Investing in nanotechnology

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The current commercial path for nanotechnology ventures mirrors the early evolution of the biotechnology industry, allowing similar strategies toward both technology commercialization and investment opportunities.

The emergence of nanotechnology and its commercialization has followed a similar path to the emergence of recombinant technology and the biotechnology industry. Clear parallels can be drawn concerning the role of the US federal government and intellectual property (IP) in driving nanotechnology's growth. This is providing new opportunities for venture capital, particularly in the area where nanotechnology interfaces with biology—the nascent field of nanobiotechnology.

Box 1 Nanotechnology patent growth

US patents have already been filed and issued for many areas of nanotechnology. One indication of this upward trend is found in published patent applications, which offer the most up-to-date numbers because the US only began publishing patent applications that have a filing date later than November 29, 2000 (see **Fig 1**). A perusal of patent applications filed after 2000 (as of August 11) reveals the following numbers:

- 884 newly published US patent applications contain the word 'nanoparticle'
- 584 newly published US patent applications contain the word 'nanotube'
- 99 newly published US patent applications contain the word 'nanowire'

In the wake of the US Bayh-Dole act of 1980, many biotechnology companies sprouted from broad university patents or groups of patents that were licensed to the start-up followed by an initial round of funding from a venture capital firm. Today, that cycle continues with nanotechnology start-up companies who have licensed university nanotechnology patents.

Stephen Maebius

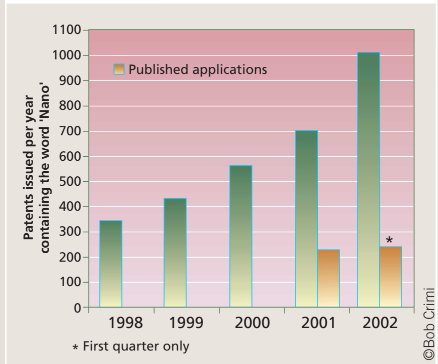

Figure 1 Trends in the patenting of nanotechnology. Source: Foley and Lardner, Washington, DC, USA

Origins

Program managers at agencies like the US National Science Foundation (NSF; North Arlington, VA, USA) provided the initial impetus for the growth of nanotechnology, culminating with US President Clinton's creation of the National Nanotechnology Initiative (NNI) in 2000. Tom Kalil, former Deputy Assistant to President Clinton for Technology and Economic Policy, was one of the NNI's early and most influential advocates. "Long-term, nanotech has the potential to be as significant as the steam engine, the transistor and the Internet," he was quoted. "There is a critical role for government in areas of science and technology that are risky, long-term, and initially difficult to justify to shareholders." According to Kalil, White House staffers thought the NNI was a good idea for several reasons, including balancing the growing funding disparity between life sciences and physical sciences, training the next generation of US scientists, and taking an international lead in a transforming technology. This created the first major US investment trend in nanotechnology.

US federal nanotechnology research funding has since surged nearly sevenfold in the past six years, starting from $116 million in 1997 to a budgeted $847 million in 2004 (see p. 1127). And this isn't just a US phenomenon. In fact, nanotechnology has become an international footrace. According to our estimates, more than $3 billion will be invested worldwide in government nanotech research in 2003, including hundreds of millions of dollars in corporate R&D. Couple that with the following statistics: academic institutions worldwide are launching nanotechnology-specific curricula, 13 of the 30 companies in the world's best known stock indicator, the Dow Jones Industrial Average, mention nanotechnology on their website, more than $900 million in venture capital funding has gone to nanotechnology startups since 1999, and mentions of nanotechnology in the popular press have surged by more than 20-fold, from ~200 in 1995 to >4,000 in 2002 (ref. 1). In short, nanotechnology has reached near celebrity status, pervading 'Main Street', 'Wall Street', 'Capitol Hill' and the 'Ivory Tower,' and gaining momentum and a critical mass of interest along the way.

At the May 2003 NanoBusiness Alliance conference held in New York, US Undersecretary of Commerce Phil Bond remarked, "Nanotechnology has reached a tipping point." The major reasons? Political support, investor recognition, and the fact that startup companies and incumbents already have some products on the market. Today, most nanotechnology products on shelves are more evolutionary than revolutionary (e.g., pants, shirts, and quilts with nanostructured textile coatings that make them wrinkle-proof or stain-repellent). In the defense industry, nanoscale ceramic coatings have recently been introduced by the US Navy to prevent sea creatures from adhering and fouling metal ship components. According to the Farmington, CT-corporation, Inframat, this has led to $1 million annual savings per ship due to corrosion protection and the reduction in drag, which leads to lower fuel costs.

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Lux Capital is a venture capital firm focused on making early-stage investments in nanotechnology. *A financial stipend was paid by Nature Biotechnology to Robert Paull for research on, and writing of, this article.*

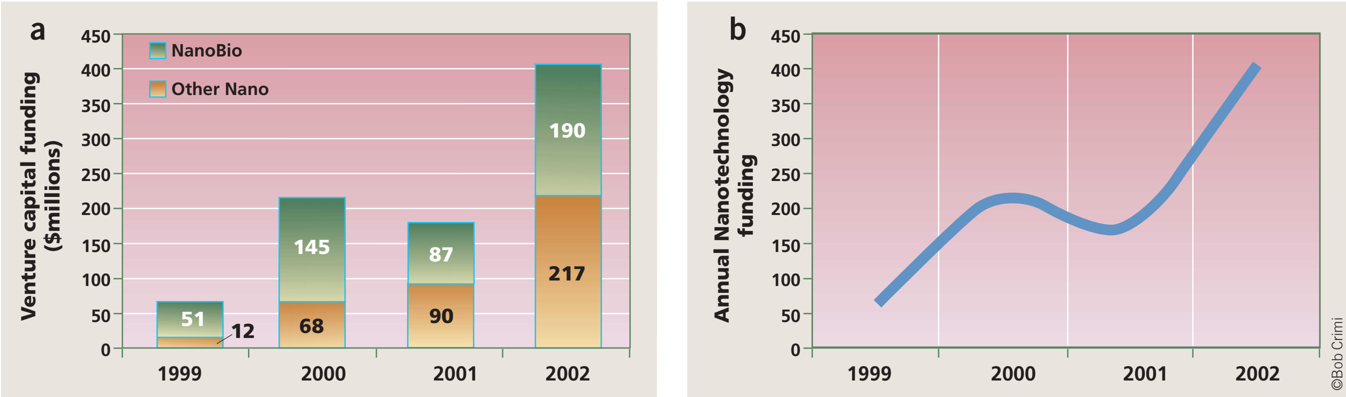

Figure 2 The increasing allure of nanotechnology to investors. **(a)** Venture capital funding in nanobiotechnology versus other types of nanotechnology. **(b)** Annual venture capital funding in nanotechnology.

Comparisons to the biotech 'revolution'

How will nanotechnology compare to the biotechnology revolution that preceded it? First, initiatives like the NNI and European Union Framework for Nanotechnology have launched a distinct new wave of government funded innovation. That, in turn, has provided a base for technology development. The congruence of recombinant DNA technology and venture capital in the 1970s sparked not only a new industry, but also an explosion of technology patents and the emergence of completely new types of products, such as Humulin, Eli Lilly's (Indianapolis, IN, USA) recombinant insulin—the first recombinant drug to be approved by the US Food and Drug Administration. Similarly, with nanotechnology, the advent and increased sophistication of scanning probe microscopes, such as the atomic force microscope, have enabled researchers to visualize and manipulate sub-100 nm matter in ways previously not possible. What has resulted is significant patent growth in materials science, a rise in patent licensing by major corporations, and an array of nanotechnology products under development, like semiconducting quantum dots for biological imaging and nanowire sensors capable of acutely detecting single molecule analytes.

Just as in biotechnology, intellectual property (IP) is critical. According to Stephen Maebius, patent attorney at Washington, DC-based Foley & Lardner, scientific journal papers on nanotechnology began to rise in the mid-1990s with patent applications accelerating in 1998 (see **Fig. 1**). Since then, huge annual jumps have been recorded, from around 500 nano patent applications in 1998 to nearly 1,300 in 2000. Coupled with estimates from the United States Patent and Trademark Office (Alexandria, VA, USA) that patent approval timelines could increase from the current 19 months to 39 months by 2006[2], the ability of companies to acquire IP in these early days will be critical. We're seeing the beginnings of nanotechnology IP land grab (see **Box 1**).

Another parallel to the early days of biotechnology, is the chronic shortage of people experienced in commercializing nanotechnology. "All the domain experts are academics," says venture capitalist Larry Bock of CW Ventures (New York, NY). "Even at the major corporations active in nanotechnology research like IBM (New York, NY, USA) and Lucent (Murray Hill, NJ, USA), their primary driver is scientific publications." According to NSF estimates, 40,000 US scientists have the skills to work in nanotechnology. But to support the NSF's estimated $1 trillion nanotechnology industry by 2015, 800,000 US workers (40% of worldwide total) will be needed (see p. 1247). For this reason, we expect management personnel and leadership to transition from more mature and slower growth industries (like specialty chemicals) and extend their expertise down to higher growth nanotechnology startups.

As with the advent of biotechnology, the confluence of these trends creates a situation ripe for venture capital investing. In recent years, however, the venture capital investment community has been deci-

Table 1: Top 10 nanobiotechnology companies based on amount of venture capital raised.

Company	Funds raised ($Millions)	Sector	Description
Immunicon (Huntingdon Valley, PA)	86.20	Diagnostics	Diagnostic screening using nanoparticles
Quantum Dot (Hayward, CA)	44.50	Biomedical applications	Semiconductor nanocrystals for biological assays
Surface Logix (Brighton, MA)	38.00	Drug discovery	Miniaturized biological assays
Genicon Sciences (San Diego, CA)	34.00	Diagnostics	Nanoscale signal generation and detection
PicoLiter (Sunnyvale, CA)	27.10	Diagnostics	Picofluidics for nanoparticle manufacturing
US Genomics (Woburn, MA)	27.00	Drug discovery	Single molecule analysis assays
Nanosphere (Northbrook, IL)	23.50	Diagnostics	Diagnostic nanoprobes and image analysis systems
Advion Biosciences (Ithaca, NY)	15.00	Drug discovery	Nanoelectrospray bioanalysis using biochips
Ferx (San Diego, CA)	15.00	Drug delivery	Drug delivery using magnetic forces
Nanogram Devices (Fremont, CA)	9.20	Biomedical applications	Nanomaterials for biomedical application components

Source: Lux Capital, Capital IQ

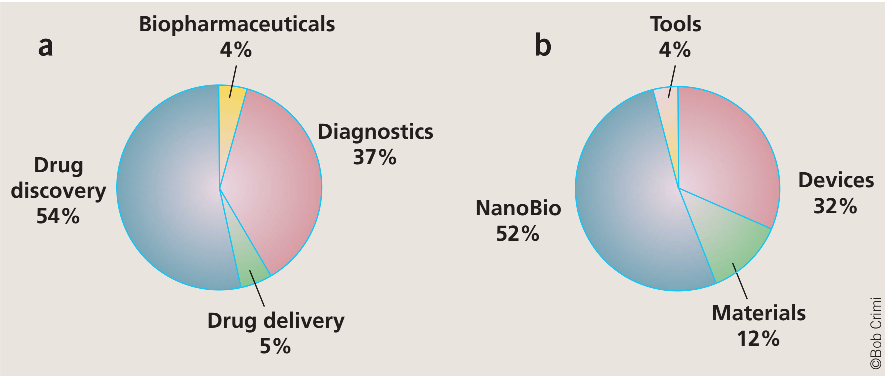

Figure 3 Where is the money going? **(a)** Percentage breakdown of nanobiotechnology venture deals from 1998 to the present. **(b)** Distribution of venture capital funding in nanotechnology from 1998 to the present

mated, decreasing for the past 12 consecutive quarters before a recent upturn. The number of new companies being financed is the lowest in eight years, and returns generated by venture capital funds have been negative over several quarters for the first time ever. Many venture investors are skeptical, shunning nanotechnology as the "new 'new' thing", instead looking to invest within existing portfolios to help ailing companies survive. Even so, some of the most successful companies are built during downturns.

Commercializing nanotech and nanobiotech

For nanotechnology in general, the earliest beneficiaries—particularly of the growing capital flows—have been companies that make hardware tools and software programs to characterize, measure, and work at the nanoscale. From an investment perspective, hardware like atomic force microscopes and resonance controllers that are being marketed for use in the biological or material sciences are a capital-intensive business with long sales cycles. In contrast, most venture capital investors prefer companies with business models that are easily scalable with large potential margins.

There are many ways to define nanobiotechnology. The term can be used to describe the interface of nanotechnology with biology. Alternatively, it may define any application of nanotechnology in biological research, drug discovery and drug delivery devices, diagnostic tools, therapeutics or novel biomaterials. Since 1999, 52% of the $900 million in venture capital funding for nanotechnology has gone to nanobiotechnology startups (see **Fig. 2a**). In fact, while total venture capital declined from 2001 to 2002, nanobiotechnology investing increased by 313% (ref 1.; see **Fig. 2b**). This growth is being driven by two key factors: the availability of government grants and the expiration of patents on pharmaceuticals.

Venture capital investors are recognizing that despite the risks associated with the drug approval process, expensive development costs, and increasing clinical approval times, nanobiotechnology firms have a window of opportunity. For one, US government grants are increasing for nanobiotechnology at places like the National Institutes of Health (Bethesda, MD, USA) BECON (Bioengineering Consortium), Small Business Innovation Research (SBIR) Bioengineering Nanotechnology Initiative and the US Army (through the Institute for Collaborative Biotechnology, University of California at Santa Barbara, Santa Barbara, CA, USA). As venture capital companies assess potential investments on the basis of pre-Internet bubble levels of risk, looking for startups that leverage government grants for development costs, revenue growth and non-dilutive financing has become the norm.

> Also driving commercialization in nanobiotechnology is big pharma's ticking time bomb: patent expirations.

One example is Hayward, California-based Quantum Dot Corporation. The start-up already has joint ventures with Genentech (S. San Francisco, CA, USA), Matsushita (Minamigata, Japan), and SC Biosciences (Tokyo, Japan) and over $44.5 million in venture funding from four leading life sciences investors. Quantum Dot has also taken advantage of grants from the National Cancer Institute (Bethesda, MD, USA) and a $5.6 million National Institute of Science and Technology ATP grant to develop semiconducting nanocrystals biomarkers. Quantum dots are a perfect example of how controlling the size of materials at the nanoscale can lead to advantages that normal biotechnology can't provide. Using nanomaterials that are chemically identical, researchers only have to change the size of the material to give a completely different functional property. A 2 nanometer diameter quantum dot glows bright green while simply increasing the particle size to 5 nanometers causes it to glow red. This effect, quantum confinement, doesn't happen with bulk materials or the leading biomarker technology, fluorescent dyes. Furthermore, these nano-enhancements lead to less photo-bleaching, greater variety of colors, and cost savings by not requiring multiple lasers of varying wavelengths as fluorescence does.

Also driving commercialization in nanobiotechnology is big pharma's ticking time bomb: patent expirations. According to a Merrill Lynch report[3], 23 of the world's top drugs are coming off patent by 2008, which will account for a loss of $46 billion dollars in annual revenue. Many of the major pharmaceutical companies are looking to nanotechnology as one angle for IP protection. For example, in 2001, Baxter International (Chicago, IL, USA) licensed Montreal, Quebec-based RTP Pharma's (now acquired by SkyePharma (London, UK) formulation and manufacturing technology that uses nanoparticulate suspensions and lipid emulsions to convert insoluble drugs to injectable, soluble formulations within six months. By enhancing the absorption of pharmaceuticals by the body, nanotechnology alters the pharmacokinetics of existing drugs, making them act more quickly.

Where's the money?

In the nanobiotechnology sector, the lion's share of funding is focusing on diagnostics and drug discovery. Blue chip investors are dabbling in both biotechnology and nanobiotechnology with the idea that complementary approaches will ultimately be integrated to produce new therapeutic agents (see **Fig. 3** and **Table 1**). For example, the portfolio of Venrock Associates (New York, NY, USA), the venture capital arm of the Rockefeller family, includes Surface Logix (Brighton, MA, USA), a nanobiotechnology

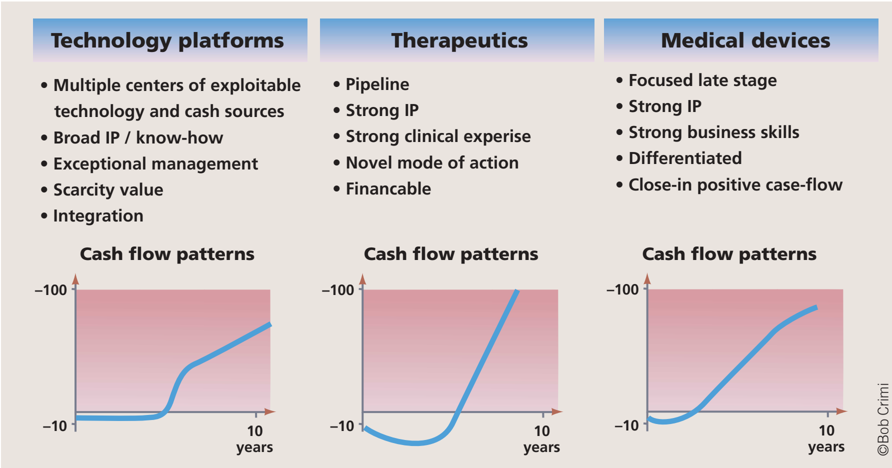

Figure 4 Cash flow patterns of life sciences companies. Source: Simon Waddington, Polytechnos Ventures, Munich, Germany.

firm developing bioassays using soft lithography technology, as well as RNA interference company Sirna Therapeutics (Boulder, CO, USA).

Despite the perceived benefits of adding nanobiotechnology to an asset allocation, venture investors must still understand the business characteristics and macro trends of the pharmaceutical and biotechnology industries. As shown in **Figure 4**, cash flow patterns of life sciences companies differ greatly and become a critical criteria in analyzing new investment opportunities. None of this is different for companies working in nanobiotechnology. Technology platform companies, such as pSiMedica (Malvern, UK), a spinoff of QinetiQ (London, UK) developing nanostructured porous bio-silicon, already have considerable IP positions ripe for licensing in many healthcare sectors.

Although cash flow from licensing partnerships may surface in the medium term (3–5 years) for many companies, profitable nanobiotechnology companies are already out there. Berlin, Germany-based JPK Instruments, for example, has adopted a medical devices cash flow pattern. Backed by two Berlin venture capital firms, JPK manufactures atomic force microscopes for the life sciences industry and reached profitability just six months after their first product launch in June 2002.

Other investment themes

Perhaps the most fitting blueprint for substantial early commercial gain in nanobiotechnology comes courtesy of the Human Genome Project. As Mark Guyer, Director of the Human Genome Project's Division of Extramural Research (Bethesda, MD, USA), points out, one company reaped the lion's share of public capital flows: tools merchant Applied Biosystems (Foster City, CA, USA), the primary supplier of high-speed DNA sequencers. "As a ballpark estimate of the total money the National Genome Research Institute spent, my guess is that 5–10% went directly to Applied Biosystems for instrumentation purchases," says Guyer. This pattern is repeating itself with the NNI. Driven by the rising number of new nanotechnology academic research centers and their need for instrumentation to work at the nanoscale, semiconductor capital equipment providers such as Veeco Instruments (Woodbury, NY, USA) and FEI Company (Hillsboro, OR, USA) are seeing academic research revenues grow at roughly a double digit pace per year. We consider tools an investment sector for the short to medium term (present–3 years), especially as it relates to nanobiotechnology (e.g., the use of atomic force microscopes/environmental scanning electron microscopes in work on tissues, cells, proteins, and other biological matter). In the short-to-medium term, materials and software (e.g., Accelrys' (San Diego, CA, USA) software for modeling polymer, crystallization, and catalysis) may also turn out to be, albeit riskier, investment opportunities for both public and private equity investing.

Many of these short-to-medium term nanotechnology investment opportunities, however, are not attractive for venture investors. Materials science companies, such as those manufacturing carbon nanotubes or nanoparticles, often face large manufacturing costs (pilot plants) and tremendous pricing pressure from incumbents. Furthermore, with instrumentation as an example, historical evidence on merger and acquisitions over the past 10 years in the semiconductor capital equipment space shows weak venture returns to other industries. Why? Instrumentation companies have required large capital equipment development costs, averaging $50 million, only to be acquired for between $100–$200 million (a mere 2–3-fold return on investment). Although biotechnology companies also require considerable and concerted funding to develop products, private equity firms and public markets apply higher valuations to later-stage drug pipelines in pharma and biotechnology because of the potential for multi-billion dollar revenue streams from one new drug. As a result, acquisition prices are often in the billion-dollar range.

Conclusions

Nanotechnology is not just a fad. It's integral to corporate R&D across a wide range of industries and sophisticated investors know that. The questions that remain for many venture investors are how are business models going to evolve and change because of nanotechnology, will industries like biotechnology consolidate greatly over the next few years, opening up even more commercialization avenues, and when will we see the initial public offering (IPO) window open again? When will there be an IPO for a nanobiotechnology company? And what will make those companies successful investments?

As we have already demonstrated, it is going to take an experienced team, an innovative business model, solid IP, and strong partnerships with established leaders. As SG Cowen biotechnology analyst Phil Nadeau puts it, in the biotechnology and pharmaceutical industries, "at end of the day, the thing that typically takes a company from IPO to a couple billion dollar market cap is one or more product candidates into phase III or into the market. There just aren't too many companies that make the leap without having a big product in development." Perhaps nanotechnology can help make it happen.

1. Wolfe, J., Paull, R., & Hebert, P. *The Nanotech Report 2003* (Lux Capital, New York, 2003).
2. Transcript of hearing before the subcommittee on courts, the internet and intellectual property, April 3, 2003, available at http://www.house.gov/judiciary/86267.pdf.
3. Risinger, D., Boris, J., Li, B., & Calone, J. *US Major Pharmaceutical Model and Pipeline Book, 4th Quarter 2002 Issue* (Merrill Lynch, New York; 2003).