company	Founding decade	Alternative investors?	Which sources of funding were accessed before advance of first therapeutic passed P.II				Therapeutic project	Type of project	First indication	Years to advance passed P.II (to nearest 3 months—E denotes estimate)	Notes
			VC?	Stock market?	Corporate alliance?	Acquirer/new parent company?					
Allergy Therapeutics	1990s	No	No	Yes	No	No	Allergy vaccine (pollen) with Monophosphoryl Lipid A	Biologic (vaccine)	Allergy	1.25	
KS Biomedix	1990s	No	No	Yes	Yes (Nycomed and others)	No	TransMID/XR-311	Biologic (recombinant protein)	Cancer (brain)	13 (E)	
Oxford Biomedica	1990s	No	No	Yes	No	No	Trovax	Biologic (gene therapy)	Cancer (renal)	11.5	
Metris Therapeutics	1990s	No	Yes	No	No	No	M-1002 Low dose HRT formulation	Reformulation	Hormone replacement	8 (E)	
Profile Therapeutics	1990s	No	Yes	No	No	No	Antibiotics with AAD system	Reformulation/DDS	Infection (antibiotics for CF patients)	5 (E)	
Intercytex	1990s	No	Yes	No	No	No	Cyzact (tissue-engineered skin)	Tissue	Wound healing	6 (E)	
Core Technologies	1990s	No	Yes	No	No	No	Miconazole Hycore-V (pessary)	Reformulation/DDS	Infection (fungal)	3	
Prolifix	1990s	No	Yes	No	No	Yes (TopoTarget)	Belinostat (PXD-101)	Novel (lead) small molecule drug	Cancer, lymphoma, T-cell	16.5	
Prostrakan	1990s	No	Yes	No	Yes	No	ResiDerm A topical formulation	Reformulation/DDS	Dematology (acne)	3 (E)	

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Table 1 Continued

Company	Founding decade	Alternative investors?	Which sources of funding were accessed before advance of first therapeutic passed P.II				Therapeutic project	Type of project	First indication	Years to advance passed P.II (to nearest 3 months—E denotes estimate)	Notes
			VC?	Stock market?	Corporate alliance?	Acquirer/new parent company?					
NeuTec Pharma	1990s	No	Yes	Yes	No	No	Aurograb (MAb specific for *Staphylococcus aureus* ABC transporter)	Biologic (MAb)	Infection (bacterial)	7.25	
Renovo	1990s	No	Yes	Yes	No	No	Zesteem (formulation of 17β-estradiol)	Reformulation	Wound healing	9.25	
Ark Therapuetics	1990s	No	Yes	Yes	No	No	Vitor (formulation of imidapril hydrochloride)	Small molecule drug	ACE inhibitor—muscle wasting	8 (E)	
Vernalis	1990s	No	Yes	Yes	No	No	Frova (frovatriptan—an 5HT1B/1D agonist (VML 251)	Small molecule drug (established strategy)	Antimigraine	5.75	
Acambis	1990s	No	Yes	Yes	No	No	Arilvax	Biologic (vaccine)	Infection (yellow fever)	5 (E)	
Chiroscience	1990s	No	Yes	Yes	Yes	No	Chirocaine (levobupivacaine)	Reformulation	Pain	1.5	
CeNeS Pharmaceuticals	1990s	No	Yes	Yes	Yes (Boehringer Ingelheim)	No	Aptiganel (Cerestat)	Novel small molecule drug	Stroke	4.5	
BTG	1990s	No	Yes	Yes	Yes (Genetics Institute and others)	No	Benefix (recombinant factor IX)	Biologic (recombinant protein)	Hemophilia/enzyme replacement	3.5	

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Table 1 Continued

Company	Founding decade	Alternative investors?	Which sources of funding were accessed before advance of first therapeutic passed P.II				Therapeutic project	Type of project	First indication	Years to advance passed P.II (to nearest 3 months—E denotes estimate)	Notes
			VC?	Stock market?	Corporate alliance?	Acquirer/new parent company?					
Vectura	1990s	No	Yes	Yes	Yes (Novartis/ Sosei)	No	NVA 237 inhaled glycopyrrolate	Reforumation/DDS	COPD	11.5	
Devco	1990s	Yes	No	No	No	No	Lexipafant (acute PAF antagonist)	small molecule drug (novel)	Surgery adjunct—cardiology	6.5	
Ineos Healthcare	1990s	Yes	No	No	No	No	Iron–magnesium hydroxycarbonate	Small molecule drug	Urological/renal	11.5	
Laxdale	1990s	Yes	No	No	Yes (Amarin)	No	Lax-101	Small molecule drug	Huntingdons disease	3	
Ardana	2000s	No	Yes	No	No	Yes (returned to licensor)	Teverelix—Gonadotrophin releasing hormone (GnRH)-antagonist	Reformulation	Hormone replacement	7.5 (E)	
Arakis	2000s	No	Yes	No	No	Yes (Sosei)	AD-923 (formulation of fentanyl)	Reformulation/DDS	Pain	8	
Plethora solutions	2000s	No	Yes	Yes	Yes (Sciele)	No	PSD502 (lidocaine + prilocaine)	Reformulation/DDS	Erectile dysfunction	4	

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discussed further here. Finally, where firms have ceased trading, or entered liquidation, they are recorded as "failed."

All dates of significant events such as founding and failure are taken from notifications with the UK Government's Companies House.[9] Figure 3 sets out the available data showing the quantitative differences in funding available to the firms obtaining stock market, VC and alternative funding. All data on financing events shown is reflated to 2010 Great British Pounds (GBP) using historic Consumers Prices Index data to allow aggregation of data across periods. It is difficult to distinguish exact amounts of funding accessed by small firms that are not subject to detailed statutory filings required for larger firms. Although near complete data are available for stock market firms, the mean investment shown in Figure 3 for VC and alternative firms is likely to be artificially high as a result of reporting bias. Nonetheless, it is reasonable to assume that firms accessing stock market funding are often able to raise the greatest sums, typically tens or even hundreds of millions of pounds, which may be in addition to substantial sums from VC investors, while firms accessing "alternative financing" can typically only access a few million pounds (with a small number of exceptions).

3.1.7 Measuring success

We use the milestone of passing P.II clinical trials to capture "success" in therapeutics development. In light of difficulties in judging objectively whether firms reporting P.II results actually achieved claimed successes, only drugs that have subsequently advanced to the start of P.III or filed for market approval as orphan drugs were counted as having completed P.II successfully (see Table 1 for full details of firms and projects). P.II trials demonstrate therapeutic proof of concept in humans and are associated with a "valuation inflection point" for drug candidates. Development costs escalate steeply afterward, disfavoring small firms, and so this is often thought to be the optimal time for small firms to out-license their projects (Kalamas and Pinkus, 2003; Murray, 2012). Achievement of this milestone is recorded positively in the case of all firms in the data set that are associated with advancing a project they own completely or partially, regardless of when the success occurs in the life cycle of the firm involved (even if it is after acquisition of the UK biotech firm that initially advanced the successful project). Data on the status of drug projects was gathered from Pharmaprojects and public sources such as company press releases. Using this measure, firms that advanced at least one project, which (ultimately) passed P.II by the time of analysis (mid-2011) are classed as "successful" irrespective of the profitability of such activities. The changing historical context complicates comparative analysis of cohorts of firms (Freeman and Louçã, 2001), and so to understand the influences on firms over the 30 years studied, we gathered

[9]It is noted that on occasion there are significant periods of time between announced events and legal events, and where this is the case we follow the dates as recorded in Companies House.

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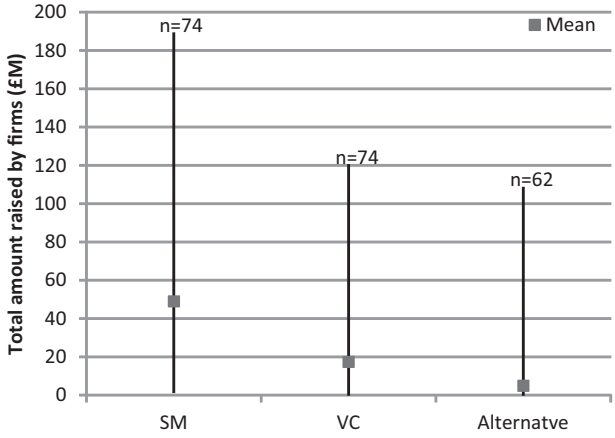

Figure 3 Finance raised by firms from the different sources of funding. *Source*: company reports (available for 210 of 247 firms—small firms are exempt from reporting).

information from a range of contemporary sources including company statutory filings, press releases, the financial press, more specialized sources (particularly Nature Biotechnology, and Biocentury), as well as a series of the UK government policy reports.

4. Funding patterns in the UK biotech

This section sets out the data on biotech firms' funding routes with firms founded in each decade tracked as a distinct cohort. Figures 4, 5, and 9 summarize the changing use of different financing options by each cohort. The choices of funding routes are contextualized by an account of institutional changes of the period 1980–2009.

4.1 The 1980s

Section 1 highlighted how established pharmaceutical firms and biotech SMEs have become increasingly interdependent. However, in the past, there have been high expectations of biotech SMEs, potentially displacing large incumbent pharmaceutical firms (Kenney, 1986). Enthusiastic investors supported a dozen US biotech IPOs in the early 1980s—dubbed biomania at the time (Teitelman, 1989). This optimism provides the context for the initial foundation of 26 UK biotech firms in the 1980s (Figure 4). During the early 1980s, the UK biotech SMEs only had domestic stock market support from the Unlisted Securities Market (USM), a junior stock market founded in 1983, as loss-making firms were not allowed to join the more prestigious main list of the London Stock Exchange (LSE) (ibid).

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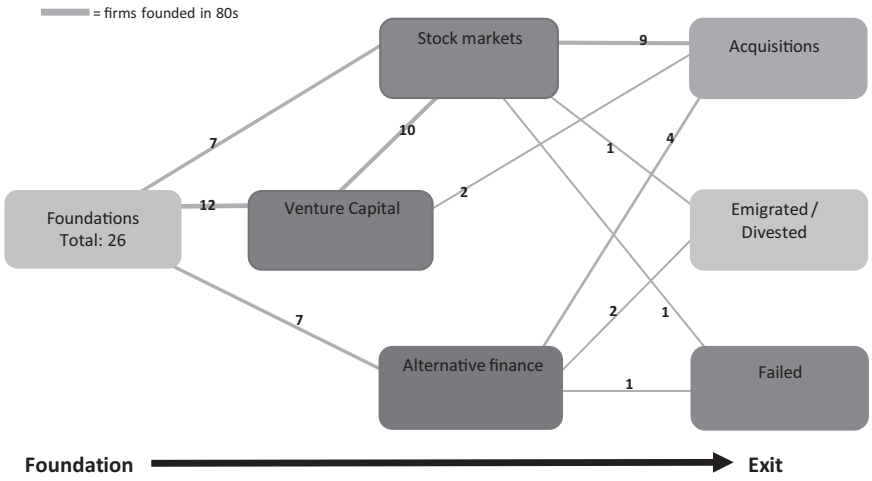

Figure 4 The funding route of the UK therapeutics firms founded in the 1980s.

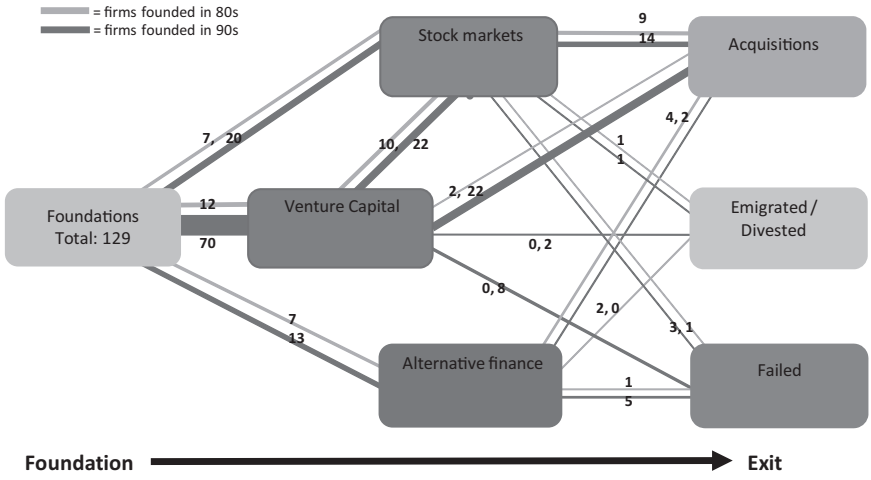

Figure 5 The funding route of the UK therapeutics firms founded in the 1980s and 1990s.

In their early years, these firms had limited support from institutional investors and only two biotech firms had IPOs on the USM in this decade. The UK Government founded Celltech in 1980, a biotech firm tasked with commercializing government-funded R&D, which it was hoped would spur private sector investment (Owen, 2001). Even as a private firm in the 1980s, Celltech had privileged access to institutional investors such as The Midland Bank, and Prudential Assurance (a pension fund),

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including the specialist fund Biotechnology Investments Ltd., which had initially been founded to invest in US opportunities (Owen 2001). The investment environment improved toward the end of the decade after the deregulation of the City of London in 1986 (Golding, 2001) and the subsequent growth of the UK VC sector. This is illustrated by membership of the British Venture Capital Association growing from 30 at foundation in 1983 to over 100 in 1990 (Owen 2001). This increasingly favorable funding environment saw more biotech firms emerge, with 19 founded from 1985–1989 compared with only 7 between 1980 and 1984 (see Figure 7 below).

Improving access to stock market funding in the 1990s (discussed below) ultimately meant that 65% or 17 of 26 of the cohort of firms founded in the 1980s managed to access stock market funding (Figure 4) at some point (albeit not during the 1980s). Of these, seven accessed the stock markets directly, while 10 out of 12 firms that accessed VC funding later joined a stock market. The remaining seven (31%) relied on alternative sources of finance.

Considerable optimism surrounded these young firms. For example, executives at Porton International, founded to exploit expertise in applied microbiology, saw the firm as "another Glaxo" (referring to an established pharmaceutical firm) and pharmaceutical executives took senior management roles in these firms (Owen, 2001). The firms founded in the 1980s were remarkably effective with 50% (12 of the 24 for which we have data) ultimately advancing at least one of their therapeutic assets beyond P.II trials (Table 1). Moreover, they seem to have been able to achieve this success reasonably rapidly. Based on available data for the firm's most advanced project in the 10 firms for which we have data, we find it took an average of just over 9 years from founding to commencement of P.III clinical trials (Table 1).

In summary, the 1980s were a time of buoyant expectations for biotech firms, despite significant uncertainties. Institutional investors increasingly supported biotech firms, and while the UK VC sector was still relatively small, it played a greater role as it grew and received more money from institutional investors. However, both biotech and VC were poorly understood asset classes for London-based institutional investors. By the end of the 1980s, the successes of the US firms and the growing access to funding in the UK gave the 1980s cohort reasonable expectations of becoming large, fully integrated firms. In retrospect, investment seems justified as several of this relatively small cohort became billion pound firms, including Celltech, British Technology Group (BTG), British Biotechnology, and Shire, although not sustainably so in all cases (Owen, 2001).

4.2 The 1990s

This section follows events in the 1990s and traces the continued efforts to seek financing of the cohort of 1980s as well as the experiences of the emerging 1990s cohort.

Figure 5 compares how the funding routes of the 103 firms founded in the 1990s (shown in the darker lines) compare with the 26 founded in the 1980s. Greater use of

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a funding route is shown by thicker lines. In the early 1990s, several UK biotech firms such as Cantab pharmaceuticals were unable to raise large amounts of capital in the UK, and successfully listed on the US NASDAQ (Owen, 2001). Shortly afterward, the LSE changed its rules to allow loss-making firms to join its list, and in 1992 British Biotechnology was able to issue an LSE prospectus despite its loss-making status. Biotech firms now had access to mainstream stockbrokers such as N.M. Rothschild, Kleinwort Benson, and Robert Fleming & Co. These brokers were ultimately able to arrange fund-raising placings of over £100 million (at 2010 prices) for some of their new clients including British Biotech, Cambridge Antibody Technology (CAT), Medeva, Oxford Glycosciences, and Skye Pharma, once they had established themselves on the stock market (i.e. after their IPOs).

The relaxing of the main list's regulations as well as the launch of London's Alternative Investment Market (AIM) in 1995 and the establishment in 1996 of the pan-European EASDAQ (an ultimately unsuccessful attempt to replicate the success of the US high-tech-friendly NASDAQ) provided important stimuli to the sector by adding funding opportunities and signaling that the prospects of high value exits for early-stage investors were improving. This was particularly favorable for the emerging specialist life sciences funds set up by established and new VCs, including Apax, Advent, Schroders, Abingworth, MVM Ventures, and Merlin Ventures. In the relatively small UK sector, these dedicated funds had limited choice in investees and in some cases these VCs would even found new biotech firms (rather than select them from applicant firms). Given these supportive conditions, more biotech firms were created than in the prior decade, and many of these eventually listed on a range of stock markets (Figures 5 and 6).

Between 1990 and 1994, seven IPOs raised a total of £155 million. However, between 1995 and 1999, this figure nearly trebled with 25 IPOs raising £456 million (Figures 7 and 8). Much larger sums of money were available in secondary (follow-on) placings through the stock market with nearly £2 billion raised in the 1990s by the UK therapeutics-focused biotech SMEs. These relatively high IPO valuations (discussed later in Section 5 and shown in Figure 11) rewarded early-stage investors and spurred growth in the sector, particularly after the opening of AIM, with 83 new firms founded between 1995 and 1999 compared with just 46 in the prior 15 years (Figure 7). The benign funding environment helped increase the number of firms per year receiving their first VC funding, which in turn sustained the growth of the biotech SME sector over the next decade. These trends are shown in Figure 7, which records the numbers of biotech SMEs receiving their first VC funding rounds each year, as well as firm foundations per year, with the two lines closely tracking each other. VC financing was more readily available in the 1990s, with 68% (70) of 1990s SMEs receiving VC funding compared with 46% (12) of the 1980s firms. Only 13 firms (13%) founded in the 1990s relied on the alternative finance route, which given the capital available from other funders, can be taken as a sign of relatively accessible finance in this decade. VC and institutional investors were not

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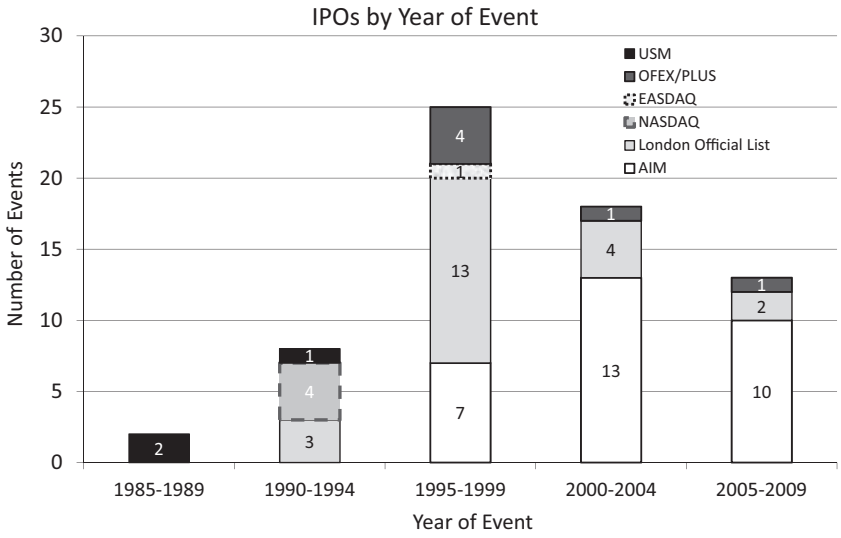

Figure 6 The changing nature of the UK Biotechs' IPOs.
Total IPOs do not sum to total firms listing on stock markets in funding route maps (Figures 4, 5, and 9) due to firms (i) obtaining dual listings simultaneously and (ii) firms entering stock markets via reverse mergers (the latter are excluded in Figure 6).

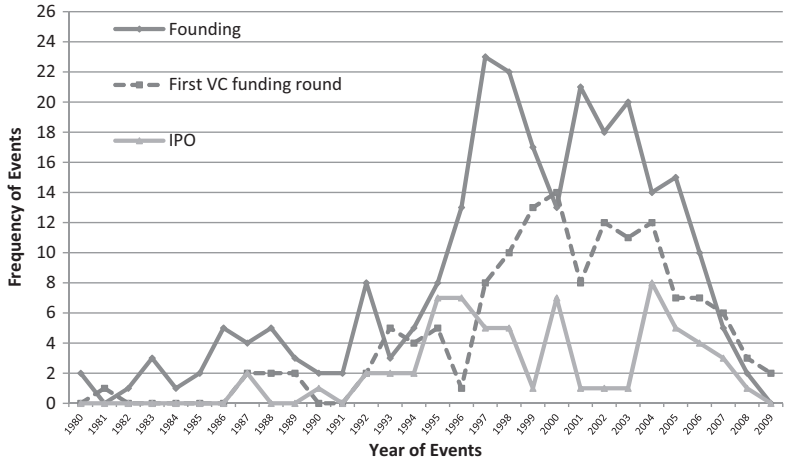

Figure 7 Foundings and initial funding from VCs and stock markets, by year of event.

being particularly selective with a high proportions of firms founded obtaining VC or stock market funding.

Although a lower proportion of 1990s firms (41% or 42 of 103) obtained a stock market listing compared with 1980s firms (65% or 17 of 26), actual numbers where

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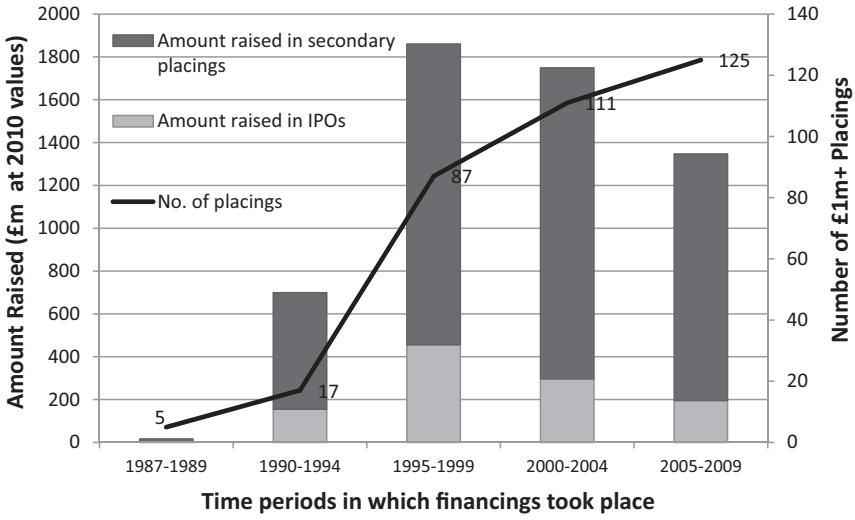

Figure 8 Money raised in IPO and secondary placings by the UK SMEs 1980–2009.

higher (42 vs. 17). Again, the majority of these arrived on the stock markets having first had VC funding (22) although nearly as many (20) joined the stock market without VC support. In a small number of cases, such as CeNeS and Skye Pharma, firms used reverse takeovers of listed firms, rather than IPOs as a less expensive "back door" onto the stock markets.

By the late 1990s a financial ecosystem had evolved based on a shared vision that staged investments, through a succession of specialist investors, could be made to work even in the absence of profitable UK biotech firms emerging onto the stock market. As a result, a well-funded biotech sector was developing with early-stage investors building firms at some scale for an investment market supported by institutional investors. Specialist life science VC funds, a small number of institutional investment funds, and dedicated stock-brokering teams that included specialist financial analysts were established. Firms founded during this period were again apparently successful at developing products that ultimately passed P.II trials. By 2011, 24% (25 of 103) of the 1990s SMEs cohort had advanced at least one project beyond P.II trials, with the average firm taking just over 6 years (based on data for 24 firms) from founding to commencement of P.III trials (Table 1).

In the 1990s, the biotech SME sector's loss-making (and sometimes productless) stock market–listed firms were seen by the Financial Times to

> "sustain capitalisations often running into hundreds of millions and regularly raise new equity capital. This is possible for just one reason. Investors believe a steady trickle of small losses is merely the prelude to a future flood of profits and big dividends." (Anon, 1998).

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The same phenomena had earlier shaped biotech in the USA, where Teitelman reports the importance amongst stock brokers of "the will to believe.... One hot [stock] issue would lead to the next and the next." (Teitelman, 1989:47). Even though stock issues were often small, there were enough of them to make it profitable for brokers to support them (ibid). Data on 75 of 77 biotech firms on public markets shows they undertook 320 placings between 1987 and 2009, which would have generated considerable income, as stock placing fees ran into the millions of pounds and averaged 10% of funds raised. The brokers with the highest number of placings are shown in Table 2 (as distinct from those raising the single largest amounts).

An important turning point in the history of the industry came in the late 1990s. In 1997 "a string of share price collapses" occurred after firms suffered failures in expensive late-stage P.III trials (Taylor, 1997). British Biotech PLC, the "flagship" of the UK Biotech sector (peak stock market value ~£3 billion) became embroiled in a scandal over an alleged cover-up of poor clinical results for key late-stage drug candidates. Dresdner Klienwort Benson's 1998 Biotech in Crisis report highlighted an "annus horribilis" for the sector (Pilling, 1998).

The share-price falls that followed clinical failures, unexpected development delays and board-level crises had lasting effects. For VC investors, late-stage failures reduced stock market interest and so destroyed portfolio value in a relatively small sector, where hedging risks was difficult. Due to the high time cost of capital, longer investment periods holding stock before exit was not desirable as investments became economically unviable. For other investors, and equity-owning founders, VC's desire for earlier exit was costly as it would require a sale before value inflection points, in a thin-market where investor trust had been badly damaged. Both cases had a lasting impact on the eventual returns the funds produced. For institutional investors, the rapid and often unexpected drops in value had a disproportionate effect on overall performance, both directly, for funds that held equity, and indirectly, for funds that had invested in VC. As a consequence, institutional investor support for large share placings waned and investors increasingly shunned biotech. Moreover, as the impact on VC fund performance became evident over the following years (in combination with poor investments during the dot.com boom), investment in the UK VC similarly declined (Owen, 2001, Smith *et al.*, 2009).[10]

One contemporary analyst noted that biotech is a field "investors find tough to understand and where there were no 6 monthly profit figures against which to gauge credibility or otherwise." He continued: "Although the rewards look high, the levels of risk is rarely appreciated by them or the stock brokers who advise them" (Anon, 1998). After suffering severe loses, institutional investors claimed they would not reinvest (Pilling, 1998). This dried up the market and the leading brokers

[10]This narrative of biotech may look like a classic investment bubble, but this only occurred in the UK, while in the USA institutional conditions continue to support an industry—indeed in some years raising even more money than in the 1990s (Huggett et al 2011).

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Table 2 Most active brokers (by number of placings undertaken involving the 77 firms in the data set)

Broker	Number of placings
Collins Stewart	22
Nomura International PLC	21
Piper Jaffray	15
Panmure Gordon	13
Credit Suisse	11

(by quantum, not frequency of placing), mentioned above, ceased to support biotech IPOs on the LSE after 1998.[11] While others continued to invest, the belief that SMEs could bring drugs successfully through clinical trials was increasingly questioned, and investors shifted their attention to firms making deals with pharmaceutical partners (Taylor, 1997; Pilling, 1998). These partnering deals provided the firms with much needed additional cash, which was secured in exchange for a share of potential future product revenues rather than further equity investments and signaled quality to other investors (McNamara and Baden-Fuller, 2007). This signaling is important because institutional investors have limited understanding of smaller firms in specialist markets, which are too small for them to devote time to understand, and are not profitable for many financial analysts to develop and sell research notes (ETB, 2006:14).[12] Again, this highlights how the scale of the investee industry influences specialization in investor industries.

The biotech firms that relied on pharmaceutical firms were now more exposed to big pharma's Chandlerian imperatives and their impact on internal decision making about their own pipeline strategies. Large pharmaceutical firms do not seek to maximize the value of each individual project, but instead maximize the value of their entire portfolio. As a result, they can make decisions that go against the interests of biotech partners, such as to delay development or product launch or shelve projects entirely. While milestone payments and capabilities from pharma may have helped advance some biotech projects, other projects that do not fit well within the

[11]There was an argument at the time that biotech had not delivered, with a lack of therapeutic successes compared with the US sector (Pilling 1998b). Various causes were advanced for this—poor management, the wrong incentives, or insufficient capital (Smith et al. 2009).

[12]Paul Myners' review of institutional investors for the UK Treasury noted in 2001 that 'long-established firms offer similar products and limited expertise in some important specialist areas, including private equity'; in particular, he noted that there were difficulties for investors getting investment advice, particularly on alternative investments p.40.

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pharmaceutical firm's (changing) strategic decision making became less attractive, and hence less attractive for biotech firms and their investors to invest in.

The 1990s cohort further suffered in the 2000s in the aftermath of the "dot.com" stock market collapse, which cast a long shadow over the UK VC sector and investors' interest in technology-based firms. As a consequence, fewer UK biotechs had IPOs on the prestigious main list of the LSE (15 listed in the 1990s compared with only 6 since 2000 and none have had an IPO since 2006, despite an overall growth in the number of firms in the sector). The long-term trend, shown in Figure 8, is that those biotech firms already listed sought more follow-on placings, but received less cash per placing. By 2010, the 1980s cohort had raised, on average, £169 million each from public markets, while the 1990s cohort raised £63.3 million and the 2000s cohort just £18.9 million. Such a trend might be expected as the older firms have had more time to raise funds. However, younger SMEs have also found it particularly difficult to raise cash as the majority of stock market funding in each 5-year period went to the 1980s cohort. As valuations and average IPO proceeds drop (Figures 8 and 11), the costs of accessing capital from stock markets increase, perhaps reflecting investor concerns about the ability of small firms to create and capture value from early-stage R&D.

In summary, during the 1980s support for biotechs was growing and those firms founded then had continued support for most of the 1990s allowing them to invest in a portfolio of projects and take some into late-stage trials, where (as might be expected in a high-risk industry) many failed, resulting in a collapse of share prices and loss of investor confidence among the relatively unspecialized the UK fund management community, compounded by more than one board-level scandal. As a result, after 2000, we see reduced enthusiasm for biotech IPOs amongst institutional investors and reduced willingness to invest in VC funds, which also failed to generate good returns in biotech (Bains, 2009). Moreover, the lack of interest in biotech IPOs created lack of interest in VCs because it closed off a key exit market for their investments. The poor performance of VC funds during the 2000s was revealed as they shut down, and institutional investors' expectations were soured (EBT, 2006; NESTA, 2011). The relatively small size of VC funds, relative to the size of the typical institutional investors' investment, meant that it was rarely worthwhile for fund managers to spend the time needed to understand the asset class (i.e. the behavior of J-curves), and trust in external advisors had been substantially reduced by losses. Failure could hit fund performance, which in turn, further discouraged interest from institutional investors from funding VCs.[13] With less institutional investor support,

[13]Ironically, some successful VCs left the sector too. As VC funds perform well, they attract more funding and grow to the point where individual investments substantially exceeded the funding requirements of start ups, creating an imperative to move into later stage, less risky Private Equity investing (EBT 2006). The prime example of this is 3i, a prominent VC investor before 2010.

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biotech firms relied more on Pharmaceutical firms, which had implications for their business models and funding.

4.3 The 2000s

This section follows events in the 2000s and continues to trace the efforts to obtain financing of the cohorts founded in the 1980s and 1990s as well as those of the emerging 2000s cohort.

The UK sector began the new millennium with a number of well-established biotech firms that had either weathered clinical failures or not experienced them (Owen, 2001). Thus, there was some optimism in the early 2000s as a joint industry-government report suggests:

> "UK companies are likely to prosper through different business models: Some companies will reach profitability through block buster products. Others will succeed by focusing on smaller products for niche indications . . . others will be fully integrated companies. Some will focus on core areas of expertise in the drug development process." (BIGT, 2003).

The need for multiple rounds of funding even in "inevitable downturns" was highlighted so that "finding and rewarding investors who understand the scientific and financial risks involved in this enterprise is a critical challenge for the industry" (BIGT, 2003). This was noted as problematic because the UK had fewer specialist investors, who invested less during each funding round than their counterparts in the USA (BIGT, 2003). By the end of the decade, the mood of BIGT's next report changed considerably:

> "There is a dearth of funding for emerging biotechnology companies from private sector finance sources. This results from the failure of most biotech companies to produce the returns needed by their investors to make the long term risks involved. [. . .] investors being increasingly reluctant to invest in emerging bioscience companies, the public markets all but closing down" (BIGT, 2009: 3–4).

The cohort of SMEs founded in the 2000s experienced a deteriorated funding environment particularly from the stock markets. For example, the AIM traded–biotech firms' lost value relative to the index of all AIM companies continuously after reaching a peak in 2003 (Andersson *et al.*, 2010). As funding declined, brokerages, such as Piper Jaffray, disbanded their specialist teams covering the therapeutics sector, or gave their analysts a wider range of sectors to research (Mishkin, 2010; Smith *et al.*, 2009).

Emerging firms had to compete with more established biotech firms for funding (as noted above), and found it more difficult to maintain investor interest. This constrained liquidity, which meant investors were even more reluctant to invest for fear of being unable to exit, further reducing demand for the stock, therefore affecting the market value of the firms. Biotech firms caught in this liquidity trap and unable to raise funding are referred to as the "living dead" at biotech networking events. This stands in marked contrast with more buoyant markets where liquidity is provided by

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deeper-pocketed and more knowledgeable investors as is the case to the situation in the USA—or alternatively, some suggest, the principle applies that there is always a "greater fool" to buy stock off the incumbent investor (Lazonick and Tulum, 2011).[14]

Despite these problems, Figure 9 shows VC continued to invest, with start-ups still receiving VC support (49% or 58 of 118). However, far fewer firms have accessed stock market funding so far (15% or 18 firms, 13 of which moved directly to the stock market, while 5 first obtained VC funding). A notable consequence is that many more of the 2000s SME cohort relative to prior cohorts, followed the alternative finance route (40% or 47 firms), which we highlighted earlier in Figure 3, provides less capital and, as we discuss in the next section, these firms are less likely to produce P.II trial passes. While some of these firms may access VC or stock market funding in the future, that is unlikely to effect the overall trend as they are already >8 years old on average, substantially older than the average age of 1.2 years at which 43 of their (equivalent 2000–2004) cohort peers obtained VC funding. We highlight this as a substantial shift in financier and biotech SME behavior.

Moreover, it appears that the alternative funding route is associated with much lower levels of capital and increased risks of failure with 9 of 67 firms (13%) taking this route having ceased to trade by 2010. This is higher than the 10% (11 of 103) of all firms that accessed VC only or the 6% (5 of 77) of all firms that accessed stock market investment. Although still relatively young, 3% (3 of 118) of firms founded in the 2000s have managed to advance a project beyond P.II, from founding in 6.5 years (on average), but all three projects were reformulations of existing drugs rather than novel molecules (Table 1).The disappointing performance of VC funds and biotech in the 2000s may partly be self-fulfilling, as lack of funding has a negative impact on biotech performance and hence on VC returns (Bains 2009).[15] Although it may be tempting to blame short-termism, this does not explain why the City of London moved from biotech to mining stocks in the resource boom in the late 2000s, which are also high risk and can take years to become profitable. The difference may be the scale of the relative industries, with institutional investors unprepared to invest the time needed to understand complex and risky areas of investment that are small (and illiquid) compared with the average size of their portfolio.

[14]Not to underestimate the difficulties of being a micro-cap US biotech firm, but overall the US sector (including therapeutic and non-therapeutic biotech) has moved into profitability in recent years, even after the removal from the sector's balance sheet of a number of successful firms bought out often in highly profitable acquisitions (Huggett *et al.*, 2010). Again this illustrates the UK bust was not an inevitable feature of a tech bubble with no underpinning of therapeutic promise.

[15]Explaining why this dynamic has worked differently (generally more profitably) in the USA is beyond the scope of this article, although because the logic of this article is on economies of scale and scope we tend toward this. Other factors also come into play—such as the suggestion that Institutional investors and VC work more closely in the USA (EBT 2006) and that US biotech firms benefit from higher valuations, which in turn allows them to build more aggressive businesses (Critical-I 2006, Bains 2006).

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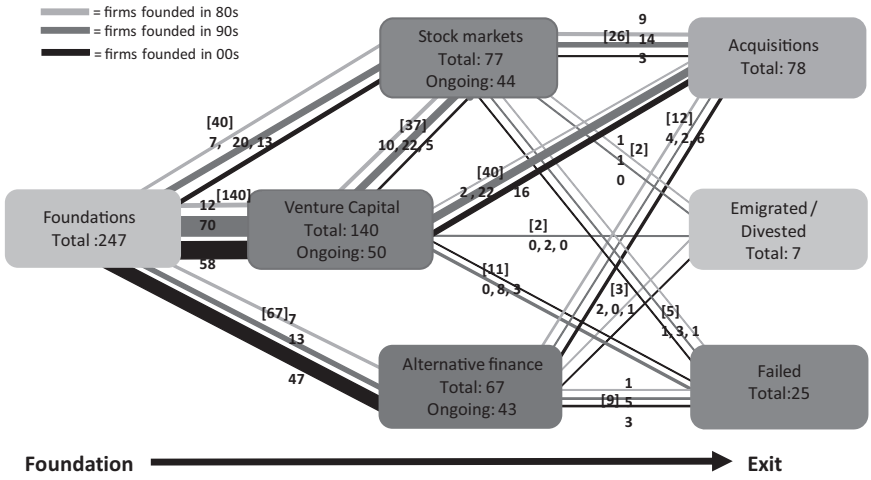

Figure 9 The funding route of the UK therapeutics firms founded in the 1980s, 1990s and 2000s.

During the late 2000s, the IPO market was much less appealing due to lower valuations, and with less frequent opportunities to exit, the importance of trade sales as an exit option increased (see Figure 8 and later "Discussion" section). However, contrasting Chandlerian imperatives are at work in this market as well. VC investors seek their returns in time windows that are short relative to the drug development process. Hence they can encourage early trade sales before biotech firms have been able to develop their assets through key clinical trials. Furthermore, during negotiations for trade sales, pharmaceutical firms can take advantage of time-sensitive VCs and cash poor biotechs by extending negotiations to drive down acquisition prices and constraining firms' other options.

4.4 CAT as a micro-level view of fundings' impact

Cambridge Antibody Technology (CAT) provides a case in point, as its experiences show how stock markets and pharmaceutical firms are pricing biotech firms at levels that make it difficult to create attractive returns. CAT was founded in 1989 to develop humanized monoclonal antibody technology from the UK's Medical Research Council's Molecular Biology Lab in Cambridge. After several years of relatively low investor funding, CAT had its IPO on the LSE in 1997 (later listing on NASDAQ), raising over £155 million (in 2010 GBP) from stock market investors, plus over £100 million in equity from commercial partners during its independent existence. This funding allowed it to become a leading therapeutic monoclonal antibody firm. It initially worked on multiple projects with a range of partner firms, effectively hedging CAT against the risks of late-stage trials. One of these collaborations yielded the world's first fully human monoclonal antibody, Humira, which was subsequently a blockbuster product for Abbott, the US-based large pharmaceutical firm.

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CAT then changed its strategy to develop its own product portfolio and in 2004 it established a substantial codevelopment programme with AstraZeneca, who took a 20% equity stake in CAT (Dickinson, 2004). Despite its successes, CAT struggled to maintain its stock market valuation, even as rival US antibody firms were acquired. As a result, when CAT's investors received a takeover offer from AstraZeneca in 2006, they accepted. Several analysts suggested AstraZeneca overpaid for the 80% of CAT (£567 million) it did not own[16] but AstraZeneca quickly sold the Humira royalty stream to Royalty Pharma for $616m (~£416 million), which when added to the ~£162 million that CAT had in cash at acquisition, meant that within a year AstraZeneca paid out £567 million and gained ~£578 million, effectively picking up CAT's capabilities and ~280 staff, clinical pipeline, and ongoing alliance deals for nothing.

According to traditional metrics, CAT's directors and advisors did not sell too low: The offer represented a 67% premium to CAT share price before the announcement, compared favorably with comparator deals, and was toward the top end of a discounted cash flow analysis undertaken by CAT's advisors. As the second highest value UK buyout over the 30-year period studied, CAT illustrates that by 2006 investors were not being rewarded with valuations of significantly more than was captured in the firm's cash and near-term tangible assets (Booth, 2009 has also observed this in second tier US biotech firms too).[17] This raises questions about the viability of long-term investment, which in turn can be expected to reduce valuations further and encourage firms' management to seek alternatives to public markets. However, as the next section highlights, in the long run, opportunitistic behavior that may be rational for individual pharmaceutical firms (exemplified here by AstraZeneca's quick turn of profit in the CAT acquisition) may be detrimental to a sector hoping to increasingly work with biotech firms to develop drugs, if biotech investing is not profitable for the wider range of supporting investors.

5. Comparing R&D performance of financing strategies over time

While biotech firms' financing patterns have changed over time, it is not clear if these changes to the frequency of funding routes used (Figure 9) have affected the ability of the sector to produce drugs. Comparing the timing of project milestones with

[16]Etain Lavelle (2006) Astrazeneca Agrees to buy partner : http://www.bloomberg.com/apps/news?pid=newsarchive&sid=akW7WEshrRKY&refer=europe and anon (2006) at http://www.zenopa.com/news/17117789/AstraZeneca__overpaid_for_Cambridge_Antibody_Technology_

[17]Another interpretation is that the remaining parts of CAT were not worth much but we reject this as in the years since AstraZeneca bought CAT, it has increased the staffing at CAT's Cambridge site from 284 (2006) to 484 (2010), and at least four MAbs originating in CAT are currently under clinical development at AstraZeneca.

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financing milestones can be used to explore whether a funding source was accessed before a firm's first development project successfully passed P.II (as in Table 1). Table 3 brings together data from Table 1 (showing firms with $\geq$1 project that has passed P.II trials) with funding route data for the remaining firms that did not have a successful P.II trial (as reported in 2011, and shown in Figure 9). This tabulation in Table 3 is necessary and helpful because a number of firms obtained VC funding sufficient to generate P.II trial passes before going on to stock markets (e.g. Celltech and Shire Pharmaceuticals).

Of all 247 UK firms, 17% (42 of 247) had at least one project that ultimately generated a successful P.II result (by mid-2011). Sufficient data from company reports was found to reconstruct the histories of 40 of 42 SMEs to ascertain the funding sources that they accessed before achieving the milestone of their first P.II pass. The 40 firms and their initial projects (detailed in Table 1)[18] can be normalized by the relative number of firms that followed each funding route to provide an approximate indicator of success. Thus, 27.5% (11 of 39) of the firms that were only funded by the stock market were successful, 39% (14 of 36) of the firms that were funded by both VC and the stock market were successful, while only 10% (10 of 103) of the VC only and 7% (5 of 67) of the alternative investment route firms produced a product that eventually passed P.II trials.

While informative, care must be taken in interpreting the results because the large number of young firms in the population (which are less likely to have had time for their drug projects to pass P.II trials) are also less likely to have obtained stock market funds and are more likely to be associated with VC investors. We therefore focus on the 127 firms that were founded in the 1980s and 1990s. This provides 37 cases with sufficient data to track development (leaving out 3 firms founded in the 2000s that had developed P.II successes and 115 that did not but that it may be deemed too early to include). Focusing only on firms founded before 2000 allows a minimum of 12 years to elapse between founding and the time of analysis (average development time across all cases in Table 1 is 7.3 years), which is enough to compare the funding routes of the 37 successful firms against their 90 unsuccessful cohort peers (data shown in Table 3) using a Pearson χ^2 test for unexpected differences between numbers of firms achieving P.II success following each funding route (i.e. deviations from a distribution of successful firms proportionate on each funding route to the number of firms taking that funding route). The results of this analysis (Figure 10) do show a distribution that is significantly different enough ($P \leq 0.002$) to reject a null hypothesis that no funding route is associated with higher than expected success in generating therapeutic projects. Thus Figure 10 shows firms

[18]The two excluded firms were Biocompatibles (supported by the stock market only) and Powderject (supported by VC and then the stock market). These are not counted as successes or failures in the charts and tables in this section or in the statistical analysis, due to this lack of data, hence Tables record 245 firms of the 247 discussed elsewhere.

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Table 3 The success of the UK Biotech SMEs in achieving P.II trial passes, by funding route and founding decade cohort

Funding sources	Project "success"	1980–1989	1990–1999	2000–2009	All years	1980–1999 only (for Figure 10)
Alternative (neither VC nor stock market)	≥1 project passed PII	2	3	0	5	5
	0 projects passed PII	5	10	47	62	15
	Alt total firms	7	13	47	67	20
VC	≥1 project passed PII	2	6	2	10	8
	0 projects passed PII	2	46	51	99	48
	VC only total firms	4	52	53	109	56
VC to stock market	≥1 project passed P.II	4	9	1	14	13
	0 projects passed P.II	3	8	4	15	11
	VC → SM total firms	7	17	5	29	24
Stock market	≥1 project passed P.II	4	7	0	11	11
	0 projects passed P.II	3	13	13	29	16
	SM total firms	7	20	13	40	27
All firms	≥1 project passed P.II	12	25	3	40	37
	0 projects passed P.II	13	77	115	205	90
	All firms total	25	102	118	245	127

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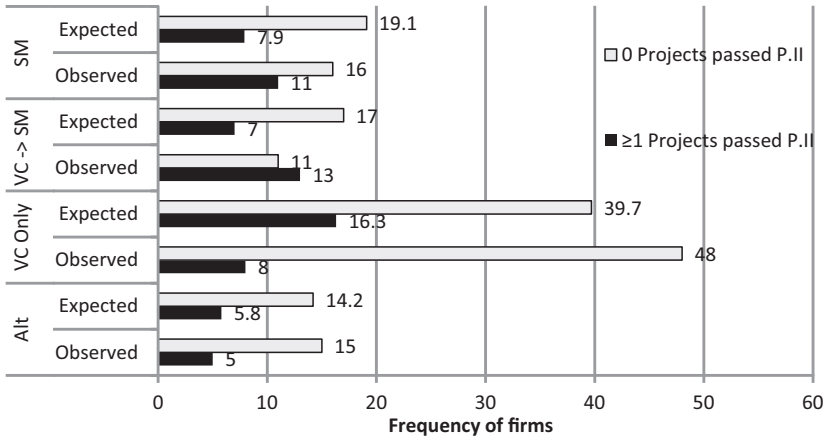

Figure 10 Comparison of observed vs. expected frequency of 127 firms founded 1980–1999 with and without successful therapeutics project, showing significance ($P = 0.002$) using Pearson χ^2 test.

supported only by VC achieved a P.II trial pass less frequently than expected (8 observed vs. 16.3 expected), while VC-backed firms subsequently joining the stock market produce more than expected (7 expected, 13 observed) as did firms with Stock Market support but no VC (7.9 expected and 11 observed).

As noted in Section 4, biotech firms have the option to use strategic deals with pharma as a substitute for investor equity.[19] It is therefore notable that of the 11 stock market-funded firms that were successful in supporting a project that passed P. II trials, only one required support from a commercial alliance partner and all remained independent entities until completion of their first P.II (Table 1). Similarly, of the 14 firms that received both VC and stock market funding, only 4 were involved in alliances to support their lead project, and all remained independent entities until after their P.II pass was achieved. However, of the 10 firms in Table 1 that produced P.II successes having only received VC funding, 3 required alliance support and a further 3 only managed to achieve a project success after they were acquired. Similarly, with the five successful firms following the alternative funding

[19]As noted in Section 3, these deals are not generally equity-investments and so are considered separately rather than as a distinct funding route option as operationalized for the analysis in the funding route maps such as Figure 9, and the tracing of firms with P.II successes shown in Table 3 and Figure 10. It should also be noted that a limiting factor of Pearson χ^2 tests where the population being tested is relatively small is that the expected number of observations in each outcome category must not be below 5 (Figure 10 shows four funding routes, with two outcomes for each). This rule would have been violated in the above analysis with the inclusion of any additional categories and was a further reason to consider separately the role of pharmaceutical funding from funding by VC, stock market, and 'alternative' equity investors.

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route, two were successful only after acquisition, one relied on support from an alliance, while another, Ineos, is the UK's largest private equity backed firm, leaving only one (Devco) that managed to reach a P.II success alone without an acquirer or alliance partner (we return to Devco's success later on).

Analysis of the funding routes taken by "successful" firms in Table 1 shows that those benefiting from access to stock market investments were more likely to succeed, and more likely to do so independently of help from larger strategic partners (whether large pharma or biotechs). Firms without stock market funding have either not been successful or have generally relied more on strategic alliances to access funding. While correlation is not causation, and there are clear challenges in ascribing causality here (which we return to in Section 6), the link between our metric of success and earlier injections of cash from stock market funding suggests this form of funding is associated with significantly higher likelihood of success in getting at least one project passed P.II trials. The next section explores how reduced entry to the stock market has changed the prospects for biotech firms.

5.1 Strategic responses to the changing funding environment

Changes in the values that different types of investor were prepared to put on biotech firms has led to a marked change in strategies in the sector. This is illustrated in Figure 11, which shows the valuations that different 5-year cohorts of firms achieved from IPOs and trade sales for all the transactions where data are publically available. Because older firms have had more time to generate value, the IPO and trade sale valuations are divided by the age of the firm to facilitate comparisons in Figure 11, which suggests firms founded before 2000 enjoyed higher stock market valuations relative to trade sale prices, while the reverse has been the case since 2000.

These higher trade sale values explain why biotech firms have shifted away from stock market exits in recent years, as shown by fewer IPOs in Figure 7 and fewer firms moving to the stock markets in Figure 9 (see also, Ernst and Young, 2010:5; Booth, 2009). The number of trade sales are up sharply in firms founded after 1995, and a sizable proportion (27% or 16 of 60) of the VC-backed firms in the 2000s cohort have achieved a trade sale to date. Although <32% (22 of 68) of VC-backed firms founded in the 1990s, there is still time for this to rise. Both 1990s and 2000s cohorts are more likely to be sold than the 17% (2 of 12) of VC-backed firms from the 1980s cohort.

Figure 12 shows the compression of the funding cycle with more firms being sold below 10 years after the 1980s, and recently more firms being bought at <5 years of age. This may reflect the increasing difficulty of obtaining the funding required to remain independent and/or VC investors' increased focus on "asset centric" business models that use less capital and more outsourcing to bring a single project to key milestones as fast as possible (Ernst and Young, 2010; Booth, 2009).

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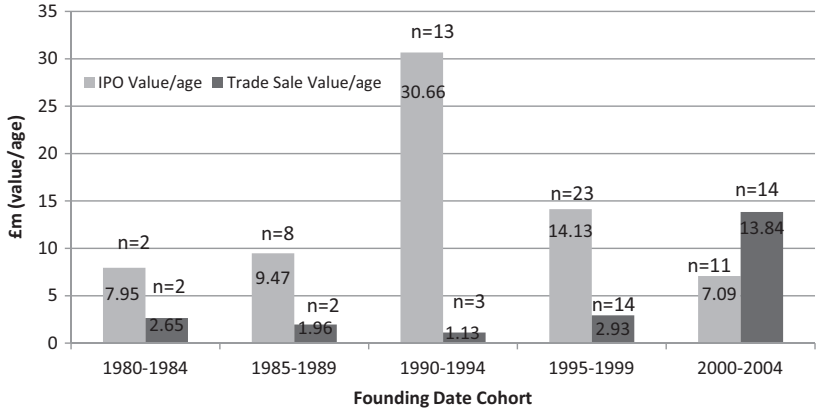

Figure 11 Age-adjusted value at sale from stock market or trade sale of the UK therapeutics firms.

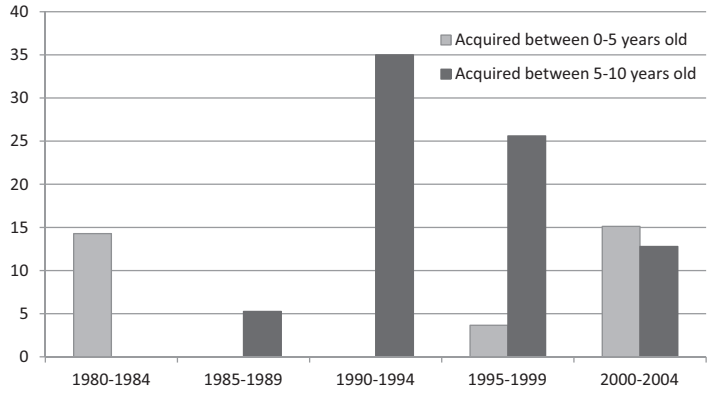

Figure 12 Percentage of 5-year founding cohorts bought before 10 years of age.

When the differences between the mean ages of firms (at acquisition) taking different funding routes are examined, a significant difference was found between firms taking stock market routes (both with and without prior VC) and VC-only firms (see results of the ANOVA test in Figure 13).[20] This result indicates that firms with stock market backing exist independently significantly longer than firms that have VC support and no stock market funding, and therefore, with the UK stock

[20]Of 40 firms VC-backed firms sold, the average age at acquisition was 7.2 years; for the 26 stock market backed firms it was 12.5 years, it was 11.5 years for the 15 VC *and* stock market backed firms; 12.5 years for the 11 firms that moved directly to the stock market; and 6.6 years for the 12 firms following the alternative financing route.

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	VC (7.2)	SM (12.5)	VC->SM (11.5)	Alt (6.6)
VC (7.2)		-0.54*	-0.50*	0.05
SM (12.5)	0.54*		0.04	0.59
VC->SM (11.5)	0.50*	-0.04		0.55
Alt (6.6)	-0.05	-0.59	-0.55	

Figure 13 Matrix showing the difference in mean of the age (real values in years are shown in brackets) at acquisition of firms, categorized by funding route. Results from an ANOVA (on logAge), with a Bonferroni post hoc test (statistically significant differences indicated by asterisk, $p = <0.05$).

market investment declining, firms sold by VCs or alternative investors had nearly 5 years less time to reach project milestones and valuation inflection points before the firm lost its independence to an acquirer. Moreover, the frequency of early-stage acquisitions is increasing (Figure 12).

Diminishing years of independence for biotech firms is an important change because different business models vary in the amounts of time they take to get products passed P.II trials. For example, Devco in-licensed a drug that had already been advanced by British Biotech for another indication, and completed early-stage trials just 1.5 years after founding, while Allergy Therapeutics was spun out of Smithkline Beecham, an established pharmaceutical firm, and rapidly took its spin-out vaccine projects into late-stage trials. At the other extreme, Prolifix's novel anti-cancer molecule entered P.III trials 16.5 years after Prolifix was founded, and >8 years after its acquisition by biotech firm Topotarget. The 37 firms for which we have data took an average of 7.3 years from founding to get their first product passed P.II, which given that the average firm sold by VC is only 7.2 years old, suggests VC investors have often not been able to wait for valuation inflection points unless they (like pharma) move their focus to later-stage development. This problem may become more acute given increasing drug development times (Pammolli *et al.*, 2011).

6. Discussion

The findings in the previous sections highlight how the structure of financial institutions and their contexts creates Chandlerian imperatives—such as rapid returns for

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VC, and for large, liquid, predicable investments for institutional investors. These have implications that cut across sectors. Cross-sector Chandlerian imperatives mean these various financial institutions interact in systemic ways, between each other and the biotech sector they fund. These interactions must generate a coherent funding system to support successful drug R&D while maintaining the scale and flow of investments and returns needed to keep its individual parts operating at minimum efficient scales. Coherence does not necessarily mean the system should be structured in a single way; for example, it is possible to spread project-associated risks by having large firms (e.g. large pharma) with many drug projects owned by many investors or conversely many firms with few drug projects (e.g. biotech) owned by few investors, as long as the scale of the combined sectors is sufficiently large for investors and biotech managers to devote resources to developing the expensive skills to manage the risks involved.

Looking over the period 1980–2009, our analysis shows how scale was pursued in the relatively new biotech sector by both VC and institutional investors, with the result that there were high investment rates in emerging biotech firms. With both these groups investing, the UK biotech firms accessed large amounts of money over a long period allowing 12 of 25 of the 1980s cohort to achieve at least one P.II trial milestone. Firms enjoying the longest support from investors were those listed on stock markets and these were disproportionately represented in the group of firms with successful drug projects (25 of 40 cases). Some of these (11 of 40 cases) even achieved success without VC funding. This is not to suggest that stock markets are intrinsically better at supporting biotech therapeutic success. Indeed the publicly listed biotech model has been criticized as broken even in the USA (Pisano, 2006). Instead, we stress the highly effective combination of relatively large-scale investment over long periods, which seems to be key for progress in clinical trials, even if the fruits are realized after the sponsoring firm's acquisition. Recent thinking in the investment community suggests that as hurdles to innovation grow, even larger and longer term investment funds than are seen at present in the USA may be needed to support drug R&D in the future (Fernandez *et al.*, 2012).

Our analysis suggests the scale of investment in the UK was, however, relatively low both compared with the size of the investment portfolios of institutional investors in the UK and also the scale of pharmaceutical R&D. To illustrate this, the entire population of publicly traded UK firms raised around £5.7 billion up to 2010 (counting all placings over £1 million at 2010 GBP and including shares bought by corporate partners). This is less than the £5.9 billion Glaxo SmithKline, the UK's largest pharma company, made in operational profit in 2009 alone. Moreover, Glaxo SmithKline is one of two UK large pharma (AstraZeneca, discussed above, being the other), each of which has an institutional share holding that would dwarf the UK SME biotech sector. Such relatively low levels of investment in early-stage technology-based firms have been discussed previously in the UK (BVCA-NESTA, 2009; ETB, 2006; BIGT, 2009) and run the risk of creating a self-fulfilling situation where

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investors will not invest because growth is poor and growth is poor because investors will not invest (see also, Bains, 2006; Smith *et al.*, 2009).

The analysis presented points to an explanation of the relative performance of the UK and US biotech sectors in terms of institutional structures, timing, and scale. Early US investors supported a small number of firms that were able to generate returns at the outset of the industry and that stimulated a virtuous cycle of investment driven by specialist investors who could understand and hedge against the failures of a high-risk sector. The biotech SME-friendly funding system that emerged has become robust enough to keep investing as the sector transformed over time, even returning to support biotech IPOs in the wake of the "dot.com" and "sub-prime" financial crashes (Huggett *et al.*, 2010).

The UK also hosted various financial innovations to support biotech investment, such as specialist VC funds, sector-specific analysts, junior stock markets, and changes to rules creating exemptions for loss making firms to access capital markets. However, despite these institutions that apparently mirrored the US investment system, as well as initial expectations and investment levels being high, the UK funding escalator was sensitive to a series of failures in the 1990s. The scale of the sector was (and remains) too small to make it worth institutional investors spending the time needed to understand it, and the UK VC sector (also young compared with its US cousin) is relatively small by both size of the industry and size of individual funds (BVCA/NESTA, 2009). After an initial period of investment did not provide institutional investors with the returns they were seeking, they reduced their investment and the system lost momentum (BIGT, 2009; Smith *et al.*, 2009). With less time and money available, biotech firm managers have made strategic choices about which projects to pursue, (e.g. increasing attention on reformulations rather than novel drugs), and focused on early trade sales rather than developing the P.II assets sought by large firms.[21] With investors increasingly unwilling to take on the risks of producing P.II assets, pharmaceutical will not be able to rely so much on the UK SMEs to develop late-stage assets, at precisely the time that they are trying to outsource early-stage development to biotech firms.

6.1 Alternative view points and further research

There are of course a number of explanations that are consistent with any data, and hence other explanations for why the stock market-backed firms from the 1980s and 1990s were more successful than their unlisted, privately held peers. Firstly, their early success in obtaining funding may have stimulated a "bandwagon" of less

[21]For example, the projects advanced into late-stage trials by the 1980s cohort of firms included six biologics, four small molecule drugs, and three reformulations/drug delivery systems. For the 1990s cohort, this has changed to 7 biologics, 8 small molecule drugs, 10 reformulations/ drug delivery systems, and 1 tissue-based project, while for the 2000s cohort all three successes at time of analysis (in 2011) are reformulations.

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capable entrepreneurs, who diluted the performance of the sector over time. Given that investors were not selective (a high proportion of firms entering the sector obtained VC and/or stock market funds) this seems credible. However, countervailing learning and networking effects (by investors and "recycled" entrepreneurs) might also be expected to lead to superior performance.

An alternative, or even potentially complementary, explanation is that the early firms captured "low-hanging fruit," or since the 1980s existing (off-patent) drugs made R&D less profitable as it made it harder to find high-value markets (see Scannell, 2012 for a critique of these ideas). However, we note that here too countervailing forces need to be accounted for as new markets have emerged because of institutional changes, such as Orphan drug legislation, and economic and demographic changes, as well as scientific advances that open new therapeutic avenues.

We have not controlled for the disease or technical focus of unsuccessful firms but note that a shift to higher risk drug projects in the global industry as a whole (reported by Pammolli *et al.*, 2011) seems to have been underway during the period studied, and that this risk has not put off continued large-scale investments by a range of investors in the US sector (Huggett *et al.*, 2011).

One explanation that might explain why stock market–backed firms succeed more often than other firms is that generalist stock market investors are better at picking investment opportunities than specialist VCs. This is controversial, as VCs are meant to play an essential role as "talent scouts, advisors, consultants, and financiers" (Powell, 1998; BVCA-NESTA; 2009), but this warrants further investigation, given the performance of European VCs (Bains, 2009) and the lack of selectivity in VC investments we highlight above (recall that 140 of 247 firms had some level of VC backing). Lastly, it may just be that while the UK firms perform well technically (given the remarkably high proportion that developed P.II drugs), they are just not as good as US firms from a commercial perspective, and have been unable to generate a decent return for their investors. However, this tautological suggestion restates the problem without providing an explanation of why this might be the case. While we advance the argument here that larger scale and longer duration of investment benefits the performance of both biotech firms and sectors overall, we also note that the alternative explanations above leave important avenues open for future research.

7. Conclusion

We set out to explore how the UK biotech firms have been financed, whether finance affects their performance, and how changes in R&D and finance influence the structure of the UK sector. During the period covered, the importance of different investors and the scale of funding they provided has varied significantly, with firms founded in the 1980s receiving more opportunity to raise high levels of stock market funding and more likely to achieve a successful P.II trial result. In later periods,

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access to stock market funding declined. As a result, biotech firms significantly compressed their life cycles and changed their business models to support, rather than attempt to displace, large pharmaceutical firms and reduce the need to access stock market funding. However, firms funded solely by VC have had less likelihood of contributing to projects that pass P.II trials.

We argue that the experience of the UK provides a concrete example of how financialization affects firm behavior, strategies, and chances of success in a context of multiple investor groups. We show how investor organizations' structures and contexts can, in some instances, generate Chandlerian imperatives that influence how they interact with firms in other sectors and help explain why short-term investments might be favored, for example, by VC funds that need to make returns rapidly given the high time cost of capital involved, and limited life time of individual funds. Hence it can be rational for them to exit investments earlier than other equity investors might like. We have seen how initial optimism and the need for scale tempted investors joining a small emerging sector, to forgo selective investment strategies, instead backing a high proportion of overall new entrants. Only once it was realized that biotech was not producing the returns they expected did interest decline, leaving investee firms to adapt their business models to the new funding environment.

These biotech SMEs became more dependent on their alliance partners or acquirers (often pharmaceutical firms) to take therapeutic assets to P.II trials. While large pharmaceutical firms at an industrial level may be keen to access R&D projects from biotech firms to address their productivity problems, individually they have little short-term incentive to see biotech firms profit from such deals. Without access to deep-pocketed investors as a counterbalance, it seems that while the "locus of innovation" may now be networks of new and established firms, rather than the older integrated firms alone (Powell *et al.*, 1996), when SMEs license projects to these partners "the locus of power" still resides with big pharma, with implications for biotech's profitability (Baum *et al.*, 2010: p.14).

In this way, we see how the Chandlerian imperatives of distinct groups of firms can conflict if they are not well balanced. Lack of stock market capital has reduced the time and financial resources available to UK biotech firms seeking to bring projects to late-stage development. Reduced support has made the sector less viable and in turn, it has become of less relevance for many investors. It would be simplistic to suggest stock market investment is the only way to support successful biotech firms—and they can be mercurial and unreliable sources of capital (Lerner, 2012). However, we suggest that funding routes that provide larger amounts of time and money than VC and "alternative" route investors in the UK typically offer are clearly required for successful drug discovery. Some have suggested that innovative funding strategies will create more capital-efficient firms, but for all the possibilities for survival in a "brave new world" of post-IPO biotech, new business models and "open innovation" (Booth, 2009; Ernst and Young, 2011, Hughes, 2009; Lessl and

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Khusru, 2010), in view of the UK's historic performance at least, the lack of investor support suggests more firms will be sold early, without advanced clinical assets.

The UK's experience may provide important lessons for other regions, as the UK had the largest SME-based therapeutics pipeline in Europe, a large and sophisticated financial sector and a strong domestic science base to support new firms (BIS, 2010; BIGT, 2009). While many countries are attempting to build biotech sectors, the UK experience raises questions about the viability of many smaller SME-based drug discovery and financing ecosystems where there are too few potential transactions for specialist investors to ensure selection of only high-quality opportunities and insufficient scale to warrant development of complementary domestic financial innovations such as specialist funds and stock market rules. Under these conditions, Big pharma may find that in the long run sourcing drugs externally from biotech firms does not boost their R&D productivity because VC and institutional investment is insufficient outside the USA. If this is the case more generally, then the emerging question for investors, big pharma and SME managers, policymakers, and scholars of technological change alike is now "who will pay for early-stage therapeutic R&D?"

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