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NCI Alliance for Nanotechnology in Cancer – from academic research to clinical interventions

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Abstract
The National Cancer Institute (NCI) of National Institutes of Health has funded and operated the NCI Alliance for Nanotechnology in Cancer - a large multi-disciplinary program which leverages research at the intersection of molecular biology, oncology, physics, chemistry, and engineering to develop innovative cancer interventions. The program has demonstrated that convergence of several scientific disciplines catalyzes innovation and progress in cancer nanotechnology and advances its clinical translation. This paper takes a look at last thirteen years of the Alliance program operations and delineates its outcomes, successes, and outlook for the future.

Keywords Cancer nanotechnology · Nanomedicine, multi-disciplinary research · Federal funding

1 Introduction

Nanotechnology has been increasingly finding new and successful applications in the medical arena. Moreover, it has been contributing to novel approaches which are significantly improving the way we diagnose and treat cancer. Nanoscale materials inhabit the same size scale as biological materials, enabling unique interactions with cells and proteins that can be harnessed for efficient delivery of drugs and imaging agents to target sites in the body. Nanotechnologies, which are capable of highly sensitive, specific, and versatile recognition of biological materials, can also be integrated into devices for use in disease detection and characterization applications.

The National Cancer Institute (NCI) recognized these unique research and clinical opportunities at the crossroads of biology, oncology, and technology early and established the Alliance for Nanotechnology in Cancer (ANC) program in 2005. The purpose of the program was to exploit nanotechnology's potential within cancer research and to the improvement of cancer care. ANC aimed to establish projects ranging from discovery-based research to translation, with a focus on innovative, clinically relevant technologies and it was the first federally-funded program to fund large scale cooperative research in cancer nanotechnology. In its original incarnation, the program focused on the development of technology platforms which were seeking appropriate cancer applications. Since the initial years, the program has matured and evolved into defining relevant biological and clinical problems, which serve as a driver for the implementation of suitable nanotechnologies. Subsequently, several technologies developed under the Nanotechnology Alliance funding have reached a level warranting the initiation of clinical trials.

2 ANC program background and history

Recognizing the potential of nanotechnology in cancer, NCI assembled a working group and held a series of workshops to structure programmatic initiatives that could capitalize on nanotechnology innovations in 2003–2004. Dr. Mauro Ferrari, spent two years at NCI at that time (away from his 'real' job as a faculty of the Ohio State University), and was instrumental to coordinating and shaping the strategies which were behind the launch of the Alliance for Nanotechnology in Cancer (ANC) in 2005 (Ferrari 2005). The goal of the program was to establish a network of interdisciplinary research teams that had the requisite collective

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expertise to develop and validate nanotechnologies applicable to cancer. ANC investigators were tasked to work in three broad research areas: i) early diagnosis using *in vitro* assays and devices or in vivo imaging techniques; ii) multifunctional nanotherapeutics, including nanoparticle-driven immunotherapies (introduced in Phase III); and iii) devices and techniques for cancer prevention and control. The ANC's development model called for the most promising ANC strategies developed in academia, to be handed off to for-profit partners for effective clinical translation and commercialization.

2.1 Program structure and network participants

The ANC Network was initially funded in 2005 through a set of Funding Opportunity Announcements (FOAs) released by the NCI. Internal and external evaluations of the program, as well as input from the extramural community (Zamboni et al. 2012), guide development of the ANC program through consecutive phases. NCI has renewed the program twice since its beginning in 2005, with Phase II and Phase III launched in 2010 and 2015, respectively. Each phase lasts five years and involves multiple synergistic funding initiatives for large research centers, smaller research projects, multidisciplinary training awards, and support of the Nanotechnology Characterization Laboratory (NCL) (Fig. 1). Figure 2 shows geographical distribution of different awards in all 3 phases of the program.

The Centers of Cancer Nanotechnology Excellence (CCNEs) are focused on integrating nanotechnology and cancer research to develop solutions that are clinically relevant. They provide infrastructure and translational support to the ANC network. The ANC program also includes smaller multidisciplinary research projects - Innovative Research in Cancer Nanotechnology (IRCN) awards, which are focused on building fundamental knowledge on interactions of nanomaterials with biological systems and mechanisms of nanotechnology-based in vivo delivery with the ultimate goal of contributing to efficient and well-informed nanotechnology translation. Multidisciplinary research training and team development initiatives were also funded to foster cross-disciplinary training of graduate students and postdoctoral fellows in nanotechnology and cancer biology. These efforts were a mix of individual post-doctoral awards; Pathway to Independence awards, allowing promising graduate students to transition to faculty positions; and Cancer Nanotechnology Research Training Centers, which conduct multi-mentor training at the cross-roads of several disciplines. The Nanotechnology Characterization Laboratory is also part of the ANC Network. NCL is an intramural laboratory serving as a centralized resource to characterize nanomaterials developed by ANC researchers and researchers from the broader academic, government, and industry research communities.

ANC researchers leverage program network resources through trans-network collaborations. These collaborative efforts are encouraged via trans-Alliance challenge projects which usually last 12–18 months, with 2–3 rounds of them being funded over the period of one phase. Many of these projects led to active collaborations and peer-reviewed publications. ANC also launched Grand Challenge competitions within the program network to fund projects in areas collectively identified by the investigators as those being most critical, yet requiring several research groups to work together to provide an adequate solution.

To chart forward strategies for the fast evolving field of cancer nanotechnology, NCI holds strategic workshops every five years (Nagahara et al. 2010; Grodzinski and Farrell 2014) and publish their outcomes in the form of a Cancer Nanotechnology Plan (https://www.cancer.gov/sites/nano/research/plan, Hartshorn et al. 2018).

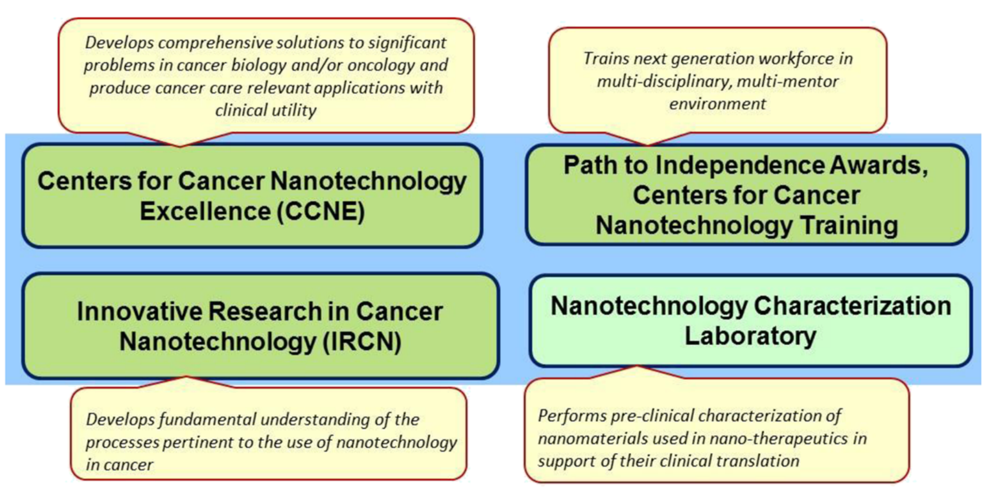

Fig. 1 ANC Program organization

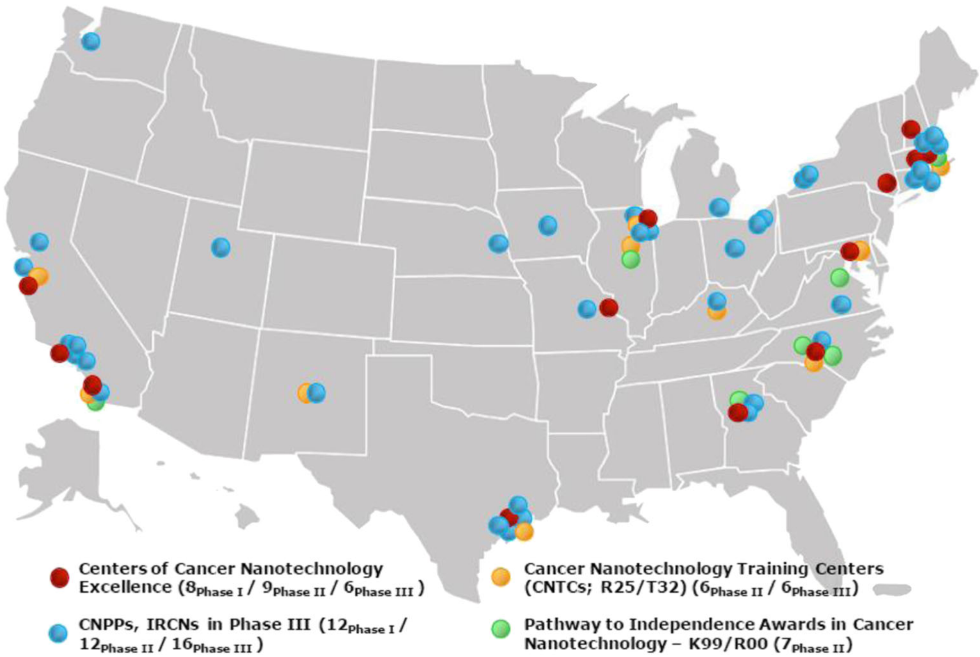

Fig. 2 Distribution of ANC awards among different academic institutions in Phases I, II, and III of the ANC program

2.2 Evolution of ANC objectives: Program Phases I to III

The ANC began with the goal of exploiting promising new technologies to improve cancer research and care. The program has since distinguished itself by pursuing additional goals of developing a strong interdisciplinary network of researchers as well as recruiting and training both physical scientists and engineers to focus their efforts on problems in cancer. The ANC was an early adopter of a multiple principle investigator (PI) model for NIH awards, and applicants have always been advised to recruit one PI from the physical sciences or engineering and another PI from the biological or clinical sciences. This has resulted in the deep integration of cancer biology and oncology practitioners into the technology design process within ANC projects.

The initial ANC awards supported development and early testing of cutting edge technology platforms in cancer settings. In some cases, these platforms adapted processes and materials from other industries, such as micro/nanofabrication techniques from the semiconductor industry (Farrell et al. 2010; Farrell et al. 2011). Many CCNE PIs were already accomplished physical scientists, and the ANC program provided support for dedicated inquiry into the most biologically-relevant applications for their work and promoted their collaborations with clinicians and cancer biologists. These Phase I projects were largely focused on technology development and the potential cancer applications were mostly used as prototypical testing platforms. Thus, most of the investigators operated in a "technology push" environment, where technology was defined first and applications for it were identified later. Phase I projects considered a wide variety of tumor types as application test beds, with many projects focused on "solid tumors," in general, rather than a specific disease or genetic sub-type. Increasing association with clinicians in Phases II and now III has focused efforts into specific interventions aimed at defined tumor types, molecular pathways, and disease markers that could benefit from a nanotechnology-based approach. Funded treatment and diagnostic modalities have evolved with time (Phase II vs III, Fig. 3), showing increasing prominence of immunotherapy applications, for example, with interest in gene therapy decreasing, while the number of projects on diagnostic tools has remained relatively constant.

3 Scientific productivity and output

Overall Alliance investigators have been highly productive and produced close to 3500 publications over the period of Phases I and II (2005–2014). To assess the impact of these publications, rather than counting individual citations, we used the metric Relative Citation Ratio (RCR) (http://www.metrics-toolkit.org/relative-citation-ratio/, Hutchins et al. 2016). Recently developed at NIH, RCR is a field-normalized citation indicator calculated based on co-citation networks which represent an article's field, as the reference set. A paper with RCR equal to 1 has an RCR higher than 50% of NIH-funded papers. The Alliance awards (both CCNEs and IRCNs) hold higher median RCRs than NCI NANO R01 awards (nanotechnology-specific projects submitted to NCI via 'parent' R01 solicitation), which already had median RCR values greather than 1 (Fig. 4).

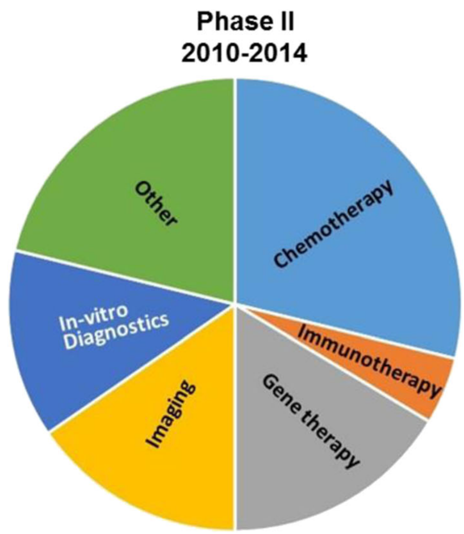

Fig. 3 Evolving focus of ANC program – change in distribution of different research topics between Phase II and Phase III

A publication-based analysis was also conducted to estimate the translational readiness of Alliance projects. Translational readiness measures were extracted using a machine learning tool (iTrans, https://itrans-beta.od.nih.gov/) and used to generate 'Triangle-of-Medicine' plots (Fig. 5, red color indicates a higher frequency of cell-line, animal, or human studies, respectively). The translation-readiness analysis showed that publications within Alliance (Phase II) resulted in significantly more animal studies and also progressed further towards studies with human samples as compared to the non-Alliance NANO R01 projects. This difference (as compared to NANO R01s) was more pronounced for CCNEs than for IRCN awards.

4 Model for translation

The translation of research discoveries to clinical application is an important goal for the ANC program. Alliance funding supports pre-clinical studies only, but members of the CCNEs and broader Alliance are expected to aggressively pursue advancements of their technologies to the clinic by leveraging ANC funding and resources. They are encouraged to seek other sources of funding for clinical trials and to partner with industry and/or establish start-up companies. Through the course of three program phases, the ANC awardees have established a path allowing for the development of innovative technologies in academic centers, allowing their maturation there, and then transitioning them to the translational stage in the commercial sector. This became a unique approach that allows for continuous input of new creative technologies, selecting those that are clinically viable, and moving them forward to the clinical trial environment. Often students and post-docs who were involved in the initial technology development within an academic group, move with the technology to start-up companies that are initiated by themselves or by their PI. Over 130 companies (Chapman et al. 2012; Lenoir and Herron 2015) were formed or associated with the ANC program since 2005. Most often these companies are funded using venture capital funding, but

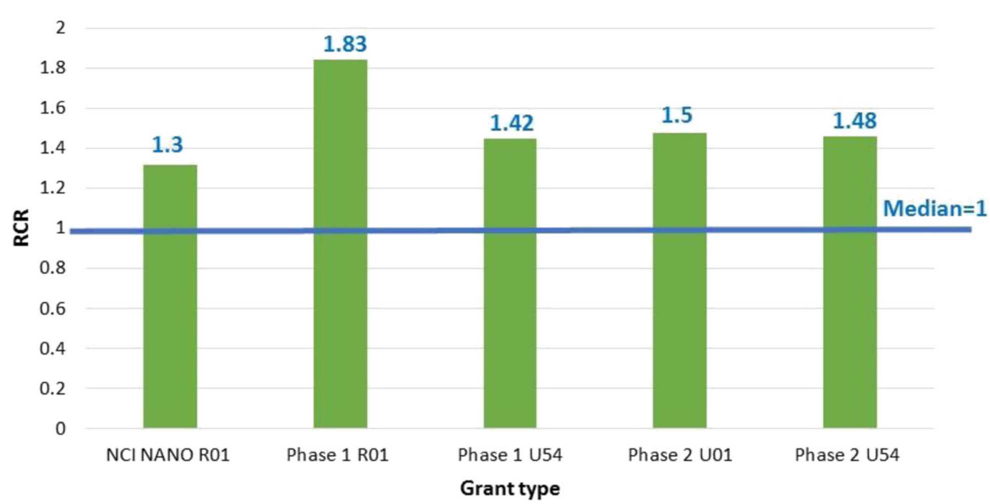

Fig. 4 RCR indices of publications produced by different grant mechanisms supporting nanotechnology at NCI

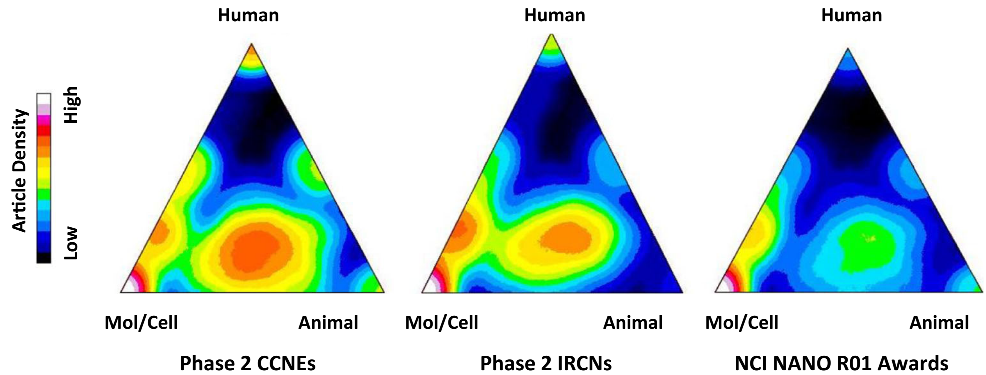

Fig. 5 Triangle-of-medicine plots for Phase II Alliance grants in comparison with NANO R01s. Heat maps of the individual cohorts are displayed with the apex of the triangle as human studies, the lower left corner as molecular/cellular studies, and the lower right corner as animal studies

many of them have also benefited from federal Small Business Innovative Research (SBIR) grants and contracts from NCI. Furthermore, several technologies that emerged from the ANC program have entered clinical trials (over 20) via these start-up companies. Majority of these trials are not funded by NCI; investigators or companies associated with them secured funds to support the trials and further technology development from other sources.

5 NCI nanotechnology translational resources

5.1 Nanotechnology Characterization Laboratory

The Nanotechnology Characterization Laboratory (NCL, https://ncl.cancer.gov/) was founded in 2005 as part of the ANC program to provide "pharmaceutical mentorship" to investigators working in cancer nanomedicine. NCL's mission was to develop an 'Assay Cascade' of scientific tests that would help determine the reproducibility, safety, and efficacy of nanotechnology-based cancer drugs and diagnostics and to provide investigators with additional tools and information required to meet regulatory requirements to move their technology towards clinic.

NCL's Assay Cascade assays had been previously tested on a variety of nanomaterial types and were developed with concurrent input from the FDA. This battery of tests and protocols has been used ever since to evaluate nanomaterials submitted to NCL by extramural investigators with the aim of generating data to support future Investigational New Drug (IND) or Investigational Device Exemption (IDE) filings to FDA. NCL has assisted more than 100 extramural investigators, tested over 300 nano-formulations in its Assay Cascade, and now has 14 collaborators with nanomedicine products in clinical trials. NCL also published over 150 scientific papers describing important trends in nanomedicine development.

Nanomedicine has been maturing, with several formulations in clinical trials, and growing interest from the pharmaceutical and biotech industry. Nanotechnology formulations are employing not only small molecule drugs and are also being considered for the delivery of peptides, proteins, siRNAs, mRNAs, plasmids, and CRISPR/Cas9-based approaches. To stay current with these new developments, NCL has been developing new capabilities in the area of drug re-formulation to reduce drug toxicities and widen their therapeutic windows through the use of nanoparticles. NCL has also participated and remains actively engaged in coordinating the formation of a sister laboratory in Europe, which has a similar mission and is funded under a European Union grant.

5.2 Data sharing

As part of the first phase of the ANC program, the Cancer Nanotechnology Laboratory data portal (caNanoLab; https://cananolab.nci.nih.gov/) was initiated as a collaborative effort with the NCI Center for Biomedical Informatics and Information Technology (CBIIT) to capture nanomaterials data generated by the research community. caNanoLab serves as a data repository that allows researchers to submit and retrieve information on well-characterized nanomaterials including compositions; physico-chemical, *in vitro*, and in vivo characteristics; associated publications; and assay protocols. caNanoLab has become an established resource designed to address the needs of the broader cancer, biomedical, and nanotechnology communities. Currently, this database holds 70 assay protocols, data on over 1200 curated nanomaterial samples, and almost 2000 publications that are available for public use. The majority of these data were curated from ANC and NCL publications by an in-house curator; however, individual users are strongly encouraged to directly submit their data to caNanoLab. Members of the NCI caNanoLab team actively work with other nanotechnology database teams, community-based programs, and federal initiatives, such as the National Nanotechnology Initiative's Signature Initiative on Nanotechnology Knowledge Infrastructure and the National Cancer Informatics Program Nanotechnology Working Group, to develop exchange standards and deposition guidelines for data submission and sharing. Through these interactions, NCI is in the process of building the framework for an organized nanoinformatics system that may lower barriers to technology development and clinical translation.

5.3 Other translational activities

To provide a better understanding of appropriate clinical applications and facilitate a better path to clinical translation of nanotechnologies, NCI promoted interactions between ANC researchers and representatives from pharma/biotech industry and established two opportunities: the Translation of Nanotechnology in Cancer Consortium (TONIC) and the Nanotechnology Startup Challenge in Cancer (NSC^2).

Translation Of Nanotechnology In Cancer consortium Established in 2011 (https://consortiapedia.fastercures.org/consortia/tonic/), with the purpose to facilitate communication and collaboration between early stage technology developers in academia and industry experienced in late pre-clinical and clinical development of cancer nanotechnology products. The main mission of TONIC was to create a consortium of the public, private, and academic sectors to accelerate the translation and development of nanotechnology-based solutions to the early detection, diagnosis, and treatment of cancer. TONIC membership includes companies currently pursuing or considering future nanomedicine applications (mostly nanomedicine start-ups) and several large pharmaceutical and biotechnology companies considering expansion of their pipeline to nanomedicines. The goals of this partnership were to provide ANC researchers with insight into industry needs in technology platforms and drug targets; promote collaborations between ANC investigators and industry partners on pre-competitive research programs; provide TONIC members with the opportunity to interact with regulatory authorities; and serve as a sustained forum for nanotechnology idea exchange. Since its inception, several round table discussions and a workshop (Prabhakar et al. 2013) have been organized to share opinions among different stakeholders of TONIC.

Nanotechnology Startup Challenge in Cancer In October 2015, NCI Nanotechnology Program Office and the NCI Technology Transfer Office partnered with the Center for Advancing Innovation (CAI) to launch the Nanotechnology Startup Challenge (https://www.nscsquared.org/). The goal of this Challenge (Currell and Bellringer 2016, Truman and Locke 2016) was to advance clinical translation of biomedical nanotechnology by developing business plans around selected portfolio of attractive nanomedicine intellectual property portfolio. Nanomedicine inventions from intramural NIH investigators were chosen to seed the Challenge using a model developed by CAI and NCI for previously operated Breast Cancer Startup Challenge (https://www.breastcancerstartupchallenge.com/). CAI then invited the formation of teams around these technologies to pursue commercialization. The teams mostly recruited from business students, currently enrolled in MBA program, who were interested in pursuing entrepreneurship and starting technology companies. Teams accepted into the Challenge received coaching from CAI and highly regarded entrepreneur mentors on best practices in business planning, formation, and development as they progressed through the stages of the Challenge – elevator pitch, business plan, and finally formation of a start-up. At the end of the first two stages, judges drawn from the business and biotechnology sectors selected winning teams to advance to the next stage. In July 2016, ten teams were chosen from the initial 28 to enter the final stage—Startup—in which they received additional advisory support from CAI on how to formally start companies, seek licensing rights for their chosen inventions, and raise funds. The Challenge was highlighted in the National Nanotechnology Initiative Strategic Plan 2016, as 'a model for engaging industry in effective technology transfer'.

6 Conclusion

ANC has become a transformative program which has delivered a strong level of innovation to medicine (Dickherber et al. 2015). This was accomplished by combining several research communities representing nanotechnology innovation, biology, and clinical practice. The program continues to foster an environment that supports the development of innovative technologies in multi-disciplinary academic centers; allows for maturation of these technologies; and their subsequent transition to the clinical stage.

Although, many metrics of success can be cited relative to this program, one of particular interest to its core mission of translation has been in the ability of ANC's investigators to attract additional funds to supplement NCI funding thus expanding upon the opportunities which the NCI seed funds provided. This is true for both additional funds raised by ANC investigators to support their academic research, as well as translation efforts pursued by companies commercializing technologies initially developed by ANC-funded academic groups. This

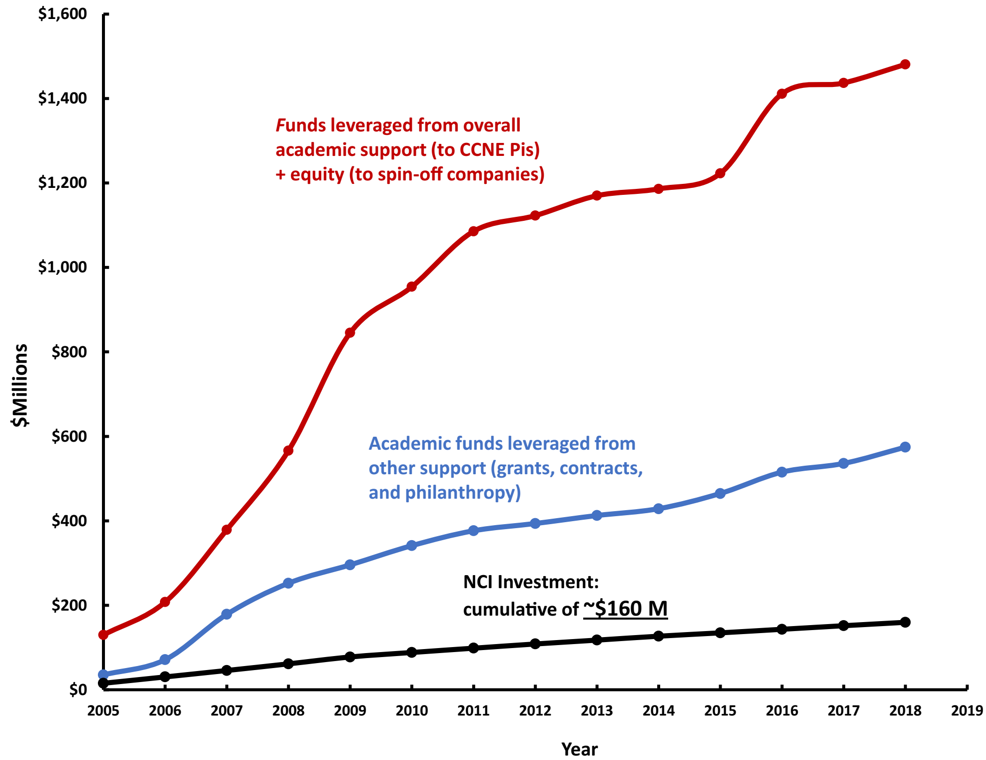

Fig. 6 Leveraging of initial NCI investment with additional academic grants and support for spin-off companies for four CCNEs funded in all 3 Phases: Stanford, Caltech/UCLA/ISB, Northwestern, UNC

'leveraging effect' of ANC awards can be seen in Fig. 6, where cumulative amounts of additional funding raised, in the form of academic grants or equity funding, are depicted for four CCNEs. Each funded through all three phases of the program (13 years), they include Stanford, Caltech-UCLA-Institute of Systems Biology, Northwestern, and the University of North Carolina CCNEs. We estimate that for each $1 invested by NCI into these four ANC awards, they generated additional ~$3 via academic grants and additional ~$5 via equity funding to companies originating from them. This very strong 8-fold leveraging factor, displays the amplification to the value of federal funding invested as well as the expansion to the scope of research and clinical translation resulting from this investment. This leveraging is particularly important in the era of tight federal funding and demonstrates a valuable model to support academic research and subsequent transition to the clinical stage. Moreover, the seed NCI award is a key enabling factor to raising of follow-up funding. The ANC investigators continue to stress the point, that having a peer-reviewed large NCI center grant award has been a critically important prerequisite to obtaining additional funding.

ANC can be also credited with increasing an overall interest of research community in using nanotechnology to address cancer. During the course of the program, we observed continuous increase of NCI NANO R01 applications (Fig. 7) reaching over 700 applications in fiscal year 2018.

Overall, the first thirteen years of the ANC make a powerful case for the influence of early investment of federal government into new research fields and technologies. The program brought several talented technologists to cancer research; they may have never used their talent and innovation for cancer applications without becoming part of CCNE teams. The initial technology-centric focus evolved and ANC-funded groups have become well integrated into biology and oncology and are capable of identifying compelling problems in these areas, while providing effective nanotechnology solutions to them. Furthermore, these teams are highly entrepreneurial and effective in raising additional funds to setup start-up companies, thus enabling technology translation and commercialization. In addition, the program became also a powerful training ground for graduate and post-doctoral students who complete their initial work in one of the ANC institutions and then move-on to obtain a faculty position in another or to join one of the start-up companies originating from ANC.

Overall, the ANC program is viewed as an example of a highly successful, long-lasting venture, which started as a science endeavor, but evolved into a complex organism involving academic investigators representing several synergistic fields working collaboratively, while being closely connected to industry.

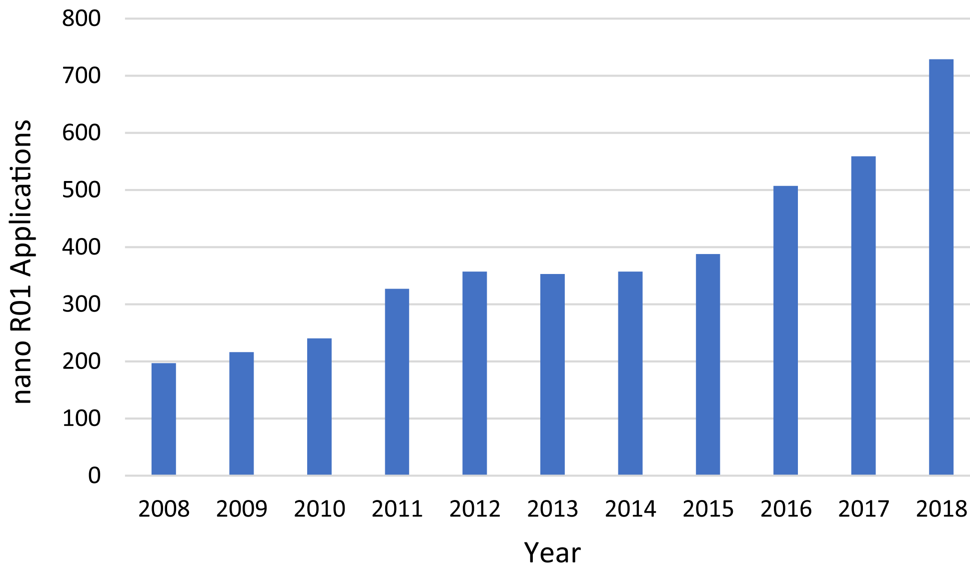

Fig. 7 NCI nano R01 applications. The number of nano R01 applications submitted to NCI increased from 200 in fiscal year 2008 to over 700

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