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NCI Alliance for Nanotechnology in Cancer – Catalysing Research and Translation Towards Novel Cancer Diagnostics and Therapeutics

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Abstract

Nanotechnology has been a burgeoning research field which is finding compelling applications in several practical areas of everyday life. It has provided novel, paradigm shifting solutions to medical problems and particularly to cancer. In order to accelerate integration of nanotechnology into cancer research and oncology, the National Cancer Institute (NCI) of the National Institutes of Health (NIH) established the NCI Alliance for Nanotechnology in Cancer program in 2005. This effort brought together scientists representing physical sciences, chemistry, and engineering working at the nanoscale with biologists and clinicians working on cancer to form a uniquely multi-disciplinary cancer nanotechnology research community. The last fourteen years of the program have produced a remarkable body of scientific discovery and demonstrated its utility to the development of practical cancer interventions. This paper takes stock of how the Alliance program influenced melding of disparate research disciplines into the field of nanomedicine and cancer nanotechnology, has been highly productive in the scientific arena, and produced a mechanism of seamless transfer of novel technologies developed in academia to the clinical and commercial space.

Graphical Abstract

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Visual Abstract Caption: The National Cancer Institute's Alliance for Nanotechnology in Cancer has produced numerous technologies dedicated towards novel solutions to cancer. The images depict nanostructures used in novel cancer therapeutics and *in vitro* or *in vivo* diagnostics developed by Alliance-funded research.

Introduction

Cancer is the most complex disease known to man. The intense research and translational efforts in this disease space have been paying off with cancer death rates in the U.S. dropping slowly, though consistently, in women by 1.4% and men by 1.8% per annum over the last decade (2007–2016) (Siegel, Miller, & Jemal, 2019). Despite these improvements in death rates and growing number of cancer survivors, it is expected that in 2019, over 1.7M new cancer cases and over 600,000 cancer deaths will occur in the U.S. These statistics continuously drive the quest for new approaches to diagnosis, treatment, and prevention of cancer.

Nanotechnology became of interest to medical researchers towards the end of 20th century. During the Clinton administration, the *National Nanotechnology Initiative* was established to expand federal funding in this area. Initially, the research in nanotechnology was mostly focused on the development and interrogation of novel materials at nanoscale and engaged predominantly chemists, materials scientists, and physicists. With time it became clear that nanomaterials could facilitate interesting applications, opening new opportunities for medical treatment, among others. Figure 1 shows the evolution of budgets supporting nanotechnology research in different federal funding agencies ("NNI Supplement to the President's 2019 Budget," 2018). In the early years, budget levels at Department of Defense and National Science Foundation were high, which was expected due to intense materials research at that time. Since then, their nanotechnology budgets have declined, while the

National Institutes of Health budget levels, which increased more slowly, have been maintained at substantial levels.

NCI ALLIANCE PROGRAM

In 2005, the National Cancer Institute of the NIH made a bold decision to invest into nanotechnology for cancer. It was apparent from the beginning that for such research to be effective in the medical arena, it needed to involve multi-disciplinary teams consisting of cancer biologists and clinicians working closely with physicists, engineers, and chemists. The Alliance program and its infrastructure have been designed to rapidly advance new discoveries and to transform them into cancer-relevant applications with clinical utility (Chapman et al., 2012; Farrell et al., 2010; Hartshorn et al., 2018; Ptak, Farrell, Panaro, Grodzinski, & Barker, 2010).

Structure and Management—The Alliance funding initiative has fostered the development of basic science to pre-clinical projects in academia, and then moving mature technology platforms forward towards prospective use in the clinic through establishing start-up companies. The program has been funded on 5-year iterations and is currently at the end of its 3rd Phase (*i.e.,* 2005–2020). At the core of the Alliance program are multi-project Centers of Cancer Nanotechnology Excellence (CCNEs), which consist of 2–5 research projects that are further supported by specialized cores. CCNEs were awarded to academic institutions in intense competition, with 6–9 different Centers funded in different Phases of the Alliance program (Figure 2). In addition to CCNEs, single (R01-like) research projects were funded as well along with a number of different training initiatives. The latter involved Path-to-Independence Awards (K99/R00) for promising post-doctoral candidates seeking faculty positions, and T32 Training Centers. NCI also recognized that the development of novel nanomaterials with a wide range of designs requires centralized characterization resources and established an intramural laboratory - the Nanotechnology Characterization Laboratory (NCL). NCL developed a comprehensive assay cascade for nanomaterials characterization and has been working with researchers from academia, industry, and government. NCL has also given back to the field by way of publishing much of the nanomaterials characterization methods they developed (Adiseshaiah, Hall, & McNeil, 2010; Crist et al., 2013; Dobrovolskaia & McNeil, 2016).

NCI Alliance investigators formed a community which is at the fore-front of the rapidly developing cancer nanotechnology field and continues to drive its progress (Farrell, Ptak, Panaro, & Grodzinski, 2011; Nagahara et al., 2010). Several principal investigators (PIs) within the program originate from disciplines that are non-traditional for NIH-sponsored research. These researchers benefit from their partnerships with biologists and clinicians in terms of understanding the needs of contemporary oncology and subsequently direct their research towards the most relevant problems in this area. In turn, they have brought new ideas and innovation to cancer, which may not have occurred without their participation. To assure involvement of oncologists and clinicians in the program to provide an effective guidance on cancer relevant interventions, NCI required multi-investigator leadership of CCNEs and recommended this leadership for smaller grants as well. These requirements led to approximately 30% of the Alliance PIs holding MDs (either MDs or MD/PhDs) on

average across all three Phases of the program. This is approximately two times higher than the fraction of investigators with MDs funded through the general NIH NANO study section's cancer applications, which remains closer to 15% (Figure 3). This points to consistently high clinical involvement among Alliance investigators.

As little progress occurs in a vacuum, an active NCI program management structure has ensured frequent and close communication between investigators and the NCI program staff members. This cooperative structure has allowed the NCI to guide, when necessary, the research direction of projects, as well as to promote and facilitate the collaborative efforts among the awardees (Anchordoquy et al., 2017; Grodzinski & Farrell, 2014).

It should be noted that the Alliance program funding constitutes only a portion (~15–20% depending on the program Phase) of the overall NCI funding dedicated to nanotechnology. In parallel to the Alliance-funded grants, the overall number of NCI grant submissions focused on nanotechnology has been growing rapidly during last 10 years, and reached over 700 R01 applications in 2018, which constitutes ~11% of overall R01 submissions (Figure 4). Initially, the majority of nano- R01 submissions were reviewed by the NIH Nanotechnology (NANO) Study Section (formed in 2008). However, as nanotechnology approaches became more mature and were shown to have broader utility, several incoming nano-R01s have started to be assigned to other study sections: Gene and Drug Delivery Systems (GDD), Clinical Molecular Imaging and Probe Development (CMIP), Developmental Therapeutics (DT), and Radiation Therapeutics and Biology (RTB). This indicates growing acceptance of highly innovative nanotechnologies into biomedical research.

Scientific Output—Over the last 14 years, Alliance investigators have published over 4,000 peer reviewed research articles that have been collectively cited more than 280,000 times ("Research Published by NCI Alliance," 2017). This represents substantial scientific dissemination to the biomedical and nanotechnology research communities. Figure 5 represents this cumulative productivity over time. In an earlier stage of the program (in the middle of Phase II), we had attempted to assess to what degree the project teams had coalesced into particular areas of research interests. We have looked at the make-up of publications originating from different investigators within the Alliance program and the evolution of topics covered in these publications (Figure 6). The evolution of topical areas from either biomedical-centric research or nanotechnology development beginnings is apparent. Specifically, we observed a convergence on publication topics centric to cancer, with physical scientists gradually moving their interests from pure nanomaterials and technology development to addressing biology and clinical issues as well as biologists integrating new technologies into their research. This is a strong indication that the multi-disciplinary model of research supported by the Alliance program has been effective and has enabled the convergence of scientists representing diverse disciplines with respect to a single research problem.

As discussed in the previous section, the Alliance program was successful in attracting a reasonable number of oncologists and clinicians to its cohort of investigators (Figure 3). We expected that their contributions would impact the translatability of research conducted in

the program, which we assessed by two measures of translatability: “Triangle of Medicine” analysis and clinical citation analysis. The Triangle of Medicine and clinical citation analyses were performed using the iTrans software developed at the NIH (Grodzinski, Liu, Hartshorn, Morris, & Russell, 2019). In the Triangle of Medicine analysis, research described in publications is weighted by three categories of biomedical research: human, animal, or molecular/cellular. This kind of analysis provides information on the level of translatability of research (or its maturity towards the clinic), with statistics heavily weighted towards molecular/cellular and animal signifying more basic research, while weighting towards human signifies clinical research. As shown in Figure 7, Alliance research is more heavily weighted towards human research than other nano-grants (reviewed by NANO study section). In addition, the Alliance generated publications had further impact in the clinical space relative to their citation by subsequent clinically-oriented papers authored by both Alliance and non-Alliance investigators, as shown in Figure 8. On average, Alliance research was cited by clinical papers 3.5 times more than research produced by non-Alliance nano-grants.

Nanoparticle and Nano-device Technologies produced by the Alliance—Since the inception of the program, a network of grantees evolved while developing innovative nanotechnologies for prospective medical applications to the biology/oncology driven Alliance program. Proposed projects have increasingly morphed from nanotechnology development to investigations of the processes underlying new therapies (*e.g.,* nanobiology) as well as the patient response to them. Currently, a third of the projects are focused on diagnostic tools for early detection and monitoring of effectiveness of therapy and the remaining two thirds are therapy-centric. But, this breakdown among different cancer applications evolved over the course of the program. The pie charts presented in Figure 9, show the fraction of total projects related to each cancer modality (diagnostic or therapeutic). We observe a strong shift from diagnostic projects (*in vitro* diagnostics or imaging) in Phase I (Grodzinski, Silver, & Molnar, 2006) to primarily therapeutic projects (*e.g.,* chemotherapy, immunotherapy, gene therapy, radiotherapy, etc) in Phase III. Since the demonstration of clinical utility of the technology is a long-term objective of the program, it was expected that initial project foci would remain on diagnostics due to less complex testing of the devices in *in vitro* environments. Later on, the therapeutic modalities became more pronounced, particularly with regards to the recent rise of nano-enabled immunotherapy.

To give the Reader further insight into various technologies produced by investigators of CCNEs, we catalogued them in Table 1. A similar follow-up table (Table 2) lists representative technologies produced by investigators of smaller grants (R01s and U01s). It is a semi-exhaustive list which allows one the opportunity to appreciate the extent of research and clinical approaches produced by investigators funded by the program. Several of these technologies have been under investigation for many years and matured from early demonstration to that warranting commercialization or even entry into clinical trials. Many of them were also diverse enough in terms of technology platform design to be employed in several cancer applications. For example, spherical nucleic acids (SNAs) were initially developed in Mirkin’s laboratory at Northwestern University to monitor mRNA levels in live

cells (Chinen et al., 2015). Later on, they became delivery vehicles used in gene therapy and novel immunotherapies (Li et al., 2018). Kabanov at the University of North Carolina and Torchilin at Northeastern University have been developing micelles for drug delivery applications in cancer for several years. Initially, these works were dedicated to the enhancement of drug loading and biodistribution studies, but gradually evolved to sophisticated nanoparticle designs with variable particle stiffness and shape enabling enhanced nanoparticle penetration into the tumour in Kabanov's lab (Han et al., 2012; Z. He et al., 2016). Torchilin researched combination therapies and reversal of multidrug resistance (Salzano, Navarro, Trivedi, De Rosa, & Torchilin, 2015). Nanoscale Metal-Organic Frameworks (nMOFs) from Lin's laboratory at the University of Chicago have become diverse tools for single and combination therapies involving delivery of single and multiple chemotherapeutic drugs and siRNA (C. He, Poon, Chan, Yamada, & Lin, 2016), therapies based on absorption of external radiation and release of oxygen radicals for deep tissue treatment (Lan, Ni, Veroneau, Song, & Lin, 2018; Ni, Lan, Veroneau, et al., 2018), and finally combination of radiation and immunotherapy (K. Lu et al., 2018; Ni, Lan, Chan, et al., 2018). These developed therapeutic platforms cover a broad range of cancer treatment modalities, demonstrating the Alliance therapeutic breadth.

Similar trends and advancement of technology platforms can be seen in diagnostic technologies funded by the Alliance program. Heath's laboratory at Caltech developed the DNA Encoded Antibody Library (DEAL) platform, a versatile array technology (Bailey, Kwong, Radu, Witte, & Heath, 2007; Kwong et al., 2009), which after integration with microfluidics was used for multiplex measurements of nucleic acids and proteins. Gradually, this measurement platform evolved into two general classes of devices which provide enabling tools for both clinical oncology and basic cancer biology investigations. The first is the Integrated Blood Barcode Chip (IBBCs), (Fan et al., 2008a; Qin, Vermesh, Shi, & Heath, 2009; Jun Wang et al., 2012), which permits large panels of blood protein biomarkers to be rapidly assayed from just a pinprick of blood. The second platform is the Single Cell Barcode Chip (SCBC). The SCBC permits highly multiplexed assays of secreted, membrane, or cytoplasmic proteins from rare cells and was used to analyse patient samples and profile the immune response to adoptive cell transfer (ACT) cancer immunotherapy (Ma et al., 2013, 2011). The Weissleder laboratory at Harvard University re-used magnetic nanoparticles developed earlier for imaging applications and applied them to the development of new sensing technique based on clustering of these particles upon contact with target proteins. This clustering, in turn, led to more efficient dephasing of nuclear spins of many surrounding water protons in the solutions and changing of spin-spin T2 relaxation time, which could be detected by nuclear magnetic resonance (Ghazani et al., 2014; Hakho Lee, Yoon, Figueiredo, Swirski, & Weissleder, 2009). These sensors were also used in the analysis of circulating tumour cells and exosomes. Wang's group at Stanford University also developed a sensitive detection platform, but theirs was based on Giant Magnetoresistance (GMR) multilayer material stacks, which undergo a change in resistance upon capturing the target protein labelled with magnetic beads (K. Kim et al., 2018). This sensor platform was also adapted further to capturing circulating tumour cells and circulating tumour DNA (Park et al., 2016; Rizzi et al., 2017). Finally, a joint effort of the Wiesner (Cornell University) and Bradbury (Memorial Sloan Kettering Cancer Center) groups produced C-dots, very small

silica-based nanoparticles containing embedded fluorescent dye. C-dots have been used successfully for delineation of tumour margins in the surgery (Bradbury, Pauliah, Zanzonico, Wiesner, & Patel, 2016), but since then are also being adapted for therapeutic applications (F. Chen et al., 2018; S. E. Kim et al., 2016). These are only a few examples which illustrate flexibility and adaptability of nanotechnology platforms in cancer. Further details can be found in Tables 1 and 2. It should be also noted that the majority of nanoparticle platforms developed in the Alliance investigators' laboratories are non-liposomal 'next generation' particles. This is in sharp contrast to the body of particles which had been previously translated to clinical use and received New Drug Approval (NDA) from the FDA, the majority of which were liposomes (Kapoor, Lee, & Tyner, 2017). Figure 10 shows the number of nanoparticle-based clinical trials for liposomes and non-liposomal particles (excluding nab-paclitaxel), with the latter occupying a much smaller fraction of the field. Several of the next generation nanoparticles developed under Alliance funding have entered early clinical trials and hopefully will move forward towards NDAs in the near future.

Clinical translation and commercialization of nanotechnology cancer interventions—The initial funding support from the NCI has allowed program participants to secure significant additional research and developmental funds from non-Alliance federal grants, philanthropic sources, industry, and foreign governments in order to further build upon research seeded by the Alliance program. These additional funds allowed for expanding the scope of research performed under Alliance awards, enabled continued work beyond pre-clinical studies, and supported commercialization. Figure 11 represents total dollars leveraged and raised by the four CCNEs that were funded in all three Phases of the Alliance. They are: University of North Carolina CCNE (*Nano Approaches to Modulate Host Cell Response for Cancer Therapy*), Northwestern University CCNE (*Nucleic Acid-Based Nanoconstructs for the Treatment of Cancer*), Stanford University CCNE (*Center of Cancer Nanotechnology Excellence for Translational Diagnostics*), and Caltech-UCLA-ISB CCNE (*Nanosystems Biology Cancer Center*). The NCI investment in these four CCNEs has cumulatively reached $165 M as of FY2019. Over the course of the same period, these CCNE's have managed to leverage these NCI funds to obtain other federally funded grants and contracts totalling more than $500 M. When including both leveraged funds obtained and commercial equity raised from companies spun out from these CCNE's, the total currently exceeds $1.48 B.

Several of the Alliance investigators have been entrepreneurial and established start-up companies based on licensing of technologies developed in their academic groups. We counted over 125 start-up companies and industrial collaborators associated with the program. Several of these companies have successfully applied for and received SBIR Phase I (*i.e.,* Feasibility and proof of concept stage of funded technology) funding through the NCI SBIR program (Beylin, Chrisman, & Weingarten, 2011; Dickherber, Morris, & Grodzinski, 2015; Narayanan & Weingarten, 2018). Additional funding from private sector was also raised by several of these start-up companies. Of these companies, the majority have successfully filed for and been awarded patents on the underlying technologies. Figure 12 represents patents awarded to companies that span different groups that have been funded by NCI Alliance grants.

The importance of this large commercial output, ultimately driving the next-generation nanoscale platforms to the clinic, comes to bear when we analyse the outcomes of this research in the clinical space – that is, the number of clinical trials originated from the Alliance investigators' research. Several Alliance-associated start-up companies and few universities have thus far entered into 34 clinical trials. A list of Alliance-related clinical trials is shown in Table 3. This table not only shows the high number of clinical trials resulting from technologies developed by the Alliance researchers using Alliance-developed nanoparticles, but also displays the aggressive push into the translation of next-generation, non-liposomal nanoparticles (Gregoriadis, 2016; Shi, Kantoff, Wooster, & Farokhzad, 2017) (e.g., Figure 10).

Conclusion

The NCI Alliance for Nanotechnology in Cancer program was established in 2005, the same year in which Abraxane was approved by the FDA. Since then, Abraxis Bioscience, the company responsible for the development of Abraxane, was sold to Celgene in 2010; Celgene, in turn, was acquired by Bristol-Myers Squibb in 2019. This scenario reflects the overall dynamism in the field of nanomedicine and cancer nanotechnology. Several iterations and combination trials involving Abraxane have been conducted – clinicaltrials.gov shows 2440 of them. Since 2005, several other nanomedicines were also approved by the US FDA including Marqibo, Onivyde, and Vyxeos – all liposomal formulations of cytotoxic drugs. Nanotherm (particles for hyperthermia treatment of glioblastoma) was recently approved in Europe (Anselmo & Mitragotri, 2016; D'Mello et al., 2017). Recent approval of ONPATTRO™ (patisiran, Alnylam Pharmaceuticals), an RNAi therapeutic agent based on a lipid complex injection for the treatment of the polyneuropathy in amyloidosis (not cancer), signals expansion of the repertoire of therapeutic molecules which can be delivered successfully using nanoparticles.

Despite these successes, nanomedicines, which have reduced life-threatening toxicities of the treatment, have resulted only in modest improvement in the overall survival of patients (Chan, 2017; Chapman et al., 2013; Goldberg et al., 2013; Prabhakar et al., 2013). Further development of nano-therapeutics will undoubtedly emphasize the improvement of patients' survival. This could be achieved through identifying "niche" applications which are uniquely positioned to benefit from nanotechnology and do not have viable contemporary solutions, expanding the scope of monotherapies to combination therapies delivering two or more synergistic drugs and/or engaging more than one treatment modalities. These strategies can be further facilitated by the implementation of companion diagnostics relying on testing the strength of the Enhanced Permeability and Retention (EPR) effect responsible for nanoparticle accumulation in solid tumours, and resulting in identification of patients for whom nanomedicines may be most effective (Ehlerding, Grodzinski, Cai, & Liu, 2018; Keating et al., 2018; Helen Lee et al., 2017; Miller et al., 2015; Wong, Siah, & Lo, 2018).

The overall landscape in the mature translational nanomedicine space associated with the development of FDA-approved nanodrugs was not directly influenced by the Alliance program, as the entire path from pre-clinical demonstration to the completion of all phases of clinical trials is very lengthy and expensive. Furthermore, many of the early stage

developments which resulted in nanomedicines approved by the FDA started prior to the establishment of the Alliance program. However, the Alliance has made a significant mark on establishing next-generation technology platforms suitable for contemporary cancer clinical interventions. This influence has been demonstrated in several areas. The majority of the Alliance nanoparticle platforms belong to next-generation, non-liposomal constructs. As a result, their designs often engage complex materials properties, which can possess therapeutic or diagnostic capabilities, making these constructs more powerful in providing the cancer intervention than simply performing the role of the delivery vehicle (Anselmo & Mitragotri, 2016). The Alliance research has been also opening doors to new areas of cancer applications for nanotechnology and moving beyond nanotechnology-based chemotherapies. As inspection of technologies listed in Tables 1 and 2 show, several therapeutic modalities have employed delivery of pharmaceutical ingredients other than small molecules including biologics, mRNA, and RNAi. The Alliance investigators also ventured into nanotechnology-based immunotherapies and their combination with other treatment modalities. Finally, they made lasting contributions in the development of multi-modal imaging constructs which can be used on different approaches to intra-operative imaging and surgery monitoring.

Many of the innovations emerging from the Alliance work would not occur without the engagement of researchers who are not traditionally NIH grantees: physical scientists, chemists, and engineers. If not for the Alliance program, many of them would not have ended up bringing their talents to focus upon cancer. For example, several of them, who were already prominent in their non-medical fields (chemistry, physics, engineering), were recognized due to their lasting engagement into nanomedicine for their impact to the medical sciences with induction to the National Academy of Medicine. They were Mark Davis, - a chemical engineer from Caltech, Chad Mirkin – a chemist from Northwestern University, Joseph DeSimone – a chemist from the University of North Carolina, and Stephen Quake – a physicist from Stanford University. They also happen to be members of other two National Academies – Engineering, and Sciences, demonstrating the level of prominence of researchers involved in the Alliance program.

The Alliance’s success can be measured not only by the scientific impact, but also by the ability of developing a seamless transition of technologies developed in academia to a further stage of maturity in industry. The Alliance NCI-funded grants supported only academic research. Due to the initiative and commercial acumen of Alliance investigators, multiple start-up companies have been established based on licensing research from their academic groups. These companies raised additional funding, often employed students and post-doctoral fellows from their “parent” academic groups, and successfully moved technologies forward into clinical trials and product development. When the National Academies review the National Nanotechnology Initiative, the Alliance program is featured as a “success story” with multi-faceted path to its success. By all accounts, the program has been considered successful in building a stimulating multi-disciplinary research environment and enriching research seeded by its initial NCI funding through collaborations, innovation, and entrepreneurship.

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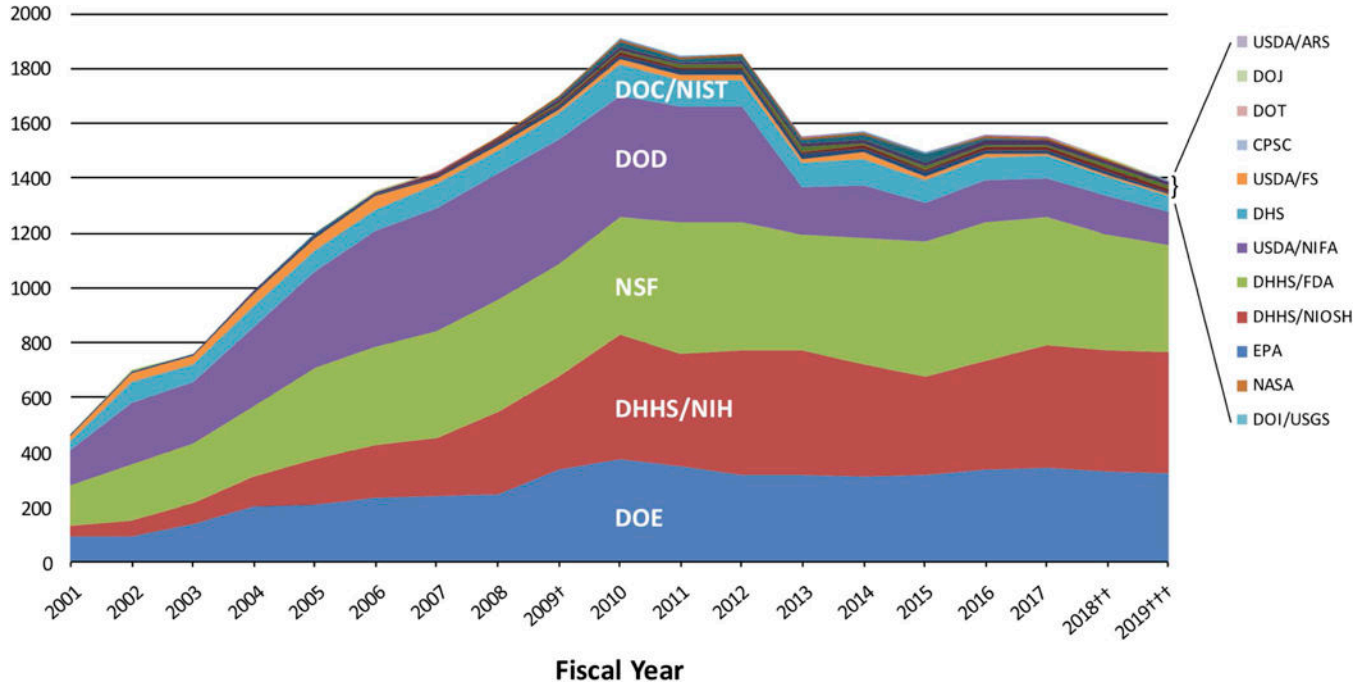

Figure 1.

The U.S. government's funding trends in nanoscale science, engineering, and technology R&D since the inception of the National Nanotechnology Initiative (NNI). The funding levels for nanotechnology by 12 agencies of the U.S. government has maintained high levels since the inception of the NNI due to the 21st Century Nanotechnology Research and Development Act, signed into law in 2003. The agencies that have continued to maintain high levels for the last decade are the National Science Foundation, the Department of Energy, and the National Institutes of Health. (source NNI Supplement to the President's 2019 Budget – https://www.nano.gov/2019budgetsupplement)

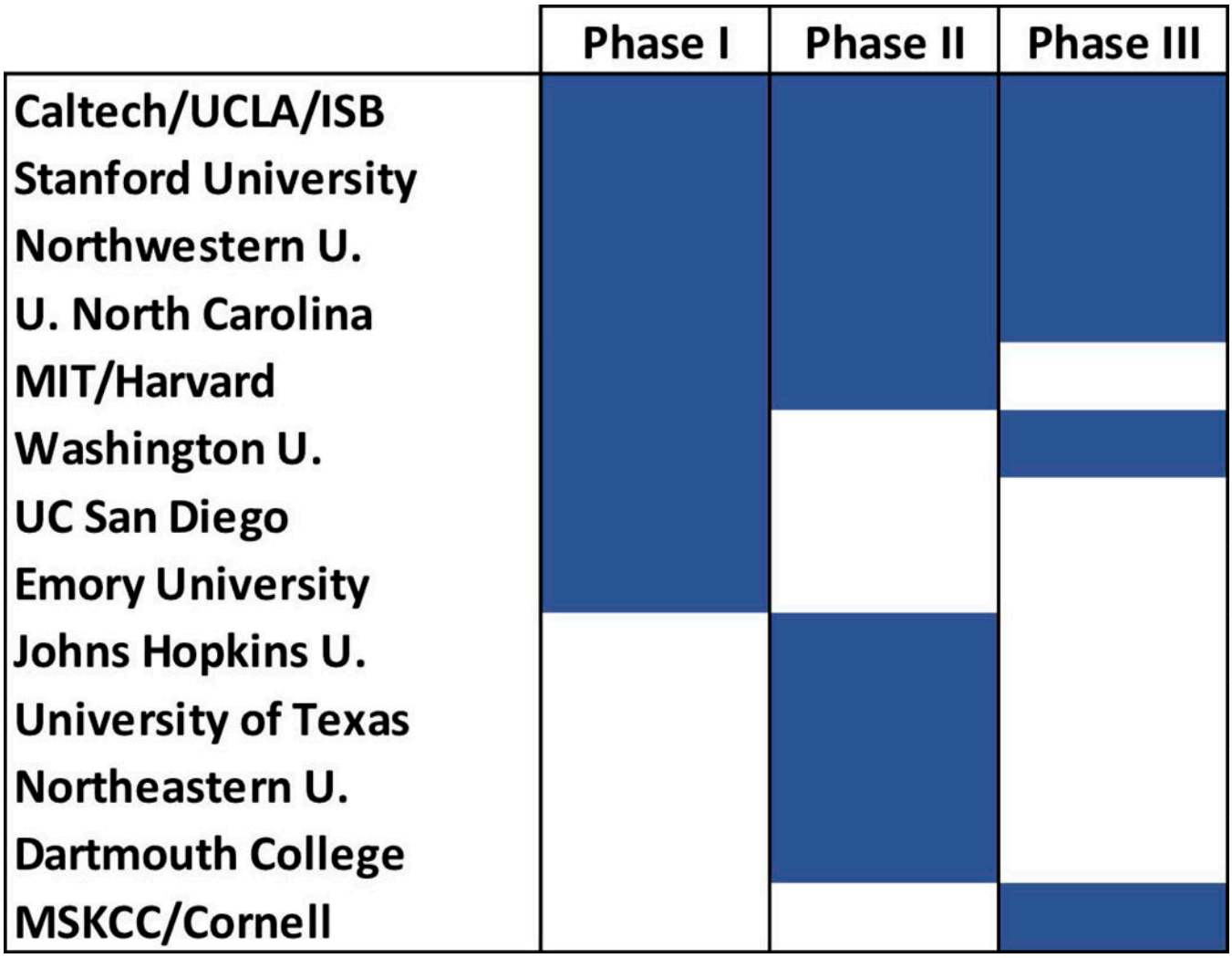

Figure 2.
CCNE awards in three different Phases of the Alliance program. Solid blue represents grant awarded during Phase.

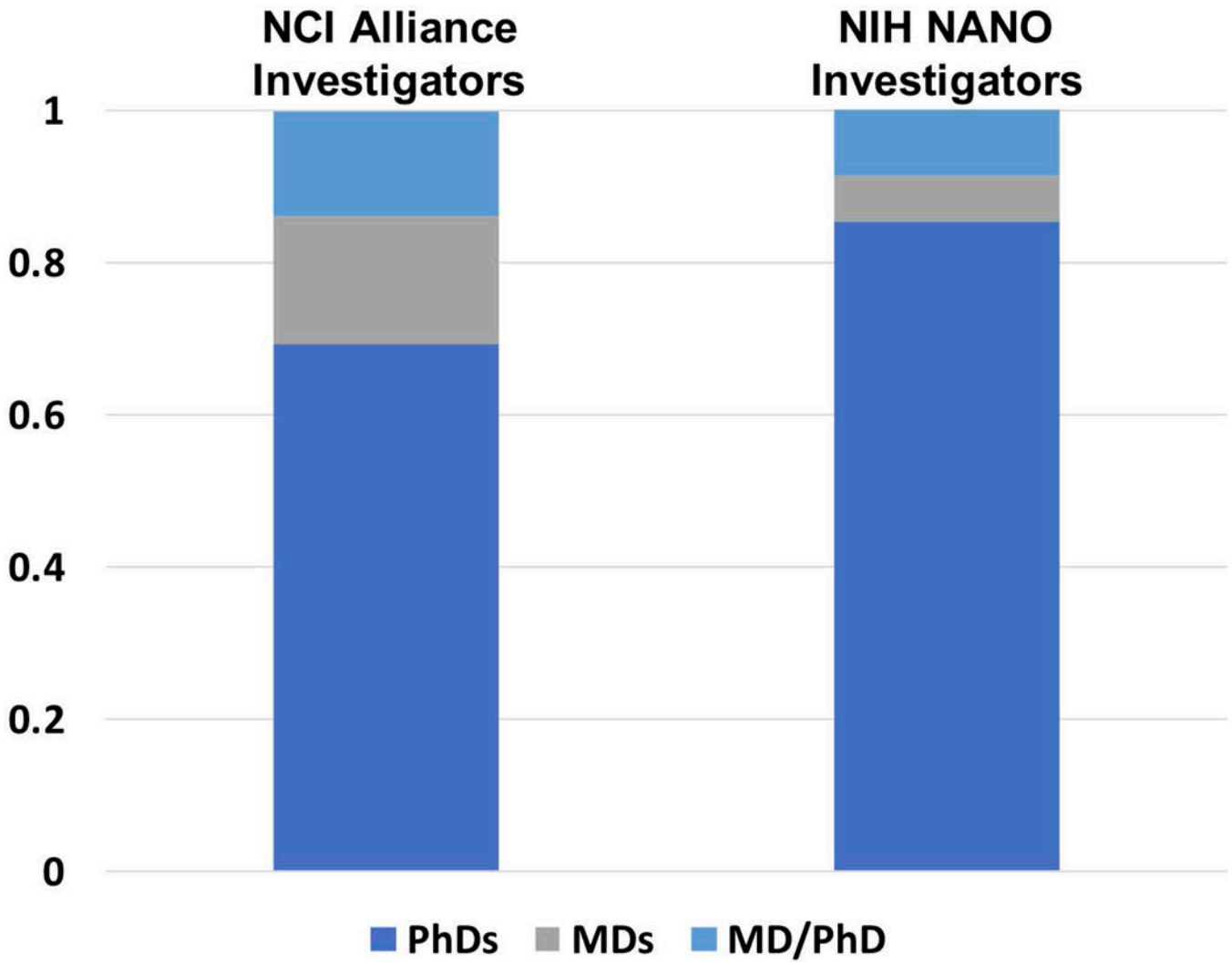

Figure 3.

Breakdown of terminal degrees held by grant awardees. In total over the course of all three Phases, Alliance grants tend to include more investigators with clinical degrees than the pool of investigators funded through the general NIH NANO study section's cancer applications. This includes fraction of funded investigators who are MDs (gray bar) and fraction of funded investigators who hold dual degrees (MDs/PhDs, light blue bar).

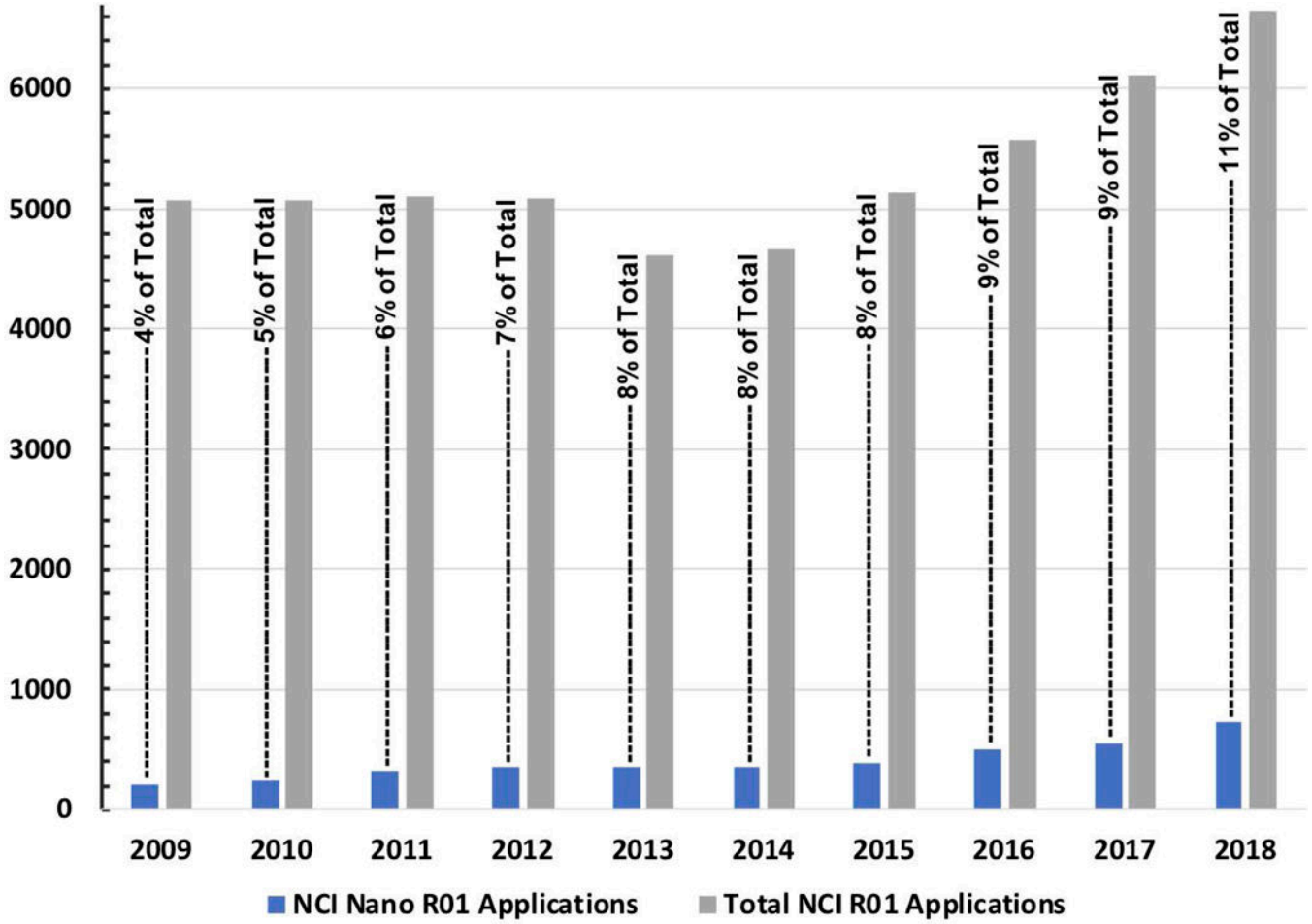

Figure 4.

NCI nanotechnology R01 applications versus all NCI R01 applications submitted. The graph highlights the changing level of investigator-initiated R01 applications submitted in the last decade. Applications received and reviewed for nanotechnology (solid blue bars) in comparison with the total number of applications received and reviewed (solid grey bars) displays persistent increase in nanotechnology for cancer being researched by the biomedical research community. The proportion (black text percentiles) of nanotechnology applications to the total submitted highlights this increase. The data was obtained using an internal NIH grant database and contains information on both new and re-submitted grants. Nanotechnology submissions were identified using a search with the NIH RCDC (Research, Condition, and Disease Categorization) term of “nano”.

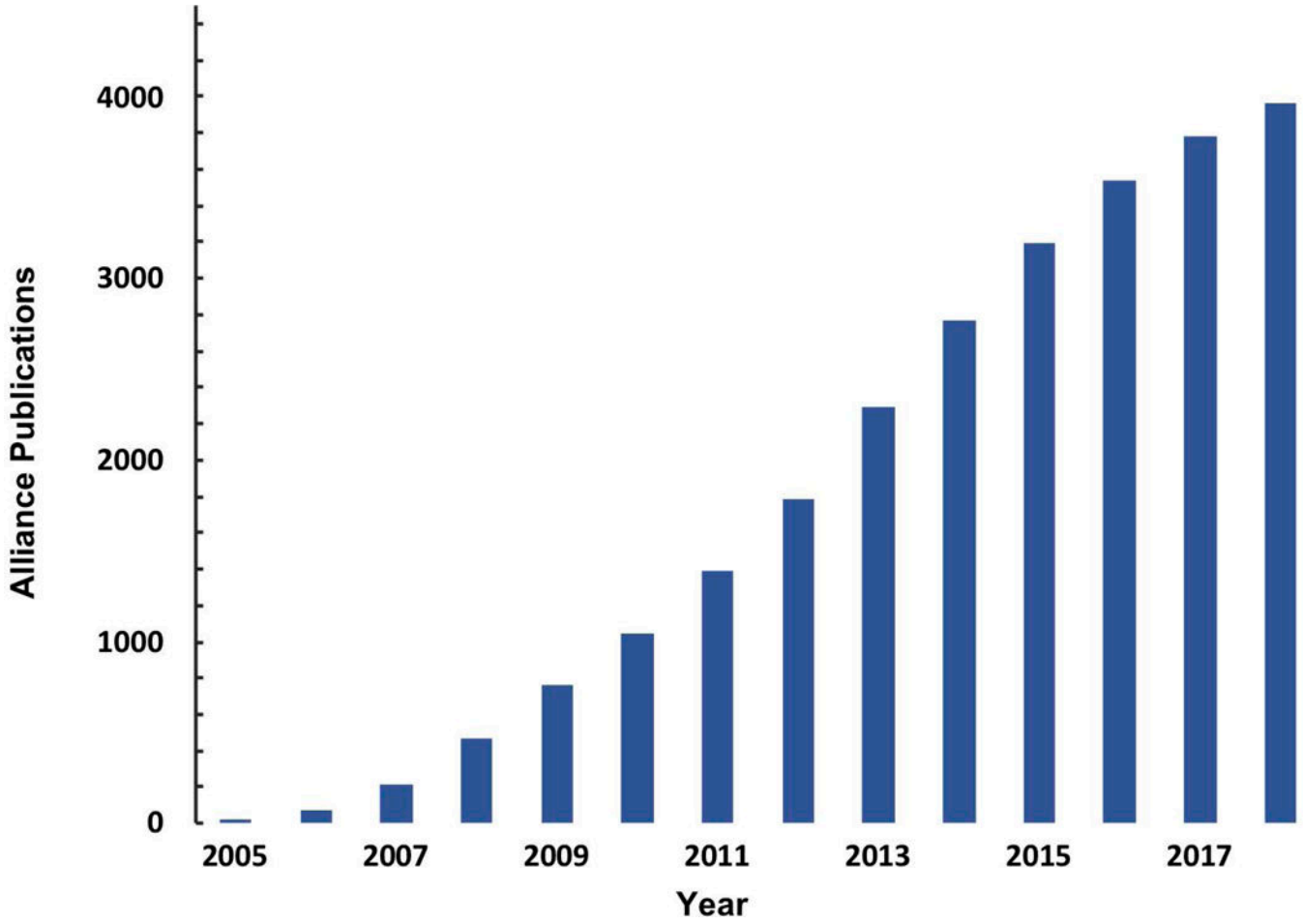

Figure 5.

Alliance published scientific output over the course of the program. The cumulative published research by Alliance investigators (dark blue solid bar) between 2005-2018. The data displayed is derived from literature search using NCBI's PubMed with Alliance-specific grant identifiers for all Alliance publications. Grants included are all Centers of Cancer Nanotechnology Excellence (U54), single research projects (Cancer Nanotechnology Platform Partnership – U01 and Innovative Research in Cancer Nanotechnology – U/R01), Cancer Nanotechnology Training Centers (R25 / T32), and Path-to-Independence Awards (K99/R00) funded under the NCI Alliance program.

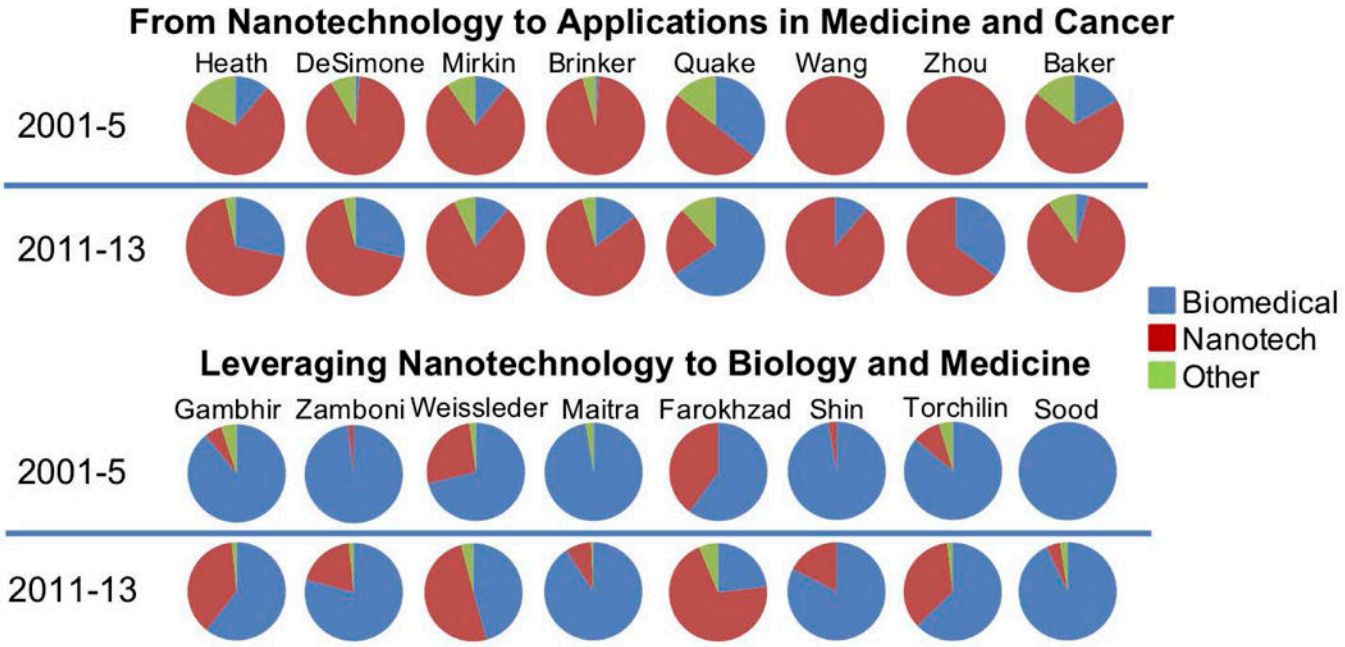

Figure 6.

Publication focus of different Alliance investigators. The upper part of the graph represents investigators originating from non-medical fields: physics, chemistry, engineering. As graph shows, prior to their involvement with the Alliance program (2001-2005, 1st, upper row of the graph), they published predominantly in non-medical nanotechnology (indicated as “Nanotech” in red). Once they started to participate via Alliance program funded grants, their focus evolved, and their overall publication portfolio gradually shifted towards medical applications of nanotechnology (visualized by growing blue portion of the pie chart corresponding to “Biomedical” in 2nd upper row). Similarly (lower part of the graph), investigators, who traditionally researched cancer and medicine, began to involve more nanotechnologies in their work as demonstrated by the red portion (“Nanotech”) of the pie chart growing after their participation in the Alliance program.

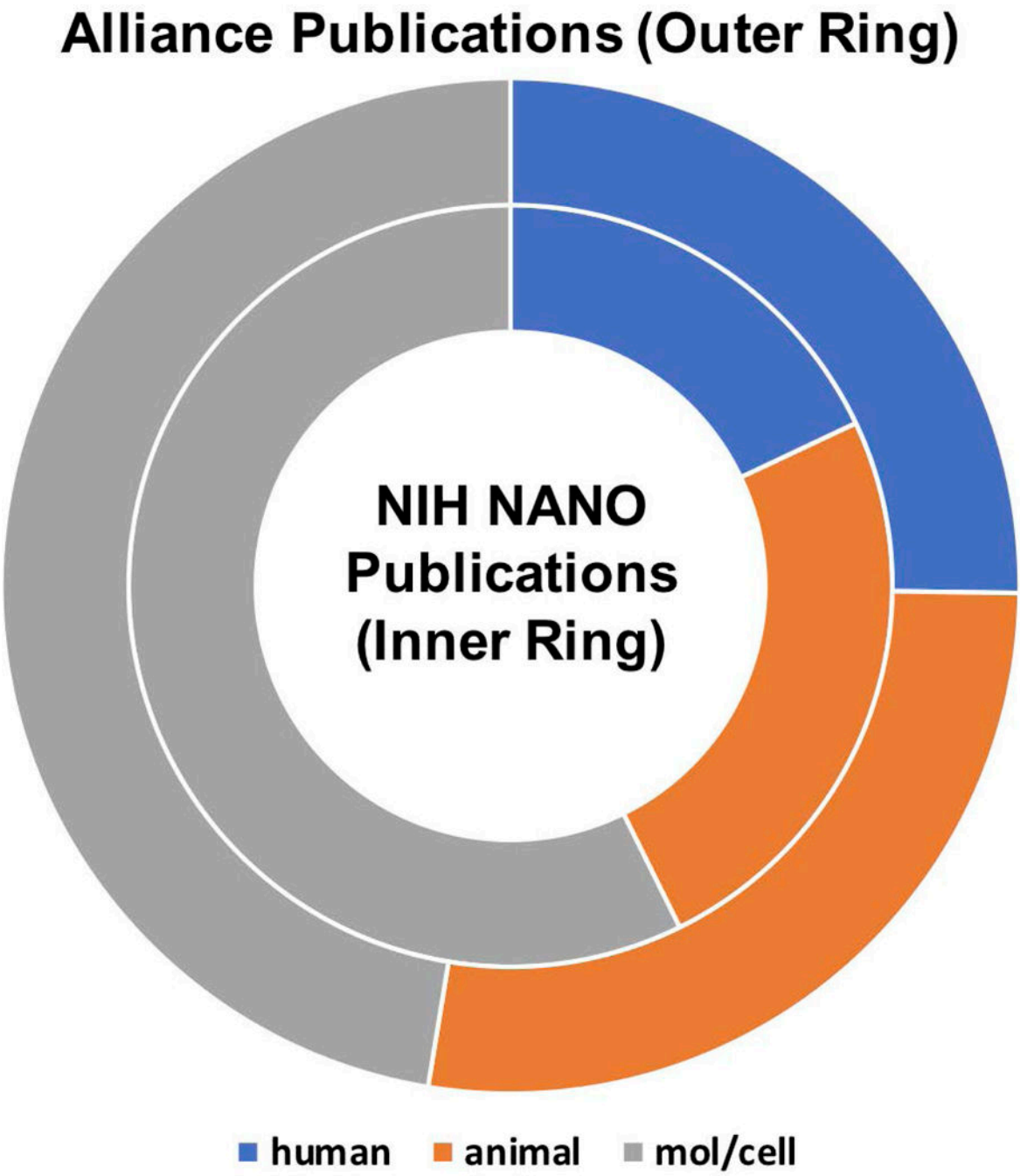

Figure 7.

Triangle of Medicine analysis. In this analysis, publications associated with a grant or set of grants are analyzed for the fractions of human, animal, and molecular/cellular research. In this case, the outside ring is representative of Alliance research, with about a quarter of the published research categorized as human (24%, blue section), slightly more than a quarter categorized as animal research (26%, orange section), and slightly less than half of Alliance research categorized as molecular/cellular research (44%, gray section). For comparison, we also analyzed the Triangle of Medicine research composition for all grants funded through

the NIH NANO study section, represented in the inside ring. In the case of NIH NANO study section funded grants, only about 16% of published research included a human research component, with 22% animal research and 51% molecular/cellular research.

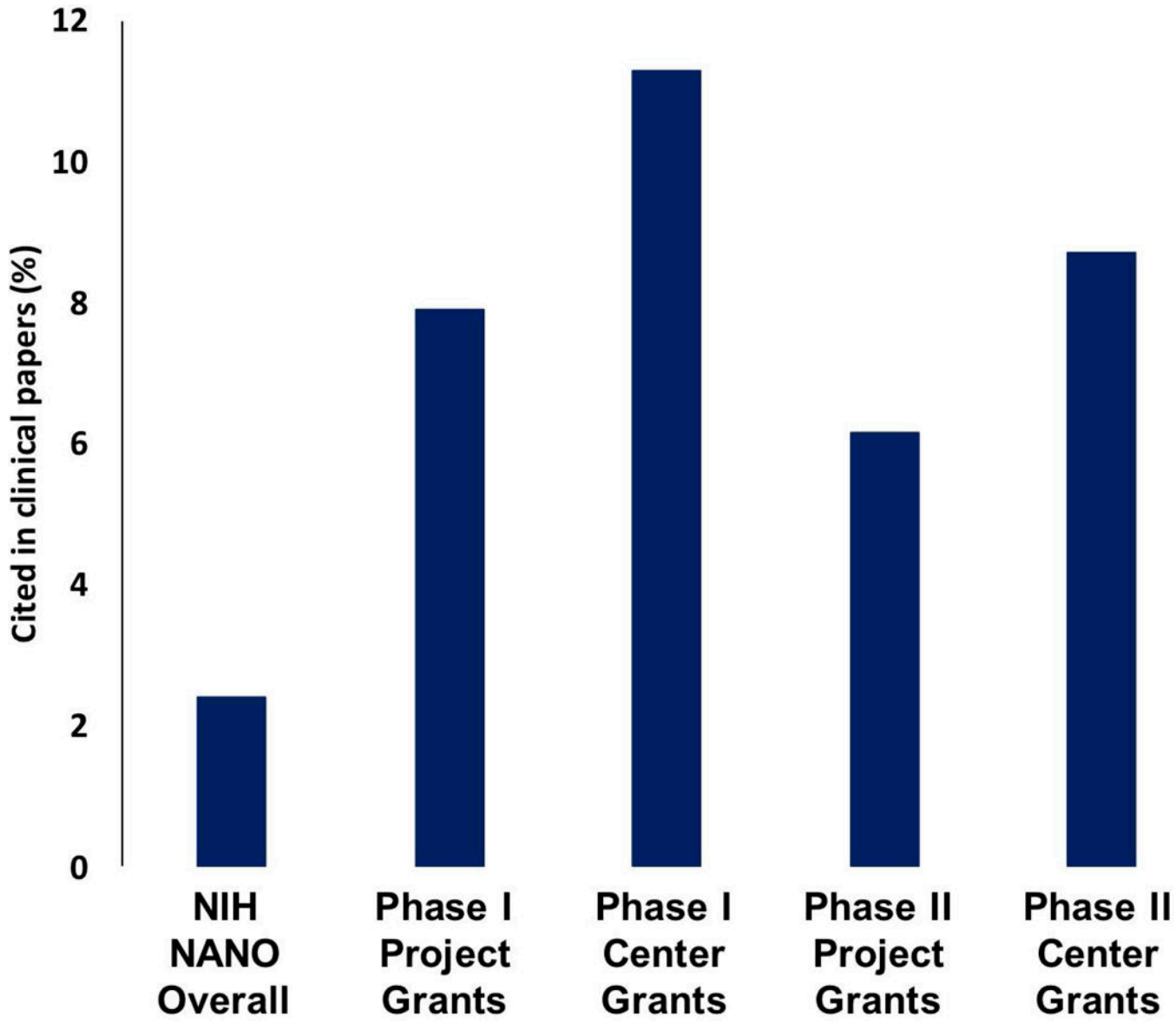

Figure 8.

Percent of the Alliance investigator authored publications that are cited by clinical papers – authored by Alliance and/or non-Alliance investigators. This analysis was carried out using iTrans software from the National Institutes of Health – by program Phase and by grant type (Du, Li, Guo, & Tang, 2019). For comparison, this analysis was performed for grants originating from the NIH NANO study section over the period of time corresponding to all three Phases of the Alliance program. The figure displays that both CCNE and smaller Alliance grants tend to be cited more often in subsequent clinical papers when compared to grants originating from the NIH NANO study section.

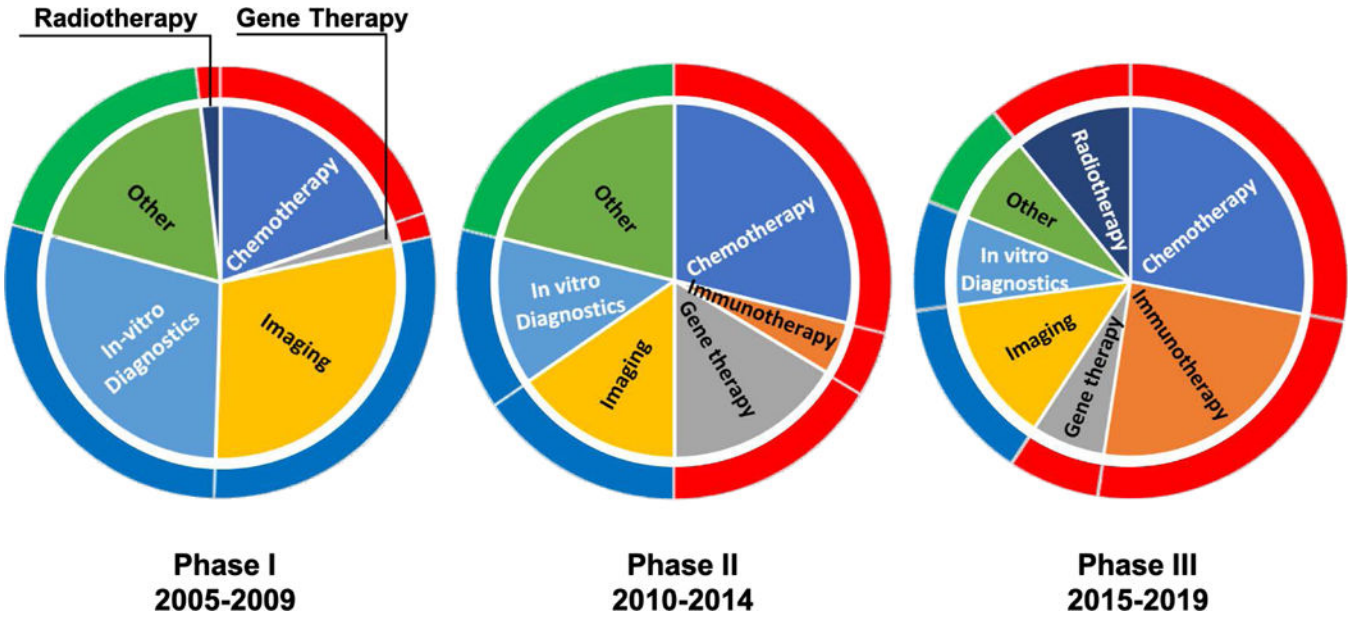

Figure 9.

Modalities of Alliance-funded projects over three different Phases of the program. These layered pie charts show the shift in modalities of Alliance-funded projects over the last 15 years. The inner pie chart displays the fraction of total Alliance projects that focused on in vitro diagnostics, imaging, gene therapy, radiotherapy, immunotherapy, chemotherapy, and other during each period. While, the outer ring is color-coded to emphasize the shift from a majority diagnostic (noted in blue) in Phase I to primarily therapeutic (noted in red) projects in Phase III. All other (materials characterization, for example) projects are noted in green.

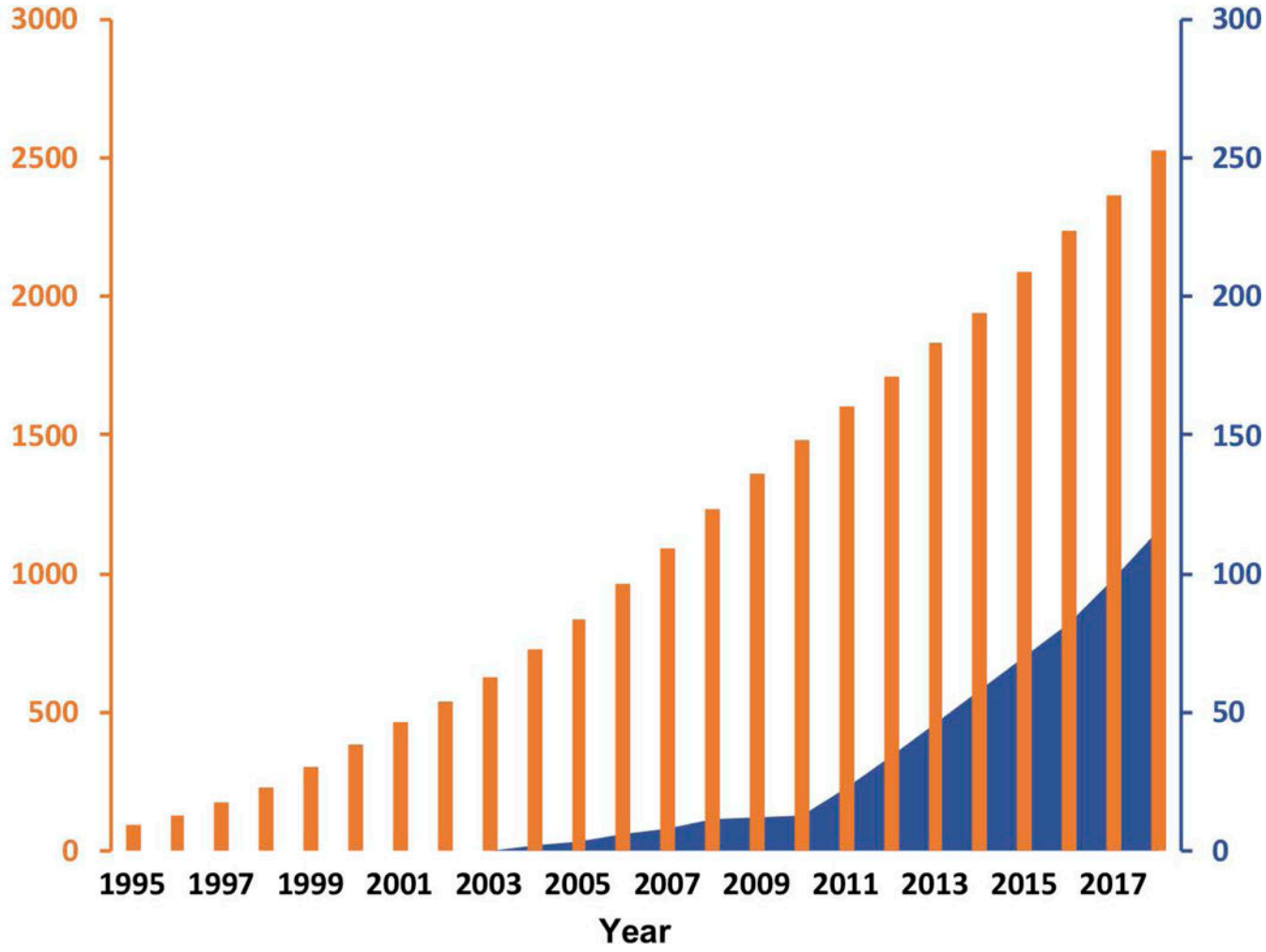

Figure 10.

Cumulative cancer clinical trials conducted for liposomal versus non-liposomal nanoparticles over time. This graph displays clinical trials performed for liposomal delivery systems (solid black bars – left axis) since the approval of Doxil in 1995. In comparison, all non-liposomal nanoparticle cancer clinical trials are displayed as solid blue fill, corresponding right axis. The information was derived from clinicaltrials.gov based on the following keyword searches '*Cancer and – liposomal, Caelyx, Myocet, Lipodox, Onivyde, Depocyt, Daunoxome, Marquibo, Vyxeos, or Mepact*' and for non-liposomal '*Cancer and nanoparticle or nanotechnology*'. The nab-paclitaxel trials that were found were excluded from non-liposomal trials count. The year on the horizontal axis corresponds to the initiation of the trial.

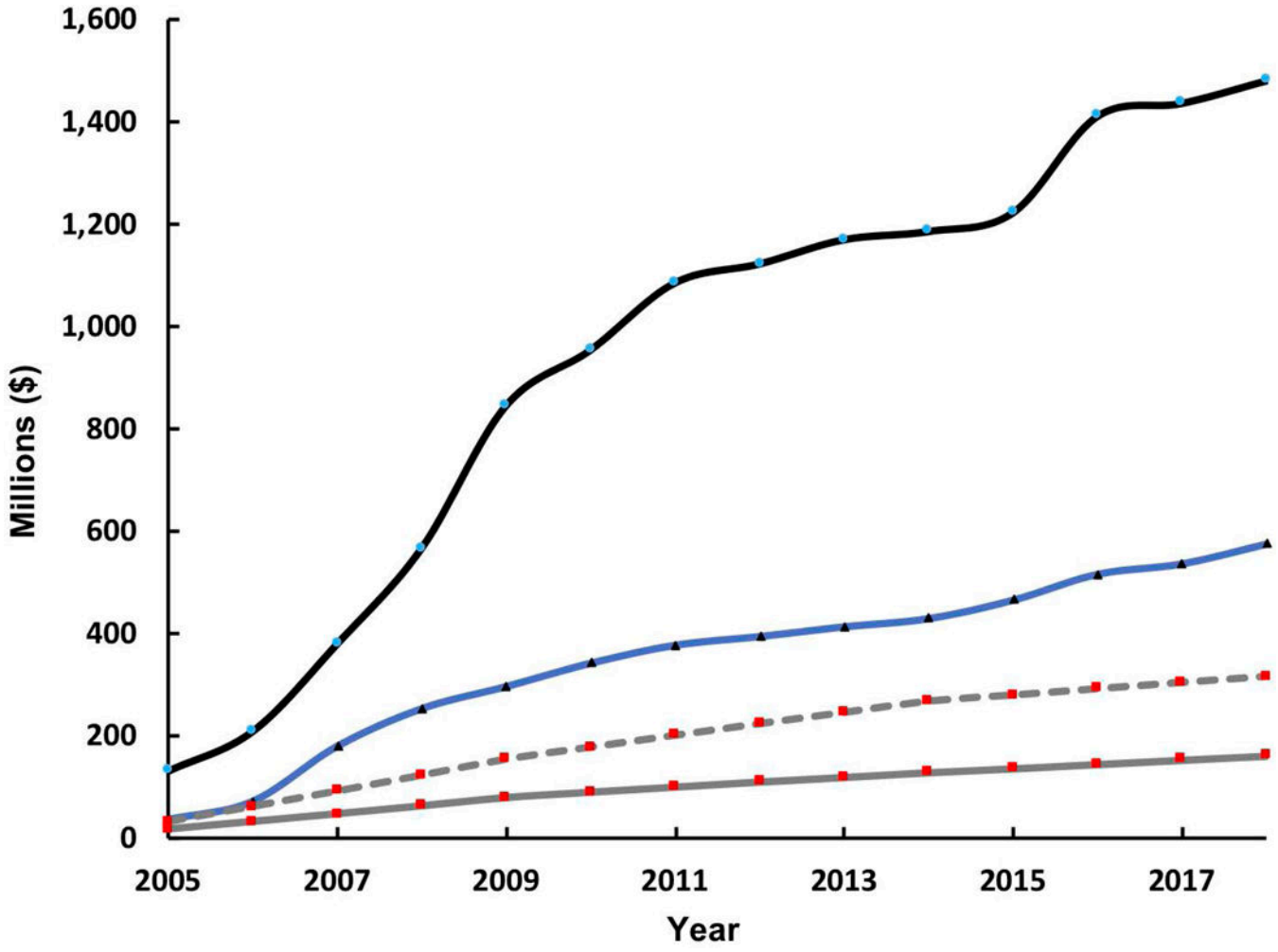

Figure 11.

The initial NCI funding and additional funding leveraged by funding to four Alliance CCNEs, which have been funded for all Phases of the program (California Institute of Technology, Northwestern University, Stanford University, and University of North Carolina at Chapel Hill). The graph represents the cumulative investment by NCI to these four CCNEs (gray solid line), the cumulative funds leveraged by these CCNEs from other public funding sources (blue solid line), and the cumulative total of both funds leveraged, and equity invested by companies that commercialized CCNE technologies (black solid line). For additional comparison, the cumulative investment by the NCI to all funded Alliance CCNEs, over all Phases, is also displayed (gray dashed line).

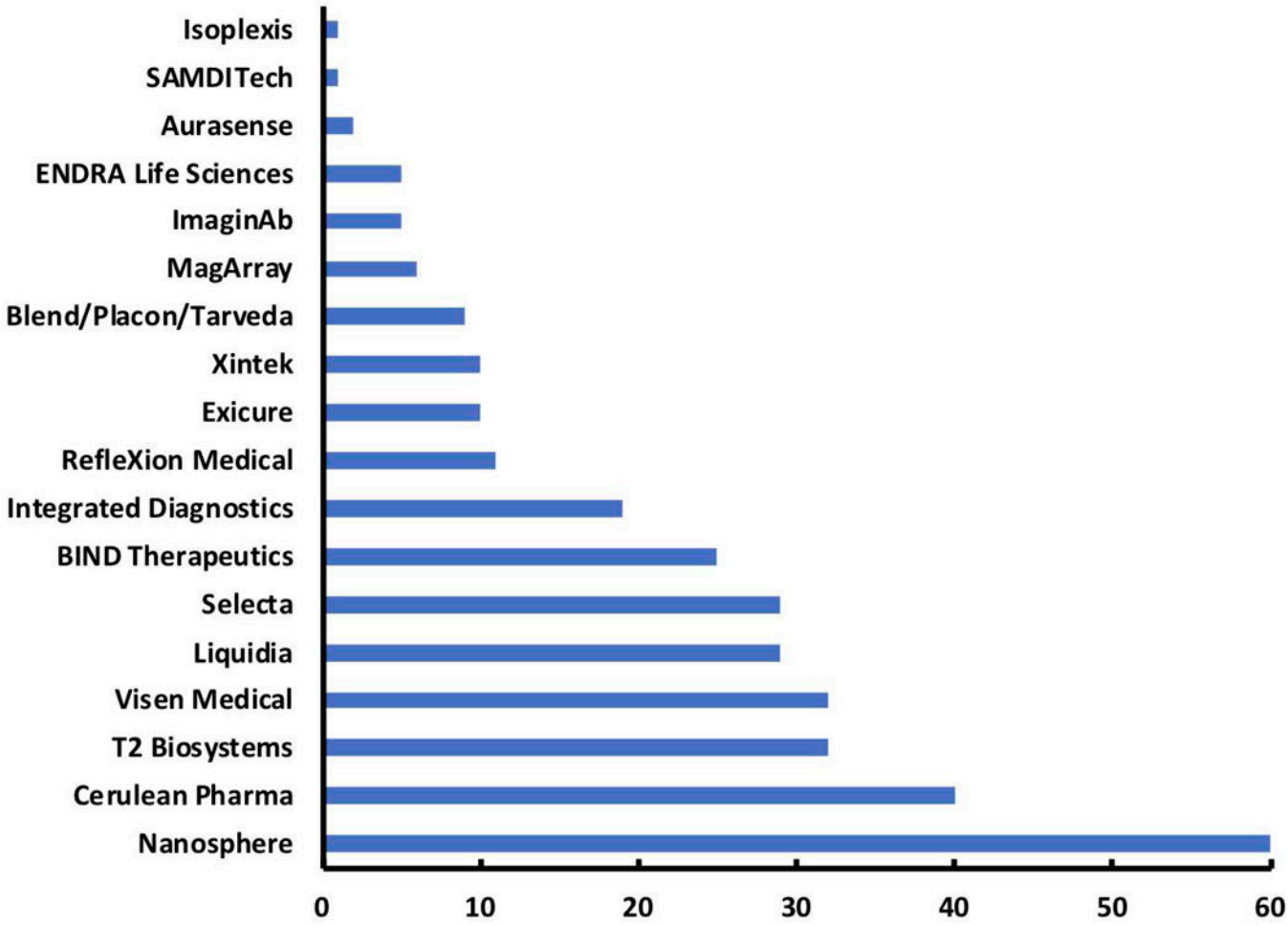

Figure 12.

Alliance-related patents. The Alliance program has funded many projects and platform technologies which have ultimately been commercialized and patented by the U.S. Patent and Trademark Office. The graph displays the total number of patents awarded to companies that were either direct spin off companies of Alliance research projects or companies that obtained the intellectual property to their technologies. The company listed do not represent the entire portfolio of companies that came from Alliance investigators and is only a representative sample that covers the most directly related. Patent data was collected using the advanced search feature of Google Patents, where the name of the company was used as the assignee and a filter for US patents only was applied. Of note, not all of the patents listed in the figure came directly from projects funded by the Alliance, as the companies have extensive portfolios and have matured. Yet these companies, and their respective patents relative to Alliance-related companies, are more directly applicable to the original research performed by Alliance investigators who either licensed to existing companies or began the companies themselves.

Table 1.

Technologies developed by CCNE awardees. The purpose of this table is to give the Reader an overview of the diversity of projects funded in CCNE grants. We were not able to include all projects – it would make the table too exhaustive. Each CCNE is represented with their most unique projects and also those which progressed to more advanced levels of maturity. The references in the table are not necessarily the most recent ones for a particular technology; they represent the status of work during the time the investigator was holding the grant. The last column in the table lists the company(ies) that licensed the technology for future commercialization and the clinical trial(s) number, if they are is being conducted for the technology.

Technology and Cancer Application	Investigator/Institution	Publications	Clinical Translation Status (companies and trials)
	Diagnostics and Imaging		
Microfluidic-based Integrated Blood Barcode diagnostic devices	James Heath *Caltech/UCLA*	(Bailey et al., 2007; Fan et al., 2008b)	Integrated Diagnostics (Biodesix)
Monitoring and predicting response to cancer therapies and immunotherapy using Single Cell Barcode Chips	James Heath and Antoni Ribas *Caltech/UCLA*	(Ma et al., 2013; Zhou et al., 2018)	Integrated Diagnostics (Biodesix), Isoplexis
Devices based on giant magneto-resistance and flow magnetic levitation to detect proteins as well as capture and concentrate circulating cancer cells	Shan Wang and Utkan Demirci *Stanford University*	(K. Kim et al., 2018; J.-R. Lee, Magee, Gaster, LaBaer, & Wang, 2013; L.-G. Liang et al., 2017)	MagArray, Levitas
Nanoparticles for multi-modal imaging in cancer	Sanjiv Sam Gambhir *Stanford University*	(X. He, Gao, Gambhir, & Cheng, 2010; Kircher et al., 2012)	ENDRA Life Sciences
Tools for transrectal ultrasound and photoacoustic imaging	Sanjiv Sam Gambhir *Stanford University*	(Garai et al., 2013; Willmann et al., 2017)	ENDRA Life Sciences NCT02365883
BarCode assays for in vitro cancer diagnosis	Chad Mirkin *Northwestern University*	(Alhasan et al., 2012; Taton, Mirkin, & Letsinger, 2000)	Nanosphere (Luminex)
Diagnostic μ-NMR devices based on nanoparticle aggregation for detection of proteins, circulating tumor cells, and microvesicles	Ralph Weissleder *MIT/Harvard University*	(Ghazani et al., 2014; Hakho Lee et al., 2009)	T2 Biosystems
Spherical nucleic acid (SNAs) nanoconstructs for intracellular imaging	Chad Mirkin and Colby Shad Thaxton *Northwestern University*	(Halo et al., 2014; Prigodich et al., 2012)	Aurasense (Exicure)
Microfluidic-based screening of DNA methylation for early cancer diagnostics and post-therapy monitoring	Jeff Wang, Stephen Baylin, and James Herman *Johns Hopkins University*	(Athamanolap, Shin, & Wang, 2014)	
Nanocrystals for multiplexed cancer detection in vitro and in vivo	Shuming Nie, Lily Yang, and Gang Bao *Emory University/Georgia Tech*	(A. M. Smith, Dave, Nie, True, & Gao, 2006; Xing, Smith, Agrawal, Ruan, & Nie, 2006)	Ocean Nanotech
Carbon nanotube (CNT) X-ray systems to develop instrumentation for radiation therapy and diagnostic medical imaging	Otto Zhou *UNC Chapel Hill*	(Hadsell et al., 2013; G. Yang et al., 2011)	XinRay Systems, XinVivo, XinNano Materials, Xintek NCT01773850
Intraoperative sentinel lymph node mapping and radiotherapy using C-dot nanoparticles	Michelle Bradbury and Ulrich Wiesner *Memorial Sloan Kettering Cancer Center/Cornell University*	(Bradbury et al., 2016; F. Chen et al., 2018)	Elucida Oncology NCT01266096, NCT02106598
Self-assembling and bio-responsive nanoparticles to probe tumor microenvironment	Jianghong Rao *Stanford University*	(G. Liang, Ren, & Rao, 2010; Witney et al., 2015)	

Technology and Cancer Application	Investigator/Institution	Publications	Clinical Translation Status (companies and trials)
Tools to monitor immune cell/cancer cell interactions in novel genetically encoded gas nanovesicles	Mikhail Shapiro and Antoni Ribas *ISB/CalTech/UCLA*	(G. J. Lu et al., 2018; Shapiro et al., 2014)	
Quantum dots and bacteriophage-inspired nanomaterials for detection of tumor spread	Angela Belcher and Moungi Bawendi *MIT/Harvard University*	(Cuneo et al., 2013; Ghosh et al., 2012)	Lumicell, Quantum Dot Corporation
Bioresponsive probes for tumor imaging	Martin Pomper *Johns Hopkins University*	(Bhang, Gabrielson, Laterra, Fisher, & Pomper, 2011)	Molecular Insight Pharmaceuticals (Progrenics)
Novel nanoparticle agents for molecular imaging of cancer	Thomas Meade and Gayle Woloschak *Northwestern University*	(Endres, Paunesku, Vogt, Meade, & Woloschak, 2007)	
Microfluidic systems for synthesis of PET probes	Hsian-Rong Tseng and Michael Phelps *CalTech/UCLA*	(Yanju Wang et al., 2009)	Sofie Biosciences
	Therapeutics		
Development and translation of targeted polymeric docetaxel nanoparticle therapies for solid tumors	Omid Farokhzad and Robert Langer *MIT/Harvard University*	(Behzadi et al., 2017; Farokhzad et al., 2006)	BIND Therapeutics (Pfizer), Blend Therapeutics (Tarveda Therapeutics) Several trials – Table 4
Development and translation of cyclodextrin-containing polymer conjugates of chemotherapeutics and RNAi	Mark Davis *CalTech/UCLA*	(Davis, 2009; Davis et al., 2010)	Cerulean Pharma (NewLink Genetics), Several trials – Table 4 Calando Pharmaceuticals NCT00689065
Strategies for crossing physiological barrier using nanoparticles	Mark Davis *CalTech/UCLA*	(Clark & Davis, 2015)	
PRINT™ nanoparticles for chemotherapy, siRNA, and vaccine delivery	Joseph DeSimone *UNC Chapel Hill*	(Mueller, Tian, & DeSimone, 2015; Perry, Herlihy, Napier, & Desimone, 2011)	Liquidia
Spherical nucleic acid (SNAs) for gene therapy and design of nanostructure vaccines	Alexander Stegh, Andrew Lee, and Chad Mirkin *Northwestern University*	(Jensen et al., 2013; Skakuj et al., 2018; Yue et al., 2018)	NCT03020017 Exicure, NCT03086278 NCT03684785
Targeted and tumor-penetrating siRNA nanocomplexes for treatment of ovarian cancer	Sangeeta Bhatia and Phillip Sharp *MIT/Harvard University*	(Ren et al., 2012)	Alnylam Pharmaceuticals
A comprehensive treatment of multiple myeloma through nanoparticle-based tumor microenvironment targeting	Kareem Azab, John DiPersio, and Gregory Lanza *Washington University*	(Azab et al., 2012; de la Puente et al., 2018)	Cellatrix, Targeted Therapeutics
Deep tissue PDT enabled through the Cerenkov radiation induced therapy (CRIT)	Samuel Achilefu *Washington University*	(Kotagiri, Sudlow, Akers, & Achilefu, 2015)	
Mucus penetrating nanoparticles for small cell lung cancer	Justin Hanes, Charles Rudin, and Craig Peacock *Johns Hopkins University*	(Nance et al., 2012)	Kala Pharmaceuticals
Multi-stage nanoparticle vectors for cancer therapeutics	Mauro Ferrari, Paolo Decuzzi, and Gabriel Lopez-Berestein *UT/MD Anderson Cancer Center*	(Martinez et al., 2013; Yokoi et al., 2013)	Leonardo Biosystems
Mining TCGA data to identify targets for nanotherapies	Anil Sood and Gabriel Lopez-Berestein *UT/MD Anderson Cancer Center*	(Shen et al., 2013)	NCT01591356

Technology and Cancer Application	Investigator/Institution	Publications	Clinical Translation Status (companies and trials)
Nano-assemblies for ligand-directed imaging and therapy of solid tumors	Wadih Arap and Renata Pasqualini *UT / MD Anderson Cancer Center*	(Hosoya et al., 2016; T. L. Smith et al., 2016)	PhageNova Bio
Nanoparticle strategies for siRNA and vaccine delivery	Leaf Huang *UNC Chapel Hill*	(Yuhua Wang et al., 2013; Xu et al., 2013)	Qualiber, Inc.
Nanoparticle strategies for siRNA and vaccine delivery	Leaf Huang *UNC Chapel Hill*	(Yuhua Wang et al., 2013; Xu et al., 2013)	Qualiber, Inc.
Nanoparticles for hyperthermia of ovarian and breast cancers	Ian Baker and Jack Hoopes *Dartmouth College*	(Stigliano et al., 2013)	
Combination therapies to overcome multi-drug resistance (MDR) in cancer	Vladimir Torchilin and Tamara Minko *Northeastern University*	(Salzano et al., 2015)	Nemucore Medical Innovations
Tumor homing peptide-nanoparticle complexes	Erkki Ruoslahti *Sanford Burnham Prebys*	(Sharma et al., 2017; Sugahara et al., 2009)	DrugCendR
Nanoparticle strategies for targeting tumor microenvironment	Roger Tsien *UC San Diego*	(Crisp et al., 2014)	
Silicon oxide porous particles for drug delivery	Michael Sailor and Sadik Esener *UC San Diego*	(Anglin, Cheng, Freeman, & Sailor, 2008; Gu, Park, Duong, Ruoslahti, & Sailor, 2010)	Genoptix
Targeting angiogenesis using nanoparticle-based imaging and therapy	Gregory Lanza and Samuel Wickline *Washington University*	(Winter et al., 2003, 2008)	Kereos
Nanoparticles for combination of radio- and immunotherapy	Andrew Wang *UNC Chapel Hill*	(Min et al., 2017)	
Tools to study cancer biology			
Nanostructured matrices for cancer cell biology interrogations	Milan Mrksich and Bartosz Grzybowski *Northwestern University*	(Kandere-Grzybowska et al., 2010; O'Kane & Mrksich, 2017)	SAMDI Tech, Grzybowski Sc. Inventions
Nanotechnologies for genome, protein secretion, and biophysical analyses at single cell level	Steve Quake, Luke Lee, and Scott Manalis *Stanford University/MIT*	(Bryan et al., 2014; Jianbin Wang, Fan, Behr, & Quake, 2012)	Fluidigm, Travera
In vivo spectroscopic quantification of ligand-nanoparticle binding	Brian Pogue and Steven Fiering *Dartmouth College*	(Sexton et al., 2013)	

Table 2.

Technologies developed by R01 and U01 awardees. Similar to Table 2, we were not able to include all projects – it will make the table too exhaustive. We selected the most unique projects and those which progressed to more advanced levels of maturity. The references included in the table are not necessarily the most recent ones for the particular technology; they represent the status of work during the time the investigator was holding the grant. Last column in the table lists the company(ies) which licensed the technology for future commercialization and clinical trial number, if one is being conducted for the technology.

Cancer Application	Investigator/Institution	Publications	Clinical Translation Status (Companies and Trials)
Diagnostics and imaging			
Devices for circulating tumor cell capture and purification based on thermoresponsive NanoVelcro templates	Hsian-Rong Tseng and Edwin Posadas *UCLA/Cedars-Sinai*	(Grossman et al., 2017; Lin et al., 2014)	Cytolumina
Rodent eye as a non-invasive window for understanding of cancer nanotherapeutics	Kit Lam *UC Davis*	(Goswami et al., 2019)	
Imaging of nanotherapeutic drug action	Ralph Weissleder *Harvard University*	(Miller & Weissleder, 2017)	VisEn Medical
Magnetoresistive sensor platform for parallel cancer marker detection	Mark Porter *University of Utah*	(Young, Blackley, Porter, & Granger, 2016)	
Nanotechnology platform for pediatric brain cancer imaging and therapy	Miqin Zhang *University of Washington*	(Fang & Zhang, 2010)	
Therapeutics			
Nanoscale metal-organic frameworks (nMOFs) and coordination polymers (NCPs) for radiodynamic and immunotherapeutic treatment of solid tumors	Wenbin Lin and Ralph Weichselbaum *University of Chicago*	(C. He, Duan, et al., 2016; K. Lu et al., 2018)	RiMO Therapeutics, Coordination Pharmaceuticals NCT03444714, NCT03781362
Mesoporous silica nanoparticles for pancreatic cancer treatment	Andre Nel and Huan Meng *UCLA*	(J. Lu et al., 2017)	Westwood Bioscience
Theranostic nanoparticles for targeted therapy of pancreatic cancer	Lily Yang *Emory University*	(Huang et al., 2016)	
RNA nanotechnology in cancer therapy	Peixuan Guo *Ohio State University*	(Haque & Guo, 2015; Jasinski, Haque, Binzel, & Guo, 2017)	NanoBio Delivery Pharmaceutical
Treatment of glioblastoma using chain-like nanoparticles	Efstathios Karathanasis *Case Western University*	(Karathanasis & Ghaghada, 2016)	
Targeted therapeutics for ovarian cancer and its microenvironment	Gabriel Lopez-Berestein *MD Anderson Cancer Center*	(Kanlikilicer et al., 2017)	
Overcoming the immune-suppressive tumor microenvironment through in situ vaccination nanotechnology	Nicole Steinmetz *UC San Diego/Case Western University*	(Hoopes et al., 2018)	
Nanovaccine platforms to combat pancreatic cancer	Balaji Narasimhan *Iowa State University*	(Banerjee et al., 2018)	
STING-activating polymeric nanovaccines for T cell therapy of melanoma	Jinming Gao *UT Southwestern*	(Luo, Samandi, Wang, Chen, & Gao, 2017)	OncoNano Medicine
High capacity nanocarriers for cancer chemotherapeutics	Alexander Kabanov *UNC Chapel Hill*	(Han et al., 2012; Z. He et al., 2016)	
Nanoconjugate based on polymalic acid for brain tumor treatment	Julia Ljubimova *Cedars-Sinai*	(Patil et al., 2012)	Arrogene

Cancer Application	Investigator/Institution	Publications	Clinical Translation Status (Companies and Trials)
Targeting SYK kinase in B-lineage acute lymphoblastic leukemia (ALL) with CD19-specific C-61 nanoparticles	Fatih Uckun *USC*	(Uckun & Qazi, 2014)	
Combinatorial nanoplatforms to overcome tumor drug resistance	Mansoor Amiji *Northeastern University*	(Ganta & Amiji, 2009; X. Yang et al., 2015)	Nemucore Medical Innovations
Toxicity and efficacy of gold nanoparticle photothermal therapy in cancer	Dong Shin *Emory University*	(Ali et al., 2017)	
Tumor targeted nanobins for the treatment of metastatic breast and ovarian cancer	Thomas O'Halloran *Northwestern University*	(S.-M. Lee, O'Halloran, & Nguyen, 2010)	
Peptide-directed protocells and virus-like nanoparticle platforms	Cheryl Willman and Jeff Brinker *University of New Mexico*	(Ashley et al., 2011)	
Preclinical platform for theranostic nanoparticles in pancreatic cancer	Naomi Halas *Rice University*	(W. Chen et al., 2014)	Nanospectra Biosciences
Photodestruction of ovarian cancer: ErbB3 targeted aptamer-nanoparticle conjugate	Tayyaba Hasan *Mass. General Hospital*	(Rai et al., 2010)	Visudyne licensed to Bausch and Lomb
Multifunctional nanoparticles in diagnosis and therapy of pancreatic cancer	Paras Prasad *SUNY-Buffalo*	(Yong et al., 2009)	Licensed to Nanobiotix
Near-infrared fluorescence nanoparticles for targeted optical imaging	Chun Li *MD Anderson Cancer Center*	(Zhang et al., 2011)	Carestream Health
DNA-linked dendrimer nanoparticle systems for cancer diagnosis and treatment	James Baker *University of Michigan*	(Myc et al., 2010)	Avidimer
Hybrid nanoparticles in imaging and therapy of prostate cancer	Kattesh Katti *University of Missouri*	(Chanda et al., 2010)	Nanoparticle Biochem Inc.

Table 3.

Table of clinical trials associated with technologies developed by Alliance investigators

Cancer Indication	Trial Name	Year Started	Phase	Sponsor	Particle Type
Solid tumor	Study of CRLX101 (formerly named IT-101) in the treatment of advanced solid tumors (NCT00333502)	2006	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Solid tumor	Safety study of CALAA-01 to treat solid tumor cancers (NCT00689065)	2008	1	Calando Pharmaceuticals	Polymeric nanoparticle
Metastatic melanoma	Study of gene modified immune cells in patients with advanced melanoma (NCT00910650)	2009	2	UCLA Jonsson Comprehensive Cancer Center	Diagnostic assay
Advanced solid tumors with liver involvement	Evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP02 in patients with advanced solid tumors with liver involvement (NCT00882180)	2009	1	Alnylam Pharmaceuticals	Lipid nanoparticle
Advanced solid tumors with liver involvement	Extension study of ALN-VSP02 in cancer patients who have responded to ALN-VSP02 treatment (NCT01158079)	2010	1	Alnylam Pharmaceuticals	Lipid nanoparticle
Non-small cell lung cancer	A Phase 2 study of CRLX101 in patients with advanced non-small cell lung cancer (NCT01380769)	2011	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Prostate cancer	Transrectal photoacoustic imaging of the prostate (NCT01380769)	2011	NA	Stanford University	Transrectal imaging device
Solid tumor, Metastatic cancer	A study of BIND-014 given to patients with advanced or metastatic cancer (NCT01300533)	2011	1	BIND Therapeutics	Targeted polymeric nanoparticle
Metastatic melanoma, Malignant brain tumors	PET imaging of patients with melanoma and malignant brain tumors using an 124I-labeled cRGDY silica nanomolecular particle tracer: A microdosing study (NCT01266096)	2011	NA	Memorial Sloan Kettering Cancer Center	Silica nanoparticle (C-dots)
Metastatic stomach, gastro-esophageal, or esophageal cancer	Pilot trial of CRLX101 in treatment of patient with advanced or metastatic stomach, gastroesophageal, or esophageal cancer that cannot be removed by surgery (NCT01612546)	2012	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Renal cell carcinoma	CRLX101 plus bevacizumab in advanced RCC (NCT01625936)	2012	1	Cerulean Pharma	Polymer-drug conjugate
Ovarian cancer, fallopian tube cancer, and primary peritoneal cancer	CRLX101 in combination with bevacizumab for recurrent ovarian/tubal/peritoneal cancer (NCT01652079)	2012	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Rectal cancer	Neoadjuvant chemoradiotherapy with CRLX-101 and capecitabine for rectal cancer (NCT02010567)	2013	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Extensive stage or recurrent small cell lung cancer	Topotecan hydrochloride or cyclodextrin-based polymer-camptothecin CRLX101 in treating patients with recurrent small cell lung cancer (NCT01803269)	2013	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Prostate cancer, Castration-resistant prostate cancer	A Phase 2 study to determine the safety and efficacy of BIND-014 (Docetaxel nanoparticles for injectable suspension) administered to patients with metastatic castration-resistant prostate cancer (NCT01812746)	2013	2	BIND Therapeutics	Targeted polymeric nanoparticle
Non-small cell lung cancer	A Phase 2 study to determine the safety and efficacy of BIND-014 (Docetaxel nanoparticles for injectable suspension) as	2013	2	BIND Therapeutics	Targeted polymeric nanoparticle

Cancer Indication	Trial Name	Year Started	Phase	Sponsor	Particle Type
	second-line therapy to patients with non-small cell lung cancer (NCT01792479)				
Breast neoplasms	Comparison of stationary breast tomosynthesis and 2-D digital mammography in patients with known breast lesions (NCT01773850)	2013	NA	UNC Lineberger Comprehensive Cancer Center	Carbon nanotubes
Metastatic renal cell carcinoma	CRLX101 in combination with bevacizumab for metastatic renal cell carcinoma (mRCC) versus standard of care (SOC) (NCT02187302)	2014	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Squamous cell non-small cell lung cancer, KRAS-positive patients with non-small cell lung cancer	A study of BIND-014 (Docetaxel nanoparticles for injectable suspension) as second-line therapy for patients with KRAS-positive or squamous cell non-small cell lung cancer (NCT02283320)	2014	2	BIND Therapeutics	Targeted polymeric nanoparticles
Head and neck melanoma, breast cancer, and colorectal cancers	Targeted silica particles for real-time image-guided intraoperative mapping of nodal metastases (NCT02106598)	2014	2b	Memorial Sloan Kettering Cancer Center	Silica nanoparticles (C-dots)
Solid tumors	Alternative dosing for CRLX101 alone, with Avastin and with mFOLFOX6 in advanced solid tumors (NCT02648711)	2015	1	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Ovarian cancer	A Study of CRLX101 in combination with weekly Paclitaxel in patients with recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer (NCT02389985)	2015	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Urothelial carcinoma cholangiocarcinoma, cervical cancer, squamous cell carcinoma of head and neck	A Study of BIND-014 in patients with urothelial carcinoma, cholangiocarcinoma, cervical cancer and squamous cell carcinoma of the head and neck (NCT02479178)	2015	2	BIND Therapeutics	Targeted polymeric nanoparticle
Advanced cancers	Eph2A gene targeting using neutral liposomal small interfering RNA delivery (NCT01591356)	2015	1	MD Anderson Cancer Center	DOPC nanoliposomes
Advanced solid tumor malignancy	Phase 1/2a dose-escalation study of CRLX301 in patients with advanced solid tumors (NCT02380677)	2015	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Advanced solid tumors	A Phase 1 study of safety, tolerability, and PK of AZD2811 in patients with advanced solid tumors (NCT02579226)	2015	1	AstraZeneca	Targeted polymeric nanoparticle
Small cell lung carcinoma, non-small-cell lung carcinoma, lung neoplasms, small cell lung cancer, and lung cancer	Trial of CRLX101, a nanoparticle Camptothecin with Olaparib in people with relapsed/refractory small cell lung cancer (NCT02769962)	2016	2	NewLink Genetics (formerly Cerulean)	Polymer-drug conjugate
Gliosarcoma, Recurrent glioblastoma	NU-0129 in treating patients with recurrent glioblastoma or gliosarcoma undergoing surgery (NCT03020017)	2017	1	Northwestern University	Gold core spherical nucleic acid
Healthy volunteers	A study Of AST-008 in healthy subjects (NCT03086278)	2017	1	Exicure Inc	Gold core spherical nucleic acid
Advanced or metastatic: solid tumors, melanoma, head and neck squamous cell carcinoma, cutaneous squamous cell carcinoma, merkel cell carcinoma	Intratumoral AST-008 combined with Pembrolizumab in patients with advanced solid tumors (NCT03684785)	2018	2	Exicure Inc	Gold core spherical nucleic acid
Advanced Tumors	Phase 1 Study of RiMO-301 With Radiation in Advanced Tumors (NCT03444714)	2018	1	RiMO Therapeutics	Nano metal-organic framework (nMOF)

Cancer Indication	Trial Name	Year Started	Phase	Sponsor	Particle Type
Malignant brain tumors	PET Imaging of Patients With Malignant Brain Tumors Using 89Zr-cRGDY Ultrasmall Silica Particle Tracers: A Phase 1 Microdosing Study (NCT03465618)	2018	1	Memorial Sloan Kettering Cancer Center	Silica nanoparticles (C-dots)
Advanced Tumors	Study of CPI-100 in Patients with Advanced Tumors (NCT03781362)	2018	1	Coordination Pharmaceuticals	Nanoscale coordination polymer
Advanced Tumors	Study of CPI-200 in Patients with Advanced Tumors (NCT03953742)	2019	1	Coordination Pharmaceuticals	Nanoscale coordination polymer