

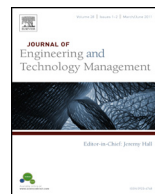


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Radical innovation from the confluence of technologies: Innovation management strategies for the emerging nanobiotechnology industry



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ABSTRACT

We investigate how the confluence of technologies can lead to radical innovation, thus creating opportunities at the firm and industry levels. To do so, we conduct a detailed examination of the development of the transistor and of two nanobiotechnology drugs – Doxil[®] and Zevalin[®] – from an innovation management perspective. We argue that three innovation management strategies are central to the development of radical innovation from the confluence of technologies, namely: importing ideas from broad networks, creating environments which allow for deep collaboration, and technology-market matching.

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Introduction

There is enormous potential for innovation from the confluence of technologies (Sharp et al., 2011), but little is known about how the confluence of technologies can lead to the creation of radical innovation and subsequently the emergence of new industries. A confluence of technologies is defined as a new combination of previously distinct technologies, and evolves when researchers begin to work at the intersection of two or more technology streams, and when products based on this intersection of technology begin to emerge. Radical innovation dramatically improves existing product attributes, enables entirely new functionality, or reduces product cost very significantly (Foster, 1986; Leifer

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et al., 2000). An often cited example of radical innovation is that of the transistor (Morton, 1971; Riordan and Hoddeson, 1999; Gertner, 2012), which was enabled by technological advances and knowledge integration across the fields of advanced materials, physics, electronics and instrumentation (Globe et al., 1973a,b). Several radical innovations have already been enabled by the confluence of biotechnology and nanotechnology streams, including effectively targeted drug delivery, rapid diagnostics, and nanoscale tissue engineering. Many firms have already been formed around these innovations (Maine et al., 2012a; Wagner et al., 2006). Further radical innovation is anticipated, from both ambitious and uncertain multidisciplinary research programs and from serendipitous discoveries (Sharp et al., 2011). Although the development and exploitation of radical innovation is an important and enduring research theme (Foster, 1986; Utterback, 1994; Leifer et al., 2000), scholars have not yet adequately explored how radical innovation is enabled by the confluence of technologies.

In this paper, we explore the innovation management strategies that connect the confluence of technologies to radical innovation by developing and analyzing a series of case studies. By innovation management strategies, we mean the purposeful actions that company founders and technology managers take to influence the productivity and impact of their scientists and product development teams. We focus on innovation management strategies so that they may guide managers at both large firms and new ventures who are attempting to create value from the confluence of technologies. We argue that three innovation management strategies are central to the development of radical innovation from the confluence of technologies: importing ideas from broad networks, creating environments which allow for deep collaboration, and technology-market matching. Importing ideas from broad networks involves a broad search and synthesis of concepts from disparate technology streams. Deep collaboration refers to interactive input and feedback between R&D groups, where “each group makes an essential contribution to different stages of the research process” (Rafols and Meyer, 2007). Technology-market matching involves recognition and prioritization of the most promising technology solutions for a market application or the most appropriate markets for a technology. Through analysis of three case studies, we demonstrate the commonality of these three innovation management strategies in enabling radical innovation at the confluence of technologies.

The context in which we explore strategies which connect the confluence of technologies to radical innovations is the emerging nanobiotechnology industry. After an analysis of the well documented development of the transistor, we provide detailed and novel case studies of two of the earliest and most significant nanobiotechnology innovations – Doxil[®] and Zevalin[®] – both in the new drug class of therapeutic nanoparticles (Burgess et al., 2010). We provide nuanced detail on the role of both the confluence of technologies and the role of specific innovation management strategies in enabling these radical innovations of liposomal drug delivery and radiolabeled antibody therapy. This context is especially appropriate to our research question as all three case studies document radical innovation enabled by the confluence of technologies. Advances in the technological streams of physics, advanced materials, electronics and instrumentation enabled the transistor, from which the modern consumer electronics industry emerged. Similarly, advances across several previously distinct technological fields enabled radical innovations in therapeutic nanoparticles, and a nanobiotechnology industry is currently emerging.

This paper contributes to three distinct knowledge domains: innovation management, opportunity creation from the confluence of technologies, and innovation management strategies for the emerging nanobiotechnology industry. The innovation management strategies that emerge from our paper are relevant across industry contexts, demonstrating how radical innovation emerged from the confluence of technologies. Further, we make a contribution by integrating streams of management literature to suggest that opportunity creation may be more likely at the confluence of technologies. Finally, we provide innovation management strategies for the emerging nanobiotechnology industry, a context in which very few studies of innovation have been conducted. Management researchers have recently begun examining opportunities created by the confluence of biotechnology and nanotechnology; however, studies to date have been dominated by patent and bibliometric analysis, which focus on invention rather than innovation (No and Park, 2010; Takeda et al., 2009; Grodal and Thoma, 2009; Pei and Porter, 2011; Barirani et al., 2013). The few valuable case study contributions in the context of nanobiotechnology innovation focus either at the lab level (Rafols, 2007; Rafols and Meyer, 2007) or extrapolate implications from the ICT industry to the nanobiotechnology industry

(Hacklin et al., 2009). The emerging nanobiotechnology industry, replete with complex relationships, is an ideal setting for conducting case study research (Yin, 2009). Thus, through reviewing literature from multiple streams and using rich, nuanced case studies, we develop innovation management strategies which elucidate how radical innovation is enabled at the confluence of technologies. We also develop specific implications for technology entrepreneurs in the emerging nanobiotechnology industry as we believe that the significant differences in terms of product development timelines and the stringent regulatory standards for toxicity and safety warrant in-depth examination of specific cases of nanobiotechnology innovation. Further, we discuss the current stage of industry evolution in the nanobiotechnology industry and compare that to the industry evolution of the transistor-enabled consumer electronics industry.

Our paper proceeds as follows. First, we review the management literatures which have relevance to opportunity creation from the confluence of technologies. Next we present the historical case study of the transistor and demonstrate the role of the confluence of technologies and the innovation management strategies that enabled radical innovation. We summarize findings from the literature review and the transistor case study before moving to a current confluence of technologies – that of biotechnology with nanotechnology. We present two detailed case studies of radical innovation: Doxil[®], which was the first targeted liposomal drug delivery process approved by the FDA, and Zevalin[®], a radiolabeled antibody therapy which has provided a remarkable increase in the efficacy of cancer treatment. We then demonstrate the confluence of technologies and analyze the role of innovation management strategies in enabling these radical innovations. We compare and contrast the opportunities and challenges of innovation management between the transistor-enabled consumer electronics industry and the emerging nanobiotechnology industry. Finally, we draw implications for technology entrepreneurs in the emerging nanobiotechnology industry.

Literature review

Although there is nothing in the innovation literature that states that radical innovation is more likely at the confluence of technologies, there are three streams of literature which provide theories and frameworks which can be used to link radical innovation to the confluence of technologies. In this section, we summarize the three broad literatures which have relevance to opportunity creation from the confluence of technologies, namely: the strategic management of technology, industry evolution, and product development literatures. Key arguments from this review are summarized in Table 1.

Strategic management of technology literature

The strategic management of technology literature explores value creation, opportunity exploitation, and competitive advantage resulting from technology development. This literature provides some evidence that broader technological inputs may lead to opportunity creation. Opportunity recognition and resource allocation routines emerge as potential mechanisms to link radical innovation to the confluence of technologies.

Resource based theory posits that a firm's resources and capabilities are developed over time, and act to enable and constrain the strategic and product development choices available to the firm (Penrose, 1959). Scholars researching technology capabilities argue that sustained innovative performance is generated through a systematic and continuous process of accumulation and regeneration of resources and competences (Hamel and Prahalad, 1994; Leonard, 1995). Tripsas (1997) further proposes that an added stream of technology competency may provide complementary or supporting elements to a firm when it develops an innovation. For example, phototypesetter firms which developed a competency in electronics were able to develop the first typewriters with electronic memory. Suzuki and Kodama (2004) provide evidence that industry entrants from outside the value chain tend to have a larger market share than industry entrants from within the value chain, and suggest that this greater success of firms entering from outside of an established industry is caused by new technologies and market linkages. Teece (1986) proposes that such novel combinations of technologies, when protected by an adequate appropriability regime, can lead to firm success. Thus,

Table 1

Literature proposing firm opportunity at the confluence of technology streams.

| Authors | Proposition about firm opportunity at the confluence of technology |
|--|---|
| <i>Strategic management of technology literature</i> | |
| Tripsas (1997) | An added stream of technology competency may provide complementary or supporting elements to a firm when it develops an innovation. |
| Teece (1986) | Novel combinations of technologies, when protected by an adequate appropriability regime, can lead to firm success. |
| Pisano (2006, p. 26) | A mix of technology streams have vastly improved drug development and advanced biotechnology. |
| Subramanian and Soh (2010) | Greater technological search breadth leads to greater technological performance in the biotechnology sector. |
| Suzuki and Kodama (2004) | Greater success of firms entering from outside of an established industry is caused by new technologies and market linkages. |
| Allen et al. (1980), Brown and Utterback (1985), Lee et al. (2001) | Successful new product innovations typically come from firms which take advantage of the different technological and market ideas available in broad networks. |
| <i>Industry evolution literature</i> | |
| Schumpeter (1934) | Schumpeter argued that the greatest opportunities for new firms were created by technological change. |
| Utterback and Abernathy (1975) | As an industry forms and grows around a technological change, there is rapid initial product innovation and a large influx of new entrants. |
| Suárez and Utterback (1995) | If technology confluence leads to greater technological developments, it also leads to greater opportunity for new ventures. |
| Adner and Levinthal (2002) | Recognizing and developing new applications for emerging technology will be key to success in emerging technology sectors. |
| <i>Product development literature</i> | |
| Checkland (1981, pp.60–66); Ackoff (1999a) | Product development decisions should be looked at holistically as the resulting system of connections and interactions produce the unexpected and disproportional outputs that are radical innovations. |
| Ackoff (1999b) | There are a greater number of unexplored, possible combinations at the intersection of academic fields than there are within a single academic field, and that this leads to greater opportunity for significant discovery at the intersection of fields. |
| Globe et al. (1973a) NSF-C 667 "Science, Technology, and Innovation" | Confluence of technology constitutes a decisive event in the development of innovations with high social impact. Decisive events are those without which the innovation would not have occurred or would have been delayed by a long period of time. |
| Leonard (1995) | A firm's chances for radical product innovation at the intersection of technologies are enhanced by nurturing both technological gatekeepers (broad search) and boundary spanners (technology integration). |
| Morton (1971), Riordan and Hoddeson (1999) | To enhance chances for radical innovation, nurture the transfer of ideas from distinct technological fields. |

resource based theory scholars propose that added streams of technology can lead to more effective product innovation.

Selecting and applying external technology competencies is generally dependent on managerial recognition of potential opportunities. Several strategic technology management authors write about the importance of opportunity recognition to technology based firms (Garud and Rappa, 1994; Kemp and Rip, 2001; von Hippel, 2001; Shane, 2005). A stream of the strategic management literature has developed the argument that dynamic capabilities are of prime importance in enabling firms to succeed in emerging technology industries (Teece et al., 1997; Eisenhardt and Martin, 2000; Maine and Garnsey, 2006). These researchers suggest that dynamic capabilities include the routines that allow for recognition of potential ways to import appropriate new resources or recombine existing firm resources, and resource allocation routines which allow firms to act on this recognition by developing new products to create or meet the needs of emerging or rapidly evolving industries. Technology-market matching is one type of dynamic capability that is vital to innovation

management for broad technologies with applications across multiple markets (Maine and Garnsey, 2006).

Other authors in the strategic technology management field have proposed that there are more opportunities and rewards in certain technological sectors or streams than others (Rosenberg, 1974; Jaffe, 1986; Klevorick et al., 1995; Shane, 2001). Rosenberg (1974) argues that the supply side is key to understanding technological opportunity, and, hence, that different firms will have different opportunities, different technological sectors will have more opportunities, and firm success in many sectors will be driven by technological change. Jaffe (1986) argues further that firms can benefit disproportionately from opportunity-rich technological sectors if they already have productive R&D in these technologies. He suggests that this effect is created both by a firm's presence in an opportunity-rich technology sector and by knowledge spillovers from a firm's competitors and/or government and university labs, from which a firm can benefit if it already has some resident capability. He also finds that firms move their technological competencies over time into more productive R&D areas, which suggests that these firms are responding to greater technological opportunity.

There is some evidence in the strategic management literature that suggests that technological diversity leads to opportunity creation. For instance, Pisano (2006) illustrates how a mix of technology streams has vastly improved drug development and advanced biotechnology: "recombinant DNA, for the production of proteins; hybridization, for the production of monoclonal antibodies; and combinatorial chemistry, for the mass synthesis of large numbers of novel chemical entities." Subramanian and Soh (2010) demonstrate that greater technological search breadth leads to greater technological performance in the biotechnology industry. These findings lend support to the idea that a unique and diverse mix of technology streams creates competitive advantage for a firm.

The last relevant stream within the strategic management of technology literature is network theory. Successful new product innovations typically come from firms which take advantage of the different technological and market ideas available in broad networks (Allen et al., 1980; Brown and Utterback, 1985; Lee et al., 2001; Chesbrough, 2003). In the knowledge intensive biotechnology industry, Powell et al. (1996) demonstrate that firm growth depends on a firm's network and on the firm's experience in managing their network ties. Bliemel and Maine (2008) argue that new technology based firms are most successful when they are moderately embedded in networks, with a mix of strong (efficiency) and weak (exploratory) ties. In the evolution of new technology sectors, Soh (2010) demonstrates that network centrality, along with broad knowledge sharing, has a positive influence on a firm's innovation performance. Thus, network theory scholars argue that effectively linking together diverse technological capabilities and ideas leads to greater firm success in knowledge based industries.

Industry evolution literature

The industry evolution literature proposes that radical innovation leads to new industry creation and greater opportunity for new ventures. It also suggests that market recognition may link the confluence of technologies to radical innovation. The industry evolution literature argues that industries develop in recognizable and even predictable ways over time (Abernathy and Utterback, 1978; Tushman and Anderson, 1986) and that there are national differences created by the impact of national systems of innovation over time (Nelson and Winter, 1982). One aspect of industry evolution is the path dependence experienced by firms. The theory of path dependence argues that the present and future are impacted by actions and experiences of the past, and that these act as a constraint on the possible evolutionary paths of firms (Arthur, 1988; Dosi, 1988; Garud and Karnoe, 2003). Industries also evolve because of technological change: Schumpeter (1934) argued that the greatest opportunities for new firms were created by technological change and that industries would reinvent themselves and change the key actors through a process of creative destruction. As an industry grows around a technological change, there is rapid initial product innovation and a large influx of new entrants. Over time, as a dominant design is established, the rate of product innovation slows, and many less successful firms exit the industry (Utterback and Abernathy, 1975; Suárez and Utterback, 1995). Industry evolution scholars propose that the greatest opportunity exists at the early stages of industry evolution, shortly after the first commercialization of the new technology. Thus, if technology

confluence leads to greater technological developments, industry evolution scholars would argue that it also leads to greater opportunity for new ventures.

Firms can also impact their chances of successful commercialization through strategic consideration of the evolution of the markets for their technologies. Rogers (1983) and Moore (1995) argue that a firm's target customer and selling strategy should change in any given market as that market evolves over time. Christensen (1997) posits that new ventures have the best chance of success if they exploit technologies and business models which will not appeal to the current customers of incumbent players. Adner and Levinthal (2002) argue that firms need not concentrate so much on technological development as on recognizing and developing new applications for emerging technology. For emerging technology industries, Leonard (1995) argues that product market experimentation is the most effective strategy for any firm: this is linked to the technology-market matching capability proposed in the strategic management of technology literature. If the confluence of two or more technologies leads to new emerging markets, these industry evolution scholars argue that new ventures' market recognition is key to their success.

Product development literature

The product development literature argues that diverse technological streams are important for significant inventions and provides some ideas of innovation management strategies which may facilitate radical innovation from the confluence of technologies. Systems scholars argue that product development decisions should be looked at holistically (Ackoff, 1999a) as the resulting system of connections and interactions produce unexpected and disproportionate outputs that are radical innovations. Ackoff (1999b) pointed out that there are a greater number of unexplored, possible combinations at the intersection of academic fields than there are within a single academic field, and that this leads to greater opportunity for significant discovery at the intersection of fields. Thus, an innovation management strategy would be searching broadly and synthesizing concepts from previously disparate fields. Systems scholars also propose that firms facing environmental uncertainty should pursue a strategy of experimentation (de Neufville, 1990; Ackoff, 1999a; Thomke, 2003). Systems scholars would argue strongly that the confluence of technologies leads to increased opportunity for radical innovation.

NSF-C 667 "Science, Technology, and Innovation", a historical study of major innovation product development, examined the decisive events¹ that led to the development of innovations with high social impact (Globe et al., 1973a). Through detailed case studies and analysis of major technological innovations they found that the confluence of technologies was important in over a third of the decisive events leading to the development and commercialization of each innovation. It also demonstrates the need for complementary innovation to enable radical product innovation. In addition to complementary innovation, a firm's chances for radical product innovation at the intersection of technologies are enhanced by nurturing both technological gatekeepers and boundary spanners. Leonard (1995) notes how these innovation management techniques enable companies to work productively at the intersection of technologies and disciplines.

The implanted heart pacemaker is an example of a radical innovation formed from the confluence of technologies. An implanted heart pacemaker is a fully implanted device that regulates a person's heartbeat. Throughout the 1950s, engineers, researchers, and medical practitioners in Canada, the US, and Sweden pursued a goal of designing, refining and implanting a device to restart the heart by electrical stimulation (Elmqvist, 1978; Hopps, 1981). Advances in multiple streams of technology were required, including cardiac physiology, surgical techniques, battery technology, biomaterials and electrodes, semiconductors and electronics (Globe et al., 1973b). The commercialization of an implantable heart pacemaker spurred Medtronic to grow into a \$4 billion biomedical firm and also created many new supplier firms. In 2005, 800,000 pacemakers were implanted worldwide (Gott, 2007).

¹ Decisive events are those without which the innovation would not have occurred or would have been delayed by a long period of time.

Another example is the development of soft magnetic ferrites, which replaced iron in such applications as inductor cores and telecommunications transformer cores because of their far greater efficiency, size and cost, and enabled many new applications such as microwaves, early computer memory storage, cellular phones, and hybrid vehicles. To develop magnetic ferrites, scientists and engineers within Philips made and integrated advances in the diverse technological fields of crystal chemistry, telecommunications, ceramic materials and magnetic theory. To do so, they overcame significant challenges in the integration of such a broad range of technologies in industrial laboratory research (Snoek, 1947). Errors and unplanned experiments also played an important role in making interdisciplinary advances (Snoek, 1947; Stijntjes and Van Loon, 2008).

Evidence of innovation management strategies to enable the exchange of tacit knowledge and serendipitous discovery – whether purposeful or not – can be found in each of these radical innovations. In the case of the implantable heart pacemaker, it can be inferred to be present in the development of the implantable pulse generator by Greatbatch, Chardick and Gage (Globe et al., 1973b). In the case of the development of soft magnetic ferrites, such managerial strategies were created and utilized at Philips Research Laboratories (Snoek, 1947; Stijntjes and Van Loon, 2008). Most famously, innovation management strategies led to the creation of the highly interdisciplinary, co-located teams with complementary skillsets which developed the point contact transistor and the planar transistor (Morton, 1971, pp. 40–43, 46–48). The ways in which opportunity was created at the confluence of technologies in the development of the transistor is discussed in detail in the next section.

Historical case study of confluence: the transistor

The development of the transistor demonstrates how a confluence of technologies can lead to radical innovation and the opportunity created thereof. A transistor is a semiconductor device that regulates electrical current. The planar transistor replaced the vacuum tube – with a major advantage being a vast reduction in size – and has since evolved into integrated circuits and has been the basis for the modern consumer electronics industry. Technological advances in the diverse fields of physics, advanced materials, electronics and instrumentation, along with the integration of these advances, were required to develop the transistor (Table 2).

At Bell Laboratories in New Jersey, researchers from very different areas of technological expertise – chemists, physicists, metallurgists, electrical engineers, and mechanical engineers – were asked to work together in a fast-moving project team, and their offices and labs were purposefully placed in close proximity to one another, to allow for unexpected transfer of ideas (Morton, 1971, pp. 40–43, 46–48; Riordan and Hoddeson, 1999, pp. 117, 120, 141; Gertner, 2012, p. 79). Bell Labs executive vice-president Mervin Kelly also selected theoreticians – Shockley and Bardeen – alongside experimentalists – Brattain, Pearson and Teal – for this high profile solid-state research group. Morton (1971, p. 43) argues that this organizational design, along with a culture and an environment at Bell Laboratories conducive to experimentation, had a major influence on the invention and refinement of the transistor. As depicted in Table 2, advances in diverse fields were required, and the key early advances all occurred at Bell Labs from 1945 to 1951, building on their longer term research competencies. Key advances were the 1947 development of the point-contact transistor, by physicists Bardeen and Brattain, the development of junction theory in 1949 by physicist Shockley, and Teal's technique for growing single crystals of germanium in 1949 and single crystals of silicon in 1951. Notably, physical chemist Teal drew not only on mechanical engineering and physics through his Bell Lab colleagues, but also on a relatively unknown materials science research paper from 1917. Continued refinement in each of these fields enabled Bell Labs to produce the first junction transistor in 1950.

The confluence of technologies that enabled the development of the transistor created enormous opportunity for new firms, profit creation, firm growth and the development of the modern consumer electronics industry. Bell Laboratories themselves made very little profit from the invention of the transistor: AT&T first licensed the patent rights to the transistor for merely \$25000. Then, in 1956, they relinquished the patent rights to the transistor, as they were deemed to be a public good. However, several new ventures formed around the transistor, furthered the technology, and profited from the commercialization of the transistor (Rothwell, 1989; Utterback, 1994). Shockley, feeling shut

Table 2

Technological advances enabling the Transistor.

| Transistor | Physics | Advanced materials | Electronics | Instrumentation |
|------------|---------------------------------|--|---|--|
| Advance 1 | Point Contact Transistor (1947) | | | |
| Advance 2 | Junction Theory (1949) | Germanium Single Crystal (1949) | Junction Transistor (1950) | |
| Advance 3 | | Silicon Single Crystal (1951) | | |
| Advance 4 | | | Diffused-Epitaxial Transistor (1960) | Oxide Masking, Photolithography (1959) |
| Advance 5 | | Thin metal films (tantalum) for interconnection, resistors and capacitors (1961) | Integrated Circuits (1961) | |
| Advance 6 | | | Beam-lead sealed-junction silicon circuits (1966) | |

out of key leadership roles, left Bell Labs and eventually started his own research intensive semiconductor company near Stanford University. Eight scientists and engineers (from six different disciplines) who had worked together at Shockley's company left in 1957 to form the highly successful venture Fairchild Semiconductor. Still in R&D mode, these scientists and engineers solved problems in metallurgy, chemistry and physics to ship their first batch of transistors in 1958, and went on to develop and commercialize the planar transistor with their breakthroughs in reliable production methods, including physicist Hoerni's idea to leave oxide over the junctions (Rothwell, 1989; Riordan and Hoddeson, 1999, pp. 262–263; Chesbrough, 2003). Fairchild's interdisciplinary team went on to develop the first Integrated Circuit, commercialized in 1961 (Riordan and Hoddeson, 1999, pp. 264–265). Fairchild's revenues grew from \$0.5 million in 1960 to \$27 million in 1967 to \$520 million in 1978 (Rothwell, 1989) and they played a key role in the emergence of the semiconductor industry, now a nearly \$300 billion industry (WSTS, 2013).

Intel was another venture created when Moore and Noyce left Fairchild, and went on to capture much further value by concentrating on production and exploiting existing R&D on the transistor and integrated circuits (Chesbrough, 2003). Entirely new industries, that of semiconductor manufacturing, and subsequently, a vast number of new consumer electronic product markets, were created from this radical innovation.

Summary: literature review and historical case study

Thus, the strategic management of innovation literature, the industry evolution literature, the product development literature, and the historical case study of the transistor demonstrate that technology confluence can be an important factor in radical innovation and opportunity creation. All three literatures support the idea that the confluence of two or more technologies increases opportunity creation. These literatures, along with the case study, provide us with the basis to propose that radical innovation is more likely at the confluence of technology streams than emanating from a single stream of technological knowledge.

Our research question is “How is radical innovation connected to the confluence of technologies?”. We aim to address this question through extended analysis of the transistor case study and through new evidence and analysis of two radical innovations enabled by the confluence of biotechnology and nanotechnology. To date, few managerial recommendations have been made which adequately guide firms attempting to profit from the confluence of technologies: the main knowledge integration recommendation made from the development of the transistor was to co-locate theoreticians and experimentalists with diverse disciplinary backgrounds (Morton, 1971, p. 43). Thus technology

managers have little managerial guidance in attempting to profit from the current confluence of biotechnology and nanotechnology.

The case study of the transistor demonstrates that the confluence of technologies can promote radical innovation, creating opportunities at the firm and industry level, including, in this case, the creation of new industries. This confluence may not lead to radical innovation in a linear fashion, as the challenges of integrating new knowledge from multiple disciplines can be substantial, and uncertainty is inherently high in radical innovation. However, despite these challenges over long timelines, the payoffs from such a confluence can exceed even the most optimistic expectations.

When re-examining the transistor case study in the light of our literature review, we see additional innovation management strategies beyond co-location of scientists from diverse disciplinary backgrounds. We also note the Bell Labs development team's exposure to broad networks, through the connections of Shockley and Bardeen, at MIT and Harvard respectively. Shockley used those networks in recruiting Bardeen. We see considerable evidence of a deep collaborative environment. Notably, Shockley acted as both a big picture thinker and a knowledge integrator, and led highly interdisciplinary teams both at Bell Labs and at his subsequent start-up firm. Although there was some personal animosity between Shockley and other members of the project teams at Bell Labs, there was definitely an environment which encouraged technical debate and disagreement. Lastly, we see the purposeful matching of technological solutions with market applications at Fairchild Semiconductor with their development of the planar transistor for more reliable large scale production.

Nanobiotechnology case studies of confluence

Next we consider a confluence of technologies currently underway, with some radical innovation already having occurred, but much earlier in the industry emergence than the confluences which led to the development of the transistor and the subsequent growth of the consumer electronics industry. In the emerging nanobiotechnology industry, the confluence of technologies is particularly notable. The novel attributes of nanotechnology married to existing biotech and pharmaceutical knowledge and techniques has enabled major leaps forward (Sharp and Langer, 2011; Allen and Cullis, 2004). Two case studies of radical innovation emanating from the confluence of nanotechnology and biotechnology are presented here, both in the new drug class of therapeutic nanoparticles. We note the tremendously long time line of discovery and commercialization, when considering the key interdisciplinary advances that led to both innovations.

Several authors have studied the patent and publication landscape to reveal emerging technological trends in nanobiotechnology (No and Park, 2010; Takeda et al., 2009; Grodal and Thoma, 2009). Four areas emerge from such bibliometric analysis as active hubs of nanobiotechnology convergence: nanostructures; drug delivery and biomedical applications; bio-imaging; and carbon nanotubes and biosensors (Takeda et al., 2009). Targeted drug delivery is the most dramatic of these nanobiotechnology applications, with the most highly anticipated potential outcomes, and with dozens of passively targeted nanobiotechnology products already clinically approved (Farokhzad and Langer, 2009; Burgess et al., 2010; Aggarwal, 2012), and several actively targeted therapeutic nanoparticles under development (Burgess et al., 2010).

The case of drug delivery exemplifies the potential that nanotechnology brings to biotechnology. A common problem faced by biotechnology and pharmaceutical companies has been excessive damage to healthy tissue using systemic treatments such as chemotherapy. More recently, when attempting targeted drug delivery, the large particulate nature of drug molecules prevented efficient uptake of the drugs into intended tissue. Low solubility of therapeutic drugs has also been a limiting factor. However, the use of techniques and concepts from nanotechnology has facilitated the synthesis of drug molecules that are vastly more amenable to diffusion, uptake and bio-assimilation and far more efficacious and accurate targeted delivery carriers, receptors, and activators. Armed with these improvements, existing drugs become more useful with wide reaching benefits for patients. New active pharmaceutical ingredients are also enabled.

Although this emerging field holds tremendous promise for economic and social value creation, there is as yet scarce management literature on the development and commercialization of nanobiotechnology innovations. The few relevant studies provide useful guidance on knowledge

integration and product development (Rafols and Meyer, 2007; Juanola-Feliu et al., 2012), but focus on the differing level of product development challenges when knowledge is more or less mature and codified. There is very little known about innovation enabled by the confluence of biotechnology and nanotechnology and less still on innovation management strategies to encourage radical innovation.

Thus, in the next section we present a case study of the discovery of the first FDA approved nano-therapeutic, Doxil[®]. Subsequently, we present a second nanobiotechnology case study of targeted drug delivery, this time of Zevalin[®], the first targeted radio immunotherapy drug delivery system. In both cases, we demonstrate the role of the confluence of technologies, the long timelines and high levels of uncertainty involved. We assess the impact of these radical innovations thus far. Although many firms have entered this emerging nanobiotechnology industry (Wagner et al., 2006; Maine et al., 2014), we argue that much is yet to come, that there is great opportunity for technology ventures, and that we can learn from the innovation management strategies utilized to facilitate radical innovation from the confluence of technologies.

Nanobiotechnology case study A: liposomes for drug delivery (Doxil[®])

Several interdisciplinary scientists were involved in the development of liposomes and using it to deliver the anti-cancer drug doxorubicin to tumors in the human body. The initial discovery of liposomes was made by a trained physician, hematologist and occasional anesthetist, A.D. Bangham, who was investigating the physical and chemical properties of cell membranes using phospholipids in 1956. Many remarkable properties of cell membranes such as selective permeability were unaccounted for mainly due to a lack of a credible cell membrane model at the time (Bangham, 1993). The 1960s were an exciting time for cell membrane researchers. While some researchers had demonstrated techniques for the creation of the Black Lipid Membrane (BLM) (Mueller et al., 1962), others with professional expertise in the physical, chemical, biological, clinical medicine and instrumentation domains, were being recruited at the Babraham Institute in Cambridge, UK (Bangham, 1995). One of the scientists who did part of his doctoral research at Babraham during this period was Y. Barenholz (Barenholz, 2012). The confluence of knowledge from these multiple domains and the coexistence of these scientists at Babraham provided a unique opportunity for the recognition and development of liposomes as an alternative model membrane system. While experimenting with a new electron microscope (funded by the Wellcome Trust), Bangham and R. W. Horne were able to visualize the cellular structure of animal membranes at the nano-scale in 1961. They found that “phospholipids in aqueous negative stain were spontaneously forming closed membrane systems” (Bangham, 1993). The microscopic pictures served as the first real evidence for the cell membrane being a bilayer lipid structure. The significance of this discovery was highlighted by Keith Miller (Massachusetts General Hospital) who said “To a field whose most powerful model nearly seven decades ago had been a jar of olive oil, the liposome’s arrival was a liberating force” (Deamer, 2010). It was considered to be the membrane equivalent of discovering the double helix structure of DNA.

Liposomes proved to be a revealing model of the cell membrane with remarkable packaging powers of interest to the pharmaceutical community. This idea stemmed from finding that liposomes were not recognized as being “foreign” by the first line defences of a living animal. Later research highlighted the ability of nano-scale liposomes to take advantage of the enhanced permeation and retention effect (EPR) which meant that tumor cells having a large number of porous blood capillaries were permeable to nanoparticles 100nm and smaller (Barenholz, 2012). This led to selective retention of such nanoparticles within tumor cells opening up the possibility of targeted drug therapy or a “magic bullet” for cancer treatment as had been visualized at the beginning of the twentieth century (Gabizon, 2001). The most effective anti-cancer drug of the time was doxorubicin which was effective against a wide variety of tumors. However, one major weakness of doxorubicin treatment was its high cardiotoxicity which could lead to irreversible congestive heart failure. It was realized that encapsulating the therapeutic drug doxorubicin in liposomes could improve the delivery of the drug to the target tumor while simultaneously reducing toxicity because of targeted delivery to tumor cells. But, as initial studies showed, liposomal doxorubicin faced several problems as the liposomes which were stable in the test tube were not as stable in human plasma (Poste, 1983). There had to be sufficient levels of the therapeutic drug within the liposomes to increase efficacy. Enough liposomes

had to pass through the tumor vasculature and the liposomes had to release the drug once inside the tumor (Fenske and Cullis, 2008).

A US based start-up company Liposome Technology Inc. (LTI), founded by Demetrios Papahadjopoulos, Frank Szoka and Nick Arvanitidis at Menlo Park in 1981, had been working on liposomal drug delivery since its inception. Arvanitidis had a PhD from Stanford in Engineering Economic Systems and had worked for a decade as a natural resources consultant before shifting to the biotechnology industry (Potterf and Sorenson, 2009). LTI had several partnerships with other larger firms for the commercialization of liposomes (Liposome Technology Inc., 1988; Jacobs, 1985). They were also on the lookout for scientists working on liposomal drug delivery. Papahadjopoulos as the scientific co-founder of Liposome Technology Inc. introduced the CEO Nick Arvanitidis to Barenholz (Barenholz, 2012). After discussions with Barenholz, LTI decided to support his research and licensed-in his technology from the Hebrew University of Jerusalem in 1985 (Barenholz, 2012).

With high uncertainty and expensive development, financing and resource allocation were key responsibilities for Arvanitidis. LTI was able to successfully raise funds through an IPO in 1987 (Financing Business, 1987). Due to a stock market crash in biotechnology stocks in 1987, investors lost interest in this sector and LTI, under Arvanitidis, had to reduce the projects they were working on from eight to three in 1988 (Fisher, 1988), with a primary focus on treating a type of AIDS-related cancer named Kaposi's sarcoma. As access to funding was critical, Arvanitidis explored a merger with The Liposome Company based in New Jersey in 1989 (Staff Reporter, 1989). This deal however fell through and LTI was able to continue its development only due to an increase in stake by biotechnology investor David Blech (Liposome Technology Inc., 1990).

With the discovery of stealth liposomes in 1991 (Fisher, 1991), LTI was able to demonstrate that the conjugation of polyethylene glycol (PEG) to the liposomes enhanced their stability, and the reduction of the liposomes to below 100nm permitted these pegylated nano-liposomes encapsulating doxorubicin to achieve better results with much lower side effects. This led to a secondary stock offering raising \$28 Million (Carlsen, 1991). After recruiting N. Goldberg from Genentech as legal counsel in 1993 (Staff Reporter, 1993), LTI was finally able to secure FDA approval for Doxil. As a result the anticancer nano-drug Doxil[®] became the first FDA-approved nano-drug in 1995 (Barenholz, 2012). The Kaposi's sarcoma drug approval was followed in 1998 by a Doxil product targeted at ovarian cancer and in 2003 by a breast cancer therapeutic product (Barenholz, 2012). The success of LTI (renamed Sequus Pharmaceuticals Inc. in 1995) attracted attention from larger players, and ALZA acquired Sequus and was itself later acquired by Johnson and Johnson (Barenholz, 2012).

This case demonstrates the use of knowledge from multiple domains, lipid biophysics, physical chemistry, biology, clinical medicine and instrumentation – that were critical in the development of this first anticancer nano-drug (Bangham, 1993; Lasic and Papahadjopoulos, 1995; Barenholz, 2012). As depicted in Table 3, key advances needed to take place in each of these fields for Doxil[®] to be realized. Deep collaboration was demonstrated, in particular at the Babraham Institute, in the discovery of liposomes, but also seen at Liposome Technology Inc. (Barenholz, 2012). As Doxil[®] was a broad technology platform, applicable to many types of cancer and in many organs, choices needed to be made as to which target markets to initially prioritize.

Following the success of the concept and formulation of Doxil[®], several other therapeutic nanoparticles are being investigated as possible drug delivery vehicles (Farokhzad and Langer, 2006). Liposomes, as a platform delivery technology, could emerge as the standard for targeted drug delivery (Allen and Cullis, 2004). This radical innovation has created enormous opportunity, primarily in therapeutic advancements, but also in economic development. Over 250 firms are now commercializing liposomes with more than 100 firms started expressly around this technology (Maine et al., 2014). Burgess et al. (2010) argue that therapeutic nanoparticles offer the potential for shorter drug development timelines and far longer peak term sales than traditional drugs, leading to more attractive venture opportunities. Liposomes have also spawned a vast industry with applications ranging from cosmetics to maturing cheese (Bangham, 1995).

Table 3Technological advances enabling Doxil[®].

| Doxil [®] | Medicine | Pharmacology | Chemistry | Biology | Instrumentation | Physics |
|--------------------|--|--------------|--------------------|---|-----------------------------|---------|
| Advance 1 | Serum therapy (1890) | | | | | |
| Advance 2 | | | | | Electron Microscopy (1930s) | |
| Advance 3 | | | | Discovery and Development of Liposomes (1961) | | |
| Advance 4 | | | PEGylation (1970s) | | | |
| Advance 5 | Development of Remote Drug Loading in Liposomes (1970 onwards) | | | | | |
| Advance 6 | First FDA approved nano-drug Doxil [®] (1995) | | | | | |

Nanobiotechnology case study B: monoclonal antibodies: Rituxan[®] and Zevalin[®]

The development of the first cancer treatment based on monoclonal antibodies *Rituxan*[®] and its nanocarrier radio-immunoconjugate *Zevalin*[®] (Peer et al., 2007) was based on several path breaking discoveries. Bringing specialized knowledge from multiple disciplines, scientists at various institutions across the world collaborated to develop this radical innovation and demonstrate the effectiveness of monoclonal antibodies for the treatment of cancer. The development of this innovation spans several decades, with critical contributions from scientists, biotechnology firms, venture capitalists and pharmaceutical companies at various stages. We show in detail the role played by each of these stakeholders in the innovation process and highlight the importance of innovation management strategies for fostering radical innovation in nanobiotechnology firms.

The first technological breakthrough reaches all the way back into the late 1800s with the discovery of antibodies. Emil Behring, a military doctor, started exploring the power of blood as a treatment for various infections. He found that he could protect a pig from diphtheria by injecting it with the blood of a pig which had survived this disease. His colleague Paul Ehrlich saw these results and suggested that there must be chemicals in the blood which acted as “magic bullets” by searching and destroying disease causing agents. Behring was awarded the first Nobel Prize in Physiology or Medicine in 1901 for this path breaking discovery of serum therapy, postulating the presence of antibodies in blood serum. As other researchers embarked on identifying antibodies in blood, they were stymied by the large number of surprisingly similar antibodies. By the 1930s, improved techniques such as the ultracentrifuge made it possible to separate antibodies by size and shape. The ultracentrifuge, developed by Theodore Svedberg using concepts from physics and chemistry, permitted the separation of subcellular bodies. This technique was improved by Jessie Beams, a physicist at the University of Virginia and his student Edward Pickels. Ultracentrifuges were commercially available in the late 1940s and contributed to the development of the field of molecular biology (Koehler, 2003).

Several decades later, researchers such as Rodney Porter (an immunologist) and Gerald Edelman (a trained physician and researcher) independently identified the chemical structure of antibodies in 1959 using various enzymes developed by chemists and biochemists (Patlak, 2009). For their discovery of the chemical structure of antibodies, they were awarded the Nobel Prize in Physiology or Medicine in the year 1972. Though progress had been made in identifying and describing the chemical structure of antibodies, several vexing questions remained, the most prominent being the ability of the human body to quickly produce an abundance of a specific antibody as an antidote in response to a disease causing agent. This question was answered by the theory of clonal selection.² For this

² Clonal selection posited that each antibody-producing white blood cell or B cell could produce only one specific antibody and the identification of a specific antigen (disease causing agent) triggered the B cell to create clones. During this process, these cells made a few subtle mistakes leading to slightly different antibodies being produced. If these newer antibodies were able to better at identifying the concerned antigen, the process would repeat itself over several iterations, leading to the antigen's destruction.

discovery of the antibody production mechanism, Frank Burnet (a virologist and trained physician) was awarded the Nobel Prize in Physiology or Medicine in 1960 which was followed by the Nobel Prize in Physiology or Medicine to Niels Jerne (an immunologist) in 1974 for further describing the functioning of the immune system.

It was still not clear how humans with only about 100,000 genes in their DNA were able to create nearly a billion different antibodies. Susumu Tonegawa, a trained molecular biologist with interests in immunology, identified in 1976 the genetic basis of antibody diversity (Hozumi and Tonegawa, 1976). At nearly the same time in 1975, Cesar Milstein (a biochemist) and Georges Kohler (a biologist) developed the hybridoma technique which combined antibody producing B cells to mouse tumor cells. The discovery of genetic diversity and the hybridoma technique permitted scientists to create monoclonal antibodies of extremely high specificity in large enough quantities and helped them diagnose various diseases and infections accurately (Mackenzie et al., 1988; Cambrosio and Keating, 1992). Understanding the abilities of monoclonal antibodies for oncology, Lee Nadler, a 33 year old hematologist and oncologist at the Dana Farber Cancer Institute of the Harvard Medical School in Boston, and his friend Phil Stashenko (an immunologist and trained dentist) developed a monoclonal antibody which could identify non-Hodgkin's lymphoma, a form of cancer. Their initial treatment using monoclonal antibodies in 1979 was not successful, as the human immune response recognized the antibody as originating from a mouse which led to its destruction within the body (Patlak, 2009). Even though the technology was not a success, his results demonstrated the safety and negligible toxicity of monoclonal antibody infusions in patients.

The discovery of recombinant DNA techniques by Cohen and Boyer in 1973 had given birth to the biotechnology industry (Zucker et al., 1998). Genentech was formed in 1976 and within a few years monoclonal antibodies were being used in diagnostic products by companies like Centocor. Firms like Biogen, Amgen, Chiron and Cetus quickly arose to take advantage of the tremendous opportunities thrown up by the development of biotechnology. Ortho Biotech developed the first commercial therapeutic murine antibody Orthoclone, targeted at transplanted organ rejection which was approved by the USFDA in 1986 (Strohl, 2009; Yoon et al., 2010). In the same year, IDEC Pharmaceuticals was created from the merger of IDEC and Biotherapy Systems (co-founded by Ronald Levy from Stanford University). With William H. Rastetter joining as the CEO of IDEC Pharmaceuticals in late 1986, IDEC gained his deep insights in drug discovery and development from his time at Genentech.

Dr. Rastetter had a PhD in chemistry from Harvard and had been working at the interface of chemistry and biology. Later on, as an Associate Professor of Chemistry at MIT, his frustration at needing to work in a very narrow discipline prompted him to move to Genentech in 1982. As the leading biotechnology company, Genentech had a highly collaborative culture and Dr. Rastetter assembled a unique interdisciplinary group of mathematicians, X-ray crystallographers, protein chemists, biochemists, microbiologists and organic chemists from very good labs across the world, to create one of the first groups working in protein engineering. He believed that "the tools that are available to people who bring together many, many disciplines' tools are, by definition, much broader" (Rastetter, 2008). His time at Genentech made him aware of the challenges faced by spin-off companies, and this business experience was invaluable during his leadership at IDEC Pharmaceuticals. He found the running of a smaller group of talented scientists at IDEC very similar to his experience at Genentech (Rastetter, 2008).

IDEC Pharmaceuticals had been focused on developing a customized approach of antibody therapy for lymphoma. However, Rastetter soon realized that developing a unique therapy customized for each patient would be prohibitively expensive. Understanding the business implications for IDEC, Rastetter changed course and focused resources on the clinical trials of an off-the-shelf broadly applicable antibody later called Rituxan (Rastetter, 2008). This decision was resisted by the founders and most of them left the company but it proved critical for manufacturing antibodies at the cost and scale required for successful commercialization. As the CEO, Dr. Rastetter realized that "a leader has to be able to motivate, to coalesce, to communicate, to cause a group of people to become much more than the sum of its parts" (Rastetter, 2008). Academic research recognizes individual excellence but corporate scientific research requires understanding the nuances of leadership and teamwork.

By choosing to relocate from Mountain View to San Diego, Rastetter conserved scarce resources and created an environment where highly interdisciplinary scientists worked closely together in synergistic teams and he could draw on the rich biosciences community at San Diego. Additionally, his decision to develop monoclonal antibodies in bulk quantities in-house drove costs down and made the development of Rituxan far more attractive (Rastetter, 2008). From his time at Genentech, he had a clear picture of the financial resources required to commercialize a new drug in-house and understood the critical role played by large pharmaceutical companies during clinical trials and FDA approvals.

The failure of Centocor in the development of a monoclonal antibody based treatment for sepsis, called Centoxin, highlighted the importance of partnering with larger, more experienced firms at later stages of drug development. Centoxin initially showed promising results but failed in tests later, leading it to be rejected by the USFDA in 1992 (Marks, 2012). One of the major reasons for the failure of Centocor with Centoxin was that it had planned to assume the whole risk of product development and manufacturing without any prior experience. As a result of this failure, Centocor initiated a partnership with Eli Lilly and was able to develop a chimeric antibody targeted at platelet aggregation post-cardiovascular surgery called Reopro which was approved in 1994. These initial antibodies, though successful, had problems of their own. One major problem was that these MABs had low half-lives which meant that they had reduced efficacy on being introduced in the human body. An additional problem with murine antibodies was that the human body recognized these as foreign agents due to the presence of the mouse component and rapidly attacked them, reducing the efficacy.

Realizing these weaknesses and learning from the experience of Centoxin, Dr. Rastetter and his colleagues at IDEC Pharmaceuticals used recombinant DNA techniques to initiate development of a chimeric antibody in 1991 which was part mouse and part human (Grillo-Lopez, 2000). Drawing on the tacit knowledge brought by recruiting experienced scientists from larger firms, Dr. Rastetter was able to lead the development of Rituxan (Rastetter, 2008). Even as the first patients were being tested with the chimeric antibody, other researchers questioned the use of monoclonal antibodies in treating cancer (Dillman, 1994). IDEC Pharmaceuticals was able to develop this first chimeric monoclonal antibody targeted at non-Hodgkin's lymphoma called Rituximab. Rituximab showed very promising results and quickly cleared clinical trials as an orphan drug in partnership with Genentech to enter the market in 1997 (Grillo-Lopez, 2004). It is now one of the foremost monoclonal antibody treatments for oncology on the market, with sales of \$3.0 Billion in the US in 2011 (Aggarwal, 2012).

Rituximab enabled targeted drug delivery. One final advance was required for the development of Zevalin: the addition of targeted radiation therapy. Although radiation has been a mainstay of cancer therapy for several decades, its major shortcoming was the damage done to healthy human tissue. Research has constantly tried to improve efficacy of radiation therapy by targeting only diseased cells and tumors (Torchilin, 2007). One of the important initiatives taken soon after the early success of Rituximab in clinical trials was the combination of ibritumomab (the murine parent of rituximab) with the beta-emitter radionuclide yttrium 90 (^{90}Y) (Milenic et al., 2004). This radiolabeled antibody was the first USFDA approved conjugated anti-CD20 MAB treatment for the treatment of non-Hodgkin's lymphoma. By drastically improving the targeting of radiation to tumor cells, this treatment added to the options available to physicians to handle non-Hodgkin's lymphoma. Zevalin[®], as this drug came to be called, was approved in 2002 had \$29 Million in sales in 2010 (Elvin et al., 2013). Zevalin, however, has not been as successful as Rituxan, mainly due to the challenges associated with administering it to patients in a clinical setting as it requires expertise in hematology, oncology and nuclear medicine.

Over the decades of separate technological advances that led to the radical innovations of Rituxan and Zevalin, environments were created to enable the exchange of tacit knowledge across the multiple disciplines depicted in Table 4. Most notably, valuable ideas and tacit knowledge were brought into IDEC Pharmaceuticals from multiple organizations through personal relations of founders and employees (Zeller, 2008, p. 36). Uncertainty was high throughout the development of Rituxan and Zevalin: at most stages the initial hypothesis of the scientists could not be confirmed (Zeller, 2008, p. 36). Dr. Rastetter played a pivotal role both in creating the interdisciplinary teams and environment that led to the development of Rituxan, and in making decisions about the most appropriate technology to meet their targeted market application. This case highlights the high levels of uncertainty in technological confluence driven emerging fields like nanobiotechnology.

Table 4
Technological advances enabling Rituxan[®] and Zevalin[®].

| Rituxan [®] and Zevalin [®] | Medicine | Pharmacology | Physics | Chemistry | Biochemistry | Molecular biology | Immunology |
|---|--|--------------|-------------------------|---------------------------------------|-----------------------------------|--|--------------------------------|
| Advance 1 | Serum Therapy (1890) | | | | | | |
| Advance 2 | | | Ultracentrifuges (1930) | | | | |
| Advance 3 | | | | | | | Clonal Selection Theory (1957) |
| Advance 4 | | | | Chemical Structure of Antibody (1959) | | | |
| Advance 5 | | | | | Recombinant DNA Technology (1974) | | |
| Advance 6 | | | | | | Genetic basis of Antibody Diversity (1976) Hybridoma Technique (1975) | |
| Advance 7 | | | | | | | |
| Advance 8 | Murine Antibody (1979) | | | | | | |
| Advance 9 | First Chimeric Antibody based Cancer Drug Rituxan [®] (1997) | | | | | | |
| Advance 10 | First Radiolabelled Antibody Zevalin [®] (2002) | | | | | | |

Summary of nanobiotechnology confluence case studies

The potential of nanobiotechnology to revolutionize human therapeutics and personalized medicine has been illustrated. In both cases above we note that there was a long gap between the initial idea and the discovery of the basic science (Tables 3 and 4). Combining and building on knowledge from different disciplines, scientists were able to surmount problems. As initial scientific discoveries were reported, several research teams across the world commenced work on facets of the identified problems. Breakthroughs often happened due to knowledge and perspectives being brought from several disciplines and through environments which enabled deep collaboration. Technological advances such as the ultracentrifuge, electron microscopy, chromatography and its refinements and recombinant DNA techniques helped to speed up the translation of scientific discoveries into commercial products. Yet uncertainty was high throughout, even when the first products were being launched, there were other researchers who were skeptical about the success of these techniques.

The picture that emerges from the cases is that of a long scientific gestation period which is punctuated by periods of rapid activity catalyzed by the availability of new techniques and tools (Weiner et al., 2010). New ventures were pivotal in experimentation and in innovations enabled by this confluence: Liposome Technology Inc. in the case of Doxil[®] and Centocor and IDEC Pharmaceuticals in the development of Zevalin[®]. The key role played by technology ventures may be because larger established firms have trouble integrating knowledge across fields (Maine et al., 2014) or in commercializing radical innovation (Maine, 2008; Langer, 2013).

In these two nanobiotechnology case studies, purposeful choices fostered the conditions in which these radical innovations developed. Knowledge was imported from a broad range of sources, including from top interdisciplinary researchers with personal networks at world leading universities. Environments were created which facilitated deep collaboration between interdisciplinary researchers. This was seen through purposeful co-location of interdisciplinary teams, through the recruitment and nurturing of top researchers, through the presence and leadership of interdisciplinary leaders who could help integrate knowledge, and through cultures which allowed for debate, disagreement and broad perspectives. Additionally, each case study featured a leader who made the strategic choices of matching potential technological solutions to market applications.

Discussion and implications of technology confluence

We presented three case studies to investigate how radical innovation can be facilitated at the confluence of technologies. The development of the transistor and the subsequent emergence of the semiconductor and consumer electronics industries illustrate the degree of opportunity creation that has been enabled by the confluence of technologies in the past. In the case of the transistor, innovation management strategies were observed which facilitated key advances across four technological fields.

We also provide two additional detailed case studies of the confluence of biotechnology and nanotechnology documenting key areas of technological advances and evidence of innovation management strategies employed. In the case of Doxil[®], the first FDA approved nano-drug, the nano-scale manipulation of pharmaceuticals into liposomes and the targeted drug delivery of those nano therapeutics combined technologies across six medical/biological and nanotechnology fields (Table 3). In the case of Zevalin[®], the first radio-labeled antibody, which increases efficacy and dramatically decreases radiation therapy side effects, knowledge was integrated and key advances were made across seven medical/biological and nanotechnology fields (Table 4).

Timelines are long for the multiple advances in distinct technological fields that underpin these radical innovations. In each case study, advances in at least 4 distinct fields were necessary for the innovation (Tables 2–4). In the nanobiotechnology case studies, multiple instances of technology combination are observed across time in the key advances: an example is the discovery of liposomes in 1961, which integrated knowledge across chemistry, biology, instrumentation and physics (Table 3). Knowledge of liposomes, in turn, was integrated with knowledge from medicine and pharmacology, and the ability to better manipulate materials on the nanoscale, to lead to the first FDA approved nano-drug, Doxil[®], in 1995. Each of the 3 innovations drew on advances made over at least 10 years.

Reduction to practice of nanobiotechnology innovations still typically exceeds 10 years (Maine et al., 2012b; Pisano, 2010; DiMasi et al., 2003).

Long timelines of innovation in these case studies reflect, in part, that the confluence of biotechnology and nanotechnology is not linear and smooth, and that there are regulatory, market, potential toxicity, and other hurdles to overcome (Maine, 2013). In both nanobiotechnology cases, there were times when the inventors thought that their invention would fail or have little impact. For example, after the initial demonstration of the structure of liposomes, research had started on their use for drug delivery. However, some researchers pointed out the dismal results of initial applications and questioned their potential (Poste, 1983). Similarly, in the case of monoclonal antibodies, the initial success of Orthoclone was moderated by the failure of centoxin in cancer treatment (Dillman, 1994).

Management of innovation takes on more importance in such highly uncertain conditions. The first innovation management strategy seen in all three cases of radical innovation from the confluence of technologies is importing ideas from broad networks. All three case studies demonstrated this strategy, implemented largely through recruiting from and networks with leading universities, as depicted in Table 5. Additionally, one individual in each case study was notable in the role they played in synthesizing the concepts accessed through these networks: Kelly at Bell Labs, Bangham at the Babraham Institute, and Rastetter at IDEC.

The second innovation management strategy is creating an environment conducive to deep collaboration. As Rafols (2007) found in his study of the bionanotechnology development of bio-molecular motors, and Juanola-Feliu et al. (2012) found in their study of nano-biomedical devices, when knowledge is emerging in two or more distinct fields simultaneously, teams need to be organized to allow for deep collaboration, essentially tacit knowledge exchange. This was seen in all three case studies, with Kelly's novel team design at Bell Labs (Morton, 1971, p. 40–43, 46–48), in the interdisciplinary team at Babraham Institute (Bangham, 1993) for the discovery of liposomes, and in advances which led to the discovery and commercial use of monoclonal antibodies (Koehler, 2003; Patlak, 2009). Thus the role of innovation management in facilitating knowledge transfer and integration across fields was vital. As depicted in Table 5, we observed four aspects to creating an environment to facilitate deep collaboration. First, recruiting and maintaining leading specialized researchers was important in all cases. Second, co-locating interdisciplinary groups to facilitate exchanges that would not happen without such intervention was seen in all three cases. Third, an active knowledge recognition and integration role was played by individuals with broad interdisciplinary knowledge, here referred to by Leonard's (1995) term, boundary spanners. And lastly, a culture and mix of individuals existed which encouraged vigorous debate, differences in perspective and constructive disagreement, while not getting derailed by personal conflict. This was also present in all three case studies, although there was some personal disagreement at Bell Labs, leading to the eventual exit of leading researchers. Without these aspects of a deep collaborative environment, the chances for the level and frequency of tacit knowledge exchange which can lead to radical innovation are far lower.

The third innovation management strategy is that of technology-market matching. The recognition of potential opportunities and prioritization of technologies and markets did not happen to a significant degree at Bell Labs or at the Babraham institute. These environments were essential to major technological advances, but led to radical inventions, not radical innovations. Rather, in the case of the transistor, it was Hoerni at Fairchild Semiconductors who made the technology-market matching choices that led to the economically produced silicon planar transistor. Similarly, as CEO of IDEC, Rastetter realized that a generic antibody technology – though not of interest to the founders of IDEC – offered the potential of a lower cost, higher efficacy anti-cancer therapy, and jettisoned the incumbent customized antibody technology around which IDEC was formed to focus resources on developing a product with the generic technology and reducing the associated manufacturing cost. At Liposome Technology Inc, Arvanitidis made the technology-market choice to abandon R&D on five market applications and to focus development primarily on Kaposi's sarcoma.

What can we learn from the case study of the transistor and from those of Doxil[®] and Zevalin[®]? Each case study demonstrates the challenging context, with evidence about timelines and levels of uncertainty. We also find evidence of innovation management strategies which facilitated the development of these radical innovations from the confluence of technologies. Thus, we argue that three innovation management strategies, observed in all of the case studies, are what enable radical

Table 5

Innovation management strategies enabling radical innovation from the confluence of technologies.

| Innovation management strategies | Transistor | Doxil [®] | Rituxan [®] and Zevalin [®] |
|---|---|---|---|
| Importing Ideas from Broad Networks | Yes, at Bell Labs | Yes, at Babraham Institute | Yes, at IDEC |
| Broad Search | Recruitment into Bell Labs, conferences, relationships with MIT and Harvard University researchers | Recruitment into the Babraham Institute, visiting scholars, Cambridge University | Recruitment into IDEC, relationships with Harvard, MIT, and Genentech researchers |
| Synthesis of Concepts | Through fast moving project team created by Mervin Kelly | By Bangham | By Rastetter |
| Creating Environments Conducive to Deep Collaboration | Yes, at Bell Labs | Yes, at Babraham Institute | Yes, at IDEC |
| Specialized Knowledge | Advanced Materials, Physics, Electronics, Instrumentation | Chemistry, Biology, Instrumentation, Physics | Medicine, Pharmacology, Molecular Biology, Chemistry, Immunology, Physics |
| Co-location of Interdisciplinary Groups | Purposefully by Kelly | By Bangham | Purposefully by Rastetter |
| Boundary Spanners | Shockley, Teal, Bardeen | Bangham | Rastetter |
| Creative Abrasion | Yes, although some personal infighting as well | Yes | Yes |
| Technology-Market Matching | Yes, at Fairchild Semiconductor | Yes, at Liposome Technology Inc. | Yes, at IDEC |
| Recognition of potential technology-market matches | Hoerni, with the idea and development of the more reliably manufactured planar transistor. Noyce, with transition to silicon from germanium | LTI' idea of PEG conjugated to liposomes for better efficacy in targeted drug delivery for cancer treatment | Rastetter saw manufacturing cost barriers to customized antibody therapies and recognized the potential of a generic antibody technology |
| Prioritization of potential technology-market matches | Yes, team decisions to shift focus from germanium to silicon and from the point contact transistor to the planar transistor | Arvanitidis focused Liposome Technology Inc.'s resources on 3 projects from original 8 | Rastetter shifted entire focus to cost-effective generic antibody technology for chosen market application, over the protests of founders |

innovation from the confluence of technologies. Such strategies could help technology entrepreneurs to better realize the enormous potential latent in current technology confluences. The case studies and literature suggest specific implications for new industry creation and for innovation managers in nanobiotechnology ventures.

Implications for new industry creation

The key events in the emergence of the new industry of consumer electronics, enabled by the transistor, are depicted in Fig. 1, with the phases of industry emergence also depicted. New firms enter an emerging industry after the introduction of a radical innovation, and their entry and consolidation often follow similar patterns (Abernathy and Utterback, 1978; Utterback, 1994, p. 31, 100). Many new ventures formed to further develop and use transistors. As the planar transistor emerged, the industry consolidated (Suárez and Utterback, 1995; Fig. 1). Over time this industry consolidated into a few large firms. The transistor, through its dramatically smaller size, lower weight and lower power consumption, further enabled the emergence of the consumer electronics industry (Fig. 1).

Fig. 2 depicts the current state of the nanobiotechnology industry emerging around targeted nano-drug delivery, partially enabled by liposomes. Drug delivery and nano-enabled therapeutics appear to

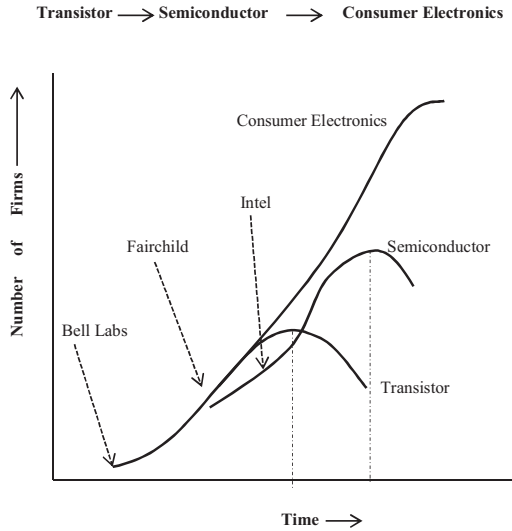


Fig. 1. Evolution of the consumer electronics industry.

Diagnostics → Drug Delivery → Nanobiotechnology

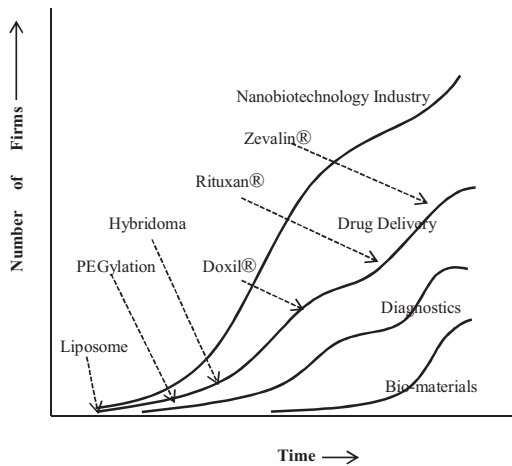


Fig. 2. Evolution of the nanobiotechnology industry.

be nearing the end of the fluid phase of industry emergence, with potential standards emerging (Maine et al., 2014). This implies that there is further growth to come in terms of firm entry, value creation, and revenue generation. Notably, in the case of the transistor, it was new technology ventures which drove the commercialization of the radical innovation and its subsequent products, with Bell Labs unable to capitalize on its invention, and start-up firms, supported financially by larger firms, best positioned to create and capture value in the emerging industry (Rothwell, 1989). Similarly, in the emerging nanobiotechnology industry, start-up firms are expected to play a leading role, with Maine et al. (2012a) finding that technology ventures account for nearly two-thirds of the firms in the industry, and Hacklin et al. (2009) suggesting that small nanobiotechnology platform firms may drive the disaggregation of the current, vertically integrated pharmaceutical industry.

Having analyzed the historical case study of the transistor and two detailed case studies of the current confluence of biotechnology and nanotechnology, we demonstrated that the opportunity created through the confluence of distinct technological disciplines may be vast, both in economic and social terms. The consumer electronics industry had a value of \$291 billion in 2012 (WSTS, 2013). The emerging nanobiotechnology industry has created more than \$20 billion in revenue in 2011 (Aggarwal, 2012). Potential future value creation has been estimated at over \$62 billion in 2015 (Elvin et al., 2013). Given this strong potential, we proffer learning gleaned from these prior examples of radical innovation enabled by technology confluence – and from the innovation literature – to help technology entrepreneurs create and capture value in the emerging nanobiotechnology industry.

Implications for innovation management within nanobiotechnology ventures

Technology ventures are best positioned both to integrate knowledge and to commercialize radical innovation from the confluence of technologies (Maine et al., 2012a). However, the long timelines, high levels of technical and market uncertainty, and large capital investment required for drug development present a big challenge for technology ventures (Lok, 2010; Maine, 2013; Pisano, 2010). Thus, the use of innovation management strategies to increase the likelihood of radical innovation from the confluence of technologies takes on additional importance.

The innovation management strategies illustrated in this paper can be implemented by technology ventures aiming to create and capture value from the confluence of technologies. First, the leaders of such ventures should look to broad networks for novel ideas and have the ability to recognize and synthesize such disparate streams of knowledge. This is dependent on leadership, but can be facilitated through partnerships with academic labs, participation in conferences, recruitment of interdisciplinary researchers from top institutions, encouragement of *boundary spanners*, and location in a strong technology cluster. For synthesis of concepts from a firm's networks, technology leaders should make time for "big picture" discussions. Ideally, a synthesis role is taken on by a leader with broad interdisciplinary expertise.

A second innovation management strategy to enable radical innovation from the confluence of technologies is the creation of an environment which encourages deep collaboration. First there must be deep specialized knowledge in two or more disciplines to be shared. This is a function of recruiting practices, ongoing learning opportunities, and the value the firm places on scientific excellence. Given this specialized knowledge, co-location of scientists from diverse disciplines within applied R&D teams is recommended to create an environment where tacit knowledge can be exchanged (Morton, 1971; Allen et al., 1980; Cardinal and Hatfield, 2000; Maine, 2008; Battard, 2012; Juanola-Feliu et al., 2012). Contrary to Avenel et al.'s (2007) view that knowledge convergence at the firm level can be achieved through either a strategy of "juxtaposition" where a firm has a broad knowledge base through the cumulative knowledge of several independent research groups, or one of "hybridization" where a firm has forged truly interdisciplinary research groups, we argue in this paper that "hybridization" is critical to opportunity creation from the confluence of technologies. The other two innovation management aspects of an environment encouraging deep collaboration are the recruitment and nurturing of boundary spanners and the facilitation of creative abrasion (Leonard, 1995). Boundary spanners are those who have expertise in two or more technological streams and can recognize important advances and connections between them. Creative abrasion results from purposefully building a development team with very different skill sets, personality types, backgrounds, and setting institutional norms where technological disagreement and experimentation is encouraged, but personal battles are not.

The third innovation management strategy involves the matching of technology to market applications. Recognition of promising opportunities to exploit is one aspect of this strategy, and prioritization through resource allocation is another. There are many factors to consider in technology-market matching, including commercialization choices to overcome some of the context specific challenges faced by nanobiotechnology ventures. As depicted in Table 5, Rastetter, as CEO of IDEC, made a controversial strategic decision to abandon the customized antibody technology around which IDEC was formed, because he felt that the value proposition was not compelling for patients, and he could not see that changing, given production, technical, and efficacy constraints. Instead,

Rastetter decided to allocate all company resources to developing a generic antibody technology for the same market application, and to drive down production costs as they scaled up production capacity in-house.

Technology entrepreneurs can make other technology-market matching choices to reduce uncertainty and the long timelines characteristic of this sector. Burgess et al. (2010) advocate the strategy of applying nanotechnology platforms to pre-validated active pharmaceutical ingredients. This strategy of utilizing therapeutic nanoparticles to deliver previously approved active pharmaceutical ingredients shortens the development and approval timeline. Another example is seen in the Doxil[®] case study: when there was no alternative therapeutic for a fatal disease, the commercializing venture successfully lobbied the FDA to speed up their clinical testing timeline. Technology entrepreneurs can choose to commercialize nanobiotechnology inventions outside of the FDA regulated therapeutics market, instead targeting biomedical devices, diagnostics, instrumentation, or even nutraceuticals (Maine et al., 2012b). Examples of ventures which have done so include: BioNano Genomics, in their development of novel instrumentation, NanoSphere's commercialization of novel diagnostics (Maine et al., 2014) and Aphios's commercialization of nanobiotechnology inventions in the nutraceuticals market (Aphios, 1999). Uncertainty can also be reduced by choosing to exploit nanobiotechnology confluence in areas in which one stream of knowledge is currently well understood. Rafols (2007) points out that innovation in more mature streams of biotechnology and nanotechnology can be modularized, such as the aspects of electronics, MEMS, analytical chemistry, cell biology, and biochemistry contributing to lab-on-a-chip products. Thus, the evolutionary stage or maturity of the confluence of technologies will impact the degree of difficulty of knowledge integration between nanotechnology and biotechnology fields and subsequent technological uncertainty. A comprehensive innovation management strategy would include consideration of these factors in making technology-market commercialization choices.

Conclusion

In this paper, we investigate how radical innovation is facilitated at the confluence of technology streams. In doing so, we make contributions to three distinct knowledge domains: innovation management, opportunity creation from the confluence of technologies, and innovation management strategies for the emerging nanobiotechnology industry. The innovation management strategies that emerge from our detailed case studies and analysis of the development and commercialization of the transistor, Doxil[®] – the first FDA approved nano-drug – and Zevalin[®] – the first radio-labeled antibody, demonstrate how radical innovation emerged from the confluence of technologies. Further, we make a contribution by integrating three streams of management literature to suggest that opportunity creation may be more likely at the confluence of technologies. Finally, we provide innovation management strategies for the emerging nanobiotechnology industry, a context in which very few studies of innovation have been conducted.

Hurdles to commercialization, including technological, regulatory, and market uncertainty, potential toxicity, and negative public perception, led to long development timeframes for Doxil[®] and Zevalin[®], which draw on a broad range of disciplines within or related to nanotechnology and biotechnology. Breakthrough advances such as the discovery of liposomes and the discovery of monoclonal antibodies happened due to knowledge and perspectives being integrated from multiple disciplines and through environments which enabled deep collaboration. We demonstrate repeated instances of similar innovation management strategies and argue that the role of innovation management to facilitate tacit knowledge transfer and integration across fields was vital. Key innovation management strategies were importing ideas from broad networks, creating environments which allow for deep collaboration, and technology-market matching. Although the development and commercialization of such innovations involves a complex, costly and long process, the resultant opportunity created at both firm and industry levels is immense (Fig. 2). The emerging nanobiotechnology industry has already created more than \$20 billion in revenue, advanced the efficacy and reduced the side effects of cancer treatment, and is considered to still be in its early stages of development.

We conclude with implications for technology ventures of innovation management strategies to create value at the confluence of biotechnology and nanotechnology. We recommend three innovation management strategies to exploit the confluence of technologies. First, technology managers should undertake a broad search and synthesis of concepts from disparate technology streams. They can do this through purposeful recruitment and networking policies, and through making time for big picture discussions. Second, an environment for deep collaboration can be created through the recruitment and nurturing of employees with specialized knowledge, co-location of employees from diverse disciplines, the use of boundary spanners, and institutional norms and practices to facilitate creative abrasion. Third, CEOs of technology ventures might combat high prolonged uncertainty and capital intensive development through their technology-market matching choices: some options include purposefully utilizing pre-approved active pharmaceutical ingredients or first commercializing nanobiotechnology inventions outside of the FDA regulated therapeutics market.

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