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# The emergence of the nanobiotechnology industry

Elicia Maine, V. J. Thomas, Martin Bliemel, Armstrong Murira and James Utterback

**Abstract:** The confluence of nanotechnology and biotechnology provides significant commercial opportunities. By identifying, classifying and tracking firms with capabilities in both biotechnology and nanotechnology over time, we analyze the emergence and evolution of the global nanobiotechnology industry.

Research in nanotechnology has expanded rapidly in the last 15 years, but the development of commercial products has been significantly slower<sup>1-3</sup>. One of the most promising areas for commercialization is the application of nanotechnology to biological processes<sup>4-6</sup>. This is due, in part, to the fact that it involves the confluence of two previously disparate research fields – nanotechnology and biotechnology – and novel combinations of ideas and approaches are known to increase the opportunities for innovation<sup>7,8</sup>.

The rate of increase in nanobiotechnology invention is well documented<sup>9,10</sup>. However, little is known about the commercialization of these inventions and the entry of firms into the field. For example, what types of companies have both biotechnology and nanotechnology capabilities, when and where did they develop them, and what applications are they targeting? And are these companies actually integrating nanotechnology with biotechnology? Here we explore the emergence of the global nanobiotechnology industry by identifying, tracking and analysing firms with capabilities in biotechnology and nanotechnology, and examining the degree to which they integrate their knowledge.

## Entry and exit of nanobiotechnology firms

Through longitudinal analysis and an extensive search and validation process, we identified 507 firms globally targeting human health that have both biotechnology and nanotechnology capabilities. We categorized our sample by firm type, location, and industry sub-sector. We then tracked the entry and exit of these firms, including mergers and acquisitions. Details on our methodology are available in the supplementary information accompanying this paper online.

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Our analysis shows that nanobiotechnology capabilities first emerged in multinational corporations in the 1980s and early 1990s (Fig. 1). Most of these multinational corporations are based in the chemical (Dow, Bayer, for example), pharmaceutical (Roche, Abbott Labs, for example) or the electronics (HP, Hitachi, for example) industries. Most have developed capabilities in biotechnology and nanotechnology in separate subsidiaries and have supplemented their capabilities by acquiring smaller nanobiotechnology firms. By 1990, there were already 10 multinational corporations with both biotechnology and nanotechnology capabilities (Fig. 1). (In fact, research areas such as liposomes, which are now considered to be within the realm of nanotechnology, have existed in polymer chemistry research since the 1960s.) Specific nanobiotechnology applications began to emerge in the early 1990s.

As of 1999, the majority of the firms in the emerging nanobiotechnology sector were *de novo* firms, which we define as new ventures founded specifically to commercialize the opportunities arising from the confluence of biotechnology and nanotechnology. *De novo* firms rapidly increased in number between 1995 and 2007 (Fig. 1), with a total of 215 entries during that time period. The timing of these entries is consistent with the claim that new ventures are more likely than large, established firms to attempt to commercialize highly uncertain technologies<sup>4,11,12</sup>. In the emerging nanobiotechnology industry, approximately two-thirds of the firms with nanobiotechnology capabilities are very small as measured by annual revenues<sup>4,13</sup>. Therefore, ventures can be considered the primary driver for innovation in such highly diverse fields. One prominent nanobiotechnology inventor and entrepreneur stated that he needed to form new ventures because when he licensed his diverse technologies to large firms they often did not develop these technologies further<sup>12</sup>. A *de novo* example is depicted in Box 1. Our data also showed a steep decline in the number of *de novo* entrants during and after 2008 and an increase in the number of *de novo* exits in the same period. It is likely that this reflects financing constraints during the period<sup>15</sup>.

We define *de alio* as incumbent firms that have chosen to enter the nanobiotechnology industry. *De alio* firms are differentiated from multinational corporations because they are smaller in size, have fewer (or no) subsidiaries, and have much less geographic scope. *De alio* firms are often established biotechnology firms, which enter the nanobiotechnology industry through development of their own capabilities in nanotechnology or by acquiring existing firms that have

demonstrated success in integrating biotechnology and nanotechnology. We find that the *de alio* firms started entering this industry in increasing numbers after 1998 – following the FDA approval of the first nanobiotechnology drug Doxil® in 1995 – with a peak in the year 2005. After a period of fewer entries after 2008, another increase was observed in 2011 (Fig. 1).

Although multinational corporations have significant nanotechnology capabilities, we find that their focus remains on their existing industries and technologies: only a very small proportion of their total patents can be classified as nanobiotechnology (on average 0.1%, compared with an average of 9.9% for *de novo* firms and 3.0% for *de alio* firms). This highlights the tensions between existing capabilities and emerging capabilities within large, established organizations, such as the pressures suppressing radical innovation in the multinational chemicals corporation Degussa<sup>11</sup>. Therefore, despite first-mover advantages and superior resources of multinational corporations, it is the small, fledgling experiments, in the form of *de novo* firms tightly integrated to universities, which appear most likely to cross-pollinate concepts from different disciplines and commercialize the resulting nanobiotechnology inventions.

### **Industry evolution across countries and regions**

Based on existing innovation literature<sup>16</sup>, we expected national and regional differences in the evolution of the global nanobiotechnology industry. Similar to other technology based industries, the evolution of the nanobiotechnology industry globally has not been homogeneous. As depicted in Fig. 2, we find that the US leads the emergence of this industry, with approximately 60% of global firms located there. Predominant regional strengths in nanobiotechnology are found in California, Massachusetts, and New York & New Jersey. Somewhat surprisingly, the rest of the US also has a substantial and growing proportion of nanobiotechnology firms, outside of traditional biotech clusters. For example, the integrative nanobiotechnology diagnostics venture, Nanosphere (see Box 1), was spun out of Northwestern University and is building its manufacturing facilities in Northbrook, Illinois. This suggests that star scientists in research universities are the most important determinant of the location of new nanobiotechnology firms, as was previously observed for the formation of the biotechnology industry in the 1970s and 1980s<sup>17</sup>. Elsewhere in North America, Canada has built a presence, with 15 nanobiotechnology firms as of 2011.

Europe holds more than a quarter of the global nanobiotechnology firms, with Germany, the UK and France all having established a significant presence in the emerging industry. Germany, with 35 firms as of 2011, has been the leading European country throughout the evolution of the nanobiotechnology industry, although their relative share within Europe has decreased from 37% to 24% between 2005 and 2011 (Fig. 2). As in the US, the entry of nanobiotechnology firms outside of the traditional biotech clusters in Europe has been extensive and continued through the financial crisis. Several countries such as Sweden, Netherlands, Spain and Italy have new entrants between 2008 and 2011. France is an interesting case, with minimal nanobiotechnology activity in 2005, but 14 firms by 2011, with a predominance of *de novo* drug delivery firms.

The leading nanobiotechnology country in Australasia and Asia is Japan, with 23 firms as of 2011. Australia, New Zealand, South Korea, China, Israel and India also have a presence. The Australasia-Asia region accounted for 14% of global nanobiotechnology firms in 2011. There was rapid growth in firm entry from 2005 to 2008, and slower growth since 2008, but little change in this region's global share during that time.

Overall, it can be seen that the global nanobiotechnology industry underwent rapid growth before 2008 (a 51% increase in the total number of firms between 2005 and 2008), but slowed down substantially after 2008 (a 17% increase in the total number of firms between 2008 and 2011). Regions have evolved in notably different ways. Massachusetts firms, for example, represent all subsectors of nanobiotechnology and have a roughly equal mix of *de alio* and *de novo* firms. France, on the other hand, has fostered impressive growth in a focused nanobiotechnology subsector, suggesting that purposeful science policy can play an important role in this emerging industry.

### **Industry evolution by subsector**

The nanobiotechnology industry consists of several subsectors with notable differences in application focus. Table 2 provides an example of the types of firms that are categorized in each nanobiotechnology industry subsector. Following studies of industry evolution that track firm entry and exit over time<sup>18</sup>, Figure 3 depicts the cumulative number of firms in the US (i.e. firm entries minus exits) into four nanobiotechnology industry subsectors: biopharmaceuticals, drug delivery, suppliers & instrumentation, and diagnostics. Bio-pharmaceutical firms, the most

prevalent subsector of the nanobiotechnology industry, were early entrants into specific areas of nanobiotechnology research, such as utilising liposomes for drug delivery. A pioneer was Liposome Technology Inc. (LTI), with the development of Doxil®: LTI was acquired by Alza which was in turn acquired by Johnson & Johnson<sup>8</sup>. The rate of entry into the biopharmaceutical subsector increased after the FDA approval of Doxil® in 1995, and further accelerated between 2004 and 2008. (Fig. 3). The drug delivery subsector experienced gradual firm entry over the first two decades, followed by a rapid increase between 2004 and 2008. Rapid entry into the suppliers & instrumentation subsector began earlier, around 2000, though this began to plateau in 2005. Diagnostics, the smallest subsector shown in Figure 3, increased gradually from 2000 to 2011.

Industries evolve over time in known patterns, moving from a fluid phase to a transitional phase to a specific phase; each phase has characteristic rates of product and process innovation, and associated changes in firm entry and exit, research and development management, organizational characteristics, market focus, and competitive focus<sup>18</sup>. In several studies of the evolution of industries, a dominant design – a standard set of product features or technological attributes that become expected by the marketplace – emerges after a period of rapid entry of firms and instigates consolidation of firms in the industry. Although easier to analyze in hindsight, our data suggests that one or more dominant designs may have emerged in the suppliers & instrumentation subsector (an example might be processes for the synthesis of nanoparticles). This shift in the phase of industry evolution is suggested by the rapid growth and subsequent plateau depicted in the suppliers & instrumentation curve in Figure 3. Consistent with this interpretation, we note higher consolidation (i.e. firm exits) in this industry subsector. Scientists and engineers in these firms should therefore be more focused on process attributes, such as reducing cost and increasing reliability, and less focused on developing new product features or technological attributes.

The drug delivery subsector appears to be toward the end of the fluid phase of industry emergence. In this phase, there are still opportunities for radical innovation, and the focus is on competing on product features or technical attributes. That said, the rate of entry has reduced in this subsector, and potential dominant designs are emerging among drug delivery technologies<sup>19,20</sup>. Our data on the degree of integration of nanobiotechnology knowledge in biopharmaceutical firms suggests that they may only adopt a dominant design from the drug

delivery firms, rather than contribute to forming it. Biopharmaceutical firms are likely to focus more on the new drug and less on the delivery mechanism, choosing to adopt and, where necessary, adapt mechanisms developed by drug delivery specialist firms. Doxil® is a good example of the delivery mechanism being developed by a specialist nanobiotechnology drug delivery venture<sup>8</sup>.

## **Conclusions**

Although the first firms to develop capabilities in both biotechnology and nanotechnology were multinational corporations, these capabilities often remained in 'silos' and were overshadowed by the multinational corporations' existing capabilities. *De novo* firm entry intensified after 1995 and appears to be the primary driver for innovation in such highly diverse fields. The US remains the dominant location for nanobiotechnology commercialization, with Germany a distant second. In terms of industry subsectors, the drug delivery sub-sector appears to be coalescing around potential dominant designs, but still competes on technological attributes: as such, the focus is still on product innovation, and establishing a dominant design. In the suppliers & instrumentation subsector, the period of rapid entry appears to have concluded, suggesting that these firms should be focussing on process innovation and subsequent cost reduction.

We argue that knowledge-based sectors drawing on a diverse range of novel inputs, such as biotechnology and nanotechnology, will be most likely to provide opportunities for radical innovation and economic growth. Integration of such disparate technological fields is not straightforward, however, especially for multinational corporations. Firms can increase their chances at benefiting from emerging industries such as nanobiotechnology by enhancing the exchange of ideas across technology fields and knowledge workers. Co-location of diverse groups, purposeful mixing of disparate expertise and insulation from an incremental innovation culture are recommended<sup>8,11,21</sup>. Hiring of scientists and engineers with an interdisciplinary education could also help bridge technology 'silos'<sup>8,22</sup>. Such practices would accelerate the transition of the significant promise of nanobiotechnology into economic and social value.

Governments can also influence innovation in industry by providing resources and by creating an environment encouraging innovation. Measures that have been proven most effective are government funding of research, ensuring a broad and strong system of education, and ensuring a robust and resilient infrastructure<sup>23</sup>. We have observed in our data here and in other

studies that new entrants in emerging industries tend to be clustered in a few locations that might be said to have a strong and balanced ecology of research centers, talented human resources, excellent transportation, communication and other assets supporting innovation<sup>24</sup>. The increasing entry of firms outside of traditional biotechnology clusters, however, suggests that science policy can play an active role in this emerging industry, with star scientists at research universities seeding new clusters.

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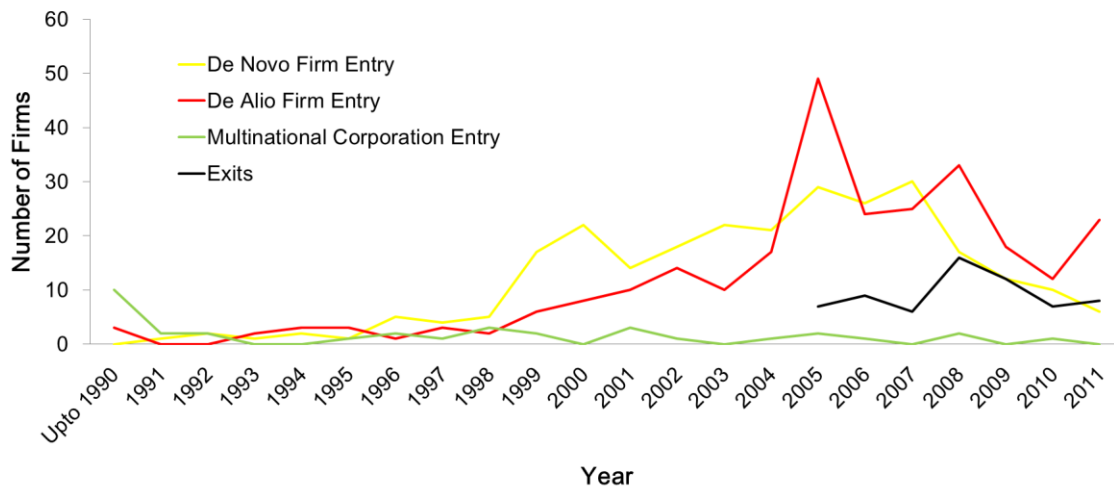
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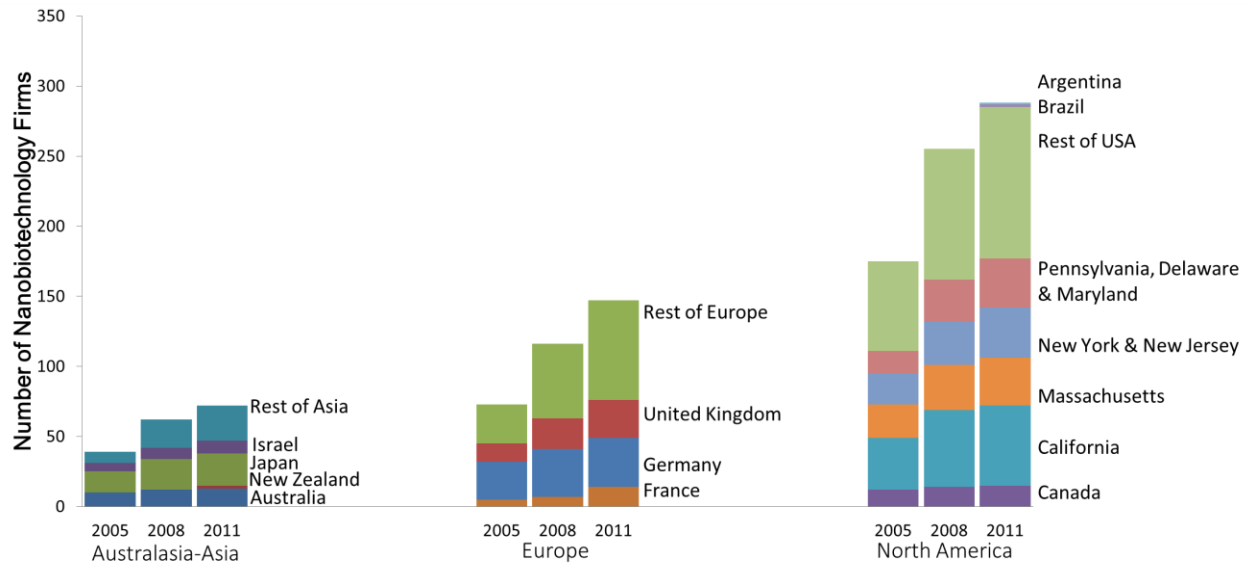
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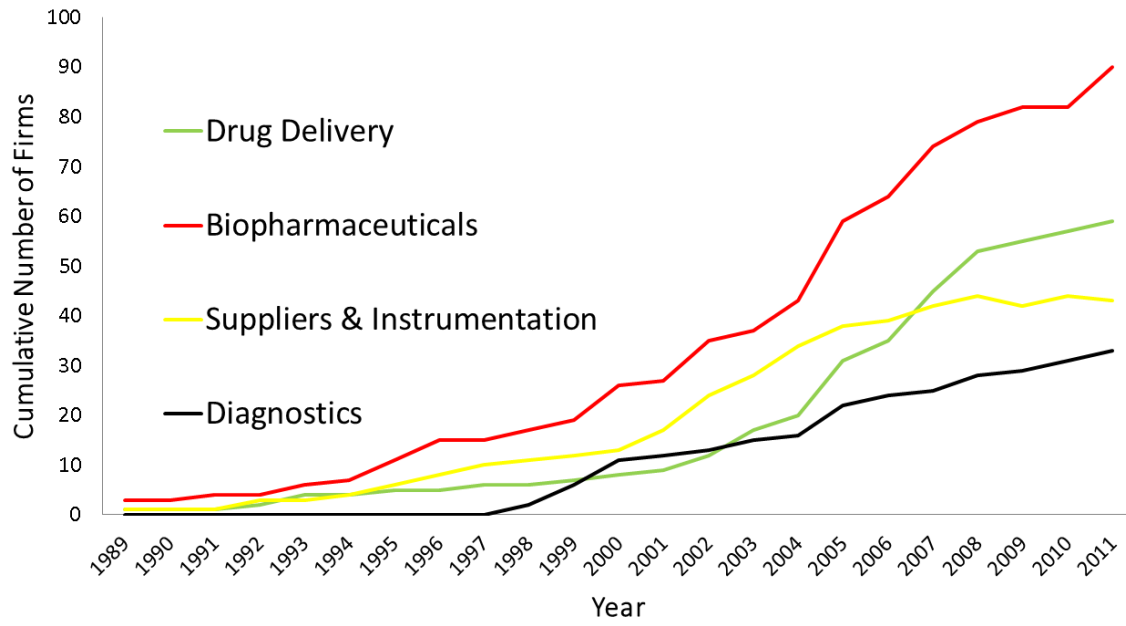
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**Figure 1. The evolution of the global nanobiotechnology industry by firm type.** Firms are divided into three categories: *De Novo*, *De Alio* and multinational corporations. *De Novo* are firms where the difference between the founding year and year of acquisition of nanotechnology capability was 3 years or less. *De Alio* are firms where the difference between the founding year and year of acquisition of nanotechnology capability was more than 3 years.



**Figure 2. Evolution of the global nanobiotechnology industry by regions.** The Australasia-Asia category includes Asian countries as well as Australia, New Zealand and Israel. The North America category includes the US, Canada and 3 South American firms which entered in 2011.



**Figure 3. Evolution of selected nanobiotechnology subsectors in the US.**

**Box 1:** Example of a highly integrated *de novo* firm: NanoSphere

- Nearly entire biotechnology or nanotechnology patent portfolio integrated
  - Founder Chad Mirkin is a pioneer in the integration of nanotechnology with biotechnology
  - 46 out of 50 US patents incorporate both biotechnology and nanotechnology
  - “We live at the boundaries of molecular diagnostics and nanotechnology” Bill Moffit, former CEO Nanosphere.
- *De Novo* Nanobiotechnology Diagnostics Firm
  - Earlier detection of disease and more targeted treatment
  - World’s first diagnostic test for sepsis, shortening time from 3 days to 3 hours
  - Utilizing functionalized gold nanoparticles to detect nucleic acid or protein targets
  - Multiple tests under development with more accurate, more specific results
- Spun out of Northwestern University (USA) in 2000
  - US\$5 million in revenues in 2012
  - Approximately US\$300 million invested since founding
  - Currently scaling up manufacturing facilities
  - Initial Public Offering (IPO) on the NASDAQ in 2007
  - Market capitalization of US\$155 million in 2013

**Table 1:** Nanobiotechnology Industry Subsectors

<b>Nanobiotechnology Subsector</b>	<b>Definition</b>	<b>Example Firms<sup>1</sup></b>
BioPharma	Firms involved in multiple sub-segments such as pharmaceuticals, drug delivery, contract research.	Roche, Merck, Bayer, Johnson & Johnson, DuPont, Celator
Drug Delivery	Firms specializing in drug delivery	C-Sixty, enGene, 3M, Siemens
Diagnostics	Firms specializing in human diagnostics and imaging	NanoSphere, NanoGen, PanBio, NanoProbes
Suppliers & Instrumentation	Firms supplying nano-materials, instrumentation, consumables, lab equipment	Dow, Degussa, Agilent, Toray, Hitachi
Medical Devices	Firms providing medical devices such as wound care products, blood care products etc.	Wilson Greatbatch Inc, Haemonetics
Biomaterials	Firms focussing on dental implants, orthopedic implants etc.	Allvivo Vascular, Mnemo Sciences, Nanovis
Bioinformatics	Firms specializing in bioinformatics and providing drug discovery services.	HP, IBM

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<sup>1</sup> We classify multinational corporations (MNCs) based on their applications in the nanobiotechnology space. For example, 3M's nanobiotechnology focus is on asthma inhaler innovation and thus 3M is classified in the drug delivery subcategory.

## Supplementary Information

We created three distinct samples (cohorts) for longitudinal analysis over the course of evolution of the nanobiotechnology industry: these cohorts consist of firms with both biotechnology and nanotechnology capabilities in 2005, 2008 and 2011. We used the DMS IndustryAnalyser, DMS NewsAnalyser, and Medtrack databases to identify a pool of biotechnology firms targeting human health which potentially held nanotechnology capabilities, whether integrated or in separate research divisions. DMS IndustryAnalyser and DMS NewsAnalyser went out of service in 2009, necessitating the use of a new database to create the 2011 cohort. Relevant firms from the 2011 cohort were added to the earlier cohorts, creating a robust sample. Similarly, firms identified by DMS in the 2008 cohort (but not by Medtrack) were added to the 2011 sample, when proof was found that they still had relevant capabilities.

Next, we verified the existence and timing of development of both sets of capabilities through web searches, press releases, publications, and US patents. Nanotechnology patents were identified using keywords adapted from recent studies<sup>1,2</sup> and biotechnology patents were identified using standard guidelines based on patent sub-classes<sup>3</sup>. Using the patent filing date from the first of the selected patents (assigned to the company or its relevant subsidiaries) and comparing with the founding year of the firm, we were able to classify firms as *de novo* if the difference between the founding year and year of acquisition of nanotechnology capability was 3 years or less. Firms with more than 3 years difference between founding and year of acquisition of nanotechnology capabilities were identified as *de alio* or incumbent firms. In cases where firms had not yet had patents assigned to them, press releases, company documents, scientific publications and industry reports were used to identify the initial year of development of



nanotechnology capabilities. These additional data sources allowed us to retrospectively supplement each cohort if these sources indicated such capability development prior to their date of entry in the three databases used. This retrospective analysis thus enables our sample to comprehensively represent the evolution of this industry across regions (Table 1). We acknowledge that there may have been some exits prior to 2005 which would not necessarily have been captured by our methodology.

Patent data also was used as a measure of the level of integration of biotechnology and nanotechnology capabilities within a firm. We gathered all biotechnology and all nanotechnology US patents issued to the firms in our sample and identified patents overlapping both searches. As of 2011, 82 firms out of the 507 nanobiotechnology firms in our global sample had issued US patents which integrated biotechnology capabilities with nanotechnology capabilities. The level of nanobiotechnology integration was higher in *de novo* firms than in multinational corporations.

**Table 1:** Global distribution of nanobiotechnology firms

<b>Cohort/ Region</b>	<b>Australasia-Asia*</b>	<b>Europe</b>	<b>North America<sup>#</sup></b>	<b>Total</b>
<b>2005</b>	39 (14%)	73 (25%)	175 (61%)	<b>287</b>
<b>2008</b>	62 (14%)	116 (27%)	255 (59%)	<b>433</b>
<b>2011</b>	72 (14%)	147 (29%)	288 (57%)	<b>507</b>

\*Asian countries as well as Australia, New Zealand and Israel.

# North America includes USA, Canada and 3 South American firms which entered in 2011.

By treating all firms as fundamental experiments in the evolution of an emerging industry and by attempting to capture all firms in the industry over time, our study adds to existing industry evolution literature by studying a case of technology confluence as it unfolds. Our advancement in granularity includes tracking firm entry and exit, firm type, and application

focus. Using data from company documents, industry reports and the DMS and Medtrack databases, we are able to classify the biotechnology firms as belonging to specific sub-sectors which helps us to examine the evolution of nanobiotechnology at the level of the sub-sector. Previous studies have concentrated on bibliometric assessments of scientific publications or patents to separately examine the biotechnology and nanotechnology industries<sup>4</sup>, or to examine specific case studies within the nanobiotechnology industry regarding the generation of interdisciplinary knowledge<sup>5</sup>. Patents, while critical to the study of invention, do not adequately represent innovation. One study which did examine firms commercializing nanomedicine identified 207 firms globally as of 2004: the study focused on new products which had been enabled by micro- and nanotechnology<sup>6</sup>. A later study identified 308 medical nanotechnology firms as of 2007<sup>7</sup>.

We extend existing studies in several ways. First, we focus on tracking the entry of firms into the emerging nanobiotechnology industry, and are very comprehensive in our identification of global nanobiotechnology firms, resulting in a broader geographical distribution than found in previous studies. Second, we also are more specific to nanotechnology by limiting our inclusion criteria to firms with nanoscale capabilities defined as less than 300 nm, as opposed to the 1000 nm criteria utilised by the earlier studies<sup>6,7</sup>. Third, we include nanobiotechnology firms which do not yet have issued patents, where there is other public evidence of both biotechnology and nanotechnology capabilities. Fourth, by adopting keywords used to search broadly for nanotechnology patents<sup>1,2</sup>, while also tracking all firm biotechnology patents, we are able to enhance our industry evolution analysis and also provide insight on integration of biotechnology and nanotechnology capabilities. Together, this approach enables us to contribute to a nuanced, comprehensive picture of the emergence and evolution of the global nanobiotechnology industry.

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