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Combining Resource Based and Evolutionary Theory: A Synthesis applied to Bio-Enterprise Networks

Elizabeth Garnsey, Yuen Yoong Leong

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A SYNTHESIS WITH EXEMPLARS
FROM BIO-ENTERPRISE NETWORKS

Elizabeth Garnsey* and Yuen Yoong Leong

Centres for Technology Management and International Manufacturing
Institute for Manufacturing
University of Cambridge
Mill Lane
Cambridge CB2 1RX
United Kingdom
Tel: 44 (0)1223 338183; 44 (0)1223 765601
Fax: 44(0)1223 766400
ewg@eng.cam.ac.uk; YYL@cantab.net

Elizabeth Garnsey is a Reader in Innovation Studies in the Department of Engineering and Judge Institute of Management Studies, University of Cambridge

Yuen Yoong Leong was a post-doctoral researcher at Cambridge University and is currently a development manager of Golden Hope Plantations Berhad's herbal business

*Corresponding author: ewg11@cam.ac.uk

Abstract

This paper explores ways in which new ventures not only adapt to but can transform their own business environment. It proposes a new way to combine evolutionary and Penrosian resource-based theories. A parallel is drawn between the proactive response to resource shortfalls and under-use in the Penrosian firm and the way entrepreneurial participants in innovative networks can build complementary capability. Two case studies of biopharm ventures show how participants cumulatively altered prevailing business conditions and selection processes. The approach shows how evolutionary theory can be used to identify overlooked connections and clarify overlooked causal processes that have collective effects. How entrepreneurial activity lays the basis for further innovation is revealed by an analysis with the wider potential to bridge evolutionary and resource based approaches.

Keywords: Biopharmaceutical networks; the entrepreneurial firm; resource-based theory; evolutionary theory.

Introduction

This paper explores ways in which new firms can alter their environment in the course of their early development. It is well attested that established companies alter their conditions of business by exerting market power (Porter 1985) or by forms of lobbying (Garud et al. 2002). Whether new firms can alter their developmental conditions is seldom addressed in the economics of the firm, including work taking an innovation perspective (Morroni 2006; Simonetti et al. 1998). Resource-constrained new ventures are *prima facie* the least likely of firms to command influence over their environment. Even among authors who otherwise depart from neoclassical assumptions, it is assumed that new entrants have to adapt to external conditions. While this is true of macro-conditions, such as rates of exchange and entrenched institutions, there are indications from network and institutional entrepreneurship studies bearing indirectly on this issue that significant features of firms' environment are amenable to change (Powell 1996; Garud et al. 2002). To make this the main object of inquiry requires an analysis of new firm development together with analysis of the shifting conditions in which new firms operate. For this purpose we apply resource-based theory of the firm and economic evolutionary theory. This choice of conceptualization embodies our parallel aim, to contribute to current efforts to unite these theoretical approaches.

There is increasing recognition of the complementarities between economic evolutionary theory and resource-based theorizing about the firm (Montgomery 1995, p. 251; Ulrich 2000). Theories of dynamic capabilities,

in particular, make use of ideas from both perspectives (Teece et al. 1997; Eisenhardt and Martin 2000; Zolla and Winter 2002; Helfat and Peteraf 2003). Our development of "resource-based evolutionary theory" differs from such earlier work in respects that include the following. We bring the combined theories to bear on the same body of case evidence. This confrontation of theory with evidence is used to cut the Gordian knot that entangles abstract versions of Darwinian theory (Buensdorf 2006). It provides a version of evolutionary theory that addresses current business issues in a pragmatic manner, as recommended by Nelson (Nelson 2006). We examine capability building in new ventures rather than by incumbent firms to see how capability-building within a network of firms enables entrepreneurial managers to alter their business environment. We identify resource mismatches that provide an impetus to entrepreneurial capability building. We show that open systems ideas provide a meta-theoretical perspective that can encompass both evolutionary and resource based theory.

The paper starts with an overview of evolutionary theorizing in economics and of resource-based theories of the firm, identifying complementarities between the two, and goes on to apply concepts from systems thinking to bridge these approaches. This review of prior work and our own position is summarized in the form of propositions that challenge previously held assumptions on the inability of new entrants to change their environment. The propositions specify how new firms can build resource complementarities in ways that impact on business conditions. A more detailed and empirically grounded exposition of the propositions is provided

in case studies of two biopharm start-ups that built network-based capabilities to implement innovations. We conclude with an overview of the wider applications of our conceptualization and findings for theory and practice.

Biopharmaceutical innovation provides the setting for the inquiry, this being a particularly demanding environment for a new firm. Innovation in biopharm relies on inter-firm partnerships of various kinds; the high incidence of such alliances among major pharmaceutical companies is shown in Figure 1.

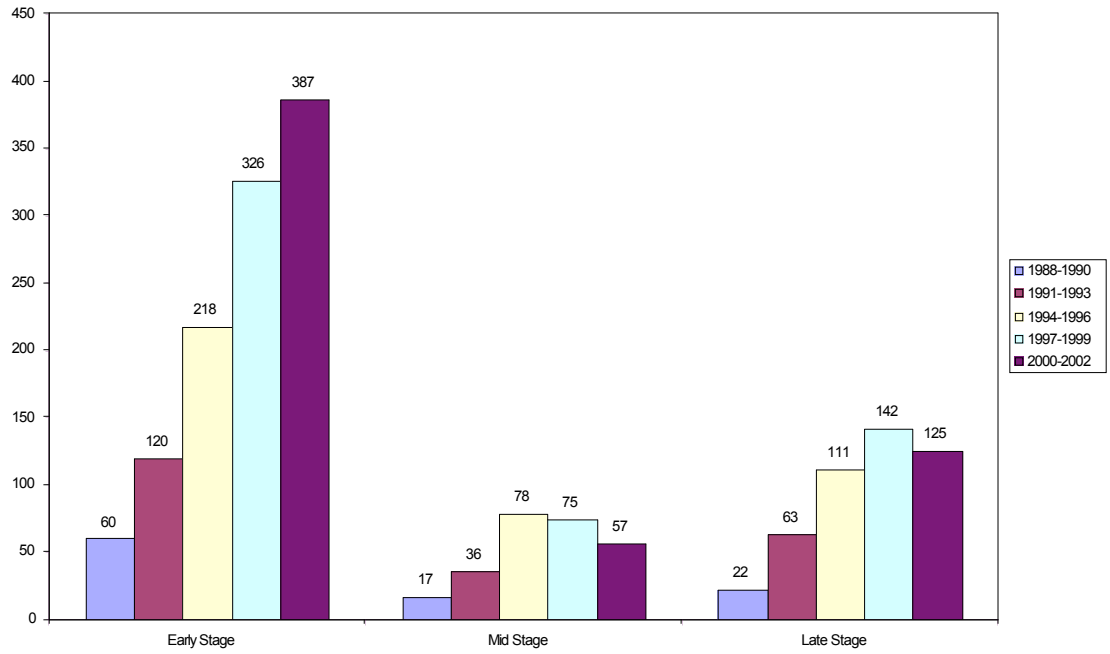
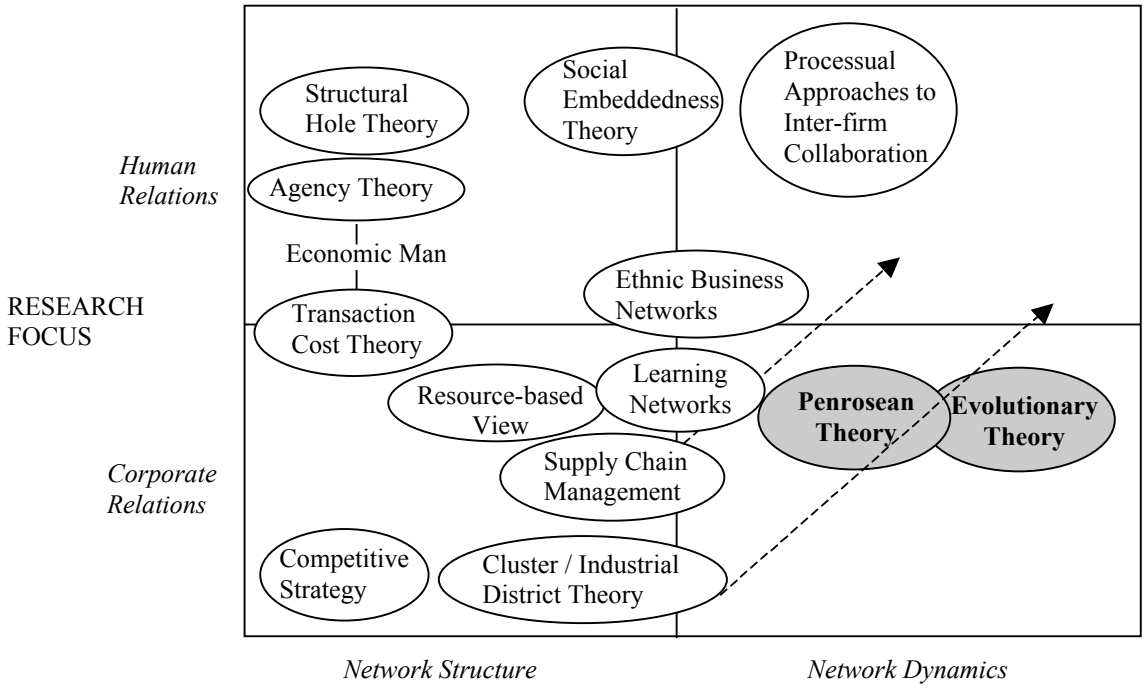


Figure 1: Biotechnology Alliances of Top 20 Pharmas 1998-2003
(Recombinant Capital 2003)

There are many competing and complementary accounts of the functions, roles and dynamics of biotech networks in the literature on networks that use diverse definitions of networks. Relevant theories include those located in the

overview in Figure 2. Our approach populates the lower right quadrant in the literature on business networks, being concerned with the creation of networks for the development of new drugs, drug delivery innovation and new supply chains.



Research Area	**References**
Agency Theory	Eisenhardt (1989)
Cluster / industrial district theory	Piore and Sabel (1984), Porter (1998) Perry (1999)
Competitive strategy	Miles and Snow (1986)
Ethnic business networks	Light (1972), Phizacklea (1990), Perry (1999)
Learning networks	Powell and Brantley (1992), Powell et al. (1996), Powell (1996)
Process approach to inter-firm collaboration	Larson (1992), Ring and Van de Ven (1994), Doz (1996)
Social embeddedness theory	Granovetter (1973; 1985), Rond (2003)
Structural hole theory	Burt (1992)
Supply chain management	Fisher (1997), Lamming (2000), Lee (2002), Liker and Choi (2004)

Figure 2: Mapping Theories and Research Related to Networks

Rationale for the study and alternative perspectives on issues raised

The wider rationale for the inquiry concerns the way in which entrepreneurial activity lays the basis for further innovation. The ability of a new firm to secure and sustain competitive advantage is a central concern in the study of strategy, innovation and entrepreneurship. How entrepreneurial innovation creates positive externalities that open up further possibilities for innovation can be informed by literature on strategic positioning (Porter 1991), on industry evolution (Klepper 1996), on institutional entrepreneurship (Garud et al. 2002) and social networks (Powell et al. 1996). Other relevant perspectives include population ecology (Hannan and Carroll 1992) and resource dependency theory (Pfeffer and Leong 1977). While these authors include material very pertinent to the relationship between firm and environment, to address our research questions and evidence we need a less eclectic conceptual framework than these diverse contributions provide. Our argument is that pragmatic evolutionary theory combined with Penrosian resource-based theory offer a conceptually coherent and comprehensive basis for explaining the relationship between the new firm, its networks and its business environment.

Complementarities between evolutionary theory and resource-based theories of the firm

Both Penrosian resource-based theory and evolutionary theories adopt a dynamic approach to reveal mechanisms and processes of change that are obscured by equilibrium frameworks (Penrose 1995; Winter 1964; Nelson

1982). Both constitute what Nelson calls 'appreciative theory' providing a basis for asking questions that cannot be addressed by less dynamic theories (Nelson 1998, p.319). Both aim to explain the heterogeneity of firms. Many complementarities have been identified between these approaches (Montgomery 1995, p. 251; Foss 1997, Witt 2000). Studies of dynamic capability, in particular, are increasingly drawing on both resource-based and evolutionary ideas (Helfat and Peteraf 2003).

Nevertheless there are apparent disparities between the Penrosian resource-based theory used here and evolutionary economics. In common usage, evolutionary means gradual, unfolding or developmental. This is the sense in which Penrose's thought on the firm was evolutionary. 'Evolutionary' also has a more precise reference to a type of change often associated with natural selection in biology (Van de Ven and Poole 1995; Nelson 2006). Penrose rejected biological analogies because she saw them as depicting "action taking place in human affairs without the intervention of human decisions based on deliberation and choice" (Penrose 1952, p. 816). She was opposed to the deterministic assumptions she believed to be embedded in biological analogies.

But understanding of evolutionary theory has moved on considerably since the early attempts at applying biological models criticised by Penrose. Indeed evolutionary reasoning could be described in the terms Penrose applied to homeostasis: "Strictly speaking, the basic principle is not a

biological one .. [but] a general principle…(Penrose 1952 p. 816)." Evolutionary theory is increasingly recognised to be a general theory of change wherever variety, systematically generated, is culled by selection processes (Nelson 2006). Processes of variety creation, selection and propagation occur not only in biology but also in the evolution of language, science and technology, among other spheres (Metcalfe 1998; Van de Ven and Poole 1995). Experimental new ventures generate economic variety. Selection in economic life is a process of elimination that culls variety among populations of units such as firms, technologies and firm routines.[1]

Propagation of selected units operates not only through biological inheritance but through diffusion processes that differ according to the specifics of different contexts: language for example is replicated and diffused by mechanisms of intergenerational learning and migration. Change of this kind in the socio-economic world involves learning on the part of agents and changes in the opportunity space in which they operate.[2] If we can show that a new venture can deliberately alter its environment and the very selection forces that operate upon it, this demonstrates the importance of the entrepreneurial decision making and motivation which Penrose justifiably viewed as a central object of inquiry.

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[1] The units of selection and propagation on which inquiry is focused depends on the level and scope of the analysis (McKelvey 1996). We show that economic networks may be a selected unit; favourable forces of selection are found in conditions where resources are made available to that network.

[2] *ICC* reviewer's observation.

Dynamic processes set off by uneven resource availability

It is still unusual to draw on the work of Penrose in exploring entrepreneurial networks since she wrote about growth in the mature and integrated industrial firm (Lockett 2005). However her ideas on knowledge building as a cumulative process driving the growth of a firm can usefully be applied to new firms (Garnsey 1998). We show here that a Penrosian approach need not be confined to the firm (nor to firms that build a production base in-house). We show that her approach to the dynamics of growth is relevant to networks of firms that engage in co-production with partners rather than developing internal production facilities. Here too, the experience and outlook of entrepreneurs shape the way opportunities are detected and activated (Penrose 1995, p. 3).

We found striking parallels in our case evidence between the proactive response to resource shortfalls and under-use in the Penrosian firm and the activities of entrepreneurial participants in innovative networks. Penrose saw that even the well-resourced mature firm is continually faced with both resource deficits and resources that cannot be put to full use. Resources are available not in convenient increments but in 'uneven multiples'. Since equipment and personnel, for instance, are never available in precisely the combination required at a given time, some overloading or under-use of resources is inevitable: "… in putting together the jig-saw puzzle of resources required in an expansion programme, the firm may find that a number of

awkward corners persist in sticking out" (Penrose 1995, p. 69). While resource constraints are obvious, the under-use of certain resources may not be recognised until managers discover new uses for unexploited resources. Penrose saw that under-used resources could actually stimulate growth if they are dealt with by obtaining or creating complementary resources, so enlarging the company's knowledge base - from which new opportunities can be pursued (Penrose 1995, p. 54).[3]

Teamwork and shared experience "not only causes the productive opportunity of a firm to change … but also contributes to the 'uniqueness' of the opportunity of each individual firm" (Penrose 1995, pp. 52-3). A generation before the pursuit of opportunity was identified as the defining feature of enterprise (Shane 2000), Penrose described the environment as "an image in the eye of the entrepreneur." That is, she held that perceptions shape the way firms respond to their environment and the business conjectures they formulate, though ultimately the success of their conjectures depend on economic realities. Penrose wrote of established firms that they not only influence their environment but know that they can do so (Penrose 1995, pp. 41-2). While acknowledging that established firms can alter their environment, Penrose put the influence of the environment 'on one side in the first instance in order to permit concentration on the firm's internal resources' in her *Theory of the Growth of the Firm* (preface p. xiii 1995).[4]

[3] "Unused productive services … facilitate the introduction of new combinations of resources … [for] the production of new products, new processes for production of old products, new organization of administrative functions." (Penrose 1995, p 85).

But as shown in the case study on which her book was based, in practice she saw firm growth as governed by "a creative and dynamic interaction between a firm's productive resources and its market opportunities" (Penrose 1960).[5] More recent work on dynamic capabilities has developed this idea more fully. In this paper we explore this interaction in early-stage companies to see how it affects the new firms' business environment.

Alternative versions of the resource-based view of the firm

Teece and others have shown how firms can adapt, reconfigure and integrate resources and skills to exploit new market opportunities (Teece et al. 1997). They built on work investigating how competitive advantage is generated by the firm's unique bundle of resources (Lockett 2005; Barney 1991; Conner and Prahalad 1996). [6] Barney had focused on the attributes (valuable, rare, inimitable, organisational support) of discrete resources that generate rents. These resources are said to be what give rise to firm attributes that are difficult to imitate and thereby enhance the firm's potential for sustained competitive advantage (Barney 1991).

In contrast, Penrose had viewed resources not as a given set of attributes but as combined and used in ways that change over time, leading to changes in "the productive possibilities that the firms' 'entrepreneurs' see and can take

[4] *ICC* reviewer's contribution

[5] Studies of technology speciation have come to focus on the way in which innovations from established firms arise from technologies that prove unexpectedly to have applications in new market domains (Levinthal 1998). The extent to which Penrose anticipated this theme in her 1960 Hercules Powder case study is not recognized in the technology speciation literature.

[6] For an overview of the controversy between Penrosian and competitive attribute resource-based approaches, see Lockett (2005) and Thompson and Wright (2005).

advantage of" (Penrose 1995, p. 31). Penrose pointed out that a firm's unique 'productive services' and 'basic strengths' (her term for capabilities) may outlive specific products (Penrose 1995, p.150). The life cycle model of capability building develops these ideas further (Helfat and Peteraf 2003). Helfat and Peteraf view the development of dynamic capability (defined as a firm's ability to use resources to perform a coordinated set of tasks to achieve its ends) as the outcome of learning-by-doing in a team context, of deliberate process improvement, problem solving and investment (Helfat and Peteraf 2003). They see dynamic capability development as a less linear, more fitful process than do Zolla and Winter, who defined dynamic capabilities in terms of systematic patterns of organizational activity aimed at the generation and adaptation of operating routines (Zolla and Winter 2002). This literature indicates that if entrepreneurial firms in biopharm networks seek to develop dynamic capabilities to coordinate the operational capabilities of their members, repeated efforts will be required before these attempts succeed in achieving their objectives reliably; capabilities are not built in a day.

Penrose emphasised that history matters in the firm; in this respect, modern theorists are justified in seeing the building of new resources as restrained by the firm's inability to move in directions incompatible with its prior experience. Just how firm specific are the capabilities that confer competitive advantage is a question on which our case evidence has bearing. [7]

[7] Recent resource-based theory has emphasised that when strategies stem from firm-specific resources, they are not easily replicated by competing firms. Dierickx and Cool (1989), for example, emphasised that competitive advantage is most likely to result from the development of unique asset stocks built up through resource accumulation.

Economic evolutionary theories have contributed relatively little to the field of entrepreneurship studies; their perspectives are absent for example in Shane 2003. [8] It has been recognised that variety generation (by new entrants) has received little attention in evolutionary economics, the focus having been on selection processes (Metcalfe 1998).[9] But resource-based concepts are also largely absent in entrepreneurship studies, with a few exceptions (Brush et al. 2001). Conceding that the modern strand of resource-based theory could be combined with other approaches, Alvarez and Barney have written that "… resource-based models of strategic advantage may need to be augmented by theories of creative and entrepreneurial process…these observations suggest a very close relationship between theories of strategic advantage and theories of creativity and entrepreneurship" (Alvarez and Barney 2001, p. 53). Penrose's original conception has much to offer here.

Evolutionary Approaches and the Firm's Industrial Environment

Evolutionary theory has rich and varied traditions outside biology (Durand 2006). Here we focus on one strand of this approach, the economic theory of variety generation and selection processes (McKelvey 1996). While Penrose was interested in how entrepreneurial firms develop their resource base and identify new market opportunities, evolutionary economists have highlighted selection mechanisms that influence the evolution of technologies and industries (Nelson 1982; Nelson 2006; McKelvey 1996). They view this as

[8] Two consecutive volumes of *Research Policy,* one on evolutionary theory (Vol. 31 nos. 8-9 Dec 2002), one on technology entrepreneurship (Vol. 32 no. 2 Feb 2003), illustrate the divide between evolutionary theory in economics and entrepreneurship studies. There is no cross-referencing of themes and authors between the two issues of the same journal, symptomatic of the wider literature.

[9] Aldrich (1999) has given useful attention to variety generation by new ventures in an evolutionary sociology approach. However Schumpeter does not appear in the index to his book; linkages between entrepreneurial innovation and the economy are not on his agenda.

the outcome of the operation of selection forces on the destinies of specific innovating firms, the incubators and carriers of innovations. In evolutionary theory, multi-level analysis can occur as the unit of selection examined shifts, e.g. from routines selected by the firm to the selection of firms by market forces and institutional arrangements. Early attempts to apply evolutionary theory to firms in the economy focused at the industry level and on the internal selection processes through which firms adopt unique routines, informed by the theory of natural selection (Nelson and Winter 1982). Nelson and Winter departed from the tradition of the representative firm of orthodox economics, proposing a focus on the way an internal selection environment within the firm can select for skills, organisational capabilities and behaviour which shape unique routines for conducting businesses and create differences between firms.

Selection forces do not function on blind basis in economic life but instead evoke learning, anticipation and deliberate responses. The transmission of learned responses is Lamarkian rather than Darwinian, but it was Darwin who provided insight into the feedback processes through which selection forces operate. Market forces that affect firm viability can be seen as a form of selection. Their operation is analysed in the industrial structure approach to strategy (Porter 1991).[10] But many sectors are too immature or volatile to

[10] Porter has criticised the resource-based theory as based on circular reasoning: *"Successful firms are successful because they have unique resources. They should nurture these resources to be successful ..."* He maintained that the resource-based theory does not recognise that *"resources are not valuable in and of themselves, but because they ... create advantages in particular markets"* (Porter 1991 pp. 108-109). This criticism does not apply to the original work of Penrose; the latter part of her *Theory of the Growth of the Firm* has much insight into the relationship between resources and market conditions, explored in detail in her 1960 case study.

have a stable industrial structure. In biopharmaceuticals for example, conditions have altered rapidly as new technologies have emerged and 'low hanging fruit'[11] have been harvested. New entrants, mergers and unstable capital markets have brought about rapid industry restructuring (Garnsey 2004). Biopharmaceutical ventures operate in an environment characterised by high drug development costs, long development periods, entrenched institutional arrangements, stringent regulations and alliance competition. Conventional industrial structure frameworks with their methodology of comparative statics (Porter 1991) are not suited to depicting evolving business environments characterized by alliance-based supply and regulation-mediated demand, the features of which are captured by the concept of a dynamic selection environment.

Bridging Conceptual Gaps

While the intellectual background to ideas from evolutionary and resource-based theory is complex, the key ideas are relatively simple. Shorn of elaborate biological correspondences and analogies, these concepts can be combined to achieve the aim of evolutionary theory: to uncover how detailed processes give rise to collective effects. Here we aim to show how resource building by and between young firms is affected by selection forces that make available or deny them the resources they need to emerge and operate.

[11] Examples include Interferon-α which was for many years the therapy of choice for use with traditional chemotherapy in certain leukemias and multiple myeloma and monoclonal antibodies such as Herceptin (trastuzumab) and Erbitux (cetuximab) (*Editorial, Nature Biotechnology* **23**(267).

Resources needed are inputs of funds, knowledgeable people and equipment - sustained by the revenues obtained from outputs.

Selection processes respond to such quantitative signals and indicators as costs and prices. Salaries and share price value are among the signals of relative reward that shape perceptions and motivations and thus drive further action and response. But in the networks of the modern economy, selection forces do not depend only on market signals. They include relationship-mediated interactions with other businesses and with regulators that differ from the impersonal forces, costs and prices of market theory. The symbolic interaction that informs and motivates material exchange is cultural as well as economic.

Systems ideas provide a meta-perspective that brings into mutual focus resource-based and evolutionary theory. Evolutionary and resource-based approaches implicitly share the idea that a firm is an open system exchanging resources with its environment (Scott 1987).[12] The firm receives inputs from resource providers, develops productive resources which it uses to transform inputs into resource outputs and obtains returns from the distributors and customers who buy its output. Firms secure investment resources by giving investors a stake in subsequent returns. We can depict the agents with whom the firm interacts as constituting its transaction environment. In Figure 3 the

[12] Systems thinking is implicit in both approaches because modern social science is infused with systems-based concepts such as resources and environment, which go back to its earliest thinkers (Mayr 1971; Scott 1987)

transaction environment graphic depicts interactions between a firm and other organisations beyond its administrative boundary.

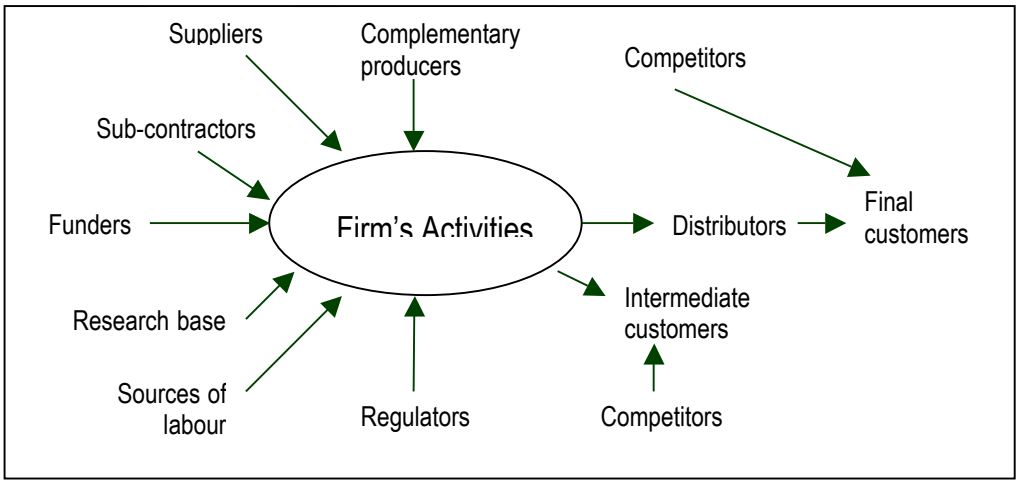


Figure 3: The Firm Experiences Selection through Interactions with Others in its Transaction Environment

This graphic provides a device for comparing otherwise dissimilar case evidence (Figures 5 and 7). Rather than viewing the firm's value chain as linear, the transaction environment represents the firm as linked into a web of related activities. Each organisation has its own transaction environment for its various activities. *Whether this develops into a lasting business network that outlives specific product development needs depends on whether transactions are recurrent and continuous.* If a business network is to be sustained, interactions must be sufficiently recurrent and intensive to create shared understanding, legitimisation and relations of interdependence. Social structure is constituted by such recurrent patterns of interaction (Giddens 1984).[13] Looking at this process from the perspective of evolutionary theory,

[13] In structuration terms, a social structure such as a network is both the medium and the outcome of action (Giddens 1984).

the network constituted by recurrent transactions between associated firms may be viewed as a unit of selection, provided with or denied resources by selection processes.

Unless the new firm has inherited resources, it must create a new resource base to generate market returns acceptable to resource providers.[14] As the firm grows, its resources may come to support a variety of productive bases.[15] Penrose pointed out that: "… movement into a new base requires a firm to achieve competence in some significantly different area of technology" (Penrose 1995, p. 110). Just as the productive base is not static, so the firm's transaction environment differs for different products and is more extensive for multiple products and multiple stages of production. As it enters different sectors, it will experience the operation of sector-specific selection forces.

Whether the new firm will be allocated or denied the resources it requires depends on how selection forces impact on it. There is deliberation in the way in which many features of economic selection operate. A firm is selected by others when they decide to do business with it, to engage with it in economic transactions. Resource providers choose to make available inputs such as investment and component supplies and customers provide revenue

[14] Companies that address similar developmental problems in a common sequence tend to experience similar phases of activity (Garnsey 1998). But there are no invariant phases of activity in new firm development because different problems arise and re-arise in ventures undertaking diverse activities. The building of different kinds of resource base involves different sequences of activity, and even in specific sectors, problems are addressed indifferently through diverse business models.

[15] The term 'productive base' is used here because Penrose's concept of production base can also be applied to service activities. For example research services require the productive capacity to generate, process, store and retrieve information and convert it into meaningful knowledge communicated to clients.

resources when they select its products. In biopharmaceutical markets, regulatory institutions play a key part in selection processes by endorsing or approving the firm and its products. Consumer preference is mediated by the product choices of physicians, hospitals and health system officials. Public opinion influences whether the activity has legitimacy. Industry regulators influence criteria defining 'fitness' for a given environment. For biopharmaceutical firms, regulators play a critical role because an unendorsed product is prohibited from market entry, whereas an innovative drug approved for the treatment of a serious disease or disorder stands a good chance of acceptance by the market.

Another approach using implicit systems thinking is resource dependency theory, which examines relations of power that stem from control by one organization over resources needed by another organization (Pfeffer 1982; Boyd 1990). This theory has much in common with the approach we propose. Resource dependency theory has been mainly used to investigate issues of organizational legitimacy and organizational structure. But a version of bridging strategies to overcome resource dependency is seen in our case evidence. Bridging strategies reduce the chances of a resource shortage, by strengthening the links between the organization and its suppliers (Scott 1987).

Our argument is summarised in a set of propositions, an early stage in theory building. These challenge previous assumptions about the need for a new

firm simply to adapt to its environment and specify means by which new ventures can influence their environment. While other interpretations of our evidence would be possible, our argument is that evolutionary and resource-based theory, integrated by systems concepts, provide a coherent and economical account of how it is that new firms can alter their environment.[16] We are not presenting falsifiable hypotheses but the elements or constructs of a theoretical perspective, connected axiomatically. This can be used to explain developments at one level of analysis (advances in biopharmaceuticals) in terms of evidence of more detailed processes (innovative networks). It would be possible to disconfirm our argument by presenting an explanation both more economical and more comprehensive of our evidence. Any such advance would be enlightening.

Proposition 1: *Selection forces that impact on the processes of development of new firms are amenable to influence by these very firms.*

P1 challenges previous assumptions in the literature that the new firm is faced with an environment to which it must adapt without prospect of changing it.

Proposition 2*: A new firm experiences via its transaction environment the forces of selection which allocate or withhold the resources it needs to survive and grow.*

P2 specifies that parties doing business with the new firm are the agents who provide or withhold the resources the firm requires.

[16] Any such account is provisional, following Popper on the provisional status of knowledge subject to a systematic intellectual selection process, and thus open to refutation by a better explanatory schema (Popper 2002).

The three propositions that follow state how relationships with such agents can be used to access and build needed resources:

Proposition 3*: An entrepreneurial firm can be proactive in shaping its own transaction environment.*

Proposition 4*: A new firm can use its transaction environment to access, via those with which it interacts, the complementary resources needed to achieve its aims.*

Proposition 5*: A network of partners can together build complementary resources.*

P5 moves the focus of analysis to the level of the network to claim that there is complementary resource building at this level, not just at the level of the firm.

Proposition 6*: Resource shortages and under-used resources encourage the entrepreneurial firm to develop complementary resources and find new domains of application. This can be termed a 'resource-opportunity dynamic.'*

P6 summarises Penrose's argument detailed above.

Proposition 7*: A resource-opportunity dynamic takes place not only within entrepreneurial firms but also between innovative firms who contribute collectively to the growth of an innovative network.*

P7 applies P6 to the network level.

Proposition 8*: Enrepreneurial learning in networks is a path dependent process influenced by the resource-opportunity dynamic.*

P8 is an inference from the previous propositions.

Methods based on correlating statistical associations depend on comparative statics that are not suited to uncovering unfolding processes. This is what Schumpeter meant when he criticised the type of statistical approach that: "keeps analysis on the surface of things and prevents it from penetrating into the industrial processes below, which are what really matters." (Schumpeter, 1939, p. 44). Case histories are here used to provide a detailed exposition of such processes. The analysis of the case histories enables us to articulate propositions P1 to P8 more fully. These sum up some overlooked firm level processes that underlie cumulative and collective outcomes at the level of industry and economy.

An empirical context for the application of resource-based evolutionary theory

Biopharm ventures face a difficult environment dominated by large corporations, regulators and impatient investors. They operate as agents of innovation because competition between the large pharmaceutical companies for new compounds provides incentives for them to turn to innovative biopharmaceutical ventures to renew their product portfolios (Simon and Kotler 2003 pp. 55 - 57; Tyebjee and Hardin 2004). The giant pharmaceuticals are concerned to set up R &D alliances with new ventures that have specialist expertise (Figure 1).[17] Pharmaceutical managers explained to us how even well resourced pharmaceutical companies cannot

[17]In-licensing from biopharm ventures has been the most prominent strategy adopted by the large pharmaceutical companies. Acquisition has become less prevalent and external sourcing has been shifting towards earlier stage compounds from the 1990s (Lane and Probert 2005). There is increasing understanding of the inter-dependence nature of biotech-pharma relationships (Lane and Probert 2005) and ways of enhancing their productivity (Leong 2005). To move beyond aggregate evidence on the incidence of partnerships (Figure 1), we need to understand patterns of interaction at the firm and network level (Larson 1992; Ring and Van de Ven 1994; Doz 1996; Lane and Probert 2005).

afford to develop expertise in the full range of emerging scientific specialisms required for drug discovery, particularly when research outcomes are uncertain and investor pressures are short term. The time taken to develop a new drug and its development costs have been escalating; one estimate is ten to fifteen years and $802 million (Tufts University, 2001). R&D alliances aim to reduce the very high upfront cost of research preceding the lengthy and costly regulatory approval process.

The two case studies were selected from a range of cases on biotech ventures prepared by the authors (Garnsey 2003; Leong 2005). The rationale for the case selection was that these ventures set out deliberately to transform their own business environment, were ambitious in aiming at integrated drug discovery and production, yet differed in terms of the type of innovation undertaken. Biopharmacetical ventures require heavy funding if they aim to add value to their intellectual property through *drug development,* rather than obtaining revenues from feeding *drug discoveries* into the pipeline of an established pharmaceutical company. They use the prospect of shared future returns to persuade investors to support their activities. Figure 1 showed that this type of alliance is relatively rare, since pharmaceutical companies concentrate on drug discovery alliances. The case study companies were unusual in aiming to co-produce their products, though without the high costs of in-house production.

The cases draw on documentary evidence and interviews with entrepreneurs, CEOs, process development, production, regulatory and commercialisation

managers at the biopharmaceutical ventures, together with interviews with their contract manufacturers and clinical research organisations on their biopharmaceutical development networks (Leong 2005; Garnsey 2004). The various accounts provided by interviewees were compared for consistency. Although some conflicting viewpoints were in evidence, a sequence of events could be constructed by comparing interviews and from documentary evidence. The cases were further checked by interviewees who corrected errors and misunderstandings.

Company A

Company A is a biopharmaceutical enterprise founded in the 1980s to develop a radio-labelled monoclonal antibody for treating cancer Y, annually diagnosed in approximately 190,000 people worldwide.[18] This new drug (Medicine A) had an annual market potential of around $850 million. It was developed from research through to phase II clinical trials at the Cherry Research Institute in the 1980s, where the positive results of the phase II trials inspired the founding of Company A. The development of Medicine A was taken through to the phase III clinical trials initiated in 1998.[19] Orphan Drug status sought in the US and the EU would have guaranteed respectively seven and ten years of market exclusivity had phase III trials gained approval. But development efforts were discontinued when phase III trials for advanced

[18] For more than 70% of target patients having advanced disease at the time of diagnosis, survival rates were poor. Medicine A was targeted at patients who have entered remission following surgery and chemotherapy, with the aim of destroying any remaining cancer cells and so preventing or delaying relapse.

[19] Phase III trials are therapeutic large-scale trials at several trial centres and on different patient populations for final establishment of the therapeutic profile, which includes indication, dosage and types of administration, contra-indication, side effects and precautionary measures. Phase III trials also need to establish proof of efficacy and safety in long-term administration. In addition, therapeutic advantage over existing drugs must also be demonstrated and any interactions with concomitant medication also need to be clarified.

disease patients treated with Medicine A showed no better results than those of patients in the comparative arm of the trials.

The case studies focus on early attempts by these bio-ventures to create a network of organizations that could provide them with the resources they needed to create and capture value. In company A, the project manager was the founder who built the necessary infrastructure for developing Medicine A from the laboratory base. A small team of specialist staff was brought together to manage the emerging development network. The skills of this team grew with experience of working together, but was greatly extended by the work they carried out with the partners whom they introduced to each other, creating a developmental network. The key development tasks involved in Medicine A defined partnership requirements and are summarised in Table 1.

Drug Development Stages	Tasks involving innovative partnerships
Primary Manufacturing	Process improvement for antibody ▪ Change of cell culture method to meet potential market demand ▪ Purification ▪ Analytical ▪ Formulation
	Linker manufacturing
	Radioisotope manufacturing
Secondary Manufacturing	Vialling
Phase III Clinical Trials	▪ Design clinical development plan ▪ Design individual clinical studies ▪ Design and write individual study protocol ▪ Identification and setup of clinical sites to take part in the studies – including interaction with regulatory authorities ▪ Selection of CROs to provide the necessary support and infrastructure for each of the clinical studies ▪ Running and monitoring the clinical studies.

Table 1: Key Development Tasks for Medicine A

Building partnerships to advance product development

The development team had difficulty finding contract manufacturers for Medicine A because of the novelty of their requirements, their limited financial resources and the small size of their orders. Medicine A consisted of antibody, linker and radioisotope. Good Manufacturing Practice (GMP) accreditation was needed for all three.

The manufacturing process developed in the hospital laboratory for producing antibodies was inadequate for regulatory approval. A contract manufacturer was sought to improve on the process and to make it GMP-compliant. Company A took up a small contract manufacturer located abroad, Mabman, which had the expertise to scale-up the laboratory process and proved adept at introducing innovations into the laboratory process (Table 2).

Cherry Research Institute	MABMAN
Upstream	
Roller bottles – suitable for small scale (could only handle tens of litres per batch). The production standards were also inappropriate for a marketed product.	MABMAN provided a hollow fibre based perfusion cell culture systems, which could handle 3000l per batch.
Downstream	
Purification using protein A, which is designed to remove DNA; sepharose – a strong anion/cation exchange medium.	MABMAN recommended a proven method to cut the cost of producing protein A.
No facilities to remove viruses.	MABMAN used a low pH=3 hold to destroy viruses, a development step based on the discovery that the antibody could survive this process.

Table 2: Critical Expertise Provided by Contractor MABMAN

After failing to engage a local chemical manufacturer to produce the linker, Company A found Linkman, a US company with scientists interested in Medicine A. While their European counterparts had dismissed the prospects of a new venture, the US company viewed phase III development as significant enough to justify commercial interest. Further supplier difficulties were experienced because of the novelty of their radioisotype requirements. The largest radioisotope-producing company in the country withdrew after six months of discussion. Company A's team had difficulty finding radioisotope contractors and meet regulatory requirements.

Very few companies provided the plastic tubing and biologics vialling needed in A's country. Once again, the main manufacturer in the country was not interested in introducing a complex process for a new company. But an entrepreneurial contract company, Vialman, realised that Company A represented new demand which made it worth developing the expertise to vial bio-products of this kind. The vialling system jointly developed with Company A was to provide the basis for the future expansion of Vialman.

In preparation for phase III trials, the clinical trials manager at Company A built a network with contract research organisations (depicted by code name in **Table 3**). Criteria for choosing partners included their lead time performance and cash position.

Tasks	1st tier Contract Research Orgs. (CROs)	2nd tier CROs
Central Pharmacy (distributing drugs to study sites)	A-C3 (Country Alpha)	
Monitoring (clinical monitoring and study site management to ensure that investigators follow protocols)	A-C4 (monitored US trials)	
	A-C6 (monitored Australia and New Zealand trials)	
	A-C7 (monitored EU trials)	A-C8 (local)
		A-C9 (Croatia and Slovenia)
		A-C10 (Israel)
Data Management (statistical advice and database infrastructure)	A-C5 (Country Alpha)	
Central Services (a) Laboratory (accreditation required)	A-C2 (EU)	A-C11 (location unknown)
		A-C12 (US)
		A-C13 (Australia and New Zealand)
(b) Histology	A-C14 (Country Alpha)	
	A-C15 (US)	
(c) CT Scan Review	A-C16 (Netherlands) (recommended by investigators)	
	A-C17 (US) (recommended by investigators)	
Dosimeter Consultant	A-C18 (US) (recommended by FDA)	
Independent Auditing	A-C19	

Table 3: Contract Research Organisations for Medicine A

Pharmaceutical alliance

Seeking a pharmaceutical partner for later stage development and commercialisation was a strategy designed to secure immediate and long-term liquidity, and to serve as a validation of Medicine A. An initial alliance with a pharmaceutical company was terminated when this company reassessed its product portfolio and abandoned Medicine A. Company A approached another big company, Pharma-A1, but 'cold' contact with them did not elicit any interest in the new venture. By chance, the Chairman of

Company A sat beside a senior executive from Pharma-A1 at a dinner and urged him to reconsider Company A's potential. Within six weeks, a contract was finalised, illustrating the impact of chance and the importance of well-connected Board members for a new company. The agreement provided Company A with the backing it required to continue its development work.[20]

Pharma-A1 had a record of partnering effectively with biopharm ventures; they knew that value could be destroyed by acquisition that resulted in staff losses. Instead of buying Company A outright, Pharma-A1 maintained Company A's autonomy and did not interfere with the products that Company A in-licensed. Pharma A-1 proved effective in gaining the confidence of A's contract partners.

A summary of the transaction environment that Company A created in the process of developing Medicine A is illustrated in Figure 4.

[20] A venture in need of immediate resources may have to forego its potential to add value on an independent basis through vertical integration. In this case, the existence of Company A was threatened and to ensure survival it was necessary to allow Pharma-A1 exclusive rights to most of Company A's product pipeline. Company A retained the right to co-develop and commercialise oncology products currently under development together with any reaching human trials during the next five years. Pharma-A1 took only a minority equity stake in Company A and agreed to payments in cash for new products entering clinical studies, and milestone payments for phase III and launched drugs. The total payments to Company A was set to surpass $500 million, if all products reached the market. Additionally, Company A would receive royalties of 10-20% on product sales.

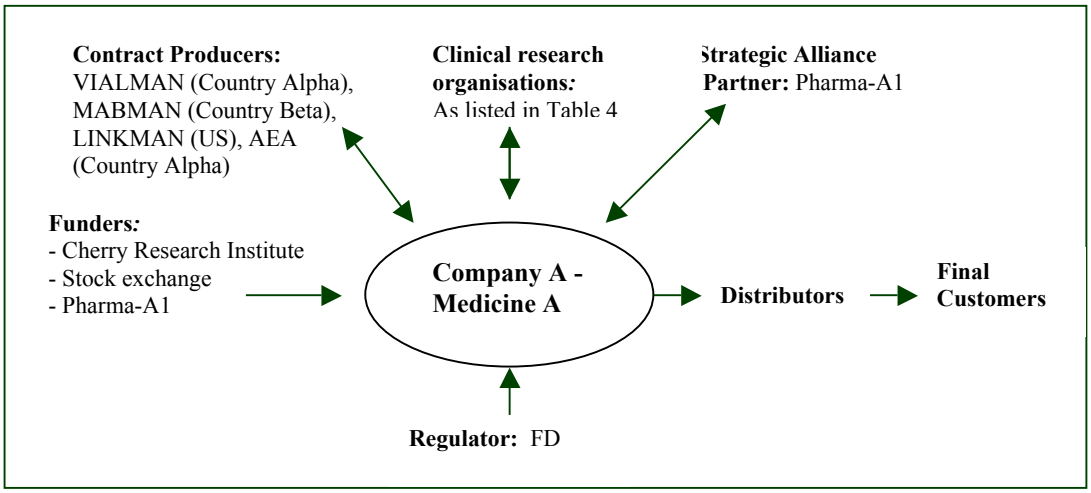


Figure 4: Company A's Transaction Environment for Developing Medicine A

Each of the relationships shown contributed resources to the network. (The relationships between the CROs shown in Figure 4 are between 1st tier and 2nd tier contractors.) Figure 5 shows how the various actors entered the new network as Medicine A was developed.

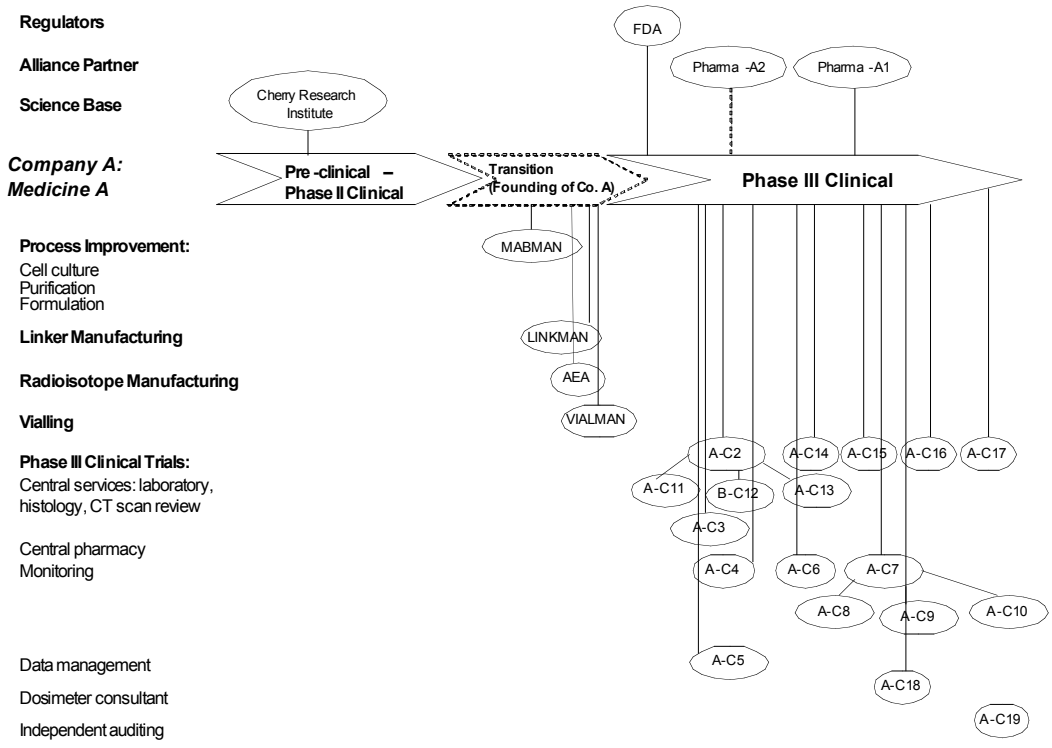


Figure 5: Drug Development Process of Medicine A

Company A's Experience Analysed

That critical features of the business environment operate as selection forces shaping the developmental processes of new firms (P2) is shown by the experience of Company A. Progress there depended on a collaboration with a major pharmaceutical company which was both customer and funder to the new venture. The collapse of the first attempt to collaborate in this way illustrates a denial of the resources the venture needs to survive and grow. But Company A's transaction environment for developing Medicine A provided the basis for a network that outlived a shift to another Pharma partnership and the unsuccessful outcome of this product's phase II clinical trials. The company were able to go on to develop other products, drawing on partnerships with companies that had collaborated in their pioneering development efforts. Thus a new firm may use its transaction environment to access complementary resources (P4).

Creating a favourable environment and formation of organisational routines

In emerging sectors, an entrepreneurial venture can build resources that are complementary with those of its partners (P5), to achieve its aims. In the late 1980s, the environment for small biopharmaceutical start-ups was unfavourable, as seen from the difficulties the venture faced when seeking contractors. Instead of going to a large clinical research organisation that provided the entire range of services needed for clinical trials, Company A adopted the strategy of using multiple contractors, many of them small, finding benefits in working with organisations of comparable size. By

choosing their partners' geographical location, size and number, Company A aimed to reduce exposure to risks and offset the uneven bargaining position of relationships with giant pharmas.

The building of capability can be seen in the way Company A developed routines for seeking contractors and managing interactions. In this venture, operational routines were selected to meet relatively stable requirements and prevent reinventing of the wheel when recurrent problems arose. However, flexible procedures rather than fixed routines were adopted to organise their search and learning processes in solving new technical problems.

Enhancing innovative capability in the network

A Penrosian process by which resource shortages were remedied was observed, though inter-firm rather than intra-firm teamwork. Unable to find contractors with proven technical competences willing to meet their needs, they selected Mabman and Vialman though neither possessed the specific capabilities that they needed. They undertook joint work so that new skills and systems were developed by these suppliers. It is of significance at the industry level that the services of these contractors became available to other small biopharmaceutical ventures developing bio-based medicines.

Proposition 6 sums up the way resource shortages and under-used resources may encourage entrepreneurial capability building. The case study shows how a Penrosian resource-opportunity dynamic exploiting uneven resource availability takes place not only within entrepreneurial firms but also between

innovative firms who contribute collectively to the growth of an innovative network (P7).

Building Partner Capability

In the early 1990s, many European contract manufacturers who had met European (EMEA) requirements were reluctant to subject themselves to approval by the US FDA who were reputed to demand costly changes in facilities and procedures. But without manufacturing facilities compliant with FDA standards, clinical trials could not be conducted in the US and the world's largest market was closed to a new drug. In the process of developing Medicine A, the project manager introduced partner manufacturers to FDA personnel to learn about GMP requirements. They were helped to overcome their reluctance to deal with the FDA and to copy effective procedures for meeting FDA requirements.

Selection processes as exerted by business partners

The deliberation inherent in economic 'selection' processes is evident when a venture is selected or de-selected as a business partner. In a collaborative network, external resources can become available to the firm through closely managed outsourcing. Competence of this kind is built cumulatively within a firm through team-based learning (Penrose 1995). After the collapse of their first major alliance, the injection of new funds and technical expertise into Company A by the new partner (Pharma-A1) improved the company's resource base and enabled it to continue to grow, though at a cost. In the

circumstances the founders had to allow a dilution of their equity and control. The alliance formed during the development of Medicine A was critical because it enabled Company A to remain in a strong enough cash position to continue developing other drugs in their pipeline after the failure of Medicine A in the phase III trials. Through the various efforts of its managers, scientists and members to create a drug development network and enhance its capability, Company A was over time able to alter the conditions in which it did business, exemplifying (P1).

Company B: introduction

Case B raises a current business issue: by what means can a new generic drug firm replicate the drugs of established firms whose drugs reach patent expiry? In biotechnology, intellectual property provides only temporary reprieve from competition. It is a common perception that the production of generic drugs involves imitation rather than innovation. However, bio-generic drugs are not produced by synthesising defined chemical identities. They involve complex processes that use living organisms to produce the desired proteins. New clinical trials on generic drugs are likely to required by the regulating authorities for patient safety. Thus Company B took up a major innovative challenge in accessing and integrating the specialist resources needed for re-engineering a bio-process for a drug newly emerging from patent protection.

Penrose showed how a vertically integrated firm can grow new capabilities by setting up new departments or subsidiaries engaged in complementary

activities (Penrose 1960). Our second case study exemplifies the capability process in a different way. In effect Company B put into practice propositions set out earlier in this paper. Thus Company B recognised P2 ("A new firm experiences via its transaction environment the forces of selection which allocate or withhold the resources it needs to survive and grow") and sought to embody P3 ("An entrepreneurial firm can be proactive in shaping its own transaction environment.") To achieve this, B set out to use its transaction environment to access complementary resources (P4) by building partnerships (P5).

Thus the second case study exemplifies propositions 1 to 5. To move the analysis further, we focus in this case on the opportunity-resource dynamic (propositions 6 and 7). We examine the ways in which entrepreneurial firms were mobilised to build capabilities initially missing among the suppliers Company B chose to work with.

Company B's experience

Two entrepreneurs founded Company B in 1997 through a collaboration and joint venture with a Chinese Research Institute. One of the founders, Dr. C, began funding research work at this Institute in 1995. He aspired to make life-saving drugs available at affordable prices in developing countries.[21] He

[21] Dr. C used mortgages to provide seed funding for Company B because he did not wish to resort to venture capitalist funds and risk losing control of his venture. The first round of external funding was sought two years after founding. Dr. C's track record in another biopharmaceutical company helped raise several million pounds through the company's listing on a national share platform for unlisted and unquoted securities. Dr. C appointed a CEO who had previously served as vice-president of another biopharmaceutical company. Together they set in motion a second round of fund-raising by listing the company on two stock exchanges in Europe and Asia on the same day. They raised £20 million and by mid-2000, a core management team was in place.

set out to acquire promising cell lines and gained the rights to the manufacture and sale of six biopharmaceutical proteins derived from the cell lines using recombinant DNA technology. The early development of these drugs had already taken place in the Chinese Institute, but its scientists lacked the know-how and funding to scale-up the manufacturing process and improve product quality, as required to launch these drugs in European and other Western countries on patent expiry. The purchase of these cell lines represents both the detection of an opportunity to develop high value medicines and the securing of critical resources, protected by intellectual property. The cell lines were used for leverage in building up the other resources needed by the company. To achieve his mission, Dr. C had to find a cost effective way of manufacturing and marketing the drugs without compromising quality. This case study tracks the efforts required to create and combine through collaboration all the resources needed to take a cell line through to market as a life saving drug.

Bio-generic Business Model

The bio-generic product Company B set out to replicate was a natural human protein produced in the body in response to viral infection and cancer. The worldwide market size for the drug was estimated to be $1.7bn, with the largest share in the US. The decision to develop Medicine B was based on its high value and the imminent expiry of patent. Company B did not set out to create or buy laboratories, nor to employ in-house scientists or a clinical development team. Their business model was one of system integration, requiring the orchestration of a complex network. All the process

development work, pre-clinical trials and future clinical trials would be carried out through partnerships with contractors or strategic partners. In making decisions about partnerships, key considerations were the detailed process of drug development and the management of an extended development network. Table 4 shows the key development tasks of Medicine B and the contractor/partner selection criteria.

The pioneering attempts to synthesise Medicine B elsewhere had incurred very high costs; attempts by the originators to recoup these had led to pricing of treatment at several thousand dollars. A second generation drug which was simpler to administer than the first product soon captured 60% of the market. Company B needed to create relative value greater than the existing second generation drug. To do this, Company B entered into collaboration with Partner-1 which owned a proven new drug delivery system.[22]

Drug Development Stages	**Tasks**	**Contractor/ Partner Needed?**	**Contractor/Partner Selection Criteria**
Process Development	• Technology transfer from the Chinese Research Institute • Re-cloning and cell bank characterisation • Fermentation • Cell breakage • Refolding of inclusion bodies • Purification • Analysis • Formulation	Yes	• Expertise in fermenting bacteria • Credibility of people on the senior management team • Management team's experience of similar products • Cost • Good Manufacturing Practice (GMP) facilities for toxicology and early phase clinical trials
Pre-clinical Studies	• Toxicity studies • Pharmacokinetics • Pharmacodynamics	Yes	• Observes Good Clinical Practice (GCP) • Location where animal trials are more easily conducted • Lower cost location
Regulatory Clearance	• Prepare dossiers for licensing authority	No	
Clinical Trials	• Clinical trials design and location • Compare therapeutic effects of new and existing products	Yes	• Clinical research organisations located in the US and Poland • N/A

[22] Their aim was to develop an extended release formulation of Medicine B, using Parter-1's technology to deliver therapeutic doses of the protein once a month in place of the current treatment's weekly injections.

Registration Launch and Sales	• Reports for product approval and user education • Prepare marketing plan • Sales • Packaging • Quality control	Yes	• N/A

Table 4 –Key Development Tasks for Medicine B

Process development

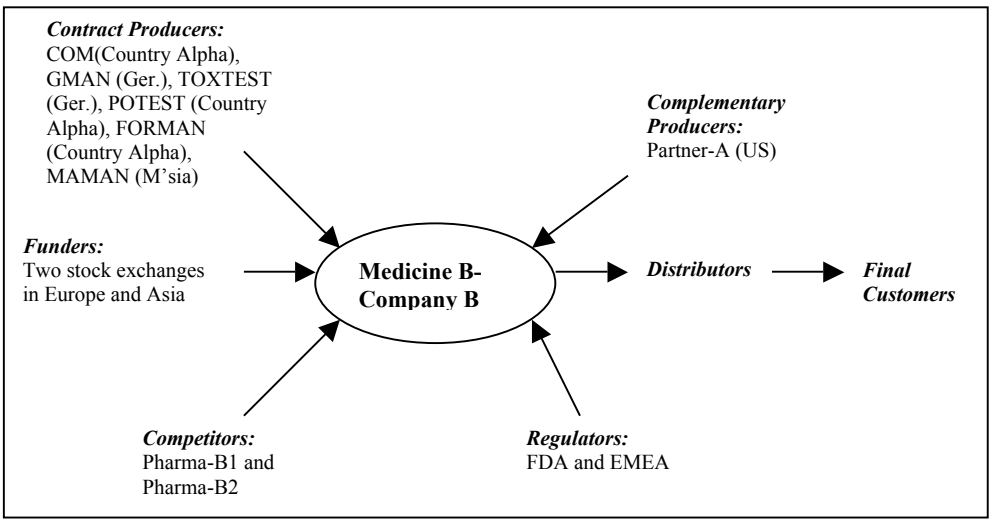
The Chinese scientists had developed a laboratory process which, it was thought, could be modified to make it amenable to scaling-up. COM, a contract manufacturer based in a different part of the country, was selected to manufacture the material for pre-clinical and clinical trials because it had accreditation for Good Manufacturing Practice (GMP). COM had not previously engaged in protein production but its scientists and senior management had experience of manufacturing products similar to Medicine B in other companies where they had previously worked. It turned out that re-engineering the process developed by the originator firm required a high degree of skill and creativity from Company B's contractors. For example, Medicine B had to be correctly refolded into the three dimensional structure exhibited naturally in the body. The protocol designed by the Chinese scientists generated a high percentage of molecules that were folded incorrectly. On redesigning the refolding procedure, COM scientists attained a refolding efficiency of around 75%.[23] It was necessary to convert the liquid formulation to powder form, better suited to hot climates. To do this without altering the structure of the target protein was a specialist art. Company B

[23] They also developed a purification process and found a German contract manufacturer to assist. When the target protein had been purified, it was subjected to a series of analytical tests as stipulated by the European Pharmacopoeia to determine its quality. COM was in a position to carry out the tests except for the potency test. This required a license and specially designated handling areas and systems to prevent viral contamination of products. Company B therefore engaged another contractor, Potest, to develop and qualify this test for Company B.

had to find a specialist contract manufacture to formulate the product and dry it by lyophilisation.[24]

The cost and risk of phase I and phase II clinical trials of Medicine B were to be jointly borne by Company B and Partner-1. Safety testing in animals was difficult in the country where Company B was started and faced less hostility and expense in Germany.[25] Company B found a toxicology laboratory in Germany, Toxtest, and assessed its suitability. A Malaysian company, Mayman, was selected to perform vialling and packaging operations for the global market.

Figure 6 shows how production processes related to the partnerships needed.



[24] Involves freezing the product under a vacuum at -42˚C.

[25] The results from the pre-clinical studies are analysed by trained personnel and statisticians prior to preparing dossiers for a licensing authority to request a license for clinical trials in a particular country. The pre-clinical results together with a draft copy of the trial design in humans are presented to an ethical committee for approval.

Figure 6: Company B's Transaction Environment for Developing Medicine B

Figure 7 shows how various companies were enlisted into the network as the development of Medicine B progressed.

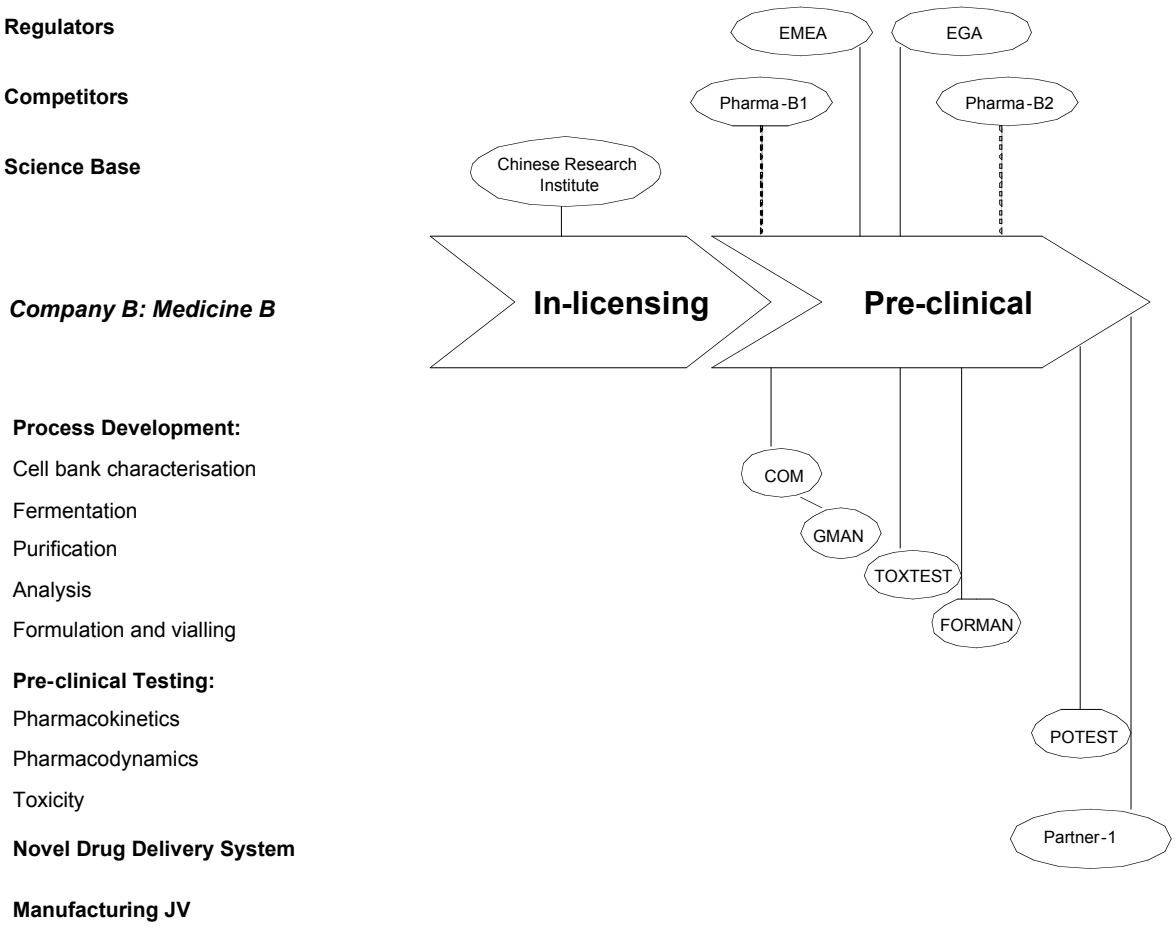


Figure 7: Drug Development Process for Medicine B

Partnerships can fall apart through factors outside a company's control; this happened when one of Company B's European partners in a joint venture to manufacture Medicine B suddenly withdrew without warning, temporarily depriving Company B of access to essential (P2). This crisis was overcome but might not have been.

Funding has been a critical issue for Company B as for most biopharmaceutical ventures. After the initial ordinary shares placing in 2000, the company succeeded in issuing new shares on five occasions between 2003 and 2005, a period of investment downturn. There were times of acute funding shortage when endorsement from partners was needed to provide the venture with credibility in the eyes of investors and thus access to the financial resources they needed for survival.

Company B's Experience Analysed

Penrosian responses to uneven resource availability among firms in the network are observed in this case study. Critical capability building occurred at the network level because of the nature of the business environment and selection forces faced by the new venture.

A reason for the relatively favourable funding position of Company B was that their post-patent strategy was believed by investors to involve less uncertainty than producing a new biopharm product. However, viability depended on B achieving cost effective development and quality-endorsed drug production. Replicating a drug to the level of quality attained by the originator required ingenuity and innovative capability among the participants in the international production network.

Effecting 'new combinations'

Competitive advantage generated through Schumpeterian 'new combinations' is exemplified in this case. Most generic pharmaceutical producers aim at price competition. Company B also aimed at improvements on existing products that would switch demand in their favour. The company's potential competitive advantage is a result of bringing together in-licensed recombinant DNA technology with Partner-1's proprietary drug delivery technology. Collaboration with Partner-1, including shared development costs and risks of phase I and phase II clinical trials, was in their mutual interests since each company's technology was insufficient to replace existing products.

Improving the capabilities of network partners

Company B scanned the market for suitable contractors and gave them the opportunity and stimulus to grow new capabilities. In the event, this proved valuable to both parties. As Penrose argued, resource shortages and under-used resources encourage the entrepreneurial firm to develop complementary resources and find new domains of application (P6). Company B achieved this by enlisting partners. Their contractor, COM, had not previously produced protein but unused resource in the form of employee knowledge built up in prior employment. This was initially largely tacit, but was shared with other employees and rendered explicit through procedures (routine building). Subsequently COM was able to build on experience gained by working with Company B to improve its share of the expanding protein contract manufacturing market. COM's improved prospects were recognised by investors, leading to an issue of new ordinary shares being oversubscribed

seven times in a stock market placement in 2003. This illustrates how the seizing of new market opportunities can take place not only within an entrepreneurial firm but also among innovative firms which form an innovative network (P7).

Creating favourable regulatory conditions

Both our cases exploited changes in external circumstances, but they were proactive in shaping selection forces in their favour. Selection forces in their business environment (P1) include regulatory requirements. The advent of new bio-generic products poses new regulatory challenges. Regulations for determining their comparability with existing products and manufacturing processes are not well established. Company B adopted a proactive stance on this matter, working with regulatory bodies in Europe both independently and through the European Generics Association (EGA). The CEO of Company B was elected to the Board of EGA and the company's Regulatory Affairs Director chairs the Biotechnology Working Group of the EGA. This group is actively lobbying the European Medicines Evaluation Agency (EMEA) to establish the regulatory pathway and data requirements necessary to register Company B's products in Europe. Regulations and policies were an integral part of the continually evolving selection environment faced by Company B, but these were not beyond their influence. (P1).

Likewise Company B demonstrates ways in which a new firm can be proactive in shaping its own transaction environment (P3). Company B sought finance in geographically dispersed capital markets as investors became less interested in the funding of new biopharmaceutical ventures in the wake of the millennial boom and slump. A critical element of influence for the new venture is its choice of product focus. B's decision to go for a generic product ensured that it was operating in a regulatory environment that was less demanding than that faced by completely new medical entities. Moreover this was influenced by participation by Company B in bio-generics standards setting.

From evidence to theory and practice

"The continual change in the productive services and knowledge within a firm along with the continual change in external circumstances present the firm with a continually changing productive opportunity." (Penrose 1995 p. 150). We called this the resource-opportunity dynamic and saw how this applies not only at the firm but at the network level. In conclusion we enlarge the detailed focus of the case studies to view the way micro-processes shaped broader developments.

(1) Entrepreneurial learning of the kind explored here responds and contributes to non-linearities in a complex dynamic environment (Marion 1999; Garnsey and McGlade 2006). From these follow implications for the understanding of innovation theory and practice. The focus on case evidence showed that:

(2) Learning in new entry firms is a path dependent process underlying the growth of dynamic capabilities.

(3) Entrepreneurial learning is an iterative process shaped by the resource-opportunity dynamic.

(4) The outcome of entrepreneurial learning is a distinctive innovation process that alters the opportunity space of a complex environment.

(5) Entrepreneurial innovation sets off changes in the conditions that impact upon it, whether or not individual entrepreneurial units achieve their objectives.

(6) Selection forces in the economy are not impersonal and deterministic forces impervious to agency. There is considerable scope for decisions by specific individuals and teams to make a difference to outcomes and conditions.

(1) Entrepreneurial learning as a path dependent process

That network learning is a path dependent process (P8) is consonant with work since Penrose on dynamic capabilities. While Teece et al. (1997) see dynamic capability as unique to a firm and difficult to imitate, Eisenhardt and Martin (2000) have argued that dynamic capabilities can be replicated elsewhere as organizational innovations. Our evidence on the way in which firms in the biopharmaceutical network learn from each other shows that these apparently conflicting accounts actually apply to different kinds of capabilities. Those that are unique to the firm are embedded in its history and its tacit knowledge base. Thus developing specialized capabilities for innovative production required the sharing of tacit knowledge and new joint

work between teams from different firms. Other capabilities depend on procedures that can be copied from those who have demonstrated their efficacy, as in the case of routines for conforming to regulatory procedures.

Either way, entrepreneurial learning promotes the application of prior knowledge to new circumstances. This has important implications for investors. If a project encounters setbacks, instead of writing off an investee team that fails to meet pre-set targets and milestones, investors could look more favourably on ways to capitalize on the firm's knowledge base in diverse rather than pre-determined ways, e.g. through the targeting of alternative patient categories for a biopharm product. This calls for thoughtful application of real options approaches rather than a target-dominated stage-gate approach (Goffin and Mitchell 2005).

(2) Entrepreneurial learning is an iterative process to which the resource-opportunity dynamic contributes

Entrepreneurial opportunity recognition and pursuit of opportunities occur as an iterative process shaped by the actual and prospective resourcing requirements of the entrepreneurial endeavour. Penrose's conception of enterprise as a dynamic matching process is in contrast with recent emphasis on the pursuit of opportunity as the driving force in entrepreneurship (Shane 2000). The latter does not accord central place to the interactive processes through which resourcing a venture and the pursuit of opportunity are in dynamic interplay. The interweaving of venture-resourcing and entrepreneurial pursuit of opportunity challenges the rationale for an

intellectual division of labour between the fields of entrepreneurship studies and new firm formation (Shane and Venkataram 2000). Entrepreneurial innovation both enables new firm development and plays a distinctive and critical role in the wider web of innovation.

(3) The outcome of entrepreneurial learning is an innovation process that alters the opportunity space in a complex environment

The cases show that firms need not be passive opportunity detectors in a given environment to which they have to adapt. The two innovative biopharmaceutical start-ups in the case studies had entrepreneurs who aimed not merely to adapt to an existing industrial environment but to construct a habitat favourable to their business models. The entrepreneurial firm sets out to create its own opportunities.[26] The emergent network represents both eventual resource-provider and a current source of opportunity for its member firms, but the opportunity must be actualized through resource sharing and building to create more favourable conditions for network interaction.[27] It is through the non-linearities of mutual feedback that the network comes to provide a business environment for its creators. There are implications for foresight exercises and corporate road-mapping practice (Goffin and Mitchell 2005). The business environment is not independent of the strategic journey but is continuously altered by strategies pursued.

(4) Entrepreneurial learning is a distributed process

[26] This supports the Schumpeterian view (1928) over that of Kirzner (Shane 2003).
[27] A social structure such as a network operates both as the medium (in which activity takes place) and as the collective outcome of such activity (Giddens 1984).

Our cases reveal new entrants contributing to the co-evolution of biopharmaceutical capability whether or not their particular projects succeed. Entrepreneurial learning and innovation operate as distributed processes to an extent obscured by investors' focus on individual firms' performance and share price. It remains to be seen how effective these companies will be in sustaining their role as system integrators in their own network and in propagating their innovations. Innovative activity is a necessary but not a sufficient condition of success for any one firm. However as a distributed process, entrepreneurial innovation collectively advances emerging technologies. There is a message for investors and policy makers here. Investors could consider supporting a network of firms on whose complementary activities the progress of a related set of promising technologies depend, rather than backing individual ventures.

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