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Review Article

Theme: Nanotechnology in Complex Drug Products: Learning from the Past, Preparing for the Future
Guest Editors: Katherine Tyner, Sau (Larry) Lee, and Marc Wolfgang

Clinical Translation of the National Institutes of Health's Investments in Nanodrug Products and Devices

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Abstract. The National Institutes of Health (NIH), a part of the U.S. Department of Health and Human Services, is the primary Federal agency for conducting and supporting biomedical research. The NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce illness and disability. In support of this mission, NIH has invested about $4.4 billion since 2001 in nanotechnology (NT) research. This investment is leading to fundamental changes in understanding biological processes in health and disease, as well as enabling novel diagnostics and interventions for treating disease. NIH scientists are developing molecular agents and methods for earlier and more accurate diagnosis and therapies aimed directly and selectively at diseased cells, and are exploring root causes of common and rare diseases at the nanoscale. Work is also underway to move these research tools and devices into clinical practice. This particular investigative review examines the NIH NT portfolio linked to clinical trials from FY2008 to FY2015 to assess the progress of clinical translation. Among the subset of trials identified, 70% target drug or combination drug-device products used in treating cancer, AIDS, and other various diseases. The review also provides insight into trends observed from studying the clinical research portfolio.

KEY WORDS: clinical trials; devices; nanodrugs; nanomedicine; nanotechnology.

INTRODUCTION

Clinical trials are known to be one of the most valuable sources of data in evidence-based medicine. The National Institutes of Health (NIH), the largest source of funding for medical research in the world, currently invests over $3.1 billion in clinical trials dedicated to the evaluation of a multitude of diseases, disorders, and conditions. The NIH conducts and supports research in the causes, diagnosis, prevention, and potential cure of human diseases. The NIH consists of 27 institutes and centers. Each of these institutes and centers has their own unique research agenda and strategic plans in support of the NIH's overall mission. The agency conducts biomedical research in its own laboratories; supports the research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the country; aids in the training of the next generation of biomedical research investigators; and fosters communication of medical information. The majority of these institutes are funding extramural nanotechnology (NT) R&D *via* specially formulated initiatives or as investigator-initiated grants, contracts, small business innovations research, and small business technology transfer initiatives. Through these strategic NT initiatives (solicitations), NIH funds basic and clinical research that impact the diagnosis, treatment, and overall management of diseases and patient care with new and emerging ideas.

Though NIH scientists began exploring how to manipulate cells and DNA and engineer liposomal delivery vehicles at the nanoscale years prior to the launch of the National Nanotechnology Initiative (NNI), the agency did not dedicate substantial set aside programmatic funds to the study of biological processes at the nanoscale until 2001. These resources were aimed at activities that included generating novel and highly effective therapeutics and addressing several challenges in biology and medicine. For example, three bioengineering initiatives were released in 2002 to promote the development and application of NT tools to solve biomedical problems. In 2005, long-term opportunities and benefits of NT were fully envisioned when three new initiatives with significant set aside funds were launched. These initiatives stimulated the creation of NT centers and networks supported by the NIH Common Fund (Nanomedicine Roadmap), National Cancer Institute (NCI Alliance Program—formally known as the Unconventional Innovations Program), and the National Heart,

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Lung, and Blood Institute (Program of Excellence in Nanotechnology). In addition to encouraging research networking for the development and utilization of tools, each program had specific goals and was organized to link basic research to clinical outcomes in 10 years. These programs later inspired the application of NT in other disease areas *via* investigator-initiated grants. The majority of NIH investments today are unsolicited, investigator-initiated grants supported by nearly all NIH institutes targeting a variety of diseases. Please refer to Part 1—NIH Investment in NT book chapter by Henderson to learn more about key initiatives and funding programs from 2001 to 2010 (1). Today, the NIH continues to remain highly engaged in the Nanoscale Science, Engineering, and Technology Subcommittee's (NSET) initiatives to accelerate NT developments in support of national priorities and innovation strategies outlined in the NNI (http://www.nano.gov).

The aims of this investigative review were to analyze the NIH NT-related portfolio in medicine from FY2008 to FY2015 and illustrate the translational progress of federally funded research projects that resulted in one or more clinical trials. This particular timeframe was strategically chosen to allow sufficient time in the initial discovery and preclinical stages of R&D, that is, it is at least 8 years after the establishment of major NT-focused initiatives.

The definition of nanomedicine has implications for many aspects of translational research including funding allocation, patents, ethical review processes, drug and device regulatory review processes and approvals, clinical trials, and general public acceptance. To be consistent with the NIH investments reported in the NNI's Supplement to the President's Budget and remain compliant with NIH policies, the following definitions were adhered to:

(1) *Definition of Nanomedicine*: Nanomedicine refers to highly specific medical intervention at the molecular scale for curing disease or repairing damaged tissues. It is at this size scale, about 100 nm or so, that biological molecules and structures operate in living cells. NT programs and projects reported *via* the NIH research, condition, and disease classification system include nanoscience and nanoengineering at the molecular and/or macromolecular levels (submicron range) with respect to phenomena, materials, and the creation of devices and systems that have novel properties and functions because of their small size. For instance, nanomedicines exploit the nanoscale manipulation of materials to improve drug delivery.
(2) *NIH Definition of a Clinical Trial*: A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html, http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html).

BACKGROUND TO NIH-FUNDED TRIALS

Research Integrity and Conduct

The NIH policies and requirement of scientific rigor apply to all health-related research with humans, regardless of funding source or degree of risk to participants. In part, this is because a diverse range of stakeholders (including clinicians, researchers, policy makers, patients, and pharmaceutical companies) rely on the information that research generates to make decisions that have important consequences for individual and public health. For example, the evidence produced in early phase research provides the foundation for subsequent studies, and methodological shortcomings can derail promising avenues of research and squander valuable resources. Many other forms of research, such as clinical trials, health-systems research, epidemiological studies, or postmarketing studies, generate data that is relevant for clinical decision-making, health and social policy, or resource allocation. Independent of the risks to participants, ensuring that studies uphold high standards for scientific quality is essential for maintaining the integrity of the research.

Type of Trials and Funding

The NIH is supporting cutting-edge clinical trials in areas such as oncology, cardiovascular disease, HIV/AIDS, *etc*. With a greater reliance on sophisticated technologies and more complex clinical trial designs, NIH has assembled a host of funding sources—programs, centers, and networks as well single institution studies—that provide important resources for researchers and institutions to lead and participate in clinical trials. These federal funds in combination with federally funded lab services and clinical trial infrastructure grants, help to reduce costs, streamline trial operations, improve efficiency of operations, and reduce administrative burdens. For instance, the clinicians and scientists in NIH's Clinical Center conduct multiple trials each year at the Clinical Center in Bethesda, MD—the only hospital in the world dedicated solely to medical research. Many of these early trials test cutting-edge treatments and technologies, often in patients with advanced stage of disease that no longer respond to standard therapy. These trials test new treatment and supportive care approaches and lay the foundation for similar trials to be conducted at NIH and across the country.

Early phase clinical trials (*exploratory, pilot, pivotal, phases 1 and 2*) build on basic and preclinical advances. Early phase trials which test promising new agents and modalities in small numbers of patients, are critical to developing new treatments and interventions and are often funded through an R01 grant mechanism for less than $500,000 in direct costs per year. These initial trials assess the safety of an intervention and sets the stage for the larger trials needed to determine whether an intervention is not just safe but also effective. Recently, the early phase trials have taken on greater importance as research on molecular profiling continues to progress. The subsequent *phase 2 and phase 3 trials* provide the additional evidence of biological effects against diseases. The purpose of phase 3 trials in particular, is to provide the definitive evidence for whether a drug or treatment is indeed effective. NIH supports a wide array of these trials through cooperative agreements exceeding $750,000 in direct costs per year. Over the past decade, nearly 14,000 investigators and more than 3100 institutions have been involved in clinical treatment and advanced imaging trials related to cancer each year. It is important to note that the NIH-funded clinical trials are not limited to therapeutic interventions as illustrated by the types of trials in Table I. Furthermore, device trials may

initially be conducted in a smaller *pilot* population with the disease or condition being studied, before moving into the larger *pivotal* population and *Post-Approval Studies*. Keep in mind that not all devices require a clinical trial. It depends on the level of risk associated with the device (Class I - Minimal, Class II - Intermediate, Class III - Substantial risk).

METHODS AND ANALYSIS OF NT PORTFOLIO

Search Methods and Results

Three main queries were conducted to identify the number and type of NT-based research projects and affiliated clinical studies on drugs, devices, and interventions. Examples include nanodrug products, nanoimaging agents, or devices comprised of nanocomponents and any combinations thereof. The NIH public database referred to as RePORT, Research Portfolio Online Reporting Tools' database (https://projectreporter.nih.gov/reporter.cfm), as well as other federal databases were used to analyze and cross reference funded research within the NT portfolio based on the NIH research, condition, and disease categories term (RCDC classification) for "Nanotechnology."

- *Query A via RePORTER: Identifies NT projects and associated trials*. Use RePORTER, select nanotechnology within the NIH spending category to generate a list of NT projects and then click on the clinical studies tab
- *Query B via RePORTER: Identifies clinical research projects in the NT portfolio*. Use RePORTER, select nanotechnology AND clinical research within the NIH spending category
- *Query C via NIH Federal Database*: Based on RCDC term for nanotechnology and linked to clinicaltrials.gov

Table I. A Brief Description of the Type of Trials Funded by the National Institutes of Health

PREVENTION TRIALS - Clinical trials that examine the risk of getting a disease and ways to reduce that risk. Most prevention trials involve healthy people.
SCREENING TRIALS - Clinical trials that evaluate new ways to detect disease and other health conditions in people early before symptoms are present. The goal is to determine whether the screening test can save lives.
TREATMENT TRIALS - Clinical trials that test the effectiveness of new drugs, vaccines, biologics, and/or new surgical procedures or medical devices. Treatment trials may also investigate known interventions that warrant further study and comparison.
QUALITY-OF-LIFE/SUPPORTIVE CARE TRIALS - Clinical trials that explore ways to improve comfort and quality of life for disease-burden patients or individuals enduring a mental/physical decline in their health (e.g., drugs for pain, depression, *etc.*,).

All searches included phase 1, 2, and 3 trials obtained from projects that were awarded between October 1, 2008, and September 31, 2015. The results from Query A & C yield a total of 64 awards and 24 identifiable grant-funded base projects among the 2373 extramural and intramural NT projects. A summary of the search results has been tabulated by search categories in Table II. The project periods varied from 5 to 25 years with the majority having more than 10 years' prior research funding. This transition from preclinical work (*i.e.*, the discovery, proof-of-concept, *in vitro* and *in vivo* testing appropriate for FDA IND approval) to early phase clinical trials takes about 10 years based on the findings of this review. Although this transition period is similar to other NIH-funded R&D platforms, it is not certain as to what extent the grant funding period (usually 5 years) and options to renew play a role in its duration. Alternatively, the NIH will create solicitations that require translational milestones or that fund clinical trials to move technologies forward. A good example applicable to NT is NCI's "*Early Phase Clinical Trials in Imaging and Image-Guided Interventions* FOA (https://grants.nih.gov/grants/guide/pa-files/PAR-14-166.html).

In addition, the NIH Office of Portfolio Analysis performed a curated keyword search within different clinical trial databases to capture domestic and international trial data. The NIH library staff also performed a PubMed search using select keywords to identify principal publications on clinical studies related to nanomedicine. This information was then used to briefly compare the state of the science of a select few investigational agents or devices with advances in the field. From the 153 publications identified, 27 were financially supported by NIH.

The grant selection process and criteria for inclusion/exclusion in this analysis required an additional level of curation. *First*, all imaging and therapeutic trials had to meet the NIH definition of a clinical trial and be entered into clinicaltrials.gov. *Second*, the clinical protocol synopsis in this database had to be examined further since many trials did not specify the underlying nanocomponent involved in the safety and efficacy test. *Third*, each imaging study that was selected had to answer specific clinical questions that could determine the value of imaging procedures for detecting, diagnosing, guiding, or monitoring the treatment of disease or assess therapeutic

Table II. Categorical Breakdown of Search Results on Clinical Trial Within the Nanotechnology Portfolio. Data Obtained from Queries on Keyword Text Terms and RCDC Classification of Nanotechnology

Number of NT-projects	Awards: 2682	Base Projects: 2373
Number of NT-clinical research projects	Awards: 242	Base Projects: 239
Number of trials from NT-clinical research projects	Awards: 64 Trials: 227	Base Projects: 24
Number of NT-drug intervention trials	158	
Number of NT-phase 1 or phase 1/2 trials	109	
Number of NT-non U.S. trials[a]	66	

[a] International trial data was derived from a keyword search in various databases

outcomes. Therefore, the 64 awards and 227 trial dataset was further curated manually by subject matter experts to verify the link between the base projects and the clinicaltrials.gov ID (*e.g.*, National Clinical Trials [NCT] Number). This involved reviewing project goals and aims to determine the NT development component and its' relationship with specific trial objectives with respect to investigational agents and devices. A subset of the curated data was then chosen to describe clinical research trends and observations in the following sections. This list of trials is cited in Table III. It is important to note that the quantitative analysis herein, is limited to the accuracies in which information has been reported by investigators and to the extent that clinical trial data can be definitively concluded as having a NT component. Limitations include technology transfer, licensing, and company sponsorship of trials that could not be traced.

Analysis of Portfolio Attributes

The trial data was also analyzed by the type of *grant funding mechanism*, *trial*, *intervention*, and *clinical indication* to establish trends in the clinical translation of nanodrugs and devices. Figure 1, for instance, shows the distribution of projects and subprojects by *grant mechanism* (with activity code in parenthesis) indicating substantial financial support for research centers and research grants from FY2008 to FY2015. Many of the base projects (*i.e.*, the leading project of multicomponent research grants) affiliated with the 227 trials were sponsored by several NIH institutes as centers, networks, and consortia. This includes NCI's Specialized Programs of Research Excellence (P50 SPORES), Comprehensive Cancer Centers (U54), and Program Research & Resource Grants (P50/P30). See type of grant programs at http://grants.nih.gov/grants/funding/funding_program.htm for more details. The most utilized mechanisms to support trials were Program Project and Center grants (P series). These are large, multiproject efforts that generally include a diverse array of research activities with multidisciplinary scientists and clinicians who share knowledge and common resources (*e.g.*, clinical trial infrastructure grants). This also explains why the number of awards released can exceed the number of base projects. Additionally, the NIH also supported novel breakthroughs in NT that utilize the U54 cooperative agreement mechanism. These differ from program project grants in that they are usually developed in response to an announcement of the programmatic needs of an institute. An excellent example of this is the NCI's Alliance for Nanotechnology in Cancer program led by Dr. Grodzinski in the Office of Cancer Nanotechnology, Office of the NCI Director (2). The Alliance program was launched in 2004 to develop NT tools and approaches to solve problems in basic and applied cancer research. Phases one and two of the program consist of four components: Centers of Cancer Nanotechnology Excellence, Nanotechnology Platforms for Cancer Research, a Nanotechnology Characterization Laboratory, and a Multidisciplinary Research Training and Team Development. It is now in phase three with emphasis on translation. See Table IV for a partial list of the Alliance's contributions to the field (5). Examples of the type of clinical studies undertaken by grantees *via* program grants and standard R01 grants are listed in Table III. These studies range from first-in-human phase 1 trials and pilot biologically focused studies to randomized phase 2 and phase 3 trials in neoadjuvant and adjuvant settings. Primary and secondary trial objective explored different imaging agents and protocols as well as combination of drug treatments. A few focused on devices for therapy such as thermal ablation and optical detection.

The results were refined further to delineate the type of trials and research under investigation. The *types of clinical studies* included prevention, screening, diagnostic, and treatment trials. The pie chart in Fig. 2 displays the percent of trials in eight separate categories defined by clinicaltrials.gov. Treatment trials represent 70% of the total NIH investments in clinical trials. Diagnostic supported trials were far less in number making up 11% of the portfolio. The majority were early phase NT drug testing studies with the remaining focused on devices or biologics. Only a few NT-related studies focused on AIDS research or novel gene therapies. Despite some demonstrated success (*e.g.*, measured by INDs that turned into new drug applications), the number of trials that looked at response to treatment or patient selection toward a given treatment was minimal. Therefore, much work is still needed to develop nano-based or nano-enabled biomarker strategies that evaluate novel therapies (*e.g.*, immunotherapy), select patients for the right treatment (*e.g.,* precision medicine), guide choice, and identify rational combination therapies for progression and drug resistance in addition to advances in delivery platforms that facilitate the schedule of drug combinations.

To ascertain the overall status of NT investments from preclinical to clinical research stages, the search results obtained from Query B were scrutinized further. There were a total of 2373 base projects in NT, 239 that focused on clinical research and 24 that led to clinical trials. The various *clinical indications* for cancer trials were also tabulated and presented in Fig. 2. Among the 227 trials, cancer research represented the largest share in both diagnostic and treatment applications. The top three cancers studied focused on the breast, leukemia, and prostate. This includes testing the safety and efficacy of known highly toxic chemotherapeutics and the assessment of second- and third-line treatments for cancer (NCT02283320). The emphasis on cancer and its focus on therapeutics was also apparent from the collection of trials associated with the NCI Alliance program for the past 14 years (see Table IV—Alliance trial listing). The NT portfolio did have treatment trials that looked at infectious diseases as well, though fewer in number (Table V). Though the mainstream of NIH investments is still in the research discovery and development stage, the NIH has clearly increased its investments in NT from 2008 to 2015 with nanomedicine research progressing beyond cancer. Nearly all institutes at the NIH support some NT grants (primarily R01 research grants, contracts, and small business innovation research) as shown in Fig. 3. In addition, 203 patents were generated from these awards. The remainder of this review will agree on such examples and trends.

HIGHLIGHTS OF TRANSLATIONAL RESEARCH

The clinical translation of NIH-funded research in nanomedicine has been catalyzed by many novel materials or advanced engineering approaches at the nanoscale. The purpose of this section is to capture translational activities in

Table III. Examples of Nanodrug and Devices Trials Affiliated with NIH-Funded Projects

Clinicaltrials.gov identifier	Intervention	Title of trial	Condition	Funding mechanism	Trial status	Nanocomponent[a]
I. PRIMARY PURPOSE: DIAGNOSTIC						
NCT01411904	Device: MagProbe™	A Novel Magnetic Needle Using Iron Oxide Nanoparticles for the Detection of Leukemia	Leukemia	R44	Withdrawn; awaiting synthesis of nanoparticles	Iron oxide NPCD34 nanoparticles incubated in bone marrow and then extracted with the magnetic needle done at the time of bone marrow biopsy
NCT01542879	Device: WB-DW-MR scan	Pilot Development of Radiation Free Whole Body Magnetic Resonance (MR) Imaging Technique for Staging Children With Cancer	Cancer	R01	Recruiting	Ferumoxytol (Feraheme): iron oxide NP coated with carbohydrate shell
NCT01671592	Drug: 19F-MRI imaging agent (tracer) Biological: dendritic cell vaccine	Safety of Labeled Dendritic Cell (DC) Vaccines and Feasibility of Tracking by Magnetic Resonance Imaging	Colorectal cancer	R01	Completed	Engineered tracer: perfluorocarbon-based nanoemulsion
NCT01336803	Drug: Feraheme Procedure: MR scan	Differentiation of Bone Sarcomas and Osteomyelitis With Ferumoxytol-Enhanced MRI	Bone cancer Chondrosarcoma Ewing's sarcoma Osteosarcoma	R21	Recruiting	Ferumoxytol (Feraheme): iron oxide NP coated with carbohydrate shell
NCT00978562	Drug: ferumoxytol nonstoichiometric magnetite; gadolinium Procedure: dynamic contrast-enhanced MRI, dynamic susceptibility contrast-enhanced MRI	DSC-MRI With Ferumoxytol and DCE-MRI With Gadolinium in Imaging Vascular Properties in Younger Patients With Brain Tumors	Childhood brain neoplasm Recurrent childhood brain neoplasm	P30	Ongoing; not recruiting	Ferumoxytol (Feraheme): iron oxide NP coated with carbohydrate shell
NCT02511028	Drug: ferumoxytol	*In Vivo* Characterization of Inflammation With Ferumoxytol, an Ultrasmall Superparamagnetic Iron Oxide Nanoparticle, on 7 Tesla Magnetic Resonance Imaging	Multiple sclerosis	NIH Clinical Center (NINDS)	Recruiting	Ferumoxytol (Feraheme): iron oxide NP coated with carbohydrate shell
NCT00660543	Drug: gadolinium Drug: ferumoxytol nonstoichiometric magnetite	MRI Study With Ferumoxytol in Assessing Early Response in Patients With Glioblastoma Multiforme	Adult brain glioblastoma	P30	Completed	Ferumoxytol (Feraheme): iron oxide NP coated with carbohydrate shell

Table III. (continued)

Clinicaltrials.gov identifier	Intervention	Title of trial	Condition	Funding mechanism	Trial status	Nanocomponent[a]
	Other: DCE-MRI; dynamic susceptibility contrast-enhanced MRI; diffusion-weighted imaging Other: MRI-based angiogram	Receiving Temozolomide and Radiation Therapy				
NCT02106598	Drug: fluorescent cRGDY-PEG-Cy5.5-C dots	Targeted Silica Nanoparticles for Image-Guided Intraoperative Sentinel Lymph Node Mapping in Head and Neck Melanoma, Breast and Cervical/Uterine Cancer Patients	Head and neck cancer Melanoma Breast cancer Cervical cancer Uterine cancer	R01	Recruiting	Targeted NP with internal silica core
NCT01521520	Observational; drug: ferumoxytol	Imaging of Type 1 Diabetes Progression	Type 1 diabetes	P01	Active, not recruiting	Ferumoxytol: iron oxide NP coated with carbohydrate shell
NCT01752166	Observational; device	Detecting Infections Rapidly and Easily for Candidemia Trial—Part 2 (direcT2 Study) (direcT2)	Candidemia	R01, U54	Completed	Functionalized SPIO NP with polymer coating; T2 BIOSYSTEMS
NCT01919762	Observational; device	Detecting Infections Rapidly and Easily for Bacteremia Trial (DIREBT)	Bacteremia	R01, U54	Completed	Functionalized SPIO NP with polymer coating; T2 BIOSYSTEMS
II. PRIMARY PURPOSE: THERAPEUTIC						
NCT02680535	Device: AuroShell particle infusion	MRI/US Fusion Imaging and Biopsy in Combination With Nanoparticle Directed Focal Therapy for Ablation of Prostate Tissue	Neoplasms of the prostate	R01 R43	Recruiting	NIR laser excited gold nanoshell with silica core
NCT02009332	Drug: ABI-009 nab-rapamycin	Combined Phase 1/2 Study of Albumin-Bound Rapamycin Nanoparticles (Nab-rapamycin, ABI-009) in the Treatment of BCG Refractory or Recurrent Non-muscle Invasive Transitional Cell Bladder Cancer	Nonmuscle invasive bladder cancer	R42	Recruiting	Albumin-bound rapamycin NPs
NCT02495896	Drug: paclitaxel Drug: cisplatin Drug: docetaxel Drug: gemcitabine hydrochloride Biological: recombinant EphB4-HSA fusion protein	Recombinant-EphB4-HSA Fusion Protein with Standard Chemotherapy Regimens in Treating Patients With Advanced or Metastatic Solid Tumors	Head and neck squamous cell carcinoma Metastatic pancreatic adenocarcinoma Recurrent gallblader carcinoma Nonsmall cell lung carcinoma	P30	Recruiting	Paclitaxel albumin-stabilized nanoparticle formulation

Table III. (continued)

Clinicaltrials.gov identifier	Intervention	Title of trial	Condition	Funding mechanism	Trial status	Nanocomponent[a]
	Other: laboratory biomarker analysis		Pancreatic cancer Gallbladder cancer			
NCT01886573	Drug: azacitidine Drug: entinostat Procedure: therapeutic conventional surgery Other: laboratory biomarker analysis	Azacitidine and Entinostat in Treating Patient with Newly Diagnosed Stage IA-IIIA Non-Small Lung Cancer Undergoing Surgery	Nonsmall cell lung carcinoma	P30, R21	Terminated	Liposomal NP
NCT02166255	Drug: TKM-080302 Biological: siRNA-transfected peripheral blood mononuclear cells APN401 Other: laboratory biomarker analysis	APN401 in Treating Patients With Melanoma, Kidney Cancer, Pancreatic Cancer, or Other Solid Tumors That Are Metastatic or Cannot be Removed By Surgery	Pancreatic cancer Renal cell cancer melanoma Recurrent melanoma Recurrent pancreatic cancer Recurrent renal cell cancer	P30	Ongoing, not recruiting	Liposomal siRNA
NCT00734682	Drug nanoliposomal CPT-11	A Phase I Trial of Nanoliposomal CPT-11 (NL CPT-11) in Patients With Recurrent High-Grade Gliomas	Glioblastoma Gliosarcoma Anaplastic astrocytoma Anaplastic oligodendroglioma	R01, U01, U10	Completed	Nanoliposome-drug NP
NCT0261733	Drug: liposomal irinotecan	Liposomal Irinotecan and Veliparib in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	Estrogen receptor negative HER2/Neu negative Neuroendocrine neoplasm Progesterone receptor negative Cervical cancer Nonsmall cell lung cancer Breast cancer Ovarian cancer	U10	Recruiting	Liposomal drug NP
NCT02022644	Drug: nanoliposomal MM-398	Study of Convection-Enhanced, Image Assisted Delivery of Liposomal-Irinotecan In Recurrent High Grade Glioma	High-grade glioma	R21	Recruiting	Nanoliposomal-drug NP
NCT01876446	Drug: pegylated irinotecan Other: laboratory biomarker analysis	Pegylated Irinotecan NKTR 102 in Treating Patient With Relapsed Small Cell Lung Cancer	Recurrent small cell lung carcinoma	P30	Recruiting	Polymer-drug conjugate NP
NCT00459810	Drug: transdermal estradiol Drug: paclitaxel poliglumex	Paclitaxel Poliglumex and Estradiol in Treating Patients With Stage IV Prostate Cancer	Prostate cancer	RO1	Terminated	Polymer-drug conjugate of paclitaxel and polyglutamic acid
NCT02769962	Drug: CRLX101 (11 trials using CRLX101) Drug: olaparib	Trial of CRLX101, a Nanoparticle Camptothecin With Olaparib in People With Relapsed/Refractory Small Cell Lung Cancer	Solid tumors Small cell lung carcinoma Carcinoma Nonsmall cell lung Lung neoplasms	NCI Clinical Center	Recruiting	Polymeric NP: cyclodextran-PEG copolymer encapsulated Camptothecin
NCT01625936	Drug: CRLX101 (Cerulean) Drug: bevacizumab	CRLX101 Plus Bevacizumab in Advanced RCC	Renal cell carcinoma; Cerulean Pharma	P30	Ongoing; no longer recruiting	Polymeric NP: cyclodextran-PEG copolymer encapsulated Camptothecin

Table III. (continued)

ClinicalTrials.gov identifier	Intervention	Title of trial	Condition	Funding mechanism	Trial status	Nanocomponent[a]
NCT00689065	Drug: CALAA-01	Safety Study of CALAA-01 to Treat Solid Tumor Cancers	Cancer Solid tumor; Calando Pharmaceuticals	U54	Terminated	Transferrin-cyclodextrin siRNA NP
NCT00111904	Drug: paclitaxel-loaded polymeric micelle	Paclitaxel in Treating Patients With Unresectable Locally Advanced or Metastatic Pancreatic Cancer	Pancreatic cancer; Theradex	U54; P30	Completed	Paclitaxel-loaded polymeric micelle
NCT02166255	Drug: TKM-080302-Biological: siRNA-transfected peripheral blood mononuclear cells APN401 Other: laboratory biomarker analysis	APN401 in Treating Patients With Melanoma, Kidney Cancer, Pancreatic Cancer, or Other Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	Recurrent melanoma Recurrent pancreatic cancer Recurrent renal cell cancer Pancreatic cancer Renal cell cancer Melanoma	P30	Ongoing; no longer recruiting	Liposomal siRNA
NCT02834611	Drug: ceramide nanoliposome	Ceramide Nanoliposome in Patients With Advanced Solid Tumors	Cancer Carcinoma Solid tumors Tumor	R44	Not yet recruiting	Nanoliposome-drug NP

[a] Comprised of polymeric NPs, polymer-drug conjugates, liposomal drugs, drug-loaded polymeric micelles, nanocrystalline, protein-polymer NPs (albumin-bound), and radionuclei-labeled NPs. These materials may also contain targeting moieties depending on their application

Fig. 1. Analysis of the funding mechanisms used to support extramural and intramural NT projects that resulted in one or more clinical trials

the field to illustrate potential impact in the different scientific areas of biomedical research at the NIH. The following portfolio examples represent the first generation of nanodrugs or nanocomponent-based devices that were formulated as a nanoparticle or engineered to increase solubility and/or payload through architectures as shown in Fig. 4. This includes nanoliposomes which are submicron bilayer lipid vesicle that can release payloads intracellularly following membrane fusion (7) (NCT00734682), superparamagnetic iron oxide particles (NCT01411904), and polymer-bound chemotherapeutics (NCT01876446). Additional information such as the type of intervention and nanocomponent involved in these select trials is defined in Table III. Readers can also find more examples of nanotherapeutic products, investigational agents, and other drug delivery designs as shown in Figure 4 in translational nanomedicine reviews (8–10).

Medical Imaging and Devices

Today, imaging performs vital roles in all aspects of clinical management of a disease including screening, diagnosis, interventions, monitoring of therapeutic response, and surveillance. The advent of effective imaging techniques has also enabled great strides in understanding the biology and pathophysiology of diseases. The NCI, for example, has invested significant resources in therapeutics and imaging, both to understand cancer biology and to improve clinical management of cancer patients. This investment has stimulated considerable research activity in the fields of new imaging devices, agents, and interventions. Below are a few illustrations of project stated aims and corresponding trial objectives that highlight the importance of this field. The NIH funding institute for each one is in parentheses.

- Radiation-Free Whole Body Imaging Technique for Staging of Children with Cancer (NICHD)

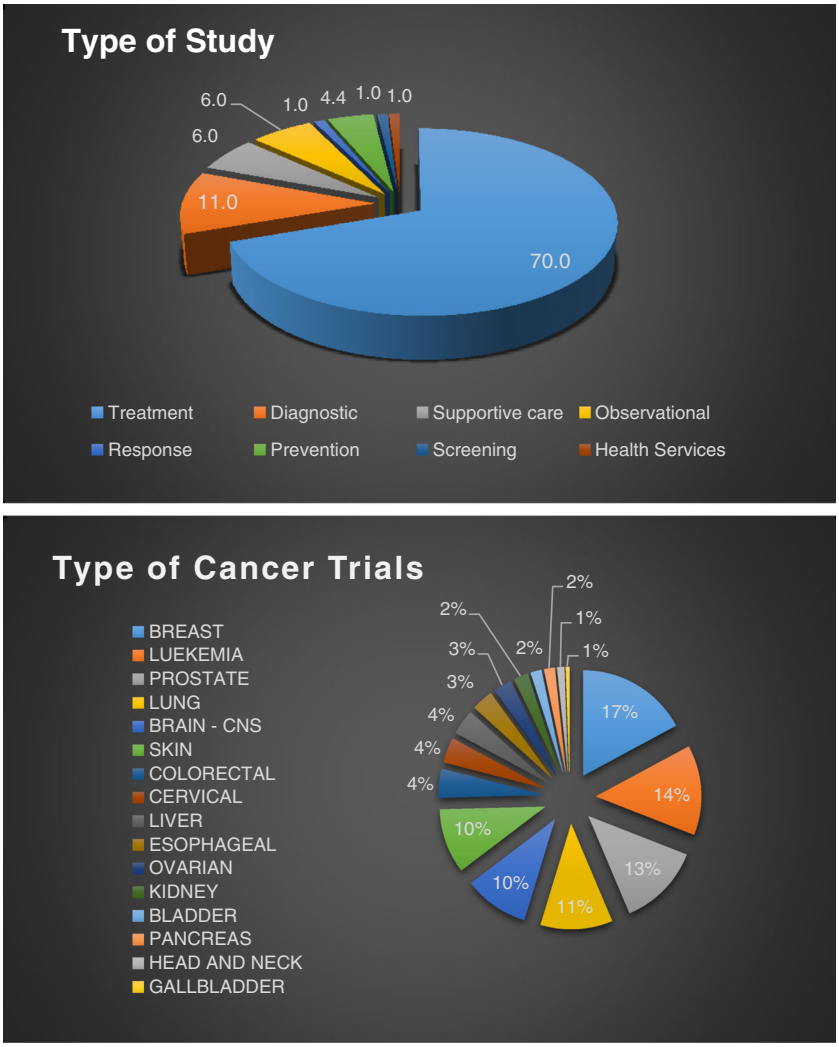

Fig. 2. Percent of trials by type of study performed (top) and cancer indication (bottom). See clinicaltrials.gov glossary for the definition of study types

More than 175,000 children worldwide are diagnosed with malignant tumors every year. Radiographic imaging tests are essential for tumor staging in children with cancer but are associated with a risk of inducing secondary cancers later in life. This project is direct at the development of a new clinically feasible imaging test that provides a customized one-stop cancer staging approach for children with cancer, save a large patient population from radiation exposure from diagnostic staging evaluations, and ultimately, eliminate associated risks of potential long-term secondary cancer development later in life. *Research focus*: To develop a new, radiation-free magnetic resonance (MR) imaging approach for whole body staging of children with cancer, based on whole body diffusion-weighted MR imaging (WB-DW-MR) and off-label use of the iron supplement ferumoxytol to improve contrast for MR imaging.

NCT01542879: To determine if the WB-DW-MR and whole body PET/MR imaging protocols can detect the extent and spread of the disease as accurately or even better than the standard tests (CT, MR, and/or PET/CT) in pediatric patients with a newly diagnosed malignant lymphoma, malignant sarcoma, or other solid tumors.

- Magnetic Resonance Imaging of Type 1 Diabetes Progression (NIAID)

Autoimmune diseases, type 1 diabetes (T1D) being a classic example, currently afflict around 7% of the population of developed countries. Type 1 diabetes results from autoimmune destruction of the insulin-producing beta cells of the pancreatic islets. A significant hindrance to both mechanistic and therapeutic advances has been the difficulty of dealing with disease entities diagnosed so late in their course. For instance, the inability to access the target organ and to evaluate the true status of the autoimmune lesion has hampered the understanding of the pathogenic process as well as monitoring of prediabetic individuals. Recent advances in the imaging field may provide solutions to monitoring the natural history of insulitis during the development of clinical diabetes and tracking the evolution of pancreatic inflammation in at-risk individuals and in diagnosed patients. In this project, the team of investigators is exploring the ability to visualize and quantitate the degree of islet inflammation in diabetic or at-risk patients to provide important insights into the mechanisms that result in type 1

Table IV. Examples of Cancer Trials Associated with the NCI's Alliance Program

Clinicaltrials.gov identifier	Intervention	Title of trial	Condition	Funding mechanism	Status/references	Nanocomponent
NCT00333502	Drug: CRLX101	Study of CRLX101 (Formerly Named IT-101) in the Treatment of Advanced Solid Tumors	Cancer; solid tumor	U54—Cerulean Pharma Inc.	Completed; no results (3)	Polymeric NP: cyclodextran-PEG copolymer encapsulated Camptothecin
NCT01380769	Drug: CRLX101 Other: best supportive care	A Phase 2 Study of CRLX101 in Patients With Advanced Non-Small Cell Lung Cancer	Nonsmall cell lung cancer	U54—Cerulean Pharma Inc.	Completed; no results (3)	Polymeric NP: cyclodextran-PEG copolymer encapsulated Camptothecin
NCT02187302	Drug: CRLX101	CRLX101 in Combination With Bevacizumab for Metastatic Renal Cell Carcinoma (mRCC) Versus Standard of Care (SOC)	Metastatic renal cell carcinoma		Active, not recruiting (3)	Polymeric NP: cyclodextran-PEG copolymer encapsulated Camptothecin
NCT01300533	Drug: BIND-014	A Study of BIND-014 Given to Patients With Advanced or Metastatic Cancer	Metastatic cancer; cancer; solid tumors	U54—BIND Therapeutics	Completed; no results (4)	Core-shell polymeric micelles—docetaxel NP for injectable suspension
NCT01812746	Drug: BIND-014	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	Castration-resistant prostate cancer	U54—BIND Therapeutics	Completed; no results (4)	Core-shell polymeric micelles—docetaxel NP for injectable suspension
NCT02283320	Drug: BIND-014	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	KRAS-positive patients with nonsmall cell lung cancer; squamous cell nonsmall cell lung cancer	U54—BIND Therapeutics	Completed; no results (4)	Core-shell polymeric micelles—docetaxel NP for injectable suspension

Table V. Cabotegravir Drug Trials to Treat Human Immunodeficiency Virus Infections

Clinicaltrials.gov identifier	Intervention	Title of trial	Condition	Funding Source	Status/ references
NCT02462772	Drug: cabotegravir (GSK1265744)	Safety and Acceptability of Cabotegravir in HIV-Uninfected Women in KwaZulu-Natal, South Africa	Human immunodeficiency virus	ViiV Healthcare	Withdrawn
NCT02345707	Drug: 4 cabotegravir tablet formulations (micronized new formulation)	Relative Bioavailability Study of Phase III Tablet Formulation of Cabotegravir	Infection, human immunodeficiency virus	ViiV Healthcare	Completed; no results
NCT02478463	Drug: cabotegravir tablet 30 mg once daily for 28 days Drug: cabotegravir injection 400 mg/2 mL IM given once a day	Pharmacokinetic Study of Cabotegravir Long-acting in Healthy Adult Volunteers	Infection, human immunodeficiency virus	ViiV Healthcare	Not yet recruiting
NCT02720094	Drug: cabotegravir tablets Drug: tenofovir disoproxil fumarate/ emtricitabine tablets	Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex With Men	Human immunodeficiency virus infections	NIAID	Not yet recruiting

diabetes. *Research focus*: To develop a clinical, magnetic nanoparticle-MRI imaging method that visualizes the changes associated with insulitis based on the increased vascular leakage and phagocytic activity in infiltrated islets. This includes decreasing respiratory artifact, increasing spatial resolution, and improving quantification through paramagnetic nanoparticles (MNP) that normally remain intravascular, changes in pulse sequences, and postprocessing software, which might yield reliable measures of pancreatic blood volume. These explorations should inform on the state of pancreatic inflammation in prediabetic individuals as a function of their risk status and eventual progression to diabetes.

NCT01521520: To assess the ability of a ferumoxytol-MRI method to detect changes in the pancreas associated with the insulitis of type 1 diabetes. Patients diagnosed with clinical type 1 diabetes, and high-risk and low-risk pretype 1 diabetes will receive pre- and post-MNP-injected MRI scans to monitor and measure changes within the pancreas associated with the development of autoimmune diabetes.

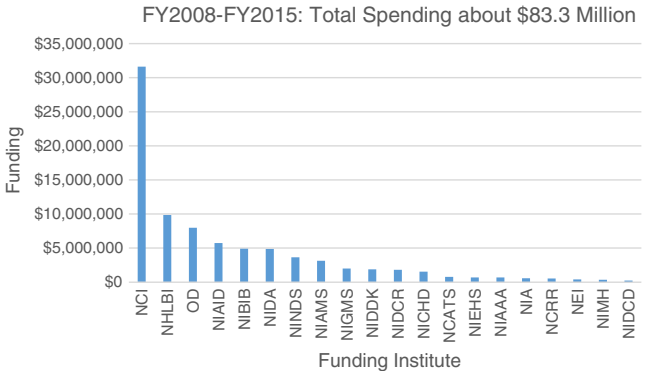

Fig. 3. Total dollars invested by the various NIH institutes used to support clinical research grants and contracts in the NT portfolio from FY2008 to FY2015

- MRI-Based Tracking of Alpha-Type-1 Dendritic Cell Vaccines in Patients with Colorectal Cancer (NCI)

Colorectal cancer (CRC) accounts for approximately 150,000 new cases annually, and CRC patients with resectable liver metastases have an overall poor prognosis and a 5-year overall survival rate between 20 and 35%, despite the presence of only minimal residual disease. Recent immunotherapeutic interventions that use dendritic cells (DCs) as live vaccines and deliver tumor-specific antigens to induce endogenous killer T cells (*i.e.*, cytotoxic T cells) may be effective in this patient population. However, a key hurdle to assessing the potential of these cell-based therapies is the inability to see the cells *in vivo* following therapeutic cell transfer. In this proposed approach, investigators have engineered a 19F perfluoropolyether (PFPE) nanoparticle MRI tracer to label

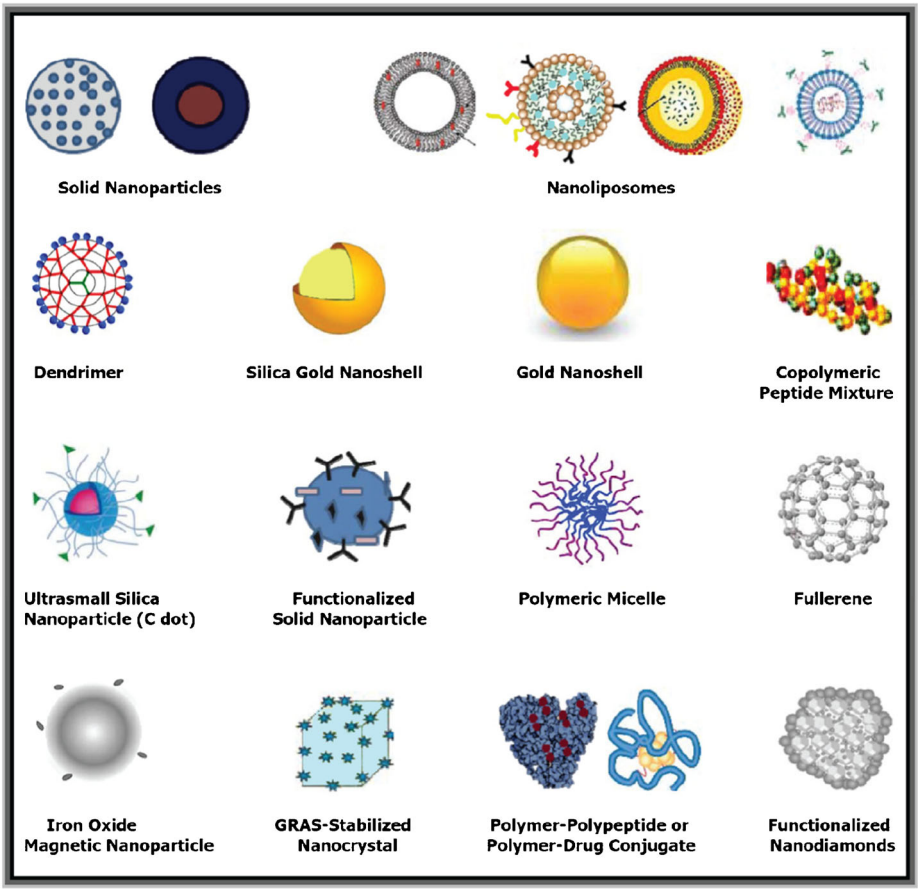

Fig. 4. Basic chemical architectures used to deliver pharmaceuticals, imaging agents, and other therapeutic products. Many of these nanomaterials are in preclinical evaluation studies or clinical trials funded by the NIH. Reprinted with permission from (6)

DC cells *ex vivo* and visualize their trafficking in humans. *Research focus*: Establish PFPE labeling protocols for immunotherapeutic DCs and develop a 19F MRI/magnetic resonance spectroscopy method on a 3T clinical MRI system. A clinical-grade version of the enabling PFPE nanoparticle reagent has been formulated and manufactured by Celsense to perform clinical studies of immunotherapy in humans. The research is now focused on optimizing pulse sequences to obtain quality images for the migration of DC-based vaccines to the lymph nodes.

NCT01671592: Evaluate the safety of labeled alpha-type-1 dendritic cell vaccines and the feasibility of tracking them by the MRI-based method. In this phase 1 study, MRI scans will be performed on patients receiving low and high doses of the vaccine.

- Improving Biopsies Using Magnetic Nanoparticles for the Detection of Leukemia (NCI)

In children with acute lymphomatic leukemia and myelodysplastic syndrome, it is extremely important to measure the minimal residual disease after chemotherapy, as this information is used to determine prognosis, efficacy, and the need for further treatments. Bone marrow biopsy is the standard method by which these measurements are obtained, but these biopsies are invasive, need to be repeated at periodic intervals, and often require multiple biopsies to obtain sufficient samples. Magnetic nanoparticles, when appropriately labeled and used with magnetic collection methods, target and attach themselves to cancer cells, which can then be collected magnetically. *Research focus*: Develop and test a new biopsy technique using magnetic biopsy needles which can increase the biopsy yield, including the sampling of metastatic rare cancer cells in bone marrow, and can provide specificity for particular leukemia cancer types. The described methodology uses magnetic nanoparticles coated with anticancer agents to magnetically concentrated cancer cells and direct therapeutic intervention at the cancer site.

NCT01411904: To determine if the magnetic needle used in combination with magnetic nanoparticles can accurately identify minimal residual disease in leukemia patients.

Therapeutic Interventions

Clinical research examples in this category are related to treatment or quality of life studies.

- Image-Guided Intraoperative Sentinel Lymph Node Detection (NCI)

Metastatic melanoma has a very poor prognosis with a median survival of less than 1 year. There are no satisfactory treatments for most patients and therapies are largely palliative. Therefore, early detection and advances in targeted radiotherapy could yield longer term benefits. This investigation takes advantage of fluorescent core-shell silica nanoparticles that are clinically promising as cancer diagnostics and radiotherapeutics due to their exceptional brightness and stability, and the success in integrating multiple functionalities in a single platform. *Research focus*: To design nanoparticle architectures with improved optical properties and favorable melanoma receptor binding capabilities using the FDA IND-approved core-shell silica NPs developed in their laboratory for detection, staging, and therapy planning of human metastatic melanoma. Surface chemistry for targeted silica NPs includes different cyclic arginine-glycine-aspartic acid-tyrosine (cRGDY) peptides and PEG chain lengths. The performance of optimally formulated chemistries established for cRGDY-bound probes will also be evaluated as a tumor response marker and a targeted, radionuclide therapeutic *in vivo*.

NCT02106598: To test the feasibility of achieving real-time optical detection of sentinel lymph nodes during surgery using nonradioactive cRGDY-PEG-Cy5.5-C dots (dye-labeled particles) and a hand-held camera system. Patients with head and neck melanoma will initially undergo imaging of their lymph nodes prior to their surgery to identify diseased nodes *via* optical scans using the Quest Spectrum^{TM} portable two-fluorescence channel camera system.

- Enhanced Delivery and Efficacy of Neuro-oncologic Chemotherapeutic Agents for High-Grade Gliomas (NCI)

High-grade gliomas (HGG) are the most common brain tumor in adults, with 15,000 new cases/year in the U.S. Median survival is only 6–12 months for patients with newly diagnosed glioblastoma multiforme and 24–36 months for patients with anaplastic astrocytoma. Moreover, chemotherapy for HGG is limited by the poor activity of available antineoplastic agents and the compromised delivery of chemotherapy across the blood-brain barrier. This study focuses on two particularly appealing delivery modalities which may improve the efficacy of neuro-oncologic chemotherapeutic agents: liposomes (nanoliposomal irinotecan) and convection-enhanced delivery (CED). *Research focus*: To develop highly potent liposomal formulations of irinotecan that reduce the toxicity to healthy tissues with the aid of real-time MR imaged CED. CED may improve chemotherapeutic delivery to brain tumors by utilizing bulk flow, or fluid convection, established as a result of a pressure gradient. MRI is used here to visualize the delivery. Their preclinical studies compared different routes of administration for liposomal irinotecan in treating mice with intracranial glioblastoma xenografts. Investigators now propose to test this combination in a first-in-human study for safety and tolerability testing.

NCT02022644: To investigate and determine the maximum tolerated dose of nanoliposomal irinotecan in adults with recurrent high-grade glioma when administered directly into the tumor using the CED method. In addition, the MR image-guided intracranial injection procedure will be optimized by correlating the observed distribution of gadolinium in HGG patients to pretreatment modeling of the drug distribution utilizing predictive imaging software.

- Ceramide Nanoliposome Therapy for Solid Tumors (NCI)

Hepatocellular carcinoma (HCC) is one of the most frequent and deadly cancers worldwide, and there are no current treatments, either approved or in clinical development, that substantially alter the course of disease for patients diagnosed with advanced HCC. Ceramide is one of the many sphingolipid metabolites known to have biological activity, serving as a lipid-derived second messenger that modulates the induction of cell differentiation, cell cycle arrest, and/or apoptosis. The combination of synergistic mechanisms of action that result in specific and selective toxicity of ceramide toward cancerous cells, along with the distinct advantages of liposomal delivery, makes the synthesis of ceramide nanoliposome (CNL) a unique and powerful potential alternative to current HCC therapies. This research builds on the preclinical studies that harvest the synergistic mechanisms of action (*e.g.*, regulation of signaling pathways, inhibition of glycolysis, and disruption of tumor-induced immune tolerance) of ceramide in a liposomal formulation that enables its use as a therapeutic by mediating solubility during circulation, suitable cell permeability, and protection from circulating catabolic enzymes as well as enhanced pharmacokinetics and biodistribution to solid. *Research focus*: To build and advance the CNL preclinical portfolio through a phase 1 clinical trial *via* a multisite clinical evaluation of the CNL as a novel anticancer therapeutic.

NCT02834611: To perform the first-in-human phase 1 clinical trial to assess the safety and maximum tolerated dose of CNL in patients with advanced solid tumors. The results of this trial will indicate the recommended phase 2 dose and support subsequent trials for the intended initial indication of HCC.

- Investigation of a mTOR inhibitor: Nab-rapamycin (NCI)

Nonmuscle invasive bladder cancer is a recurrent disease, and an effective molecularly targeted intravesical therapy especially after failure of first-line therapy, is highly desirable as there are no proven effective options for patients in this setting. Several chemotherapeutics have been explored in the second-line setting with only limited efficacy, forcing many patients into a radical cystectomy. ABI-009 is a macrolide antibiotic rapamycin bound to nanoparticle albumin with immunosuppressant and potential antiangiogenic and antineoplastic activities. *Research focus*: Develop an effective molecularly targeted intravesical therapy *via* the inhibition of the mTOR (mammalian target of rapamycin) signaling pathway.

NCT02009332: To determine appropriate dosing of Nab-rapamycin ABI-009, albumin-bound rapamycin nanoparticles, and evaluate the safety and antitumor activity of ABI-009 in the treatment of nonmuscle invasive bladder cancer in a combined phase 1/2.

DISCUSSION

Summary of Nanofeatures and Impact

After a review and analysis of the portfolio and select trials, NIH-supported nanomedicine research seems to target a number of major diseases and conditions such as heart disease, asthma, diabetes, and cancer. The analysis further concludes that nanoscale drug delivery represents the majority of developments in the NIH nanomedicine portfolio. This investment is leading to fundamental changes in understanding biological processes in health and disease, as well as enabling novel diagnostics and interventions for treating disease. NIH scientists are developing molecular agents and methods for earlier and more accurate diagnosis, therapies aimed directly and selectively at diseased cells, and are exploring root causes of common and rare diseases at the proper length scales. The following lists key features from summing the R&D projects and illustrates the impact that these nanoscale delivery formulations had on achieving efficacious treatments or interventions:

- Novel nanodrugs and nanocarriers overcome poor water solubility issues, alter unacceptable toxicity profiles, enhance bioavailability, and improve physical/chemical stability. These platforms transport active agents to their target binding sites to impart maximum therapeutic activity. Other examples include therapeutics that have side effects due to triggering an immune response (*e.g.*, complement activation) or clearance by the reticuloendothelial system.
- Various liposomal, solid nanoparticle-based, antibody-drug conjugate, and polymer-drug conjugate delivery platforms are underway to overcome the hurdle of low solubility (*e.g.*, trastuzumab work), and side effects related to high doses of free drug (Doxil, DaunoXome).
- Reformulation of old shelved therapeutics into nanosized dosage forms (*e.g.*, nanocrystalline products like Rapamune).

NIH-funded scientists are also employing a variety of chemical synthetic approaches to improve the properties of nanodrugs and nanodevices and unique strategies for its utility. Recent advances are exploring:

- Alterations in signaling pathways involved in brain cancer stem-like cells' resistance to radiation
- Nano-encapsulated drugs with radiosensitizing properties in synergy with external X-ray beam radiation therapy
- Nanogel-conjugated reverse transcriptase inhibitors as novel antiviral agents that could potentially reduce the mortality from HIV/AIDS
- Modalities of administration and passive/active targeting of nanomedicines to overcome radioresistance in glioblastoma
- Formulations that reduce the frequency in drug therapy (*e.g.*, reducing Cabogravi from four times/year to twice/year)
- Nanomaterials that enhance the bioavailability of self-carried curcumin (natural compound with promising anticancer and anti-inflammatory activities)
- MicroRNAs for posttranscriptional control of cellular phenotype to redirect tumor cell fate toward therapeutically beneficial phenotypes

In addition to those selected examples, NIH is supporting exciting clinical research and trials in areas that build nanosensors for diabetes, bridge nanoneuromedicine with bioimaging, apply innovative pharmaceuticals for gene therapies, and engineer viruses to produce vaccines. However, the results from the nanotherapeutic trials have not yet successfully demonstrated improved efficacy. The impact has been on improving the quality of life for patients by reducing adverse side effects (see HIV trials).

The following points highlight the major impact of nanoscale drug delivery and therapeutics:

Fight against HIV - Cabotegravir, a long-acting drug for treatment of HIV-infected patients, is in several clinical trials. It is an integrase inhibitor with a carbamoyl pyridone structure similar to dolutegravir. The agent has been incorporated into specific nanoparticles with a half-life of 21–50 days following a single dose. This would make possible the suppression of HIV with dosing once every 3 months compared to the frequent administration of current medications. Several trials were performed to determine PK of this nanoformulation and its use in combination with other drug candidates. See Table V for a track record of its use in HIV. Their main purpose is to test different formulations for injectable and oral administration that would increase drug payload and reduce drug frequency to improve compliance and overall quality of life. Current HIV research also focuses on bridging antiretroviral therapeutic nanoformulation (nanoART) synthesis, viral tissue reservoir targeting, and pharmacodynamic testing in rodents and large animal confirmatory studies

Progress against Cancer - Advances in NT in this field build on the understanding of cancer biology and identification of cellular mechanisms and pathways for drug targeting. Nanotherapeutics in cancer addresses several challenges in the field. The main platforms are primarily delivery vehicles that focus on the synthesis and engineering of liposomes, polymers, micelles, albumin-bound chemotherapeutics, and polymer-bound and chemo drugs. These delivery systems are designed to improve properties or address technical challenges associated with bioavailability, drug stability, and solubility. Unlike the HIV trials above, the subset of trials mentioned here has not yet demonstrated improved efficacy over current therapeutic regimens. Their benefit primarily improves quality of life by reducing toxicity and side effects of the chemotherapeutics. Though this is generally true, exciting new evidence from the Celator Pharmaceutical-sponsored randomized, controlled, phase 3 trial (NCT01696084) using VYXEOS has shown statistically significant improvement in overall survival in patients with high-risk acute myeloid leukemia. As a first-line therapy, VYXEOS (also known as CPX-351), a nanoscale liposome co-formulation of cytarabine and daunorubicin, was compared to the conventional cytarabine and daunorubicin treatment regimen. Because of these results, Celator Pharmaceutical plans to submit a new drug application (NDA) in late 2016.

In 2015, a review of cancer nanotherapeutics in clinical trials was published by Langer *et al.* (11), describing 35 trials

in terms of their delivery vehicle and clinical indication. It includes a description of the FDA approval process as well as clinical trials resulting from NCI Alliance R&D. Rather than elaborating further on the details of such studies, we refer the reader to Langer's report on the status of this field. Details such as the phase, clinical indication, and clinicaltrials.gov ID are also described in their review.

The NCI's Office of Cancer Nanotechnology also performed an assessment of the clinical translation of the Alliance program, which found that at least 14 trials were underway in 2013 based on the network's innovations (2,5). The Alliance program has proven to be a great model for developing and moving nanotherapeutics into clinical trials. Today, there are 22 cancer nanotechnology-related trials associated with the Alliance program. These trials, interestingly enough, were not funded by the NCI award but rather through start-up companies and industry sponsorships. This approach taken by the NCI Office of Cancer Nanotechnology led to a successful public-private partnership that consists of a number of pharmaceutical and biotech companies and cancer foundations. For example, the Translation of Nanotechnology in Cancer Consortium (TONIC) serves as consultants to assist in translating the nanodrugs and devices that were developed by the investigators. Table IV lists a few examples of the Alliance's contributions to the field. Learn more about of the program, their perspective on cancer nanotherapeutics, and the trials supported by companies, Alliance members, and/or start-up companies by visiting nano.cancer.gov. Today, there are several clinically approved nanoparticle cancer drugs.

Factors Affecting Trial Success—Lessons Learned from Cancer Trials

In this review, *progress toward regulatory approval* was defined as a measure of success. The NT clinical trials portfolio was thus analyzed in terms of the percentage of identified trials in different clinical stages (pilot, pivitol, phase 1, 2, or 3), as well as whether it was an observational or interventional study. This examination was further supplemented with information on current status (active, recruiting, completed, *etc.*) for the trials listed from 2008 to 2015 as well as the query of publications during this timeframe. Among the 227 affiliated studies, 109 are phase 1 or 1/2 studies, 86 phase 2, and 12 in phase 3 testing. This evidence combined with the fact that 15% has been completed with others still recruiting, suggests that the community is making progress down the clinical pathway. It is a slow process, in part, due to reluctance from some academicians to move in this direction because of the lack of institutional support/interests/recognition as a priority compared to basic R&D. Institutional viewpoint is not often aligned with product development activities, and thus, academicians generally are not acknowledged for such efforts compared to advancing research. Therefore, NIH encourages academicians to collaborate through the multi-PI mechanism, public-private partnerships, and other opportunities for early- and late-phase trials such as the NCI Experimental Therapeutics Clinical Trials Network and NCI National Clinical Trials Network. For additional information regarding these networks and other clinical trial infrastructure support or expertise, please visit https://dctd.cancer.gov/.

NCI also reviewed its phase 1, 2, and 3 therapeutic and primary imaging trials in oncology funded through research grants, cooperative agreements, and contracts to determine factors that influence trial efficiencies, performance, and completion. NCI's *Cancer Imaging Program* recently performed an analysis of its R01 and R21 portfolio that involved clinical trials to assess the performance of novel imaging agents (including nanoscale contrast agents), imaging technologies, and image-guided interventions. As a result, several factors were identified that contributed to the inability to reach trial completion according to their research plan within the specified grant period. Patient recruitment and retention proved to be the most common cause of failure often driven by complex trial designs and improper planning by trialists. Below signifies a few plausible reasons that were noted for not reaching accrual targets or achieving statistical endpoints: No direct therapeutic benefit to the patient since many imaging research trials are investigational and therefore cannot be used for making clinical decisions; Lack of compliance to the protocol due to heavy demands placed on sick patients (e.g., multiple scans, multiple visits, long scan times, etc.,); Inadequate plans for recruiting, trial activation, and conduct due to the limited experience of the investigative team (e.g., new versus established); and lack of dedicated resources throughout the life cycle of a trial.

In addition, NCI requested the Institute of Medicine (IOM) to assess the state of NCI's phase 2 and 3 oncology trials performed by the Cooperative Groups to keep pace with scientific advances. In 2010, the IOM released a report of their findings that led to the newly restructured National Clinical Trials Network program to achieve a more efficient design, review, and conduct of clinical trials (NCTN; see https://dctd.cancer.gov) (12). Meanwhile, the NIH has also taken on the task of improving data quality and efficiencies in NIH-funded research grants that have a clinical trial component with the goal of enhancing scientific rigor, promoting follow through, and yielding more definitive clinical outcomes. In summary, proper planning and trial designs were key elements identified from all analyses undertaken and therefore, any measures to *predict* the likelihood that a trial will be *successfully completed* or is *unable to advance* is crucial.

Regulating Nanomedicine

To advance their discoveries, NIH investigators need to better understand the regulatory needs and requirements in this field early in the development process. Thus far, those researchers that sought entrepreneurial developments in this area have benefited from continuous support by both the FDA and NIH. NIH has also contributed to FDA's understanding of nanomaterials through several funded and collaborative projects/programs. Emerging technologies are particularly problematic for governmental regulatory agencies, given their novelty and lack of precedence in the field. To move technologies forward, NIH works closely with the FDA and gives presentations at professional societies, hosts joint workshops, and serves as advisors on translational activities. For instance, the NCI Cancer Imaging Program in collaboration with the International Society of Image Guided

Surgery (ISIGS) and the World Molecular Imaging Society (WMIS) held a workshop on the *Regulatory Pathways for Clinical Use of Optical Imaging* in July of 2016 (https://videocast.nih.gov/summary.asp?Live=19048&bhcp=1).

Among the largest challenge is the lack of harmonization of trial data and standardized protocols and procedures employed during the preclinical development and characterization of nanomedicines. To address this serious and inhibitory effect in translation, the NIH supports multiple infrastructure programs to meet investigators' needs in standardized testing to characterize properties and toxicities of nanomaterials or nanotherapeutics. Examples include the NCI's National Nanotechnology Characterization laboratory, NCI's Developmental Therapeutics Program, NCI's Biopharmaceutical Development Program, the NHLBI's Science Moving towArds Research Translation and Therapy (SMARTT) program, and translational guidance from the NIH's National Center for Advancing Translational Sciences. Other opportunities include standardized reporting, data sharing, and informatics support for community consensus building and exchange (NanoHub, NCIP, TCIA, *etc.*). In addition, the NIH offers our small business investigators (SBIR/STTR) funding to obtain market analysis for potential start-up companies based on their funded technology developed *via* the Niche Assessment Program. Investigators also can compete for the Commercialization Accelerator Program which provides access to domain experts and focus on outcomes that will enhance commercialization.

From our perspective, the FDA's approach to regulating nanomedicine has made progress in delineating *the confusion of complex products* containing nanomaterials (13,14). The FDA has produced several *draft* guidance documents, position papers, and gave presentations at societies and other agencies' grantees meetings. At present, this information is short on specifics and reflect strong policy-based directives. In order to streamline regulatory issues, there is a real need for regulatory guidelines that follow a science-based approach *versus* policy that respond to changes in knowledge and risks as they evolve. Another critically important factor is the potential to culminate data and findings across thematic clinical studies, a transnational regulatory harmonization, to move this field forward and accelerate common platforms into the U.S. regulatory approval process. For instance, our preliminary search on international clinical trials in nanomedicine shows that the NIH-associated trials are pursuing very similar disease targets and clinical indications enabled by nanotechnologies. A total of 66 trials resulted from our query using a prespecified keyword search and were cross-referenced against the World Health Organization's International Clinical Trials Registry Platform and previous reviews in the area to make this claim (9).

Effective translation of nanomedicine candidates also requires a technological breakthrough coupled to a clinical demand, which is bridged by logical and appropriate intermediary data that mechanistically demonstrate the efficacy and safety in biological systems. In order to understand the effect of manipulating materials at the nanoscale has upon biological or clinical outcomes, improvements in correlative sciences and training a new generation of NT researchers are needed. The need for training is primarily due to the differences in interpretation of nanomedicine data between physical scientists, biological scientists, and clinicans.

CLOSING REMARKS

NIH contributions to the field is primarily preclinical at this time. FY2008-FY2015 represents a ramping-up period in translating nanotechnologies with a significant number of projects focused on engineering nanomedicine in four categories: Dental Implants and Regeneration, Early Detection and Diagnosis, Drug Development and Improved Therapies, and Medical Instrumentation and Devices. The vast majority of the NIH landscape focused on cancer and to a much lesser extent, cardiovascular disease, diabetes, HIV/AIDS, and other infectious diseases. Cancer nanotherapeutic in clinical trials have been sponsored by companies with interests in obtaining NDAs. The data collected thus far has illustrated the benefit of reformulating highly toxic drugs that currently exist with less adverse side effects. Diagnostic devices that incorporate nanosensors are also making their way to 510K or PMA status. The release of focused FOAs that created research centers, provided infrastructure, and specified network collaboration contributed greatly to the clinical translation of both drugs and devices. Much of these activities are still underway with the advent of specialized research communities for translational nanomedicine.

There is also significant preliminary evidence from the NIH nanomedicine research portfolio that demonstrate the potential for nanotechnology to enhance the therapeutic effect of current standard treatment modalities and quality of life. During the 8 years studied, a variety of nanoparticle-based drugs or devices have been developed and evaluated preclinically for their ability to enhance the effect of chemotherapy, radiation therapy, surgery, medical diagnosis, and image-guided interventions. NIH also supported a vast number of nanodevice detection platforms based on their optical and magnetic properties. Although the number of clinical trials only represents about 10% (227 trials from 2373 NT-projects) of the NIH-funded portfolio with the majority of publications in the field on cancer nanomedicine, we anticipate a significant number of new drug/device products (besides cancer drugs) will undergo clinical evaluation in the next 5-7 years.

Nanomedicine is still an emerging area and warrants continued support by the federal agencies especially with respect to biology and medicine. Much work is still needed to modify selective targeting agents to advance precision medicine, elucidate biological mechanisms to develop innovative therapies, pursue solutions to high-value imaging for patient-centered outcomes, and to manufacture and multi-dimensional nanomedicine products and patient-centered radiological outcomes. Therefore, NIH remains committed to supporting the best solutions in pursuit of the various missions of the NIH Institutes utilizing effective grant mechanisms (*e.g.*, research centers, cooperative networks and infrastructure, public-private partnerships) to facilitate the clinical translation of nanomedicine under investigation today. Besides supporting great scientists, NIH staff participates at the national level by collaborating with other agencies and the White House Office of Science and Technology Policy through the NNI and other Presidential programs like the Brain Initiative, Precision Medicine, and Cancer Moonshot Initiatives. For instance, the author, Dr. Henderson, serves as a co-chair of the NSET Subcommittee.

This subcommittee operates under the auspices of the National Science and Technology Council, a cabinet-level council chaired by the president.

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