Building a conducive environment for life science-based entrepreneurship and industry clusters

Mark J. Ahn and Michael Meeks

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Mark J. Ahn
is Professor and Chair, Innovation and Entrepreneurship at Victoria University of Wellington. Dr Ahn's teaching and research interests include technology-based entrepreneurship, management and innovation in life science industries, strategy-based transformation, leadership and organisational learning, and venture philanthropy. Prior to Victoria, he was founder, President, and Chief Executive Officer of Hana Biosciences, Inc., a biopharmaceutical company he led from private to NASDAQ-listed company. Prior to Hana, he served as Vice President, Hematology and corporate officer at Genentech, Inc., as well as positions at Amgen and Bristol-Myers Squibb Company. Dr Ahn also serves on the Board of Directors of Transmolecular, RXi Pharmaceuticals, and Access Pharmaceuticals.

Michael Meeks
is an assistant professor of strategic management, San Francisco State University. He is the founding director of SFSU's Family Business Center, where he serves as chief executive. He teaches the undergraduate and MBA capstone business course, family business courses, business negotiations, business ethics, and management of technology. He is currently engaged in six streams of research: (1) strategic management, (2) entrepreneurship, (3) family business, (4) the wine industry, (5) the bio- and nanotech industries, and (6) higher education. He founded and managed over 25 successful local Bay Area Ventures.

Abstract

The global biopharmaceutical industry, with over $70bn in revenues and 700 publicly listed firms posting double-digit growth in North America, Europe, and Asia-Pacific in 2006, represents an attractive and promising high-growth industry of the future. Broad scientific advances and commercial successes have captured the attention and aspirations of policy makers, business people, and investors alike in spurring sector growth. An understanding of the fundamental forces that shape the industry, including the challenges faced by entrepreneurs, as well as many promising industry trends, offer several implications for investors and policy makers. This study explores industry dynamics affecting growth patterns, biotech industry cluster evolution in an era of increasing globalisation, and enabling factors which support entrepreneurship activity, productivity, and sustainability. Governments and investors seeking to create and enhance biotech entrepreneurship face several enabling trends including increasing numbers of science graduates worldwide, accelerating pace of scientific advancement, dominating role of globalisation enabling greater collaboration, democratising forces of the internet, and the relentless competitive pressure to innovate. As such, policy agendas should focus on increasing factor conditions to enhance start-up formation, alliances, and skilled employment, rather than attempt to select specific winners and losers among specific sub-sectors or individual firms.

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Correspondence: Mark J. Ahn, Victoria Management School, Victoria University of Wellington, Rutherford House, Thorndon, Wellington 6140, New Zealand
Tel: + 1-650-218-7934
E-mail: mark.ahn@vuw.ac.nz

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INTRODUCTION

After three decades, the biotechnology industry has emerged to hold great promise for addressing a wide range of critical challenges in developed and developing countries, including healthcare, security, alternative energy, environmental remediation, and increasing agriculture crop yields with reduced pesticide use. This paper focuses on the evolving industry cluster dynamics of the largest segment of the biotechnology industry: human healthcare. The global biopharmaceutical industry, with over $70bn in revenues and 700 publicly listed firms posting double-digit growth in North America, Europe, and Asia-Pacific in 2006, represents an attractive and promising high-growth industry for the future.[1] Broad scientific advances and commercial successes have captured the attention and aspirations of policy makers, business people, and investors alike in spurring sector growth.[2,3]

In particular, local, regional, and national governments are keen to identify means to compel start-up firms to locate, grow, and remain in a particular geographic area. As California Governor, Arnold Schwarzenegger remarked about enhancing the birthplace of the biotechnology industry: 'Opportunities to work at the cutting edge of science in fields like genomics and stem cell research draw the world's leading researchers to California. Once here, many of them expand their careers beyond basic science, founding companies that translate laboratory discoveries into practical treatments for patients. These breakthrough products benefit people around the world and deepen our medical understanding. At the same time, the revenue and jobs our companies and institutions generate enable us to provide vital services for people right here at home.'[4]

Thus, this paper will explore three questions. First, what are the key biotechnology industry dynamics affecting growth patterns and competitiveness? Secondly, does location and proximity continue to matter to cluster development with increasing globalisation? If so, is there a framework for determining enabling factors of competitiveness for entrepreneurship? Thirdly, what are the implications for biotech entrepreneurship and firm productivity? Does innovation emerge or can it be shaped?

BIOTECHNOLOGY INDUSTRY DYNAMICS

Since the US FDA approved the first biotechnology drug (recombinant insulin, developed by Genentech and licensed to Eli Lilly and Company) in 1982, the biopharmaceutical industry has had 254 drugs approved for 385 indications with over $70bn in sales in 2006. In addition, more than 300 drugs are currently in clinical development targeting more than 200 diseases. The industry employs more than 200,000 people and spends more than $20bn in annual research and development.[1,3]

Despite this tremendous investment, productivity over the years has been decreasing, with higher costs of drug development and longer clinical development timelines. The average drug takes over $1.0bn and 12 years to go from laboratory to approval.[5] Part of the reason for rising development costs is the high failure rate of product candidates in clinical trials due to increasingly specific molecular targets for unmet diseases – which necessarily increases development risk – complexity of biologic systems with compensating mechanisms, overlapping intellectual property claims, and shifting regulatory requirements. For the drug candidates that progress from animal testing into human clinical trials, the overall success rate is 11 per cent. In other words, nine out of ten products entering clinical trials will fail, and some disease areas are proving to be even more challenging – for instance, oncology success rates are approximately 5 per cent. Furthermore, getting approval is no guarantee of commercial success.[6] To date, only four of ten products that reach the market achieve profitability. This lack of development productivity (either increasing the value

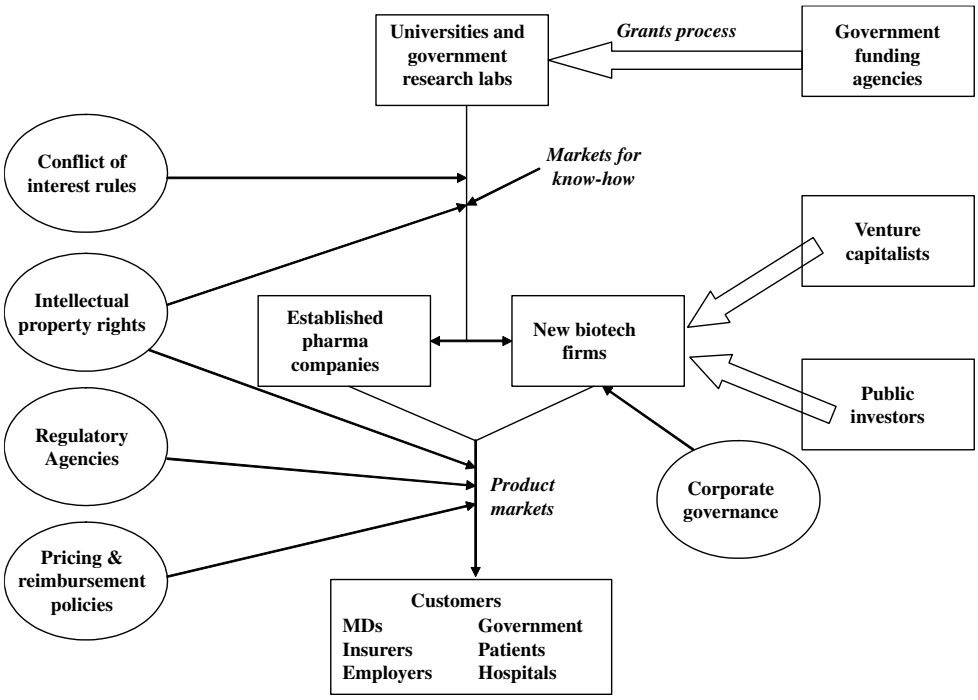

Figure 1: Biopharm industry architecture

created or decreasing the time required to create value) has taken its toll on industry financial performance. Out of the nearly 350 publicly traded biopharmaceutical companies, fewer than ten reached sustainable profitability.[1,7,8] As illustrated in Figure 1, the heavily regulated, high complexity–high velocity biopharmaceutical environment makes choosing specific winners and losers virtually impossible because success and failure can come from several sources outside a given firm's control. The highly complex environment facing all biopharmaceutical firms, disproportionately impacts the sustainability of start-ups.[9]

Fundamental forces shaping the biotechnology industry in the first decade of 21st century include: (1) the gap between the low cost of creating a biotech company around an exciting scientific discovery and the extremely high costs of converting novel technologies into approved drugs; (2) a steady evolution of the perception of value by investors in the biopharmaceutical industry value chain; (3) the irregular nature of the biotechnology financial markets resulting in increased operating risk and uncertainty; and (4) demand by multinational pharmaceutical companies for product pipeline to insure against their own declining productivity and growing market penetrations by generics.

First, a persistent issue is the gap between the low cost of creating a biotech company around an exciting scientific discovery and the extremely high costs of converting novel technologies into approved drugs. Academic research is more likely to result in a higher number of potentially breakthrough innovations due to the large numbers of scientists, resources, and patience with the scientific process. Ever-broadening access to molecular biology tools, a rapidly growing body of knowledge about basic biological processes, and the use of information-based research technologies in academic laboratories and research institutes makes it relatively easy to form a new company by spinning the basic technology out of academia. While the core competency of academia is basic research (defined as laboratory-based target validation and lead

optimisation), most universities are not resourced to translate discoveries from the lab into the clinic, a process which typically requires manufacturing know-how, *in vitro* and *in vivo* toxicology testing, regulatory filings with the US Food and Drug Administration, and mobilising physician investigators to enrol patients into early-stage clinical studies. Fuelled by the expanded access to research tools and biological insights from initiatives such as the human genome project, the excitement of creating new companies has resulted in large numbers of small, undercapitalised start-ups focused on discovery of novel drug targets but lacking resources needed to convert these targets into drug candidates and to validate them in the clinic.

Secondly, perceptions of the biopharmaceutical industry value chain have steadily evolved among investors. As the risks inherent in drug development have made themselves known, biotechnology investors and Big Pharma partners have increasingly sought to place their bets on companies that are further in their evolution to achieving marketable products. In the early 1990s, the highest market valuations went to companies with technology platforms which could potentially lead to biologic targets (ie, Human Genome Sciences, a biotech start-up, granted GlaxoSmithKline access to its gene-based drug technology in a partnership valued at $125m). Gradually, over the course of the last decade, the biopharmaceutical value chain has evolved from valuing novel drug targets (ie, Bayer paid five-year old Millennium Pharmaceuticals over $1.0bn to deliver 225 drug targets over five years); to focusing on product leads (ie, Hoffman-La Roche acquired a 60 per cent stake in Genentech in exchange for right of first refusal to all Genentech products outside the US); to acquiring development candidates in clinical trials (ie, Amgen entered into an alliance with Abgenix to co-develop monoclonal antibodies over five years and subsequently acquired the company for $2.2bn after positive Phase III clinical trial results for Vectibix); to paying for revenues from approved products that led to increased merger and acquisition activity (ie, Pfizer acquiring Agouron, Johnson & Johnson acquiring Centocor, etc). Following Big Pharma's lead, over the course of three decades, biopharmaceutical industry investors went from ascribing value solely to platform technologies to requiring clinical-stage product candidates to expecting revenues and finally, to demanding sustainable profitability. That is, as in all other industries based on technological breakthroughs, investors in biopharmaceutical companies increasingly demand commercially realisable opportunities to justify additional capital.[10]

Thirdly, the irregular nature of biotechnology financial markets increases operating risk and uncertainty. As a result of large capital requirements, long lead times, and episodic successes and failures, biotech financing cycles have been characterised by periods of high euphoria, only to be followed by deep disillusionment after a cluster of high-profile product failures occur. This subjects early-stage companies to high degrees of financing risks, regardless of their operational progress. While the industry has matured, the predominant venture capital financing model – one product platform or one product, a few investors who provide seed capital, and a long incubation period leading to sale or an IPO (initial public offering) – has not markedly changed, despite reduced numbers of exits and modest overall risk-adjusted rates of return. Recently, the early-stage financing environment has entered a period of dramatic realignment due to the entry of private equity hedge funds into earlier rounds of funding for private and small publicly traded companies.[3,11]

Fourthly, despite intense competitive pressure, product pipelines remain highly valued because large multinational pharmaceutical companies increasingly need more products given declining productivity and growing generic penetration due to loss of patent exclusivity. The incessant need for pipeline products is accentuated by increasingly narrow

molecular targets, large development and commercial infrastructures, and patent expirations. Moreover, the stock market appears to be quite efficient at discerning the qualitative differences among biopharmaceutical companies in terms of market valuations and price-earnings multiples. Thus, the conventional wisdom that new product pipelines are the lifeblood of the biopharmaceutical industry is well founded in historical operating experience and market valuations.[12,13]

In turn, large biopharmaceuticals often turn to small biotechnology companies to augment their pipelines due to a persistent lack of research productivity.[14] It estimated that 30–50 per cent of new molecular entities (NMEs) came from in-licensing versus internal development in the last five years. As a result, the number of pharma-biotech alliances has risen from just 69 in 1993 to 502 in 2004.[15]

While the increasing value of in-licensing is often spurned as a failure of internal development, it often serves as a source of innovation and energy for both because large multinational pharmaceutical firms can allow internal and external programmes to compete, then choose which to move forward after proof-of-principle studies are complete.[16] The paradox is that despite the need for pipeline products, in-licensing is generally viewed as a failure within large companies due to the 'not invented here' syndrome (or persistent corporate or institutional culture that avoids using research or knowledge because of its different origins).

Further, distinctions between traditional Big Pharma companies and smaller biotechs have increasingly blurred due to alliances and converging research interests. This trend is producing increasing competitive intensity in the marketplace, as multiple players pursue drugs with the same mechanisms of action in overlapping indications (ie, multi-kinase inhibitors Sutent by Pfizer and Nexavar by Onyx/Bayer in renal cell cancer; or EGFR inhibitors Tarceva by Genentech/OSI, Erbitux by Bristol-Meyers Squibb/Imclone, and Vectibix by Amgen). A consequence of increasing competitiveness for the same molecular targets is shorter periods of effective intellectual property exclusivity and increasing profit margin pressure.

In sum, the biotechnology sector represents an attractive and promising high growth industry of the future. Despite the formidable odds, the excitement surrounding biomedical enterprises remains high. New business models, however, are needed due to the high-complexity, high-velocity environment in which new biological insights are unfolding, as well as the lack of sustainable productivity to date resulting in success being unusually concentrated in a few firms. While technology and firm success have been highly stochastic, the relative industry-wide market valuations for biotechnology companies have surpassed big pharmaceutical firms in the last few years despite comprising a minority of current sales.[6] Thus, many local, regional, and national governments are focused on identifying and investing in means to strengthen industry cluster competitiveness by enhancing factor conditions to compel start-up firms to locate, grow, and remain in a particular geographic area.

BIOTECHNOLOGY INDUSTRY CLUSTER DEVELOPMENT: FROM LOCAL INITIATIVES TO GLOBAL COMPETITIVENESS AND COLLABORATION

Industry clusters are geographic concentrations of interrelated individuals, firms, and institutions which are both competing and collaborating by accumulating know how and intellectual capital (IP). Firms in clusters often compete for the same employees, technologies, and infrastructure. Importantly, companies in industry clusters routinely sell outside their local or regional markets. In addition, these firms are influential forces for economic development and government policy in their home markets while competing in the global marketplace.[17,18]

The notion of industry clusters is fundamentally about compounding advantages by concentrating the economic factors of production – land, labour, capital, and entrepreneurship. In the 19th century, British economist Alfred Marshall characterised early industrialisation clusters in terms of concentrating natural resources and/or industrial production capacity to create advantages in marginal costs.[19] Breaking away from the economic world of perfect information and placing the entrepreneur as central to delivering value through innovation, Joseph Schumpeter's (1942) observation that the creative destruction wrought by entrepreneurs in close proximity to one another was the driving force for progress.[20] Beginning in the 1950s–1960s, economists Paul Romer and Robert Solow studied the impact of technological progress on industry growth, productivity, and welfare.[21,22] Deindustrialisation in 1970s and early 1980s led to renewed focus on industrial location and regional competitiveness in free trade agreements such as NAFTA, ASEAN, and EEU; and high value-added industries to replicate the successes of knowledge-based clusters such as Silicon Valley which exploits synergistic relationships between industry and academia.[23]

In the 1990s, Michael Porter's influential work on the competitive advantage of nations, based on a study of ten leading trading nations, characterised the drivers of firm productivity with which companies compete rather than the traditional view of natural resources and employment pool. Porter's industry paradigm describes four interlinked factor conditions and activities between companies operating in clusters which can be influenced by government policy – (1) firm strategy, structure, and rivalry in which direct competition spurs competitive intensity, innovation, and productivity; (2) demand conditions of customers which put constant pressure on companies to drive process and product innovation; (3) related supporting industries such as the ecosystem of Silicon Valley which drives innovation through vendor and partner collaborations; and (4) factor conditions which can be created versus inherited such as skilled labour, capital, and infrastructure – all of which require continuous, large-scale investment to be a sustainable competitive advantage.[24] This paradigm argues that governments should invest in specialised factor creation, such as education, and increase firm rivalry by vigorously enforcing anti-trust statutes. This framework has been adopted by many governments in designing economic development policies aimed at creating and growing industry clusters.[16]

A paradox of the importance of firm and industry cluster location is that in an increasingly global world, proximity in high value-added industries are increasing in importance. While globalisation and the ability to operate virtually makes access to the biotech ecosystem – contract manufacturers for process development, research organisations with unique testing capabilities, patent lawyers, venture capitalists, and others who enable start-up formation and development – increasingly accessible. However, these same forces make ongoing collaboration and geographic proximity of knowledge-based industries more important because productivity, rather than natural resources, determines the long-run prosperity of any nation. Consequently, specialised factor conditions tend to be both more vulnerable and more important with increasing globalisation. Location does matter as evidenced by the power of regional innovation clusters, access to management talent, proximity to contract labs and universities, and venture capital tends to converge. Moreover, peer pressure increases competitive intensity, enhances the capacity of firms to scale operations, reduces transactions costs of acquiring talented employees, and lowers the risk premium on the cost of capital.[16,25]

Based on the observed compounding effects of proximity on productivity, competitiveness

and rates of technology diffusion, regions and localities globally have adopted policies to create and enhance the competitiveness of technology industry clusters.[26,27] Moreover, since governments generally have a poor record of choosing individual firm winners or losers, policy makers should focus on enhancing conditions for collaboration and technology transfer.[28] Additional tactics to increase levels of economic activity and productivity include focusing industry cluster efforts in areas where local firms are already competitive, promoting a shared sense of competitiveness and establishing industry trade offices to promote start-up formation, spur economic activity, overcome obstacles, and promote private investment.[29]

Thus, building a conducive environment for technology-based entrepreneurship takes both collaboration and cooperation, which represents another way of flexibly organising a firm's value chain which may be preferred to vertical integration. Clusters promote entrepreneurship because they stimulate new business formation, allow firms to access the benefits of being in large firms with expansive resources, and maintain operational flexibility which enhances sustainability in a highly stochastic, knowledge-based environment.[16] Next, we consider the impact of cluster development and entrepreneurial activity in the context of biotechnology industry development.

Development of biotechnology clusters

Recognising that the biotechnology industry represents an enormous commercial opportunity with tremendous upside potential, communities worldwide are trying to recreate the success of US bioscience clusters in Cambridge, LaJolla, Research Triangle Park, and the San Francisco Bay Area.[30] The most successful biotech cluster initiatives are taking advantage of unique local strengths to create scalability and synergies across functional areas such as biology, information systems, and engineering to drive economic activity and growth.[31] Local, regional, and national governments in nearly all the US states, as well as other developed and many developing countries, have put in place programmes to enhance biotechnology industry activity through a range of incentives including research grants, subsidised office and lab space at research parks, education, and tax credits to spur sector development.[32,33]

Typical of the policy response, Pennsylvania Governor Edward Rendell stated 'the bioscience industry has emerged as one of Pennsylvania's key economic drivers, aided by the state's investments. By bringing together world-class academic and financial institutions, top medical providers, and other organisations, Pennsylvania has developed a mechanism that encourages and supports innovation along the entire bioscience continuum – everything from research and development to commercialisation to early-stage company formation.'[34] The state formed the Pennsylvania Bio organisation with a mission 'to be a catalyst to ensure Pennsylvania's position as a global leader in the biosciences'. The state features 80 per cent of the world's pharmaceutical companies having presence within 50 miles of Philadelphia, $1.6bn in National Institute of Health (NIH) funding with over 1,500 research grants awarded, six National Cancer Institute (NCI)-designated Cancer Centers, 40,000 biological scientists in the region, and over 1,500 biotechnology, device and diagnostic, pharmaceutical, and bio-agricultural enterprises are located in the Greater Philadelphia Region.[35]

Thus, identifying and enhancing decision-making factors for locating start-up and growing biotech companies is critical success factor for policy makers and investors. At the firm level, location decisions can enable success in a highly competitive industry because collaboration with high-status academic institutions increases the probability of success for technology transfer.[26] Proximity also enhances alliance formation due to firm and institutional affiliations which enhances the likelihood of firm survival, organisational

learning, innovation, and credibility among investors.[36]

In a survey of 600 biotechnology companies in 18 countries the following factors, in order of priority, were found to be critical in deciding on the location to start a firm: (1) proximity to world-class research science centres where basic science is being pursued and translated; (2) access to highly skilled staff and a deep talent pool; (3) access to funding from a variety of sources to support various phases of company development; (4) quality-of-life factors such as schools, community, and services; (5) appropriate, adaptable, and affordable lab and office space; (6) entrepreneurial environment which supports and rewards serial entrepreneurs and management teams to start and grow companies; (7) availability of support service providers to create an ecosystem to support virtual product development; (8) access to patients and markets; and (9) favourable government financial incentives and tax treatment.[37] Interestingly, the authors found that the critical factors influencing location decisions were the same for new and established companies alike. Also, the authors concluded that there were ample 'greenfield' opportunities from unexploited and emerging technologies (ie, stem cells, RNAi, etc) to create and influence levels of sustained industry activity.

Recognising the opportunity, 42 out of 50 States, as well as most developed and many developing countries, have started life science economic development initiatives with varying degrees of success to date.[9] The pattern of growth is quite different based on a region's existing economic interest and infrastructure, with drug development around major medical research centres and agriculture applications such as biofuels being pursued in the Midwestern US for example. In general, policy agendas seek to leverage local strengths and resources to provide high-quality jobs, economic vibrancy, increasing tax base, quality of life, and improved standards of living of their constituents.[28]

However, policy agendas are generally supportive of, but not necessarily the same as a financial agenda (Figure 2). Investors, for example, seek financial returns, and capital has no nationality. Having experienced investors who can help enable, govern, and translate science into a business is critical. Further, strategic alliance partners such as large pharmaceutical firms may have yet another agenda (ie, pursue or lock up intellectual property in a class of products).[9] Another policy issue is exit strategy for start-up firms. Particularly in smaller countries, there can sometimes be a public policy tension from the notion that sale to a Multinational can reduce local industrial activity.[38] Ironically, ease of exit is a huge multiplier effect on start-up activity.[39]

	Economic development	Financial return	Pipeline/ Commercialization
Government	√		
Research institutes/Universities	√	√	
Angel		√	
Venture Capital		√	
Public investors		√	
Strategic Investors/Alliance partners		√	√

Figure 2: Access to funding: What's the agenda behind the capital?

In sum, enhancing industry cluster activity must address unique elements of the biopharmaceutical market including: (1) high capital costs and lengthy product development cycles nearing $1bn from discovery to market; (2) addressing unmet medical needs usually increases net cost to healthcare system; (3) Medical systems are uniquely 'de-linked' among the prescribing physician, user (patient), and payor (insurance); and (4) All companies compete globally for intellectual property and capital, and the presence of asymmetries in the agendas of those who provide financial capital drives strategy.

CONCLUSIONS

Broad advances and commercial success, particularly in biopharmaceuticals have captured the attention and aspirations of economic development officials, business people, and investors alike. In the case of biopharmaceutical industry specifically, local, regional, and national investors and governments are keen to identify means to strengthen industry cluster competitiveness and productivity by enhancing those conditions necessary to compel start-up firms to locate, grow and remain in a particular geographic area.

This paper has explored three interrelated issues in understanding and enhancing entrepreneurship in biopharmaceutical industry clusters. The framework of analysis was first to identify industry dynamics affecting growth patterns and competitiveness. Next, the nature of industry clusters and biotech industry evolution was investigated to determine the impact of location and proximity in an era of increasing globalisation. Finally, enabling factors and frameworks which determine biotech entrepreneurship activity, productivity, and sustainability were reviewed for potential investor and policy implications.

First, the global biopharmaceutical industry represents an attractive and promising high-growth industry of the future with over $70bn and 700 publicly traded firms posting double-digit growth in North America, Europe, and Asia-Pacific in 2006. A paradox, however, is that despite tremendous investment, productivity over the years has been decreasing, with higher costs of drug development and longer clinical development timelines. The average drug takes over $1.0bn and 12 years to go from laboratory to approval. Part of the reason for rising development costs is the high failure rate of product candidates in clinical trials due to increasingly specific molecular targets for unmet diseases which necessarily increases development risk, complexity of biologic systems with compensating mechanisms, overlapping intellectual property claims, and shifting regulatory requirements. In terms of policy making, a key insight is that the heavily regulated, high complexity–high velocity biopharmaceutical environment makes choosing specific winners and losers virtually impossible.

Secondly, the nature of industry clusters and biotech industry evolution was investigated to determine the impact of location and proximity in an era of increasing globalisation. Industry clusters are important, particularly in knowledge-based industries where the benefits of proximity such as socialisation, employment, and shared services can be leveraged into compounding advantages and lowered transaction costs. Location and proximity continue to matter, but rapid disruption is afoot as enabling technologies increase the 'virtual proximity' of global collaboration and coordination. Thus, proximity matters but the importance of physical location appears to be less so or as one venture capitalist stated, 'Silicon Valley as a locality matters less and less every day, but the Silicon Valley mentality matters more and more globally.'

Thirdly, these industry trends offer interesting implications for enhancing biotech entrepreneurship and firm productivity, as well as investor and policy makers. Foremost, frameworks for determining and enhancing regional competitiveness can be nurtured. Governments and investors seeking to create and enhance biotech entrepreneurship face many enabling trends,

including: the increasing numbers of science graduates worldwide, accelerating pace of scientific and technological insights, globalisation, which is enabling collaboration, democratising forces of the Internet, and a relentless competitive pressure to innovate.

Start-ups come in three parts: ideas, financing, and people. The forces that shape the pace and intensity of business activity include the nature and speed of innovation, stock of human capital, and structure and incentives of capital markets. As such, policy agendas should focus on increasing factor conditions to enhance start-up formation, alliances, and company development. Science-based entrepreneurship in a fast-paced and complex environment is more likely to succeed with the right mix of technology and talent – in other words, advantages compound and they compound dramatically via access to better funding, employees, customers, and other aspects of competitive advantage.

Areas for future research

There are several areas to extend the biopharmaceutical industry cluster formation and competitiveness issues explored in this paper. One area is to determine the impact of globalisation on reducing or enhancing the competitive advantages of existing industrial clusters. Another area of interest is the role of culture and risk taking in innovations by conducting a comparison and contrast of key players across geographies – that is, venture capitalists, scientists, university technology transfer offices, management from large and small companies, etc – to determine factors of competitiveness such as preferences for localisation in collaboration, exit strategies and time horizons, and degree of focus versus diversification in pursuing technologies. Finally, the dominant presence of current industry clusters constitutes a formidable barrier to entry favouring incumbents. It would be interesting to consider asymmetric approaches for emerging entrants into biotechnology sectors.

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