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The NCI and the Takeoff of Nanomedicine

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Abstract

This paper presents an analysis of the role of US National Nanotechnology Initiative's Federal funding in the takeoff of nanobiotechnology and nanomedicine. Our comparative analysis of leading nanobiotechnology and nanomedicine scientists funded by the National Cancer Institute highlights the programmatic efforts of the NCI's Alliance for Nanotechnology in Cancer beginning in 2005. We use a data science approach combining web data extraction, bibliometrics and social network analysis to identify leading nanomedicine and nanobiotechnology scientists and profile their research and commercialization efforts. By coupling leading nanomedicine researchers profiles to NNI Federal funding data we discover and document the relative importance of the US National Cancer Institute's Alliance for Nanotechnology in Cancer (NCI Alliance) to the takeoff of nanomedicine. The NCI appears to be achieving its stated goal of contributing to both the scientific and commercial infrastructure of translational nanomedicine. Using Gilsing et al.'s innovation network embeddedness model from 2008 we find that the creation and strategic placement of NCI Alliance Centers at critical positions in the Alliance network has enhanced the ability of the NCI to build a sustainable architecture for nanomedicine and foster potentially disruptive pioneering innovation.

Keywords: Nanomedicine; Assessment; Innovation; Research funding; Alliance networks; National Cancer Institute; Pharmaceutical industry

Highlights

- Performs data-intensive analysis of the NCI's role in the takeoff of nanomedicine
- NCI Alliance outperformed NSF and other NIH initiatives in commercializing bionano
- Network analysis reveals key features of NCI strategy for pioneering nanomedicine
- First 5-year NCI Alliance plan has created a sustainable path for nanomedicine

MSC Classification: 91D30

JEL Classifications: D85, H51, O32, O38

Introduction

Assessing the US National Nanotechnology Initiative (NNI, www.nano.gov) is a complex problem. Over the last century the assessment of research projects has been increasingly treated as a scientometric one, that is to say, one that requires a statistical investigation of the impact of scientific research publication productivity through the analysis of scientific publications, patents, and their citations [1]. Scientometrics began to take its more contemporary form as a tool of assessment through such efforts as Eugene Garfield's *Science Citation Index* and the research of Derek de Solla Price in the early 1960s, and the US National Science Board's creation of *Science and Engineering Indicators* in 1973. Since the early 1970s bibliometrics has assumed an ever-increasing role in the evaluation of national science programs. By the time the NNI was being framed in the 1990s, scientometrics had become the standard means for assessing research output [2]. In the first decade of the 21st century the US National Nanotechnology Advisory Panel declared that publication and patent metrics were "the most salient metrics" for assessing the NNI [3]. Accordingly the more notable assessments of US nanotechnology strategy have relied on bibliometrics [4-8].

Given that NNI objectives go beyond R&D to include sustainable societal development, metrics based on patents and publications provide an incomplete means for evaluating the NNI. While scientometrics can be used to construct indicators for commercialization, *e.g.*, linkages between scientists and commercial entities, patent and publication indicators can reveal only a fraction of the NNI's societal impact. A broader array of factors such as private investment commitments, company formation, product creation, employment, economic development, environmental impact, national competitiveness, and human health are needed for a more robust assessment.

Evaluating efforts to generate novel and efficacious nanomedicines complicates assessment of commercialization efforts. Perhaps the most significant limitation to evaluating a program engaged in producing nanomedicines is that of time. New medicines can take anywhere from six to twenty years to reach the marketplace, a period of time that dwarfs the funding cycles of even the longest-standing grant programs. Practical time constraints leave only the opportunity to assess nanomedicines in mid-development at best. Quarterly, annual and biennial review periods complicate evaluations of any nanomedicine's impact on human health, the economy, and national competitiveness. Any assessment of long-term projects must involve evaluations of developments in intermediary states, however provisional such developments may be.

Another limitation is that patents and publication metrics tell only a small part of a nanomedicine research program's ability to both generate complex pioneering innovations and translate those innovations to the marketplace. We need additional tools if we are to improve assessment

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of nanomedicine and nanobiotechnology commercialization. One place where standards for evaluating commercialization may be found is in the efforts of the US Small Business Administration (SBA) to benchmark the commercialization of their Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) award recipients, particularly commercialization that extends or derives from SBIR/STTR support while also receiving outside support.[1] The SBA's commercialization benchmark uses three data points: total patents, total sales or revenues, and total investment applied to commercialization [9]. The latter two are not scientometrics but rather economic metrics that point toward a broader set of societal impacts, indicators not captured by publication and patent-based measures.

Increasing the number of measureables for assessment adds complexity that may be appropriate for nanotechnology. Specifically, there are two ways in which a more comprehensive understanding of the complexity of nanomedicine is critical to a nanotechnology program's assessment. First, nanomedicine requires participation from diverse disciplines such as chemistry, pharmacology, physics, mathematics, computer science, medicine, epidemiology and public health. Second, the competitiveness of state economies depends upon diversified and interdependent (*re:* complex) product portfolios [10,11]. An ideal nanomedicine research program, then, is the very picture of complexity: a diverse portfolio of efficacious nanomedicines and nanobiotechnology products that enhance human health, the economy, and national competitiveness. An ideal assessment of such a program would therefore appreciate nanomedicine's complexity by striving to diversify and integrate its inputs and outputs.

In 2007, in order to support the development of a more expansive and complex form of quantitative research policy assessment, the authors began developing a software platform named GLOBONANO. The platform has been designed and constructed to support the real-time quantitative analysis of nanotechnology, from publications and patents, to state and private investments, to the formation of firms and products, to the creation of jobs and the environmental impact of nanotechnologies. During this period we have been expanding the GLOBONANO platform beyond the nanoscience research and patent literatures to incorporate investment and commercialization information, including state research funding records, private investment records, product and materials inventories, clinical trials data, company profiles, and collaboration networks. The expanse of data and data analyses in GLOBONANO has been enabled by recent technological developments in web data extraction, natural language programming, text mining, and social network analysis; and by government programs making data available to the public such as the Open Government Initiative. Using GLOBONANO we have been able to discover the rise of nanobiotechnology and nanomedicine in China [12], temporary periods of decreased international collaboration of nations during nanotechnology globalization and diffusion [13], and the importance of diversification to national nanotechnology research strategies [14]. The present analysis of NNI funding impact marks the first attempt to incorporate commercialization-relevant data into GLOBONANO.

In what follows we use GLOBONANO to compare the results of the funding efforts of the NSF, NIH, and NCI in stimulating the takeoff of nanobiotechnology and nanomedicine. We compare the leading scientists funded by these agencies from 2000-2010 in terms of numbers, quality, and impact of publications, numbers of nanomedicine and nanobiotechnology patents granted, companies founded, products on the market, in the pipeline, and in clinical trials. From this comparative analysis the distinctive contribution of the NCI Alliance for Nanotechnology in Cancer stands out. The NCI Alliance for Nanotechnology in Cancer program was funded in two different phases, with phase I from 2005 - 2010, and phase II from 2010 - 2015. In addition to identifying and quantifying the scope and impact of the Alliance program, our goal is to analyze the effectiveness of the first phase of the NCI Alliance program from 2005-2010 while establishing a means for analyzing the second phase after the data become available. To this end, in section 5, we draw upon social network analysis to assess the effectiveness of the NCI Alliance program's strategy for launching nanomedicine.

The current project is unique in several respects. First, it provides a first attempt to assess NNI investment in nanomedicines and nanobiotechnology. Second, no analysis of nanotechnology commercialization has attempted to incorporate such a broad array of data and measures as is attempted here. The present study provides a broad view of US nanomedicine by integrating data and analyses of knowledge capital and finance capital with a quantitative analysis of a government-industry-university research network. Given the wide variety of data in the present study, a full inventory of the inputs and outputs used are listed in Table 1.

The following study begins with an in-depth description of the efforts of the NNI to fund nanomedicine and nanobiotechnology R&D. The data and methods are then introduced followed by a comparative analysis of NSF, NIH, and NCI-funded scientists. We perform a closer analysis of the NCI, leading us to examine the NCI Alliance for Nanotechnology in Cancer and its commercialization efforts. We conclude our study with a social network analysis of the NCI Alliance, examining the importance of the structure of the alliance to nanomedicine innovation and translation.

Background

The US National Nanotechnology Initiative was formally established in 2000 as an umbrella organization to coordinate the activities of several federal agencies responsible for research and development aimed at exploiting the ground breaking opportunities for research and discovery at the first level of organization of matter ranging from a single atom to 100 nanometers. The framers of the NNI argued, "with potential applications in virtually every existing industry and new applications yet to be discovered, nanoscale science and technology will no doubt emerge as one of the major drivers of economic growth in the first part of the new millenium," a market predicted to climb to $1 trillion worldwide by 2015 [15]. From 2001-2012 the combined agencies of the NNI invested $16.5 billion in research related to nanotechnology, nearly $3 billion of which was devoted to areas of nanobiotechnology and nanomedicine. To date there has been no systematic study of the US effort in nanobiotechnology and nanomedicine. We are interested in exploring the impact that federal funding by the NNI has had on the development of nanotechnology in biology and medicine, nanobiotechnology (nanobio), nanobiopharma, and nanomedicine.

Despite the enthusiastic predictions of massive economic growth related to nanotechnology, in contrast to other technology sectors, large pharmaceutical companies have been slow to join the party. Over the period 2003-2009 the pharmaceutical and medicines sector averaged $35.6 billion annually of nonfederal company supported R&D, making it the largest industry subsector supporting R&D [16,17]. However, this massive investment in R&D by the pharmaceutical industry has

[1] This phase of a company's development is referred to by the SBA as "Phase III."

Approach	Input	Input Sources	Methods	Outputs
Knowledge/	Nano journal articles	ISI Web of Science	Web data extraction	Publication and citation counts
Intellectual	Patents	EPO PATSTAT	Data engineering	Publication quality
		USPTO	Data aggregation	Co-authorship networks
			Text mining	Nanomedicine-specific patents
			Bibliometrics	Home institutions of stars
			Social network	Linkage maps
			visualization	Regional and national maps of stars
				Nanomedicine literature stars Stars
				Nanomedicine patenting stars
				Nanomedicine-specific patents
				Nanomedicine literature
				Star profiles
Material capital	NNI investments	NSF funding records	Web data extraction	NSF funding for nano
	Private investments	NIH funding records	Data engineering	NIH funding for nano
	Products	NCI funding records	Data aggregation	NCI funding for nano
	SEC filings	SEC online records		Firms founded
	Employment figures	Corporate websites		Private funding proceeds raised
		Company profile dbs		Employment numbers
		Clinical trials records		Firms in operation
		News releases		Creation of nanomedicine products
		Research literature		Participation in NCI centers
				Nanomedicine funding stars
Organizational/	Business partnerships	NCI Alliance websites	Web data extraction	Dynamic social network
structural/	Triple helix alliances	University websites	Data engineering	visualization of NCI Alliance
alliance networks		Company websites	Data aggregation	Regional and national maps of
		Center websites	Social network analysis	Alliance participants
		Cinical trial records		Regional and national maps of
		Partnership websites		all US nanomedicine stars and firms

Table 1 An inventory of Inputs, Methods, and Outputs

included only lukewarm support for research in nanobiotechnology and nanomedicine. In their two-year study for the European Science Foundation, which drew upon extensive interviews and surveys of literature, patents, and company filings in 2004, Wagner et al. identified 200 companies worldwide with nanomedicine activities, 98 of them in the US [18,19]. The businesses identified in Wagner et al. included 92 start-ups, 67 small-to-medium enterprises (SMEs) and 41 large pharmaceutical or medical device companies. 71 of the 159 new SMEs and start-ups were entirely focused on nanomedicine alone [19]. In contrast, the 41 remaining large pharmaceutical or medical device companies had little in the way of nanomedicine projects or products, entirely foregoing R&D programs committed to nanomedicine and nano-based drug discovery programs. In other words, nanotechnology was not poised to make significant contributions to the business activities of large pharmaceutical and medical device companies [19].

The Lux Research group reported similarly tepid findings for US pharmaceutical firms. Lux reported that a mere $204 million or 4% of total corporate R&D in nanotech was devoted to healthcare applications in 2006. Lux reported that big pharma companies like Merck and Pfizer had not yet bought into new approaches like nanoparticulate drug reformulations or novel nanomaterials-based therapies, preferring to wait on the sidelines and license these technologies once they are developed further by startups [20]. Indeed, confirming this prediction Lux reported in 2010 that 34 out of the 50 companies reported to be developing nanoparticle-based medicines were startups and small firms that had been created since 2006 [21]. Lux predicted that until a blockbuster drug proves its full worth to pharmaceutical companies, big pharma will stay entrenched in its traditional methods of drug discovery and continue to set a low priority to investigating or using nanotechnology innovations, preferring instead to license nanoformulations once they reach advanced clinical trials [5,20].

Big pharma's reticence to embrace nanomedicine reflects the uncertainty and complexity facing companies hoping to open up and exploit the frontiers of nanobiotechnology and nanomedicine. Papers exploring the future potential of nanotech for medicine may justly rhapsodize new nanotech innovations on the horizon in medicine as revolutionizing the way medicine will be practiced, providing not only new discoveries in cell and molecular biology but also a broad spectrum of new approaches and capabilities for the pharmaceutical industry [22]. Indeed, nanomedicine promises to realize the earlier vision of personalized medicine articulated in the Human Genome Initiative that was further developed in the NIH Precision Medicine Initiative formally launched in 2015 [23]. But from the perspective of the pharmaceutical industry, nanomedicine and nanobiotechnology

are game changers, disruptive technologies that introduce a paradigm shift in previous practices.

Facilitating the development of nanomedicine will require implementing new manufacturing processes and training highly interdisciplinary R&D teams of scientists, engineers, and clinicians. In addition to these challenges nanomedicine and nanobiotechnology research introduce unprecedented issues for regulators at the Food and Drug Administration [24]. Protocols for characterizing new nanoparticles and nano-enabled materials used in drug research and delivery systems need to be established. Addressing these problems makes the already vexing lengthy drug approval process even more daunting and expensive [25]. Considering the scientific discoveries, regulatory hurdles, commercial and industrial infrastructure needed to realize their visions for a therapeutic revolution in medicine, the formulators of the goals for medicine of the National Nanotechnology Initiative must have felt they needed to cross a vast chasm to reach the Promised Land of nano-based therapeutics in one, two or even three decades [26].

A Central Policy Concern

The case of the NNI investment in nanobiotechnology and nanomedicine is situated at the center of policy debates about the role of federal funding and specific programmatic efforts targeted at transforming industry and even launching entirely new, possibly revolutionary and disruptive new industries. What role should the federal government play? Should federal funding be targeted for basic research alone, leaving the development and translation of basic research into commercially viable products completely in the hands of private industry? Should large federal funding initiatives such as the NNI actively engage in architecting and building the commercial infrastructure needed to realize their transformative visions? Or should this be left to private initiative and the forces of the market place? Apart from providing funding for basic research, can such large-scale federal initiatives be effective in realizing their goals? How do we measure the efficacy of such programs? In what follows we argue that the National Institutes of Health working through the National Cancer Institute has engaged in a well-organized programmatic effort to stimulate innovative research in nanobiotechnology and nanomedicine. In many ways their goal has been to overcome the structural and economic problems hampering the revolution in nanomedicine. We will provide data demonstrating that the programs initiated by the NIH went far beyond simply providing research funding for innovative science and potential breakthrough therapeutic discoveries in hopes they would find commercial funding and eventually have a transformative effect on medicine. The programmatic efforts we will discuss have funded innovative research through a rigorous peer review process [27], but they have also been instrumental to building necessary infrastructure for addressing the structural and economic problems we have identified above to translating these discoveries into clinical practice and the market place.

The NIH Roadmap for Nanomedicine

The formulators of the National Nanotechnology Initiative and the key officials at the National Institutes of Health (NIH) and National Cancer Institute (NCI) were keenly aware of the potential "Valley of Death" impeding the successful development of nanobiotechnology and nanomedicine we have outlined above, and they implemented a number of innovative policy instruments to accelerate basic science research in nanomedicine and the translation of research in nanobio and nanomedicine into clinical practice. After a five-year period of doubling its budget, the NIH launched its NIH Roadmap Initiative in 2003 [28]. The NIH Roadmap Initiative for Nanomedicine set out a multi-institutional long-term ten year plan for research and development of nanomedicine [29,30]. Funding for several types of center was arranged to begin in 2005. The first of these was a Network of eight NIH Nanomedicine Development Centers, each focused on a different aspect of basic science research into protein-protein interactions, intracellular transport, and biomolecular dynamics, with an initial total funding of $6 million [31]. The National Heart, Lung, and Blood Institute (NHLBI) also initiated its Programs of Excellence in Nanotechnology (PENs) in 2005 with a $53 million investment in multidisciplinary teams "capable of developing and applying nanotechnology and nanoscience solutions to the diagnosis and treatment of cardiovascular, pulmonary, hematopoietic, and sleep disorders [30]."

The NIH's largest nanotechnology program was the National Cancer Institute's Alliance for Nanotechnology in Cancer, funded for a five-year commitment of $144 million beginning in FY 2005. The Alliance supported eight Centers of Cancer Nanotechnology Excellence (CCNEs) designed to serve as research & development hubs for producing nanotechnology-based technology purposed for cancer prevention, diagnosis, and treatment [30]. The programs of these centers supported basic research, but the primary mission was explicitly focused on translational medicine. Our focus in the remainder of this paper is on the NCI Alliance programs in nanomedicine.

Addressing the Problems of Pharma R&D: The NCI Alliance for Nanotechnology in Cancer

The leaders of the NCI, Piotr Grodzinski, Gregory Downing, and Scott McNeil launched an all-out campaign to create a new paradigm in translational medicine with efforts focused on translational cancer research as the catalyst designed to "ignite" nano-product development and commercialization encompassing the public and private sectors [32-34]. The creation of alliances between academic research centers, startup companies closely connected to them, and progressive involvement of big pharma companies was a cornerstone of the NCI program.

The directors of the nanomedicine program at the NCI were well aware that the reticence of big pharma to take on new and risky-seeming research and development programs related to nanomedicine was attributable to multiple problems facing the industry. The increasing costs of drug discovery and development, along with stagnant and declining success rate of drug discovery programs, increasing length, complexity and cost of clinical trials were all contributing factors. The total R&D cost of bringing a new compound to market is estimated to be between $1.2-$1.3 billion [35-37]. In the face of higher development costs, pharma companies have gradually shifted the allocation of R&D expenditures away from basic and applied research towards development. Whereas in the 1970s almost 70% of the R&D budget went into discovery and preclinical research, since 2005 those categories have been reversed with discovery and preclinical research receiving less than 30% of pharma's R&D budget [38,39]. The clinical stages of R&D have received the bulk of R&D funding [40].

The impact of reductions in preclinical research on discovery compared to the impact of such reductions on other areas of R&D efforts is not understood [38]. One of the most telling statistics for the shifting fortunes of pharma R&D is the decline in new molecular entities (NMEs), the active ingredients in new drugs, filed with the Center for Drug Evaluation and Research (CDER): NMEs reached a

high of 50 in 1995 and declined steadily to 22 in 2008. While new drug application approvals by FDA CDER were stagnant relative to increases in R&D, FDA Center for Biologics Evaluation and Research's (CBER) Biologic License Application (BLA) approvals for protein therapeutics produced via recombinant protein synthesis rose from 11 during 1989-1996 to 17 during 1997-2002. Interestingly, biotech firms received more approvals (17 of 28) than traditional pharmaceutical companies (11 of 28) [38,41]. Was this a sign of the future? As a proportion of funds invested in R&D, basic and applied research by industry is waning, and R&D investment is being apportioned increasingly to clinical development and regulatory requirements, large pharma companies may be forced by the increasing costs of clinical trials to outsource their research and discovery to innovative startups and small firms rather than maintaining a vertically integrated company structure [35]. Indeed, Dixon, Lawton and Machin have speculated that the future of the drug industry may be one in which major pharma exists only to fund late stage clinical trials and to market drugs [42]. It is not clear whether this preclinical research and discovery gap is being filled by academic researchers and small firms that are the spinoffs of federally funded research, but in the case of the rise of nanobiotechnology and nanomedicine, we suggest that the leaders of the NCI Alliance program were betting on this as the course of the future.

Indeed, in order to address some of these problems alliances among biotech and pharma companies became a major strategy in bringing research products to market from the late 1990s through the mid-2000s. An extensive list of studies by economists and policy analysts have pointed out that while university spinoffs by academic entrepreneurs have been key factors in the evolution of biotechnology, alliances among small and large firms have been critical to ramping up potentially ground breaking innovations into commercially successful technologies. This is particularly the case with pharmaceutical products. Rather than conducting all their R&D in-house, pharmaceutical firms expand their research options by forming external partnerships and alliances. They will then acquire the company and its patents once the drug, therapy, or medical device has advanced beyond Phase 1 or 2 clinical trials [43-51]. Studies by Danzon et al. and Nicholson have shown that drugs developed in an alliance in recent years have tended to have a higher probability of success in navigating the clinical trial gauntlet, especially for the complex phase 2 and phase 3 trials. The superior performance of co-developed drugs is largest when the licensee (usually a pharmaceutical firm) has a good deal of experience conducting phase 2 and phase 3 trials [52-54]. During the first decade of the 2000s, the number of alliances with market valuations of $100 million or more increased several-fold between the beginning and ending years of the decade [55].

Modeled on the successful NIH Bioengineering Research Partnership programs initiated in 1999 [56], even before the official launch of the NNI, the NCI established the Unconventional Innovations Program (UIP) as a pilot program to work with university research groups and small companies to evaluate potential nanotechnology applications in cancer. As its first pilot project the UIP funded Kereos in 1999, a startup founded by Gregory Lanza and Samuel Wickline from Washington University in St. Louis on patents assigned by Lanza and Wickline to Barnes-Jewish Hospital, to develop a multifunctional nanoparticulate platform for imaging and drug delivery. The Kereos platform was developed in a partnership with Dow Chemical, Philips Medical Systems, and Bristol-Meyers Squibb Medical Imaging. The company received $20 million in Series B financing in 2005, by which time it had numerous products undergoing human trials.

Building upon this successful UIP model, the NCI launched the Alliance for Nanotechnology in Cancer (ANC) program in September 2004 [57-61]. The NCI Alliance for Nanotechnology in Cancer was funded initially as a five year program funded at a modest $144.3 million to create several academic centers of excellence (initially seven funded with $26 million but ultimately nine) sponsoring research but also encouraging the formation of startup companies connected to the Centers of Excellence and alliances between groups of researchers and firms in the field [62]. "The overarching goal of this program," writes the NIH Center for Strategic Scientific Initiative (CSSI) Office of Cancer Nanotechnology Research (OCNR) in their November 2010 Cancer Nanotechnology Plan (caNanoPlan), "has been to discover and develop nanotechnologies for applications ranging from discovery through translation and delivery of innovative, clinically relevant technologies for cancer prevention, diagnosis, and treatment." OCNR continues, "The Alliance's development model calls for the most promising strategies discovered and developed by Alliance grantees to be handed off to private sector partners for clinical translation and commercial development. In its first five years, the program focused on basic research and developmental efforts in six major challenge areas: molecular imaging and early detection, in vivo nanotechnology imaging systems, reporters of efficacy, multi-functional therapeutics, prevention and control, and research enablers" [63]. In addition to the nine Centers for Cancer Nanotechnology Excellence, the Alliance funded twelve Cancer Nanotechnology Platform Partnerships (CNPPs) totaling $35 million for five years [64]. The CNPPs were designed to translate transformative basic and preclinical cancer research discoveries into next-generation cancer diagnosis and treatment tools in a product-centric way. The CNPPs were individual research projects linked to the Centers of Excellence designed to develop the technologies to underpin new products in the six key programmatic areas listed above and reflected a cross-section of technologies, disciplines, cancer types, geographies, and risk/reward profiles. As these programs matured the goal was to form, in the words of OCNR Director Piotr Grodzinski, "a consortium involving government, pharmaceutical, and biotechnology companies" which would "evaluate promising nanotechnology platforms and facilitate their successful translation from academic research to clinical environment" [65]. In the second phase of the Alliance (2010-2015) the consortium was formalized as a public-private industry partnership called TONIC (Translation Of Nanotechnology In Cancer) to promote translational research and development opportunities of nanotechnology-based cancer solutions [65].

Two other key components of the first five-year program of the Alliance for Nanotechnology in Cancer were the Nanotechnology Characterization Lab (NCL) and a large program for Multidisciplinary Research Training and Team Development. The NCL was established with an initial outlay of $4 million at the NCI's Frederick, MD facility and was charged with developing analytical tests to guide the research community, support regulatory decisions, and help identify and monitor environmental, health and safety ramifications of nanotech applications [39,66]. The aim in creating the NCL was to provide a stable and standardized environment for intramural and extramural researchers to bring their nanodevices and nanomaterials for assessment and development. The NCL was established as a collaborative effort by the National Institute of Standards and Technology (NIST) and FDA for supporting the characterization of nanomaterials in a central location--and is in fact located on the same premises as NIST. The NCL's role in the Alliance was to perform standardized characterizations and safety evaluation of nanoscale materials developed by researchers

from academia, government, and industry. The NCI designed the NCL also to act as a technology incubator where new public-private collaborations could take shape in order to accelerate the translation of basic discoveries into useful clinical developments [57].

Data and Methods

We have constructed several databases to help us in identifying stars and tracking their impact across science and technology into commercialization. They are:

- Nanotechnology peer review literature metadata database
- Customized EPO PATSTAT / USPTO database
- NSF nanotechnology funding
- NIH nanotechnology funding
- NCI nanotechnology funding
- Nanobio firms & products with SEC and clinical trial events
- Social network data matrices for co-authorship linkage and the NCI Alliance

First, we have constructed a database containing detailed metadata records for all nanotechnology publications and queried the database to identify nanobio publications and authors working in nanobio after 1999 in the US. We have also created a patent database, enlisting a modified version of the European Patent Office's PATSTAT database, while also extracting data from the USPTO patent search engine for US nanomedicine and nanobiotechnology patents[2] granted after 1999. In addition we have created a database of all nano funding listed on the NIH, NSF and NCI websites, querying for all records of all nanobiotechnology and nanomedicine support over the years 2000 to 2011. Finally we have created a database of key nanobio firms and products containing corporate profiles, patent portfolios, financial event timelines based on events recorded and made available by the SEC, and clinical trial data from clinicaltrials.gov.

Having identified the leading US nanobio authors in the scientific literature of nanotechnology, we then look for the nanobiotechnology and nanomedicine patents of these star nanobio scientists that were granted by the USPTO from 2001-2011 along with the assignee affiliations of the patents. We then cross-reference those authors to the principal investigators and institutions receiving funding in our NIH/NSF/NCI funding database.

Finally, we generate a list of leaders in NCI funding over the period of interest. We examine the productivity and impact of these leading NCI-funded scientists in terms of nanobio publications and patents, companies founded, and performance measures of these companies. We note where these initial nanobio publishing stars coincide with stardom in patenting and funding raised, but we also track what they patent in the nanobiotechnology and nanomedicine space, how they affiliate with and startup firms, and how their firms perform. Our effort will be to determine the extent of involvement of "star scientists[3]" and of federal funding in commercial ventures contributing to nanobiotechnology and nanomedicine.

Literature Stars

We are interested in identifying and tracking the most prolific authors in the nanobiotechnology area by numbers of publications, citations received by their work from other papers, and the overall quality and impact of their work. However, given that nanobio is a nascent and highly interdisciplinary field, we are not only interested in the most prolific authors in nanobiotechnology, but rather we are interested in identifying those top nanobio authors who are the most prolific within the larger sphere of nanotechnology. For this reason we introduce a multi-tiered approach to identifying "literature stars" in which we identify highly prolific and influential authors within a set of papers identified strongly as nanobio and select from that group of authors those who have published the most in the broader area of nanotechnology.

The first step in our identification of star scientists in the nanobio literature is a search for a candidate list of authors using a term-based search originally developed in [12] to identify pharmaceutical nanobiotechnology articles published between 2000 and 2010 (a more complete description of our search method is included in Appendix A). The term-based procedure searches title, abstract, subject category and two different keyword fields for matching keywords in ISI Web of Knowledge metadata records in order to identify nanobio papers and the top 20-30 authors of nanobio papers. Three ranked lists of author names were produced from this initial list of papers: the top 300 names with the most total papers published (TP), the top 300 names with the largest totals of times cited (TC), and the top 300 names with the highest quality (Q, or TC/TP). All of the nanobio papers matching at least a last name from any one of the three lists were downloaded and examined manually to disambiguate the author list in order to properly attribute publications to individual authors and ultimately yield an exact list of top authors. Unlike many ISI-based papers, we chose to match names in all available author name fields and manually disambiguated authors by a manual review of approximately 900 associated papers[4] authored by individuals with last name matches. This procedure is the most precise and accurate way of handling name ambiguity for the purposes of identifying top nanobio authors, short of manually disambiguating author names for all nanobio papers, of course. While automated author name disambiguation has become an active area of research in recent years, computational methods not only continue to suffer from erroneous author assignments for 10-20% of papers but also limit themselves to last name plus first initial name representations [67].

The resulting list of authors was filtered down to authors who had published at least 3 nanobio articles with a minimum of 25 times cited combined. The resulting 174 authors from this process were chosen on a combined average rank scale of TP, TC, and Q. (See Table 2 below for the ranking in terms of publications—PubRank—for this first

[2] Throughout this study we identify nanomedicine and nanobiotechnology by following the guidelines of the USPTO's definition of Class 977 (USPTO 2010). We provide a full description of the process we use for querying the USPTO database for identifying patents as nanobio in Appendix B. In the simplest terms, a patent must be classified both as 977 Nanotechnology and also be classified under another class and/or subclass that is unambiguously bio/nano/life/med. We also discuss the advantages of the USPTO's approach to classifying nano in Appendix B and provide some examples that illustrate these advantages for sorting out problematic cases of assignment as nanobio.

[3] Our notion of the "star scientist" has its grounding in the work of Lynne Zucker and Michael Darby dating back to 1994, where a star scientist is simply one who is particularly successful at publishing and/or patenting within a specific field. Like Zucker and Darby, we identify stars by publishing success. Unlike Zucker and Darby we identify stars by finding leading recipients of research funding and do not identify stars by levels of patenting activity.

[4] According to Strotmann and Zhao [67], in order to identify a list of top authors, as many as ten times that number of top cited papers is needed. We use the complete list of possible papers, about 20 times larger than the intermediate list of top authors of nanobio papers, and about 30-40 times the number of authors produced on the final list of top authors in nanobio.

Literature Star	Locations, 2000-2012	NSF Funding in millions USD 2000-12	NIH Funding, in Millions USD (not incl. NCI) 2000-12	NCI Funding in Millions USD 2000-12	Pubs	Cites	Quality (Cites / Pubs)	Pubrank*	Pubs in co-author network	Co-author network rank	Nanobio Patents	Nanobio Assignees	Firms founded after 1999	Total Proceeds in Millions USD
Weissleder, Ralph	Harvard Medical School, Boston, MA	0	39.68	13.39	34	1090	32.06	5	107	7	1	General Hospital Corp.	2	96.5
Wickline, Samuel A.	Washington Univ, St. Louis, MO	0	14.94	16.46	24	861	35.88	7	57	14	0		1	0
Lanza, Gregory M.	Washington Univ, St. Louis. MO	0	4.79	7.87	23	860	37.39	6	53	16	0		0	0
Labhasetwar, Vinod D.	Cleveland Clinic, Cleveland, OH; Univ Nebraska, Lincoln, NE	0	3.36	0.14	24	1301	54.21	1	33	23	1	Univ. Nebraska Med. Center	0	0
Langer, Robert S.	MIT, Cambridge, MA	0	4.61	24.63	33	712	21.58	15	91	10	3	MIT	19	1034.2
Webster, Thomas J.	Brown Univ, Providence, RI; Purdue, West Lafayette, IN	0	0.43	0	50	902	18.04	19	108	6	3	Purdue Res. Found, Rensselaer Polytech	3	0.2
Josephson, Lee	Harvard Medical School, Boston, MA	0	4.42	0	14	518	37	13	49	17	1	General Hospital Corp.	1	37.7
Mumper, Russell J.	UNC-Chapel Hill, Chapel Hill, NC; Univ Kentucky, Lexington, KY	0	2.21	1.00	24	748	31.17	10	34	21	2	Valentis, Inc., Genemedicine, Inc.	5	13.2
West, Jennifer L.	Rice Univ, Houston, TX	0	0.93	0.43	10	765	76.5	9	28	24	0		1	1.7
Lakowicz, Joseph R.	Univ Maryland, College Park, MD	0	13.74	0	17	401	23.59	29	104	8	0		0	0
Baker, James R.	Univ Michigan, Ann Arbor, MI	0	1.71	8.82	18	399	22.17	31	72	12	2	NanoBio Corp., Univ. Michigan	1	6.7
Wang, Joseph	UCSD, La Jolla, CA; Arizona State, Tempe, AZ; New Mexico State, Las Cruces, NM	0.25	0.54	0	10	249	24.9	45	228	1	0		0	0
Stupp, Samuel I.	Northwestern Univ, Evanston, IL	0.81	11.70	0	16	268	16.75	39	99	9	1	Northwestern Univ.	2	3.4
Johnston, Keith P.	Univ Texas, Austin, TX	0.33	0	0	20	269	13.45	43	81	11	1	SkyePharma Canada	0	0
Geddes, Chris D.	UMBC, Baltimore, MD	0	1.90	0	12	251	20.92	42	70	13	0		0	1.5
Gryczynski, Ignacy	Univ of North Texas, Denton, TX; Univ Maryland, Baltimore, MD; Univ Pennsylvania, Philadelphia, PA	0.56	1.05	0.37	12	253	21.08	40	54	15	0		0	0
Mirkin, Chad A.	Northwestern Univ, Evanston, IL	1.18	3.81	24.04	18	206	11.44	58	225	2	23	Nanosphere, Inc., Northwestern Univ.	3	352.4

Williams, Robert O.	Univ Texas, Austin, TX	0	0	0	26	294	11.31	44	35	20	0		0	0
Grimes, Craig A.	Penn State, State College, PA; Univ Kentucky, Lexington, KY	0	0	0	10	190	19	65	110	4	0		1	0
Desai, Tejal A.	UCSF, San Francisco, CA; Boston Univ, Boston, MA; U of Illinois-Chicago, Chicago, IL	0.17	0.98	0	14	212	15.14	56	41	19	1	Nanosys, Inc.	0	0
Sun, Ya-Ping	Clemson Univ, Clemson, SC	0	0.55	0	10	154	15.4	77	109	5	2	Clemson University	0	0
Prasad, Paras N.	SUNY-Buffalo, Buffalo, NY	0.03	0	3.39	15	145	9.67	83	132	3			0	0
Gryczynski, Zygmunt	Univ of North Texas, Denton, TX; Univ Maryland, Baltimore, MD; Univ Pennsylvania, Philadelphia, PA	0.56	0.98	0.33	9	160	17.78	79	42	18	0		0	0
Yong, Ken-Tye	Univ Buffalo, Buffalo, NY	0	0	0	6	60	10	145	34	22	0		0	0
Number of Lit Stars = 24		**3.89 Millions USD**	**112.33 Millions USD**	**100.87 Millions USD**	**Avg= 18.7**	**Avg= 469.5**	**Avg= 25.1**		**Avg.= 83.2**		**Total Nanobio Patents=41**		**Total Number Firms = 38**	**Total = $1472.6**

- Multiple locations reported in order of most recent location first
- Pubrank is the author's rank, from 1 to 174, in the original nanobio literature set. It is a rank score based on ranking the average of their rank for number of publications among the list of 174 candidates, their rank for number of times cited among the list of 174 candidates, and average quality per paper among the list of 174 candidates. 'Pubs' and 'cites' reflect the total number of nanobio publications in the data set authored by the star, and the total number of times those papers were cited by other papers, respectively.
- Co-authorship rank is the rank order of the author in terms of numbers of co-authored papers in nanobiotech.

Table 2: Overview of Nanobio Literature Stars' Federal Funding Sources, Publications, Publication Rankings, Patents, Firms Founded and Capital Raised (Sources: ISI Web of Science, NSF Award Search, NIH RePORT, NCI Funded Research Portfolio, USPTO, SEC Edgar, Hoover's)

stage in our selection of literature stars; and see Appendix A for a full description and examples).

The steps outlined above result in a list of 174 of the most prolific and highly cited authors in the field of nanobiotechnology. We now want to go further and explore the wider impact of their work and potential involvement across the wider domain of nanotechnology by considering the nanotechnology publications of these 174 authors. By doing so we acknowledge that nanobio researchers are often active in more pure nanotechnology research and that lexical methods for identifying nanobio papers may lead us to miss relevant papers otherwise contained in a broader set of nanotechnology papers that are nonetheless relevant to nanobio. In this set of papers we do not limit the field to nanobiotechnology but consider their publications in all fields of nanotechnology. Our search determined that these 174 authors published 2676 nanotechnology articles published between 2000-2009. A list of authors ranked by number of publications in the set of 2676 papers was generated, and a natural break in the number of publications below 23 publications per author was identified. Using that break as a cutoff point, all authors in the set of 174 top nanobio authors that had at least 23 papers in the larger set of 2676 papers were selected. The resulting 24 authors, our Literature Stars, authors who qualify as top nanobio and top nanoscience researchers, are listed in Table 2. In addition to identifying the top 24 authors we include information in Table 2 on the funding sources for their work provided by the NSF, NIH, and NCI, the number of nanobio patents they have been awarded, the assignees of those patents, and the number of firms they have founded.

NCI Stars

In the previous section we focused on the most prolific authors in nanobiotechnology and nanomedicine, and we have drawn attention to their patenting and commercial activities. Six of the 24, or 25% of the literature stars were primarily funded by the NCI. In this section we present data on the role of the NCI-funded scientists and their impact on the development and commercialization of nanobiotechnology and nanomedicine. We begin by identifying the leading recipients of NCI funding. We then compare the quality of their scientific publications and depth of their relations with commercial firms with that of the group we identified above as Literature Stars. Our group of top NCI-funded scientists was identified by gathering all 98,585 NCI funding records for fiscal years 2000 through 2011 inclusive from the NCI Funded Research web site (http://fundedresearch.cancer.gov). The NCI funding records were filtered for records containing 'nano' in multiple text fields. Duplicate records were removed from the resulting set, and names of PIs and locations were disambiguated, resulting in 2529 nano-relevant funding records. The nano-relevant records were aggregated on disambiguated names of funded investigators, and those names receiving $5 million or more of funding during fiscal years 2000

through 2011 were identified as stars and listed below in Table 3. The $5 million of 'nano'-explicit funding is a restrictive criterion. Some individuals who may be informally considered stars or considered stars by more direct bibliometric means may not make the list either because the grants they received were not explicitly 'nano' or they were not listed as PIs for grants exceeding $5 million for the given time period. Central to our evaluation of the success of the strategies and policies of the NCI for launching and nurturing the fields of nanobio and nanomedicine is data on the success of NCI-funded scientists in translating their research into nanobio and nanomedicine patents, successful companies, and products on the market. Tables 4 and 5 summarize our findings on the firms founded by NCI-funded star scientists and the product offerings of those firms.

Comparison and Analysis of Literature Stars and NCI-Funded Scientists

The data presented in Tables 2-5 offer some interesting comparisons of the different programmatic emphases of the agencies involved in funding nanobio and nanomedicine efforts. The largest funder of research from 2000-2012 resulting in major publications and impact in nanobio/nanomedicine is the NIH (total of $112.33 million), with the

Name	Home Institution, 2000-2012	NCI dollars 2000-2011, in millions USD	Nanobio Patenting by NCI Stars 2000-20012	Nanobio Patent Assignees	Number of Firms Founded by NCI Stars 1999-2009	Total Proceeds of NCI Star's Companies in Millions USD
Arteaga, Carlos	Vanderbilt Univ, Nashville, TN	10.0				
Baker, James R.	Univ Michigan, Ann Arbor, MI	8.8	2	Nanobio Corp., Univ. Michigan	1	6.7
Bhujwalla, Zaver	Johns Hopkins, Baltimore, MD	8.0	1	Johns Hopkins Univ.		
Contag, Christopher	Stanford Univ, Palo Alto, CA	7.3				
Desimone, Joseph	UNC-Chapel Hill, Chapel Hill, NC	5.1			1	63.4
Dewhirst, Mark	Duke Univ, Durham, NC	11.7				
Dubinett, Steven	UCLA, Los Angeles, CA	8.5				
Esener, Sadik	UCSD, La Jolla, CA	20.7			3	0.9
Ferrari, Mauro	Methodist Hospital, Houston, TX; NCI, Bethesda, MD; Ohio State, Columbus, OH	5.6	1	Univ. Texas System	2	6.3
Gambhir, Sanjiv	Stanford Univ, Palo Alto, CA	27.4			1	60.5
Golub, Todd	Harvard Medical School, Boston, MA	7.4			3	610.0
Gray, Joe	Oregon Health Sci Univ, Portland, OR	11.1				
Heath, James	Caltech, Pasadena, CA	22.9	2	Hewlett Packard, Cal Tech	1	50.0
Jain, Rakesh	Harvard Medical School, Boston, MA	6.8	1	General Hospital Corp.		
Juliano, Rudolph	UNC-Chapel Hill, Chapel Hill, NC	17.7				
Kern, Scott	Johns Hopkins, Baltimore, MD	11.3				
Kopelman, Raoul	Univ Michigan, Ann Arbor, MI	12.4				
Langer, Robert S.	MIT, Cambridge, MA	24.6	3	MIT	19	1034.2
Lanza, Gregory M.	Washington Univ, St. Louis. MO	7.9				
Mirkin, Chad A.	Northwestern Univ, Evanston, IL	24.0	23	Nanosphere, Northwestern Univ.	3	352.4
Mitchison, Timothy	Harvard Univ, Cambridge, MA	6.3				
Nie, Shuming	Emory Univ, Atlanta, GA	25.0				
Piwnica-Worms, David	Washington Univ, St. Louis, MO	8.1				
Ross, Brian	Univ Michigan, Ann Arbor, MI	12.7			2	32.0
Scardino, Peter	Sloan Kettering, NY, NY; Baylor, Houston, TX	9.0			1	0
Schnitzer, Jan	Sidney Kimmel Cancer Center, San Diego, CA; Proteogenomics Research Institute for Systems Medicine, San Diego, CA; UCSD School of Med, La Jolla, CA	11.7				
Searson, Peter	Johns Hopkins, Baltimore, MD	5.3	1	Johns Hopkins Univ.		
Torchilin, Vladimir P	Northeastern Univ, Boston, MA	8.4			3	19.8
Volkert, Wynn	Univ Missouri, Columbia, MO	9.1				
Weissleder, Ralph	Harvard Medical School, Boston, MA	13.4	1	General Hospital Corp.	2	96.5
Wickline, Samuel A.	Washington Univ, St. Louis, MO	16.5			1	0.3
Number of NCI Stars=31		**Total = $384.7 Million**	**Total Patents = 35**		**Number of companies founded = 41**	**Total Proceeds NCI Stars' Firms = $2294.8 M.**

Table 3 : Overview of NCI Stars, 2000-2011, Funding, Nanobio Patents, Number of Firms Founded, and Total Proceeds of NCI Stars' Firms (Sources: NCI Funded Research Portfolio, USPTO, SEC Edgar)

Company	Location	Founder	In operation	Year Founded	Employment	Total Proceeds in Millions USD	IPOs, sale of company, acquisitions of other firms
Avidimer	Ann Arbor, MI	Baker, James R.	No	2003	5	6.7	None
Liquidia Technologies	Morrisville NC	Desimone, Joseph	Yes	2004	50	63.4	None
Parallel Solutions, Inc	Cambridge MA	Esener, Sadik; Langer, Robert S.	No	2001	9	0.9	None
Ziva	San Diego CA	Esener, Sadik	No	2002	6	0.0	None
Optical Micro-Machines	San Diego CA	Esener, Sadik	No	2010	1	0.0	None
Leonardo Biosystems	Houston, TX	Ferrari, Mauro	Yes	2005	2	1.3	None
NanoMedical Systems	Austin, TX	Ferrari, Mauro	Yes	2007	9	5.0	None
Lumera Corp	Bothell WA	Gambhir, Sanjiv	No	2000	80	60.5	IPO $41.7M 05-2004; Acquired by GigOptic 12-2008
Forma Therapeutics	Watertown MA	Golub, Todd	Yes	2008	90	124.4	Acquired SolMap Pharmaceuticals 10-2008
Foundation Medicine	Cambridge MA	Golub, Todd	Yes	2009	5	86.0	None
H3 Biomedicine	Cambridge MA	Golub, Todd	Yes	2011	30	400.0	Acquired by Eisai Inc., $200M, 01-2011
Integrated Diagnostics Inc	Seattle WA	Heath, James	Yes	2009	5	50.0	None
Combinent Biomedical Systems	Lexington, MA	Langer, Robert S.	Yes	2000	2	12.7	None
PureTech Ventures	Boston, MA	Langer, Robert S.	Yes	2000	15	0.0	None
Momenta Pharmaceuticals	Cambridge, MA	Langer, Robert S.	Yes	2001	197	348.9	IPO $34.8M 06-2004; Acquired Sialic Switch assets $51.5M 11-2011
Pervasis Therapeutics	Cambridge, MA	Langer, Robert S.	No	2003	10	240.2	Acquired by Shire PLC, $200M, 04-2012
Pulmatrix	Boston, MA	Langer, Robert S.	Yes	2003	35	53.4	None
Arsenal Vascular (medical)	Brookline, MA	Langer, Robert S.	Yes	2005	3	23.8	None
InVivo Therapeutics	Cambridge, MA	Langer, Robert S.	Yes	2005	16	51.4	IPO $17.4M, 02-2012
Living Proof	Cambridge, MA	Langer, Robert S.	Yes	2005	33	10.9	None
BIND Biosciences	Waltham, MA	Langer, Robert S.	Yes	2006	20-49	63.6	No
Semprus BioSciences	Cambridge, MA	Langer, Robert S.	Yes	2006	13	54.1	Acquired by Teleflex, $30M, 06-2012
T2 Biosystems	Lexington, MA	Langer, Robert S. ; Weissleder, Ralph	Yes	2006	25	37.7	None
Selecta Biosciences	Watertown, MA	Langer, Robert S.	Yes	2007	30	55.6	None
Seventh Sense Biosystems	Cambridge, MA	Langer, Robert S.	Yes	2008	6	15.2	None
TARIS BioMedical	Lexington, MA	Langer, Robert S.	Yes	2008	8	30.7	None
Kala Pharmaceuticals	Waltham, MA	Langer, Robert S.	Yes	2009	5	12.2	None
ModeRNA Therapeutics	Cambridge, MA	Langer, Robert S.	Yes	2009	25	0.0	None
480 Biomedical	Watertown, MA	Langer, Robert S.	Yes	2011	60	20.1	None
Blend Therapeutics	Watertown, MA	Langer, Robert S.	Yes	2011	6	2.8	None
NanoInk	Chicago, IL	Mirkin, Chad A.	Yes	2000	27	77.0	None
Nanosphere	Northbrook, IL	Mirkin, Chad A.	Yes	2000	51-200	267.5	IPO $98M 11-2007
Aurasense Therapeutics	Evanston, IL	Mirkin, Chad A.	Yes	2009	15	7.9	None
Molecular Imaging Research	Ann Arbor MI	Ross, Brian	Yes	2002	20	32.0	Acquired by Charles River, $12.5M, 09-2008
Imbio	Minneapolis MN	Ross, Brian	Yes	2007	1	0.0	None
Oncovance Technologies Inc	Houston TX	Scardino, Peter	No	2003	0	0.0	None
Encapsion/Anterios, Inc.	New York, NY	Torchilin, Vladimir P	Yes	2006	80	19.8	None
Nemucore	Wellesley, MA	Torchilin, Vladimir P	Yes	2008	10	0.0	None
MitoVec Inc.	Boston, MA	Torchilin, Vladimir P	No	2000	5	0.0	None
VisEn Medical	Boston, MA	Weissleder, Ralph	No	2000	11-50	58.8	Acquired by PerkinElmer, $23M, 08-2010
PixelEXX Systems	St. Louis, MO	Wickline, Samuel A.	Yes	2008	4	0.3	None
Number of companies=41 Avg.=1.3		**Number of stars founding firms=14 (45.2%)**	**Total=32 Avg.=1.0 per star**		**Total employment=1025**	**Total= $2294.8M**	

Table 4 Overview of firms founded by NCI stars, 2000-2012 (Sources: Hoovers, LinkedIn, Manta.com, Indeed.com, secinfo.com, SEC EDGAR, Xconomy.com, 480biomedical.com, NIH ClinicalTrials.gov, KalaRx.com, hotstocked.com, glassdoor.com)

Company	Products or services
Liquidia Technologies	PRINT particle design for vaccines; fluoropolymer materials
Leonardo Biosystems	Entered into a partnership with NanoMedical Systems mentioned below to manufacture nanoporous silicon particles for Leonardo's multi-stage drug delivery system
NanoMedical Systems	Drug Delivery Devices or Systems: PMDS-1, PMDS-2+
Imbio	Parametric Response Mapping (PRM)
Forma Therapeutics	Drug discovery services
Foundation Medicine	FoundationOneTM genomic profile assay
Integrated Diagnostics Inc	Protein-Catalyzed Capture Agents
H3 Biomedicine	Formed strategic partnership with Compendia 02-2012 to license and offer Compendia's full suite of oncology data mining tools including Oncomine Concepts Edition and Oncomine Power Tools Edition
Oncovance Technologies Inc	Kattan Nomograms
T2 Biosystems	T2Dx, T2Hemostasis machines which utilize the T2 Magnetic Resonance (T2MR) technology allows for direct detection in complex matrices
Combinent Biomedical Systems	Transvaginal drug delivery vaginal ring for reproductive endocrinology
Momenta Pharmaceuticals	Enoxaparin Sodium Injection (generic Lovenox), M356 (generic Copaxone)
Pervasis Therapeutics	Vascugel® for hemodialysis, PVS-10200 for the treatment of PAD, PVS-30200 for oncology
Pulmatrix	Dry Powder iCALM for COPD, Asthma, and respiratory infections
Living Proof	>25 (anti-frizz technology beauty products)
Arsenal Vascular (medical)	AxioCore™ nanofiber drug delivery technology
InVivo Therapeutics	Biopolymer scaffolding to treat spinal cord injuries (SCI)
Semprus BioSciences	Semprus Sustain™ Technology˚ which is a long-lasting, covalently bonded, non-leaching polymer that is designed to reduce the attachment of platelets and blood proteins at the device surface.
BIND Biosciences	Accurins™: BIND-014, chemotherapeutics
Selecta Biosciences	SVP™ platform, tSVP™ - fully-integrated synthetic nanoparticle vaccines engineered to mimic the properties of natural pathogens to elicit a maximal immune response, t2SVP™ - designed to induce an antigen-specific immune tolerance
Seventh Sense Biosystems	TAP Touch Activated Phlebotomy™, TAP 20
TARIS BioMedical	LiRIS to treat the pain and discomfort associated with Interstitial Cystitis (IC) and ureteral stent symptoms
Kala Pharmaceuticals	Mucosal Penetrating Products (MPPs)
ModeRNA Therapeutics	RNA-based drugs, explore modified mRNA to create a new class of drugs, native™ protein therapeutics.
Blend Therapeutics	Maestro™ platform: long-circulating nanoparticles
480 Biomedical	The Stanza™ Bioresorbable Scaffold
NanoInk	>30 (nanolithography, bioarrays, advanced materials, repair, instrumentation)
Nanosphere	15-20(Clinical Microbiology Tests, Cardiac Tests, Human Genetic Tests, Pharmacogenetic Tests, Instruments)
AuraSense Therapeutics	SNA™ Gene Regulation Platform

Table 5: Current product offerings of firms founded by NCI Stars, 2000-2012, in operation as of January 1, 2013 (Sources: Hoovers, LinkedIn, Manta.com, Indeed.com, secinfo.com, SEC EDGAR, Xconomy.com, 480biomedical.com, ClinicalTrials.gov, KalaRx.com, hotstocked.com, glassdoor.com)

NCI close behind (total of $100.87 million). Nineteen of the twenty-four (79%) most important authors were funded by the NIH and twelve of the twenty-four (50%) received funding primarily from the NCI. One-third of the scientists producing the most highly influential research were funded by the NSF (with a total of $3.89 million).

A central concern of our analysis is with the linkage of NIH- and NCI-funded research to commercial firms and to the founding of new firms involved in translating nano-enabled drugs and devices into clinical medicine. Table 6 and Figures 1 and 2 provide a comparative assessment of the networks of leading star scientists in the nanobio/nanomedicine field in terms of their co-authorship of papers with scientists at firms and their impact. We have compared the production of scientific articles published by our group of top 24 Literature Stars with the production of scientific articles published by the top 31 NCI-funded scientists listed in Table 3. Since 6 of our top 24 Literature Stars are NCI-funded authors (see Table 2), for sake of comparison we also present data on the two groups of authors with the overlapping group of 6 authors removed. This turns out to be crucial due to the incredible high productivity of these 6 NCI-funded stars. The two groups with the overlapping 6 NCI-funded authors removed are indicated as Lit-Only (i.e. Literature Stars excluding the NCI-funded authors) and NCI-Only (i.e. NCI-funded authors excluding authors that are also a subset of the 24 Literature Stars). Also for the sake of comparing citation rates despite differences in dates of publication we have normalized all citation counts to the average citations for a paper from the year 2000. In addition, we compare the number and impact of papers co-authored with industry scientists in both the Literature Stars and NCI sets (identified as Linked Papers in Table 6).

Judging from these data, the most prolific authors, our Literature Stars, are not only authors of high-impact papers but also engaged in co-authoring papers with industry scientists. Twenty-two, or 92% of the 24 most prolific authors in the nanobio/nanomedicine field co-authored 141 papers with industry scientists at 68 independent firms from 2000-2011. Literature Stars co-author with a wide range of startup companies as well as large firms such as Philips, Merck, Pfizer, Dow Chemical, Monsanto, Genentech, Bristol Meyers Squibb, DuPont and others (See Figure 1). The Literature Stars are considerably more prolific than the NCI stars, averaging 137 papers per star versus 35

Measure		Lit	NCI	Lit Only	NCI only	Lit + NCI
1.	Number of Stars	24	31	18	25	6
2.	Original Paper Count 2000-2011	3,287	1,086	n/a	n/a	n/a
3.	Avg. papers per star	137	35	n/a	n/a	n/a
4.	Total Cites	144,420	67,569	n/a	n/a	n/a
5.	Normalized Cites adj. to 2000 Standard	292,211	129,382	n/a	n/a	n/a
6.	Quality, normalized	88.9	119.14	n/a	n/a	n/a
7.	Number of Stars with linked papers	22	22	16	16	6
8.	Number of distinct linked firms	68	54	49	34	20
9.	Number of linked papers	141	109	85	53	56
10.	Linked papers times cited	6,923	6,574	4,048	3,699	2,875
11.	Linked papers, normalized times cited	13,770	12,775	7,270	6,275	6,500
12.	Quality of linked papers normalized	97.66	117	85.53	118.4	116.07

Table 6 Comparison of article production and impact of NCI-funded authors with Literature Stars and distribution of co-authorship linkages with industry scientists. (Source: ISI Web of Science)

for NCI authors, and producing more than 3 times the total number of papers. However, the scientific papers of the NCI stars have much higher quality rankings (standardized citations per paper) indicative of greater impact on the field. Both groups co-authored relatively few articles with industry scientists during the period we have considered, but among these co-authored papers the NCI stars have twice the rate of linked papers compared with the Literature Stars (4% for Literature Stars versus 10% for NCI stars). Also, the papers co-authored with industry scientists by NCI stars have significantly higher impact rankings than the papers of Literature Stars (see Table 6, row 12).

The major differences between the group of Literature Stars and NCI-funded scientists is in terms of the far greater number of patents, companies, and commercial products resulting from the work of the NCI-funded stars. While 12 of the 24 Literature Stars have been granted 41 patents in nanobio and nanomedicine, and 11 of the 24 literature stars have founded some 38 firms, the stars leading these efforts were funded primarily by the NCI. In Table 2 we see that NCI-funded scientists are the founders of 26 out of 38 or more than two-thirds of the companies founded in the nanomedicine field by the leading scientific authors. Two of the leading literature stars, Robert Langer of MIT and Chad Mirkin of Northwestern, have started 22 of the 38 firms and hold 26 of the 41 nanobio patents assigned to the Literature Stars in Table 2. Robert Langer, who has founded 19 companies since 1999, of which 18 are still in operation, is perhaps the most remarkably prolific scientist on the nanomedicine scene today. Langer's companies have garnered over $1 billion in funding.

Expanding on this NCI story, Tables 2-5 set out an astonishing story of success for the NCI funding program. The 31 scientists receiving the top funding awards from the NCI have been major contributors to the scientific literature in the field of nanobio and nanomedicine, and they have been significantly more productive as patentees and founders of companies. Six of the top 24 Literature Stars are among the NCI-funded stars. Collectively the 31 NCI stars have been awarded 35 nanobio and nanomedicine patents from 2000-2012. Two-thirds (23) of those nanobio patents have been awarded to Chad Mirkin, comprising one-third of the 69 patents granted to him by the USPTO from 2000-2012. Fourteen of the NCI most-funded scientists have founded 41 companies. Mirkin, Golub, Torchilin, and Esener have each founded 3 companies; Weissleder, Ferrari, and Ross have each founded two firms; and Robert Langer has founded a staggering 19 firms since 2000. The total proceeds of the firms founded by NCI-funded scientists are $2.3 billion compared to the combined $1.5 billion in proceeds (series funding offerings plus gross proceeds from IPOs and other sales of securities plus proceeds from sale of company) (See Table 2, last column) generated by firms founded by Literature Stars. The companies founded in the period of a little over a decade from 2000-2012 by the NCI-funded scientists have employed over 1,000 persons, and the 29 companies in operation listed in Table 5 currently produce more than 100 nano-enabled products and medical services (see Table 5). Scientists receiving funding from the NCI have been more active in patenting, founding companies, and bringing medically relevant nano-enabled products into clinical trials and to the market. We argue that this emphasis is attributable to the NCI Alliance for Nanotechnology in Cancer's emphasis on developing translational medicine and building the infrastructure for launching nanomedicine.

In this section we have examined the success of NCI-funded "stars" in translating their research in nanobiotech and nanomedicine into biomedical devices, drugs, and commercial products through patenting and licensing their inventions and through the formation of startup companies. The overwhelming conclusion we derive from this initial exploration is that the NCI-funded scientists have been extraordinarily successful in launching the field of nanomedicine. In our concluding section we examine the extent to which these results are linked into the programs of the NCI Alliance for Nanotechnology in Cancer and can be considered a validation of the NCI's programmatic vision.

The NCI Alliance: Network Effects in Launching Nanomedicine

Responding to the alarming deceleration of the rate at which new medical therapies are entering the regulatory pipeline, the NCI launched the Alliance for Nanotechnology in Cancer program in September 2004 to accelerate the invention and translation of nanotechnology to cancer treatment, prevention and diagnosis [33,65]. A key feature of the program was the stimulation of startup companies in nanobiotechnology and nanomedicine and the formation of alliances with existing pharmaceutical firms and device companies. The NCI Alliance was an investment in the belief that nanotechnology research could drive advancements in cancer therapies and clinical trials alike while cutting drug development and approval costs by delivering the necessary platform technology [33].

In its first phase, from 2005-2010, the NCI Alliance program funded academic clusters supporting training programs as well as interdisciplinary projects, such as the CCNEs and CNPPs. During this first phase, the NCI also established the NCL in order to centralize nanomaterial characterization and accelerate the nascent field of cancer nanomedicine [65]. Table 7 below lists the lead scientists,

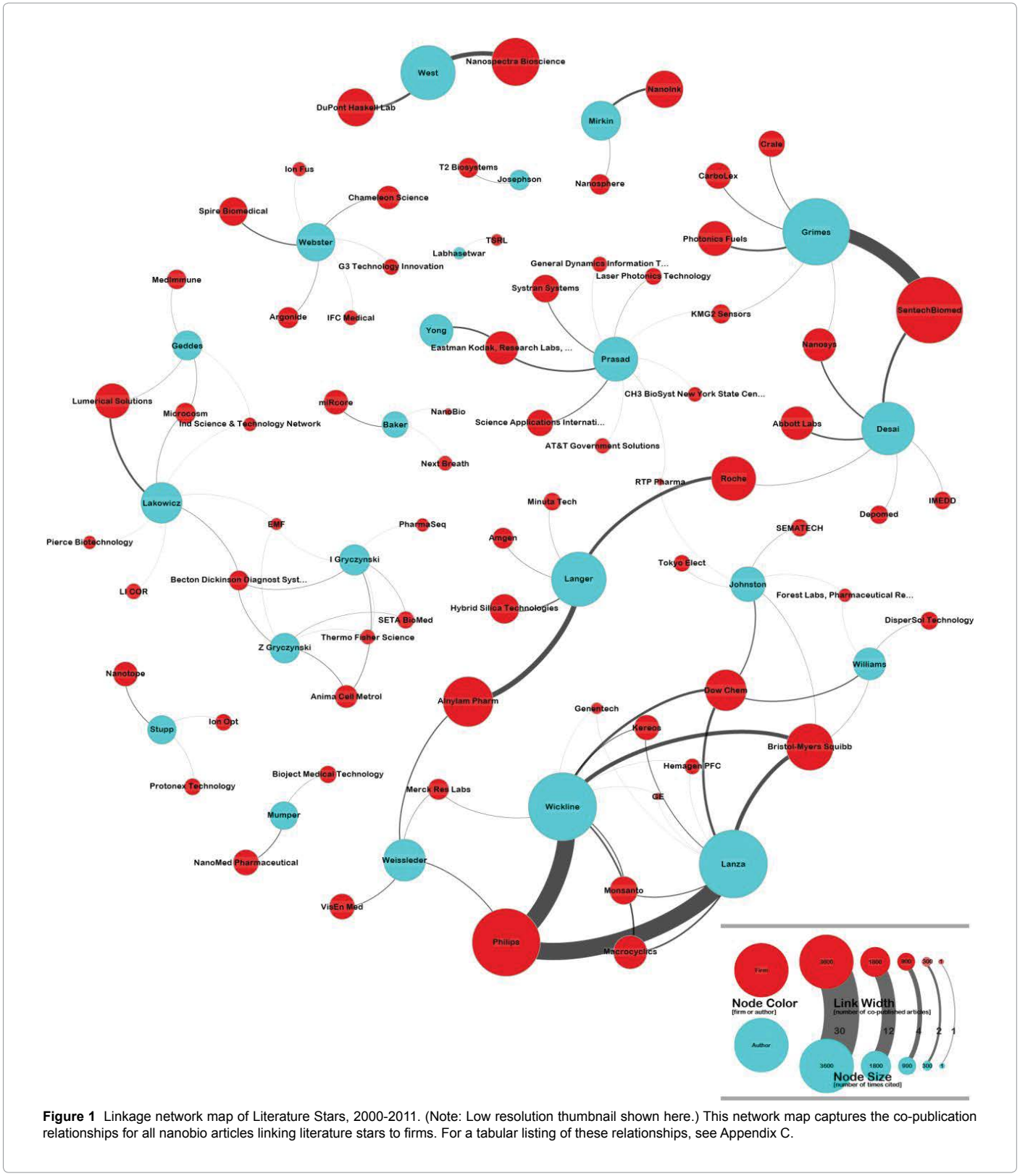

Figure 1 Linkage network map of Literature Stars, 2000-2011. (Note: Low resolution thumbnail shown here.) This network map captures the co-publication relationships for all nanobio articles linking literature stars to firms. For a tabular listing of these relationships, see Appendix C.

federally funded centers, and firms in the NCI Alliance between 2005-2012. The table includes NCI Stars who were PIs or directors of NCI Alliance Centers or assigned patents to these organizations, and firms partnering or collaborating with NCI Alliance Centers and Platform Partners in the period 2005-2012. Each listed star is either a founder of one or more NCI Alliance firms, has nanobiotechnology or nanomedicine patents assigned to affiliated institutions, or is a PI for one of the centers. The goal of the NCI in establishing the Alliance

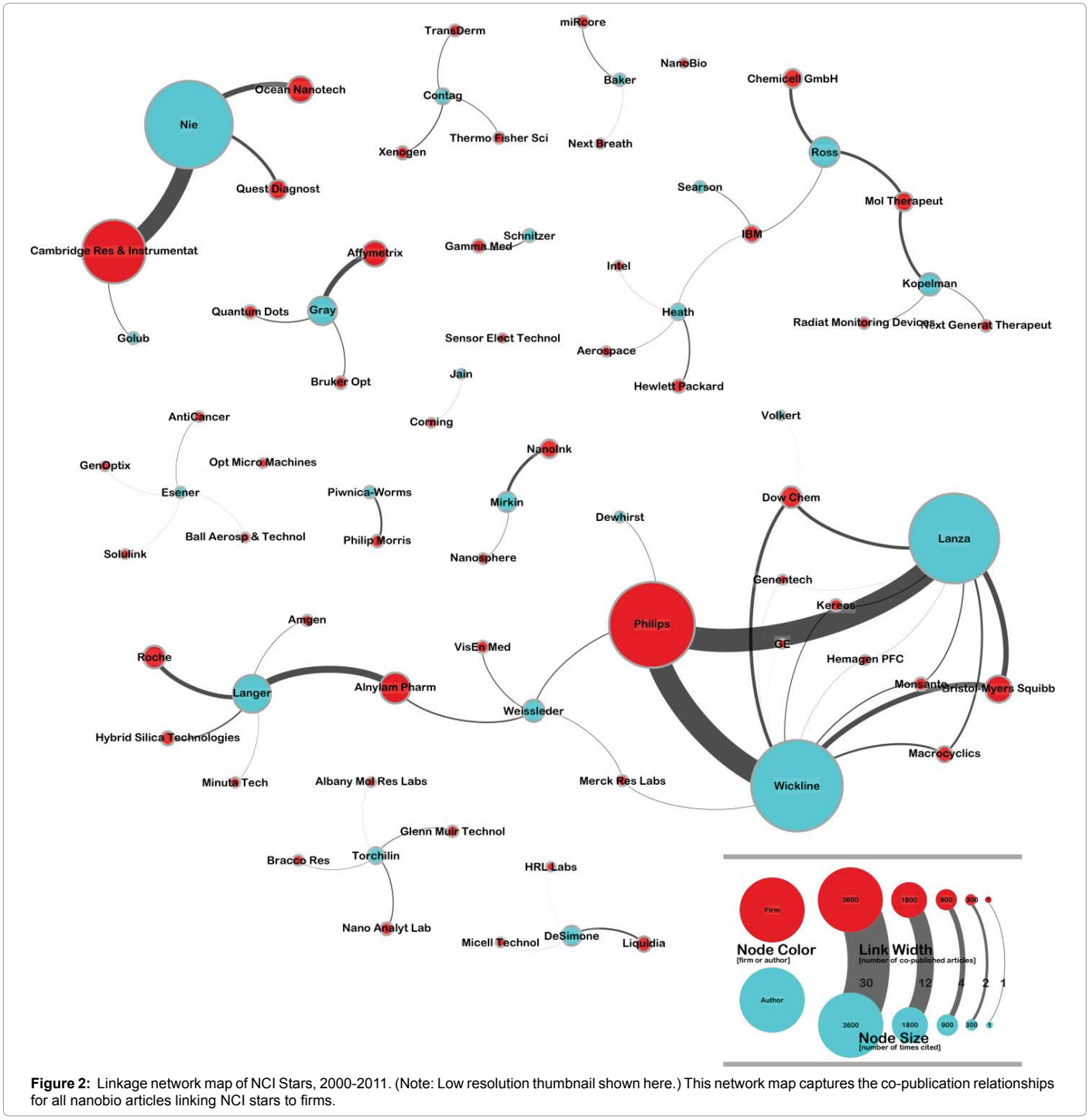

Figure 2: Linkage network map of NCI Stars, 2000-2011. (Note: Low resolution thumbnail shown here.) This network map captures the co-publication relationships for all nanobio articles linking NCI stars to firms.

was to create an interlocking network of firms and research labs with complementary capabilities that would provide critical synergies for the takeoff of nanomedicine. In this section we describe some of the successes of participants in the NCI Alliance, drawing upon the social network analysis concepts of strategic holes [68], betweenness centrality and alliance networks in [69] to assess the strategic policies of the NCI Alliance for launching nanomedicine.

In addition to having a pipeline of technologies being developed by companies founded by NCI stars and companies affiliated with the NCI Alliance, a key measure of success of the program is the steady stream of products in clinical trials generated by Alliance firms. We have indicated (in Table 5 above) that 29 of the 41 companies founded by NCI-funded stars have products and services already approved for market. Table 8 below expands on this by listing the products of firms founded by NCI stars or alliance partners that are currently in clinical trials. In all 18 companies founded by NCI-funded stars or members of the NCI Alliance currently have products in 32 early phase clinical trials. By contrast, the top five pharmaceutical companies in terms of revenues and R&D expenditures; namely, GlaxoSmithKline,

Pfizer, Novartis, Merck, and Roche have a combined total of 57 clinical trials relevant to nano. The top two companies, GSK, and Pfizer are responsible for 44 of those trials (Source: ClinicalTrials.gov). Such comparisons suggest that within a brief window of 5 years, the NCI Alliance program has emerged as an effective potential partner for big pharma in building the future of nanomedicine.

In order to rapidly architect a revolution in nanomedicine, the strategy of the NCI has been to build a network of university research/clinical centers each focused on a key area of nanomedicine, startup companies connected to those centers, and form alliances as bridge structures to big pharma companies. Thus a useful measure of the success of the program is its effectiveness in creating these alliances. Table 9 illustrates the numerous partnerships formed between firms founded by NCI-stars and big pharma and medical device companies, such as Siemens, Roche, Pfizer, Genentech, Novartis and other large firms. Examples such as the investments by Boehrringer Ingelheim, Genentech, and Novartis in the drug discovery platform developed by NCI-star Todd Golub's firm Forma Therapeutics illustrates the partnership forming between big pharma companies and the NCI alliance in stimulating the formation of the nanomedicine industry. Table 9 provides a roadmap to over a dozen new relationships likely to facilitate the production and absorption of critical innovations in the burgeoning industry.

A Social Network Analysis of the NCI Alliance's Strategic Management of Innovation

Outcomes such as the number of companies with products and services on the market along with the number of clinical trials emerging from members of the NCI Alliance in a brief period provide strong empirical evidence for the success of the NCI's strategy in creating a program of translational medicine for nanomedicine but do not tell the entire story. In our concluding section we turn to a social network analysis of the formation of the NCI Alliance in order to demonstrate how the management choices of the NCI in building the Alliance have contributed to recent successes in nanomedicine. A number of studies have examined the structural characteristics of networks and network dynamics that facilitate the diffusion and absorption of innovations by firms in alliance networks. We draw upon this work, as well as the SBA's commercialization benchmarks for SBIR and STTR, in providing a baseline of comparisons for evaluating the effectiveness of the programs initiated by the NCI Alliance. Studies of strategic management have argued that participation in alliance networks may convey otherwise unavailable benefits to network members [70-75], and quantitative studies of the performance of organizations in alliance networks have shown that the particular details of a network structure and the positions of organizations therein can influence behavior and outcomes [76,77]. Sastry [78] and Fidler and Welpe [79] have argued that the uncertain nature of nanotechnology places top priority on inter-organizational alliances, a strategy that numerous nanotechnology firms have adopted [80,81]; and as we have argued above, the formation of alliances has been particularly critical to new directions in the pharmaceutical industry over the past decade. Drawing upon tools of network science, our analysis will show how the structure of the relationships between centers and firms in the rapidly growing and increasingly complex alliance network created by the NCI has stimulated innovation in bionanotechnology and has accelerated their translation into technologies and therapies of nanomedicine. It is important to note that the purpose of the social network analysis is to demonstrate that the structure of the network emerging from the NCI Alliance stimulated pioneering innovation. The network merely

NCI Center/Platform Partnership	NCI Funding Stars & PIs	Partner/Collaborating Firm(s)
Cancer Nanotechnology Platform Partners		Arrogene, Kylin, Nanospectra, Ocean Nanotech, Tactic Pharma, Valence
Caltech CCNE	James Heath	Calando, Calhoun, CellFluidics, Insert, Integrated, Materia, Molecular Biomarkers, PETNET, Sofie
	Leroy Hood	
Dartmouth CCNE	Ian Baker	Adimab, Aspen, Philips
	Keith Paulson	
Emory-GA Tech CCNE	Shuming Nie	Beckman Coulter, CRI, CrystalPlex, Hewlett-Packard, IBM, Microsoft
Johns Hopkins CCNE	Zaver Bhujwalla	BioSante, Cancer Targeting Systems, Celldex, Immune Design, Kala, MDxHealth, OncoMethylone, Regis, SignPath, SurModics
	Peter Searson	
MIT/Harvard CCNE	Robert Langer	Alnylam, BIND, Lumicell, MicroCHIPS, Siemens, T2, Tempo, VisEn
	Ralph Weissleder	
Nanotechnology Characterization Laboratory Collaborators		Alnis, Avidimer, Azaya, Carigent, Celator, CytImmune, Dendritic Nanotechnologies, Evident, GE, Luna NanoWorks, NanoScan Imaging, Nanospectra, PDS Biotechnology, Tego
Northeastern CCNE	Vladimir Torchilin	Nemucore, NovaBioMed (Canadian)
Northwestern CCNE	Chad Mirkin	Abraxis, American Bio-Optics, Aurasense, Grzybowski Scientific Inventions, NanoInk, Nanosphere, Nanotope, Ohmx, Pharocore, PreDX, SAMDITech, ScinoPharm, Inc.
Stanford CCNE-TR	Sanjiv Gambhir	Endra, Enlight Biosciences, Genentech, GE, ImaginAb, MagArray, Nodality, Visual Sonics, Zymera
Texas CCNE	Mauro Ferrari	AM Biotechnologies, BioPath, Leonardo
UC San Diego CCNE	Sadik Esener	
UNC CCNE	Rudolph Juliano	B3 Biosciences, Hologic, Liquidia, NanoMed Pharma, Qualiber, XinRay, Xintek
	Joseph Desimone	
Wash U CCNE	Samuel Wickline	Bristol-Myers Squibb, Dyax, Genentech, IBM, Kereos, Philips
	Gregory Lanza	

Table 7: NCI Stars and Firms partnering or collaborating with NCI Alliance Centers and Platform Partnerships, 2005-2012. Each listed star is either a founder of one or more NCI Alliance firms, has nanobiotechnology/nanomedicine patents assigned to affiliated institutions, or is a PI for one of the centers. (Sources: NCI Alliance Center websites, researcher profiles, and company websites)

Company	Product	Recruitment/trial status	Last updated
480 Biomedical* & Arsenal Vascular	Arsnal Vascular Bioresorbable Scaffold System	Currently recruiting	2011-Nov
Azaya Therapeutics	ATI-1123 (active drug = docetaxel)	Phase 1- completed	2012-Sep
BIND Biosciences	BIND-014	Study demonstrated safety and tolerability, and showed evidence of anti-tumor activity with six of 17 patients with advanced or metastatic solid tumor cancers.	2012-Apr
Celator Pharmaceuticals	CPX-1 (Irinotecan HCl:Floxuridine) Liposome Injection	Phase 2- Completed	2012-May
Celator Pharmaceuticals	CPX-351	Phase 3- currently recruiting	2012-Nov
CytImmune Sciences, Inc	Aurimune (CYT-6091)	Phase 1- completed	2012-Dec
CytImmune Sciences, Inc	AURITOL™ (CYT-21001)	Preclinical development	2006-Mar
Hologic	Hologic digital mammography units	This study is ongoing, but not recruiting participants.	2012-Mar
Hologic	Hologic's new 3D Hip(TM) software	This study is ongoing, but not recruiting participants.	2011-Jul
Hologic	TIGRIS System	Device approval	2012-Oct
Luna NanoWorks	HYDROCHALARONE™	Preclinical- not currently recruiting	2008-Apr
MicroCHIPS, Inc.	hPTH 1-34 implantable delivery system (Implantable, Wireless MicroChip Drug Delivery Device)	Pharmacokinetics of long-term parathyroid hormone (hPTH 1-34) delivery in women with osteoporosis; Successful human clinical trial	2012-Feb
Nanospectra Biosciences	AuroLase® Therapy	Pilot study- currently recruiting patients.	2012-Oct
Nanospectra Biosciences	AuroLase® Therapy	Pilot study- currently recruiting patients.	2013-Jan
Nanosphere	Gram-positive blood culture test	De Novo classification granted by FDA Jun-12	2012-Jun
Nanosphere	Multi-Analyte, Genetic, and Thrombogenic Markers of Atherosclerosis	Recruiting Jun-10; completion date Dec-12	2011-Oct
Nanosphere	Serial Troponin Testing	Officially unknown; changed from active/not recruiting Jan-10	2010-Jan
PDS Biotechnology	Versamune™	Phase 1- completed	2010-Mar
Pervasis Therapeutics	Vascugel	Completed phase I and II as of Jun-2010; awaiting phase III; no study results posted	2011-Oct
Pulmatrix	CALMs	Completed Apr-2011; no study results posted	2011-Apr
Pulmatrix	PUR003	Phase I drug trial completed nov-2011; no study results posted	2011-Nov
Pulmatrix	PUR003	Phase I completed Apr-2010; no study results posted	2010-Apr
Pulmatrix	PUR118	Currently recruiting participants 09-2012	2012-Sep
Pulmatrix	PUR118	Currently recruiting participants 09-2012	2012-Sep
Pulmatrix	PUR118	Phase I completed Sep-2012; no study results posted	2012-Sep
Selecta Biosciences	SEL-068 Vaccine	Currently recruiting participants for Phase I Biological 11-2011	2011-Nov
Semprus BioSciences	PRISM - 1	This study is not yet open for participant recruitment.	2012-Apr
T2 Biosystems	DIRECT T2 Candida Assay	This study is currently recruiting participants.	2012-Mar
TARIS BioMedical	LiRIS	This study has been completed.	2011-Nov
TARIS BioMedical	LiRIS	This study is ongoing, but not recruiting participants.	2012-Jul
TARIS BioMedical	Taris Placebo System	This study has been completed.	2010-Jan

Table 8: Products in clinical trials from firms of NCI stars and NCI Alliance partners (Sources: Clinicaltrials.gov, individual corporate websites)

describes the social structure created by the Alliance; we do not assume that the management team drew upon quantitative models of social networks in designing the NCI Alliance.

For our purposes the model developed by Gilsing et al. [69], Gilsing and Nooteboom [82], and Nooteboom [83] provides an excellent framework for understanding how strategic choices in managing an alliance network can stimulate innovation and the capacity of organizations in the network to disseminate, explore and absorb innovations that may lead to major disruptive change. Key elements of Gilsing et al.'s model are the notions of absorptive capacity, network density, structural holes, and betweenness centrality. Several scholars, including Gilsing et al. [69], have sought to modify and extend the model of innovation and absorptive capacity as originally proposed in Cohen and Levinthal [84]. Absorptive capacity, according to Cohen and Levinthal [84], describes the ability of an organization to acquire information from its network and translate it into new products and services. Cohen and Levinthal [84] demonstrate that among the criteria favoring a firm's ability to absorb innovations from a network are the similarities and complementarities of that firm's core competencies to those of other organizations in the network. Managing the dyadic relations of firms via similarities and complementarities of core competencies is sometimes described as the optimization of technological and cognitive distance between firms. At issue is the criticism that the Cohen-Levinthal model describes how well-positioned firms in alliance networks can incorporate and exploit existing knowledge and technological advantages already present in the network, but by emphasizing closeness of cognitive fit and tight integration between firms and organizations in a network as keys to success, the model risks lock-in effects and network redundancy that hinders new knowledge creation [83,85,86].

The Cohen-Levinthal notion of absorptive capacity in an alliance network is based on stable networks of firms with routinized practices

NCI-affiliated firm	Partnership	Other Firm(s)	Date of record
Molecular Imaging Research	Partnership to expand luciferase reporter cancer cell lines for preclinical *in vivo* imaging	Dana Farber Cancer Institute	Dec-11
BIND	Joins Nanomedicines Alliance	Nanomedicines Alliance: BIND, Cerulean Pharma, CytImmune, Eli Lilly, NanoCarrier, NanoViricides, Pfizer, Roche	2012
Liquidia Technologies	Signs licensing deal with GlaxoSmithKline	GSK	Jun-12
Liquidia Technologies	Joins Nanomedicines Alliance	Nanomedicines Alliance: BIND, Cerulean Pharma, CytImmune, Eli Lilly, NanoCarrier, NanoViricides, Pfizer, Roche	Jun-12
Leonardo Biosystems	Signs collaboration deal with NanoMedical Systems for manufacturing scale up of Leonardo's drug delivery nanoparticles	NanoMedical Systems	Nov-11
Forma Therapeutics	Partnership with Boehrringer Ingelheim ($65M up front; up to $815M)	Boehrringer Ingelheim	2012
Forma Therapeutics	GENENTECH (ROCHE) acquires Forma's pre-clinical cancer program	Genentech; Roche	2011
Forma Therapeutics	Partnerships	Novartis, Cubist Pharmaceuticals, Esai Pharmaceuticals, Experimental Therapeutics Centre (Singapore), TGen Drug Development (TD2)	2012
Foundation Medicine	Partnership	Novartis, Celgene and Johnson & Johnson Pharmaceutical Research & Development	2013
Integrated Diagnostics	Partnership; Agilent will add blood-based early cancer detection to their diagnostics platform; Integrated Diagnostics will acquire several Agilent LC and MS machines	Agilent	Jan-12
H3 Biomedicine	Partnership	Horizon Discovery	Oct-12
H3 Biomedicine	Partnership/funding	Esai Co.	Dec-11
H3 Biomedicine	Partnership	Compendia Bioscience; Life Technologies	Feb-12
MicroCHIPS, Inc.	Received 13.4 million dollar round of investment funding led by Novartis Venture Fund	Novartis	Apr-07
Xintek	Forms joint venture with Siemens to develop nanotechnology-enabled multi-pixel X-Ray tubes	Siemens	Sep-07

Table 9 Strategic partnerships of firms founded by NCI stars and NCI Alliance members, 2005-2012 (Source: individual corporate web sites)

operating with technological certainty. Innovation, according to Gilsing et al. [69], however, is not just about optimizing the network as a channel for diffusion of existing knowledge and practices for exploitation; the search for new technologies and new opportunities is uncertain, and strategically building in features of uncertainty is actually a source of strength. Drawing upon the work of Hagedoorn [87] and Phelps [88] Gilsing et al. [69] argues that innovation alliances require the recombination of heterogeneous knowledge stocks, as similarity in the knowledge stocks of firms can be counterproductive. While coherent tightly integrated networks with strong partner similarity may be optimal for absorbing existing innovations, loosely integrated or even disintegrated networks with structural holes and cognitive distance between partners are vital sources of new innovations [48,89-91].

Gilsing et al. [69] set out to combine the best features of knowledge-based and social network-based approaches to demonstrate how a balance between the 'twin tasks' of innovation stimulation and technology absorption can be achieved by modulating structural features of an alliance network. Gilsing et al. [69] proposes a model that leverages the productive tensions between the structural holes in disintegrated networks that are necessary for making new things, and knowledge proximity in dense coherent networks that favors absorptive capacity. They show how technological distance, network density and betweenness centrality directly affect the ability of organizations to acquire external knowledge, begin innovating, and increase absorptive capacity. Specifically, Gilsing et al. [69] observe "high levels of network density in combination with high levels of centrality also offer a fairly high impact on exploration. In short, we can say that at average technological distances, central companies in (fairly) dense networks have an advantaged position to develop explorative innovations." (p. 1728). The consequence is that the careful placement of firms at pivotal locations that bridge structural holes in a large dispersed network of technologically and cognitively diverse, dense subnetworks can result in high levels of both innovation and absorption for the entire network.

In our view the Gilsing et al. model for simultaneously maximizing innovation and absorptive capacity offers a striking prescription for launching and strategically managing disruptive technological change of the sort we observe being attempted by the NCI Alliance for Nanotechnology. The model suggests identifying and investing in core innovative projects at firms or university centers and building dense subnetworks of other closely linked firms (particularly startups) and research teams around them to create, rapidly explore, and develop new innovations. A second element of the strategy prescription is to identify structural holes among the heterogeneous subnetworks and bridge them with organizations and firms with core competencies in terms of knowledge stocks, technical resources, and management skills capable of absorbing and developing these innovations into potentially blockbuster technologies for the market.

In order to use the insights from Gilsing et al.'s [69] framework we introduce the network science concepts of *average degree*, *connected components*, *modularity class*, *betweenness centrality*, *preferential attachment*, *network density*, and *structural holes*. Each of these social network concepts or measures is in itself useful for examining potential impacts of strategic alliance formation choices on desired outcome, allowing us to analyze the way in which the NCI Alliance contributes to the formation of the nanomedicine industry.

Social network measures

Table 10 below provides an inventory of social network concepts and measures used in the following section. *Connected components*, or *components* for short, are subgraphs of a network supergraph that are connected to the supergraph by a single edge. A component will appear in a graph as a cluster of heavily connected nodes connected to other nodes/clusters in the supergraph. Components can help identify distinct communities in a network, though *modularity class* is more frequently used to do so. The modularity class of a node, also referred to simply as its module or community, is a computed cluster of nodes representing a local community [92]. The *average degree* of a network is the average number of connections per node, while *average path length* captures the average distance between any two nodes in a network. *Network density* is calculated as the number of edges in the network divided by the maximum number of edges possible. A network's *average clustering coefficient* captures the average percentage of a node's neighbors that are connected to one another; the average clustering coefficient is one way to measure the global interconnectivity of a network. Connected components and clustering coefficients are useful because organizations in an alliance network with lower numbers of connected components and higher clustering coefficients will have greater reach towards knowledge resources within the alliance network and greater innovative output [93]. Further, for the purposes of the analysis of the NCI Alliance, we must take into account not only the positioning of individual organizations but also the creation and positioning of entire communities.

As we demonstrate below, a key element of the NCI Alliance's success has been the construction of critical nodes of "betweenness centrality", organizations that bridge otherwise potentially disparate parts of the Alliance network. *Betweenness centrality* quantifies how often an organization is found on the shortest paths between others [69,94]. Betweenness centrality is generally interpreted as a measure of social power and represents the relative ability of a node or cluster of nodes to broker between other parts of a network [95]. Betweenness centrality has been used to characterize access to resources at both intraorganizational [96] and interorganizational levels [97]. In general, the greater the betweenness centrality of a member organization or cluster, the more other organizations and clusters depend on the go-between organization/cluster to connect with other network members. Betweenness centrality is the leading indicator of *preferential attachment* in collaboration networks: new nodes prefer to join a network by attaching to the existing nodes with the highest betweenness centrality. Preferential attachment is fundamental to the growth of tightly interconnected networks, including science co-authorship collaboration networks [98]. For example, because new authors joining scientific co-authorship networks prefer to co-author with authors exhibiting high betweenness centrality, identifying and connecting with organizations having high betweenness centrality has been discussed as an effective growth strategy for science policy makers [99]. Expanding on the notion of centrality, Robert Burt's theory of *structural holes* argues that individuals or organizations placed at strategic locations of centrality between otherwise disconnected networks are uniquely able to broker relations between them. Such organizations exhibit high betweenness centrality and are therefore better able to bridge gaps in the network and enhance the productive flow of information and innovation production [68,100].

Visualization and Analysis of the NCI Alliance network

Figures 3 and 4 offer visualizations of the formation of the NCI Alliance network. The figures contain graphs illustrating the relationships between CCNEs, CNPPs, and the firms and universities affiliated with the CCNEs and CNPPs, before and after the influence of the NCI Alliance. Figure 3 (the 'before' view) gives a view of the participants in the NCI Alliance for Nanotechnology in Cancer *absent* both the relationships created directly by the NCI Alliance itself and the firms started after the creation and influence of the program. The entities depicted as nodes in the 'before' view were created either prior to or independently of the NCI Alliance-created centers and firms. The 'before' view provides a view of the network of strategic relationships among these participants had the NCI *not* created the NCI Alliance. Figure 4 (the 'after' view) shows the NCI Alliance network. This network includes firms started by CCNE and CNPP PIs after joining the NCI Alliance. While it cannot be ascertained that all credit is due to the NCI Alliance for firms started by PIs after the alliance's creation, the influence is significant and cannot be excluded from the web of relationships. Types of organizations in the networks, represented by nodes in the figures, include the home institutions of the stars, PIs and centers; the NCL, CCNEs, and CNPPs themselves in Figure 4; the companies founded by both NCI star scientists and Center PIs; and the companies formally collaborating or parterning with the NCI Alliance centers. Node size in Figures 3 and 4 represents the betweenness centrality of an organization. Edges, the connections between nodes, represent formal relationships between organizations.

Modules in Figures 3 and 4 are distinguished by color (the colors are based on the module scheme of Figure 4 in order to provide continuity). The densest modules in Figure 3 are the large network (in gold) of Langer-founded firms and the members of the Nanomedicines Alliance in pink, including Liquidia, Cytimmune, Pfizer and others. Several private firms stand out in this 'before' network, including the pharmaceutical giant Roche, a firm more enthusiastic in its commitment to nanomedicine than the other large pharmaceutical firms, and Forma and BIND, two important nanobiopharma startups.

A strong indicator of changes to the innovative capacity of the NCI Alliance is a reduction in the number of components along with increases in the overall clustering coefficient or in network density, crucially without a significant increase in overall average path length [93]. The 'before' network of Figure 3 has 229 edges, an average degree of approximately 6.7 relationships, an average path length of 2.9 edges, and an average clustering coefficient of approximately 0.69. With the introduction of the NCI Alliance, the number of edges grows dramatically to 1524 and the average degree jumps up to 15.9 while the average path length shortens to 2.8 and the average clustering coefficient increases to 0.82. The number of connected components changed from 7 in the 'before' network (Figure 3) to 2 in the 'after' network (Figure 4). Despite the 200% increase in the number of nodes the density changes very little, from 0.101 to 0.083. While the size of the network grows dramatically between 3 and Figure 4, the network density has remained stable, the average path length has shortened, and the number of modules or communities has remained constant at 11. The network has maintained an overall high level of interconnectivity while intensifying the network's ability to share information. These additions to the network have provided an overall increase to the innovation capacity of the NCI Alliance. A summary table of measures for the alliance networks depicted in Figures 3 and 4 is provided in Table 11 below.

Social network concept	Definition	Usefulness in network analysis & alliance networks
Average degree	Average number of connections per node	Provides a baseline against which to compare the degree of individual nodes and/or clusters
Average path length	Average distance between any two nodes	A reduction in the number of components along with increases in either overall clustering coefficient or network density and without a significant increase in overall average path length is an indication of increased innovation capacity (Schilling and Phelps 2007)
Average clustering coefficient	Average percentage of a node's neighbors that are connected to one another	Global interconnectivity of a network; see connected components
Connected component/ component	Subgraphs of a network supergraph that are connected to the supergraph by a single edge	Similar to modules: help identify distinct communities in a network; Organizations in an alliance network with lower numbers of connected components and higher clustering coefficients will have greater reach towards knowledge resources within the alliance network and greater innovative output (Schilling and Phelps 2007)
Modularity class/ module	Computed optimized cluster of nodes	Similar to components: help identify distinct communities in a network (Blondel 2008)
Betweenness centrality	How often a node (or node cluster if we extend the model) is found on the shortest paths between others (Freeman 1977)	Measure of social power and represents the relative ability of a node to broker between other parts of a network; leading indicator of preferential attachment (Wasserman and Faust 1994)
Structural holes	Position in a network between two or more clusters containing different information	Individuals or organizations placed at strategic locations of centrality between otherwise disparate networks are uniquely able to broker relations between them. Such organizations have high betweenness centrality making them better able to bridge gaps in the network and regulate the flow of information (Burt 2002)
Preferential attachment	New nodes prefer to join a network by attaching to the existing nodes with the highest betweenness centrality	Fundamental to science collaboration networks (Barabási and Albert 1999)
Network density	Number of actual edges in the network divided by the maximum possible number of edges.	High levels of network density in combination with high levels of centrality offer a fairly high impact on exploration; at average technological distances, central companies in increasingly dense networks have an increasingly advantaged position to develop innovations (Gilsing et al. 2008)

Table 10: Social network concepts and measures used, along with their applications

Gilsing et al.'s [69] model provides us with a means to interpret some of the complexities of the effective strategy behind the creation and insertion of NCI Centers and the NCL in locations of high betweenness centrality in light of overall network density and technological distance. However Gilsing et al.'s [69] model and the NCI Alliance network differ in at least one crucial respect. The networks Gilsing et al. [69] examines are explorative networks seeking to recombine and absorb existing innovations into the network. Their model concentrates on technological knowledge newly created by an organization. The model defines knowledge as 'novel' and the surrounding knowledge creation activtities as 'exploratory' if they are outside of an organization's body of knowledge, even if such knowledge already existed outside the firm. Gilsing et al. [69] point out that their focus differs from the sort of exploration yielding knowledge new to an entire industry, or knowledge new to the entire world. These latter two types of knowledge constitute what they call, respectively, 'newly emerging' and 'pioneering' technologies, representing more extreme forms of exploration as seen from the point of view of firms with their own R&D efforts [82,86]. The NCI Alliance by contrast is focused on generating pioneering innovations and new technologies.

The NCI Alliance differs from the explorative alliances examined by Gilsing et al. [69] in that the NCI Alliance has been fashioned as an incubator network of disruptive nanomedical therapies and is dedicated to pioneering new technologies and putting them on a pathway through clinical trials to translation into the medical market. While Gilsing et al. [69] do not propose extending their model to networks dedicated to pioneering or emerging technologies, we find that doing so fits the case of the NCI Alliance rather well. In fact the network constructed by the NCI Alliance is in many respects a feeder or precursor network, the goal of which is to engender the types of relationship between academic centers, closely allied startup firms, and large incumbent pharmaceutical firms that [82] identifies in terms of their learning regimes 1 & 2. In the case of pharmaceutical biotechnology in Holland Gilsing and Nooteboom identify "learning regime 1", the dominant mode of organization in the period from the late 1970s through the late 1980s as having focused on exploration embedded within a network of dedicated biotechnology firms (DBFs) with academia, while "learning regime 2", the dominant mode from the late 1980s through the 1990s focused on exploitation embedded within a network of DBFs and large pharma. The difference between the cases studied by Gilsing and Nooteboom and the NCI Alliance we are describing is that whereas the two learning regimes described in [82] depict the network of relations between the dedicated biotech firms, academic research units and big pharma in Holland during the 1980s (Learning regime 1) and 1990s (Learning regime 2), as being separately sequenced phases in a cycle of exploration and exploitation, the NCI has attempted to accelerate these developments to a time frame of less than a decade and has effectively collapsed both phases into a continual cycle of reciprocal innovation, exploration, and exploitation.

There are important similarities between the alliance networks in Gilsing et al. [69] and the NCI Alliance. Specifically, the networks depicted in Figures 3 and 4 are of a similar size to the alliance networks examined in Gilsing. The 'before' and 'after' networks have the same order of magnitude of alliance relations and firms as those in Gilsing's study: 229 in our 'before' network, 1524 in our 'after' network compared to 762 alliances examined by Gilsing; and 68 organizations in our 'before' view, increasing to 192 in our 'after' view compared to 85 firms in Gilsing's study. Also, Gilsing's networks are comprised mostly of a complex mixture of alliances in the pharmaceutical and chemical industry, a composition that overlaps well with the complex mixture of the participants in the NCI Alliance. Both our 'before' and 'after' networks demonstrate network densities significantly higher than the networks investigated by Gilsing et al. [69]: our 'before' and 'after' views have network densities of 0.101 and 0.083 respectively compared to the network densities reported in Gilsing et al. [69] of 0.013.

The 'before' graph of Figure 3 reveals several structural holes that are shown to be filled in the 'after' graph of Figure 4. The firms shown in Figure 3 are densely connected with one another but only weakly connected to universities. The nodes with highest betweenness centrality

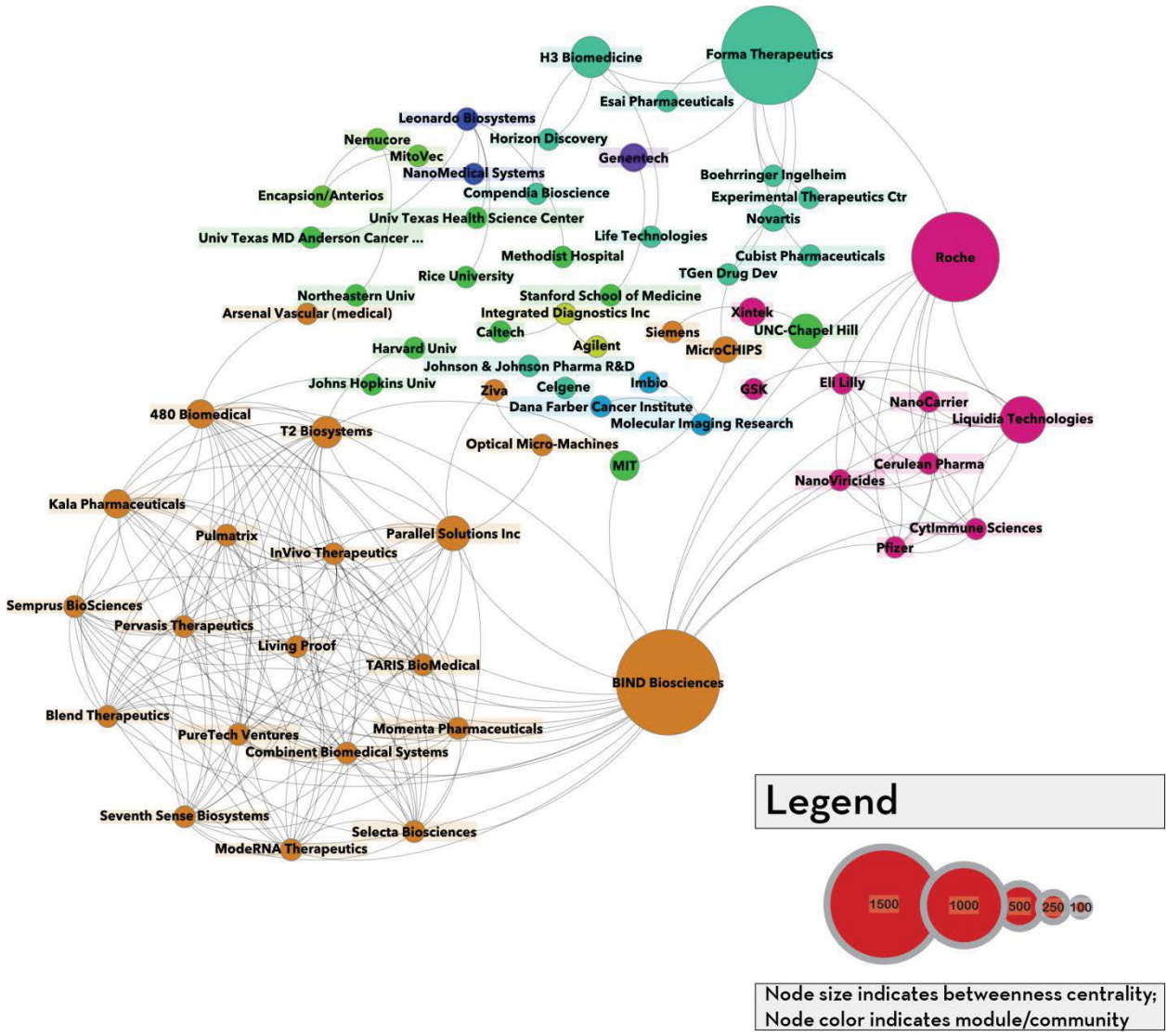

Figure 3 NCI Alliance Organization Network, 'before' view. (Note: Low resolution thumbnail shown here.) Nodes scaled by betweenness centrality. Colors distinguish different modularity classes or communities.

in 3 exhibit centrality between the firm-centric modules in pink and orange only. Figure 4 illustrates the energizing effect of the NCI centers, especially the Nanotechnology Characterization Lab (blue nodes), in interconnecting a number of universities with capable people already working in nanobio, and linking them to private firms. The locations of preferential attachment for filling structural gaps are occupied in Figure 4 not only by governmental organizations but also by startup firms (Forma Therapeutics, BIND Biosciences, Kala Pharmaceuticals, T2 Biosystems, MicroCHIPS, H3 Biomedicine, and Liquidia), large biopharmaceutical firms (*e.g.,* Genentech), more traditional large pharmaceutical firms (*e.g.,* Roche), information and computational technology-centric firms (IBM), firms with strong medical imaging capabilities (GE), universities (*e.g.,* Northwestern), and the CCNEs themselves. Highlighted here are both the interconnected group of CCNEs and the NCL as the two primary organizing modules of the graph (blue nodes) linking universities (green nodes) to otherwise separate clusters of private firms.

The sequence of Figure 3 to Figure 4 shows that the Nanotechnology Characterization Laboratory has been a cornerstone for forming new university-industry relationships. The NCI Alliance builds a community of nanomedicine research centers to fill the major structural holes identified in Figure 3. The NCL is installed as the most instrumental constituent of the bridge. The NCL, shown in Figure 4 with a betweenness centrality of 1375.7, improves the ability of the Alliance to generate and disseminate information, distribute resources between private firms, government, and universities, and stimulate continued growth of the entire network. The blue module in Figure 4, of which the NCL is a member, exhibits one of the highest average betweenness centralities of all modules, at 317.8, second only to the green university module, at 332.9. Comparatively speaking, the Alliance relationships bring up the betweenness centrality of the green university-centric community nearly six-fold along with that of the orange startup firm module by about 5%, while dropping the average betweenness centrality of the pink big pharma-centric module about

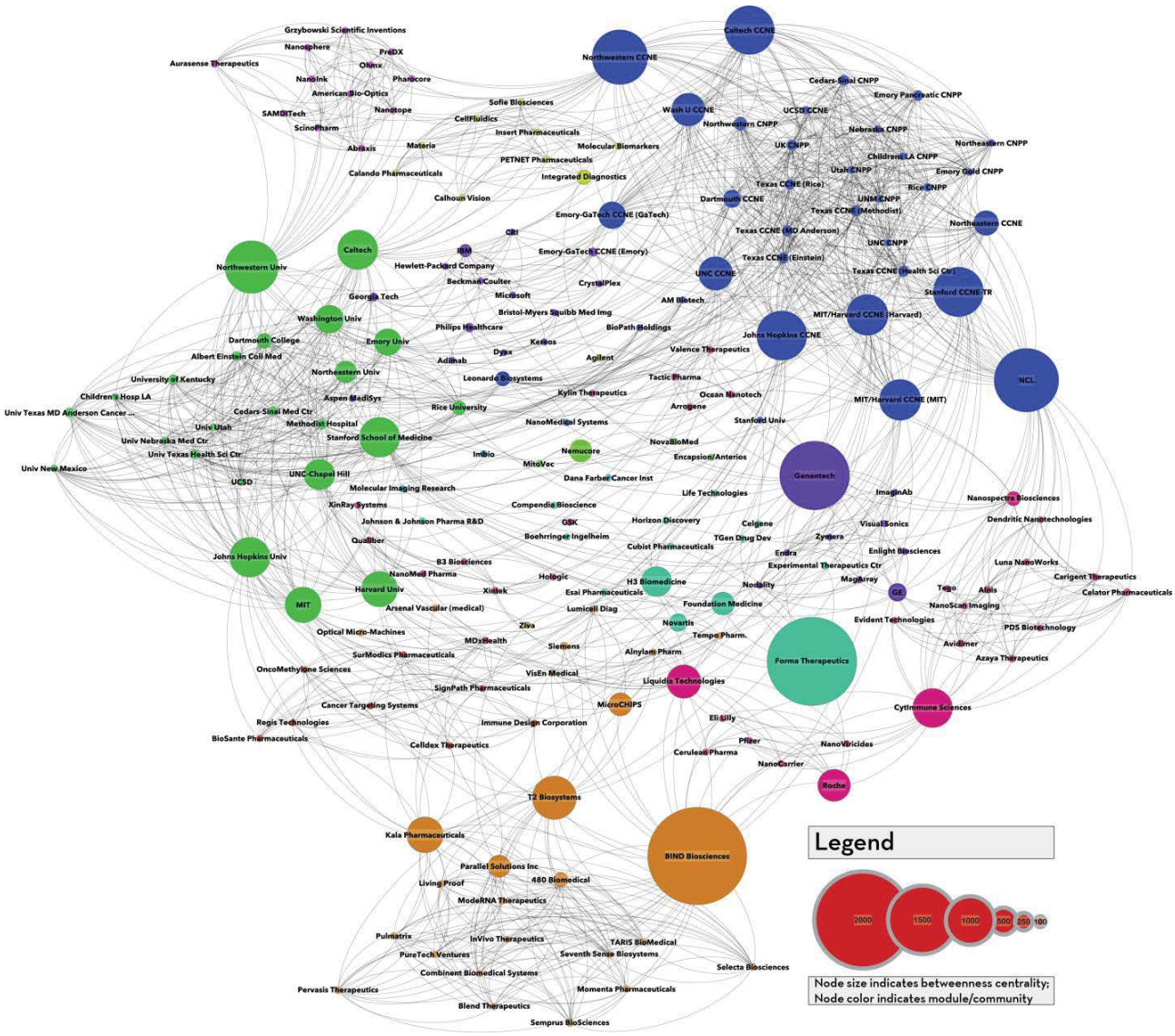

Figure 4 NCI Alliance Organization Network, 'after' view. (Note: Low resolution thumbnail shown here.) Nodes scaled by betweenness centrality. Colors distinguish different modularity classes or communities.

four-fold.

What is visible from these measures is a shift in the mediation of this network towards more innovation-centric organizations: universities and startups, a shift that moves big pharma from a role as arbiter of early-stage innovation to a role further downstream. Universities, startups and collaborative research centers have been created in or placed in structural holes by the NCI Alliance, giving them significant access to resources and ultimately significant roles in innovation and absorption. Drawing upon Gilsing et al.'s [69] model, then, we can understand the effects of the twin activities of preferentially attaching organizations and maintaining a relatively high overall network density. The NCI Alliance at once enhances the ability of these preferentially attached highly central organizations such as the NCL to accelerate innovation while increasing the absorptive capacity of the entire network.

The goals of the NCI in forming the Alliance were to generate innovative technologies and translate them into clinical practice. A key strategy in accomplishing this was to create pathways and opportunities for the incumbent big pharma firms to partner with Alliance firms, acquire the most promising therapeutic interventions that had made it through Stage 1 and Stage 2 clinical trials, and to enlist big pharma's greater financial resources and expertise in late phase clinical trials to bring these new therapeutic agents into the marketplace. The NCI Alliance of small firms allied to major university research centers and medical clinics working in consort with several major pharmaceutical firms has the sort of collaborative structure advocated by a number of industry insiders and policy experts as opening the way for an explosion of major therapeutic advances [101]. It is precisely the way in which the NCI Alliance structures the relationships that facilitates a rapid explosion

Network Metric	Before	After
Nodes	68	192
Edges	229	1524
Average Weighted Degree	6.77	16.84
Network Diameter	7	7
Graph Density	0.10	0.08
Average Path Length	2.95	2.79
Modules	11	11
Modularity	0.44	0.63
Connected Components	7	2
Average Clustering Coefficient	0.69	0.82

Table 11: Social Network Metrics, Before and After the Formation of the NCI Alliance

and absorption of disruptive nanobio and nanomedicine technologies.

Conclusion

We consider the output of the network of firms, university medical centers, and federally funded labs, particularly the Nanotechnology Characterization Lab, constituting the NCI Alliance for Nanotechnology in Cancer to offer powerful empirical measures of the effectiveness of the NCI's polices for launching nanomedicine. Our study suggests that in its first five years the NCI Alliance for Nanotechnology in Cancer has been successful in architecting a sustainable path toward the takeoff and development of nanomedicine. In our view the measure of success of the NIH/NCI policies is not only that they have fostered a large body of high impact research evidenced in research publications and a significant number of nanobio patents; but more importantly for our argument, the efforts of the NCI have resulted in the startup of successful firms with a steady stream of products in clinical trials along with a robust pattern of alliance network growth.

We have argued that a major strategic goal in creating the NCI Alliance was to build an infrastructure that would sustain the development of the revolutionary new materials and therapeutic platforms of nanomedicine. Given the disruptive character of nanomedicine, the increasing costs and stalled productivity hampering the old drug development model, and given the reticence of big pharmaceutical companies to take on the risks of conducting extensive preclinical research and discovery themselves, their strategy has been to partner with universities, innovative startups, and even other major pharma companies for the research and discovery phase of new drug development. The leadership of the NCI was well aware that from the late 1990s through 2005 the most successful drug and medical device developments had emerged from alliances of university researchers, startups and partners in the pharmaceutical industry. In constructing the NCI Alliance they managed to fashion organizations at relatively low overall cost that harness the optimal features of networks that promote innovation. The strategic placement of Centers at critical positions in the Alliance network has enhanced and accelerated the ability of the NCI to create a sustainable architecture for nanomedicine. Whether the NCI's positioning of centers at locations of preferential attachment is a product of either the processes of social networks or deliberate choice remains to be seen.

The current study has certain limitations. The methods employed in this study are strictly quantitative. Because of the stated goal of being able to perform assessment in near-real-time, more distant outcomes such as long-term impacts of novel treatments, or changes to clinical guidelines, standards of care, or health policies are not assessed. The linkages between outputs (publications, patents, companies) and federal funding are not always based on specific award numbers, so only general trends can be inferred from this analysis.

There are three directions the authors wish to take this work. Environmental health and safety (EHS) is critical to assessment and deserves further examination. Medical toxicology data arising from clinical trials does not cover the spectrum of EHS. The authors are addressing this limitation by attempting to uncover nanomaterial and nanoproduct value chains, identifying upstream and downstream nanorisks particularly at the exposure points of manufacturing, assembly, and disposal. Secondly, Phase II of the NCI Alliance program demands a similar assessment to that of Phase I provided in the present paper. Finally, it remains unclear how social network analysis tools can be used not merely to describe an emerging network as we have attempted here but rather to design a new organizational network, optimize existing networks, and predict outcomes from different proposed network structures. Developing predictive tools for network analysis would make a desirable contribution to policy studies.

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