2013

NCI Alliance for Nanotechnology in Cancer

Annual Bulletin

Contents

INTRODUCTION

BY DOROTHY FARRELL

The third year of Phase II of the NCI Alliance for Nanotechnology in Cancer was a busy and productive one for the Alliance. Our investigators published over 300 papers in 2013, bringing the total number of Alliance publications over the past three years to approximately 1,100. Alliance research continues to be high profile and high impact, as measured by the quality of journals in which Alliance research is published, as well as the high citation rates for these papers. The program office's analyses indicate that Alliance publications have consistently high citation rates when compared to other NIH programs and investigator pools, a testament to the quality and importance of Alliance research. The value of contributions our researchers are making to the translation of nanoparticle therapeutics into clinical practice and in extending nanotechnology's reach into global health applications has also been recognized by multiple outlets in the scientific and lay literature. More details about coverage of Alliance research can be found in the Nano in the News section of the Bulletin. News about individual Alliance members, including new faculty appointments, can be found in the Transitions section.

This year also saw Alliance researchers pool their expertise and experiences to publish pieces that go beyond basic research and provide valuable perspective on important issues in nanomedicine development, including biotargeting, nanoparticle imaging techniques, and clinical considerations when relying on the Enhanced Permeability and Retention effect for drug delivery. Information about these efforts, which highlight the importance of the Alliance network in moving the field of cancer nanotechnology forward, is given in the Alliance Working Groups' Updates section of the Bulletin.

Throughout 2013, the Alliance program office was also busy as it undertook extensive efforts to reach out to stakeholders in the research, industrial, and patient communities to identify needs and opportunities in cancer nanotechnology research. These efforts included crowdsourcing strategies coordinated through a dedicated website (nanocancer.ideascale.com) and a Request for Information on the Directions and Needs for Cancer Nanotechnology (grants.nih.gov/grants/guide/notice-files/NOT-CA-13-017.html). The insights gained through these forums are discussed in the Crowdsourcing section of the Bulletin. The office also organized a Strategic Workshop on Cancer Nanotechnology in June 2013 that brought together leading clinicians, researchers, and industry representatives to discuss the outlook for cancer nanotechnology research over the next five years. Following two days of scientific talks and focused breakout sessions, workshop participants prepared recommendations to present to the program office on the highest priorities and best next steps for NCI support of cancer nanotechnology research. Workshop discussions and recommendations were distilled into a report published online by Cancer Research in January 2014 (Grodzinski and Farrell, "Future Opportunities in Cancer Nanotechnology – NCI Strategic Meeting Report"). The responses received to these outreach efforts are helping to shape NCI's plans for its next stage of dedicated support for cancer nanotechnology research, as well as clarifying the role nanotechnology research can play in other initiatives at both NCI and NIH. Some initiatives that stand to benefit most from nanotechnology and that offer opportunities for strong engagement from the Alliance community are detailed in the Funding Opportunities section of the Bulletin.

As we progress through the Alliance program's fourth year, it seems clear the third year was another successful one for the program. This has also been a year marked by several diverse efforts to reach out to the wider scientific community, as demonstrated by the myriad news stories, perspective articles, and solicitations for community input, all focused on advancing the cancer nanotechnology field. The following pages offer a snapshot of these efforts, which we hope you will enjoy reviewing and find helpful in your next endeavors.

For more information on Alliance programs and members, please visit http://nano.cancer.gov/action/programs.

NIH Funding Opportunities Extend the Range of Cancer Nanotechnology in Biomedical Research

BY STEPHANIE A. MORRIS

The application of nanotechnology to medicine has been seen by the NIH as a means to develop cutting-edge research that can drive biomedical innovations. From the involvement of several NIH institutes in the Nano-science and Nanotechnology in Biology and Medicine Initiative (PA-11-148 and PA-11-149), which identifies nanotechnology as an area of increased priority, to the NIH Common Fund Nanomedicine Initiative, NIH's recognition of the importance of nanotechnology in advancing biology findings to clinical application can clearly be seen. The NIH Nanomedicine Initiative, a 10-year program, was specifically developed because of the potential high reward of nanotechnology when used to address clinical problems. The initiative supports the necessary collaborations between basic biologists, physical scientists, and clinicians to speed the development of nanotechnology-based solutions. The outputs of these initiatives are evidence of the varied ways in which nanotechnology can be utilized, as well as of the potential for collaborations to rapidly speed the process of innovation. With this in mind, other programs and initiatives with opportunities for nanotechnology strategies are in the midst of development or newly funded.

Research Answers to NCI's Provocative Questions

Currently in its third year, the purpose of NCI's Provocative Questions Initiative is to study what the community considers to be understudied problems in cancer research. Prior to the issuance of the first Requests for Applications (RFAs) in 2011, the NCI sponsored a website accessible to the community and 16 workshops were held across the country to identify unresolved basic, translational, clinical, and population-based cancer research issues. Collectively, these were defined as a set of 24 "Provocative Questions" (PQs) that, in some cases, were long-standing scientific questions that could only now be answered because of advances in scientific discoveries or technologies. By raising these questions the goal would be for scientists to develop new approaches and solutions to address specific gaps in current knowledge.

The first year's PQs (2011) covered three broad areas: (1) new questions that could be asked because of new technical advances and scientific discoveries; (2) neglected scientific problems that yield new value due to current knowledge; and (3) questions that reshape current cancer conceptions. More than 750 applications were received in response to the 2011 RFAs, utilizing R01 research project (RFA-CA-11-011) and R21 exploratory/developmental grant (RFA-CA-11-012) funding mechanisms. Fifty-six of the applications submitted were funded. Interestingly, 11% of these awards utilized nanotechnology to address several different topics such as cancer risk and prevention, detection, diagnosis, tumor development, and treatment, thus highlighting the innovative nature of these technologies. Plans to annually invite requests for applications for another two years were in place at the start of the initiative. The objective of the second issuance of the PQ RFAs was to continue stimulating cancer research into areas considered difficult to address, neglected, or understudied, using a revised set of 24 PQs. The selection of new PQs was based on the questions funded in the prior year, as well as recommendations from the research community and NCI program staff, with the goal of identifying novel and innovative answers. The PQs were also divided into four thematic groups to aid applicants in identifying the most appropriate topical area: Group A, Cancer Prevention and Risk; Group B, Mechanisms of Tumor Development or Recurrence; Group C, Tumor Detection, Diagnosis, and Prognosis; and Group D: Cancer Therapy and Outcomes (NOT-CA-12-014; RFA-CA-12-015—RFA-CA-12-022). With two opportunities to submit applications in the program's second issuance, approximately 227 applications were received by the first receipt date in December 2012, and 29 of these were awarded. The average number of nanotechnology-related applications is consistently ~4% for each receipt date, including those received during the first year. By the end of the second receipt date in June 2013, more than 700 applications combined were received. It remains to be seen if any of those awarded following this second date will utilize nanotechnology in their planned approach.

Although award decisions from the Initiative's second issuance have not all been made, the PQs for the 2013 RFAs, the third issuance for the initiative, are now available on the PQ website along with background, feasibility, and implications of success for each question (http://provocativequestions.nci.nih.gov/rfa). There are now five, rather than four, categories of PQs that can be addressed in R01 and R21 research projects. The number of PQs has also been reduced to 20. The five categories are:

- Group A: Cancer Prevention and Risk (R01) (RFA-CA-13-016); (R21) (RFA-CA-13-017)
- Group B: Mechanisms of Tumor Development and Recurrence (R01) (RFA-CA-13-018); (R21) (RFA-CA-13-019,)
- Group C: Tumor Detection, Diagnosis, and Prognosis (R01) (RFA-CA-13-020); (R21) (RFA-CA-13-021)
- Group D: Cancer Therapy and Outcomes (R01) (RFA-CA-13-022); (R21) (RFA-CA-13-023)
- Group E: Clinical Effectiveness (R01) (RFA-CA-13-024); (R21) (RFA-CA-13-025)

In this current round, some of the previous PQs were adjusted or removed. This was due to a combination of factors, such as the number of applications previously received for a given PQ, but also to give new PQs a chance to be addressed. The newest category, Clinical Effectiveness, is an opportunity for researchers and clinicians to develop new strategies and programs that can guide clinical care and more effectively treat patients. Each set of PQs was issued as a separate R01/R21 application solicitation (see above), and was published in October 2013. There are two receipt dates: January 15, 2014 and June 20, 2014, with letters of intent due on December 16, 2013 and May 20, 2013, respectively. For each group of PQs, NCI intends to fund approximately four to six R01s and three R21s, corresponding to a total up to $2-3 million and $0.5-1 million, respectively. However, the final number of awards will be contingent upon the number of meritorious applications and funds available. As in previous rounds, applications that address any of these posted PQs will be accepted, but they must be responsive to only one of these questions and must indicate the PQ addressed in the proposal. In response to the PQs, applications are expected to display a high level of innovation as well as thoroughness. Successful grants will hopefully spawn new research areas. In turn, because these applications will in most cases focus on understudied or perplexing research areas, preliminary data will not necessarily weigh as heavily as the rationale and experimental design of the proposed research. With that said, scientific rigor is extremely important. It is also expected that innovative ideas are likely to be derived from researchers who are new to the field, which will be considered during proposal evaluations.

Cancer Detection, Diagnosis and Treatment Technologies for Global Health

Access to cancer screening, detection, diagnosis and treatment are significant challenges in low resource settings and countries, especially in rural areas with limited medical infrastructure. Yet, the incidence rate of cancer is increasing in many of these areas, and cancer remains a leading cause of death. Further, most of the currently available cancer detection and treatment technologies are not practical in these environments because of cost or the need for extensive medical infrastructure. Recently developed technologies such as in vitro analyses using biosensors, cryotherapies, lab-on-chip, and imaging modalities/technologies have the potential to be adapted for low cost settings, but there is very little data to validate their application and effectiveness. To address these needs, the NCI Center for Global Health launched a new funding initiative in October 2013 called The Cancer Detection, Diagnosis, and Treatment Technologies for Global Health.

While the majority of NIH funding opportunities focus on novel discoveries, this new initiative (RFA-CA-13-015) asks applicants to take existing or emerging technologies, and apply or adapt them into next generation cancer technologies, devices, assays, and treatments that are useable in low and middle income countries with a focus on user-friendliness, and low cost for use. Applications were due in early January 2014 with awards to be made towards the end of spring 2014. This particular award uses a less common funding mechanism, the UH2/UH3 phased innovation awards cooperative agreement. Under this agreement, the award supports a two-phased support mechanism in which the UH2 phase (up to two years) serves as the initial exploratory phase to demonstrate the feasibility of the proposed technology for clinical potential. The most promising of the funded projects will be selected for the UH3 validation phase (up to 3 years) after the exploratory phase is completed. The proposed projects had to be based on a working prototype

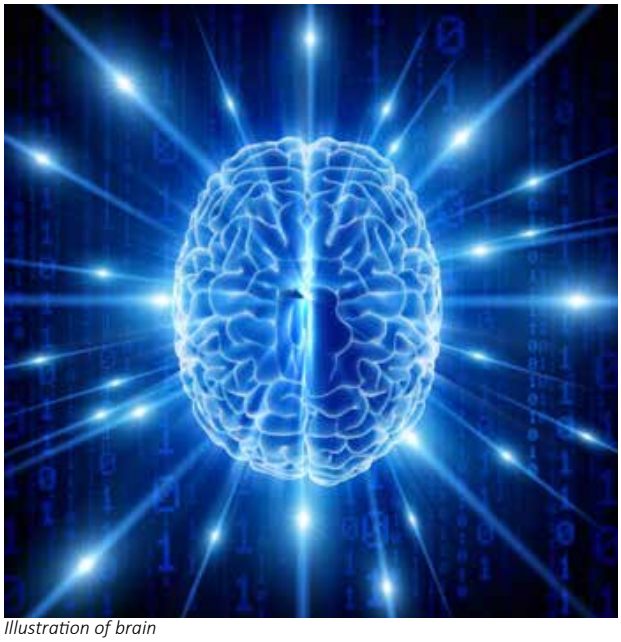


Illustration of brain

or an existing device with preliminary data at the award start to demonstrate its potential to achieve low cost, and for diagnostic devices the potential to serve as point-of-care tools with fast detection and accuracy. After implementation, proposed projects are expected to provide tools that are comparable to currently established technologies. Additionally, because of the nature of the award and purpose of the initiative, projects were required to establish multidisciplinary teams with expertise in oncology, global health care delivery, business development, and engineering to increase their potential success. NCI expects to fund up to six awards for the exploratory, UH2 phase. The amount of funds available is $3 million total for this first year.

Concurrent with application submission, a Cancer Detection Diagnostics and Treatment Technologies for Global Health symposium was held on January 10, 2014 at the NIH campus, and was sponsored by the NCI Center for Global Health. The purpose of the symposium was to promote the development of low-cost, portable cancer technologies, concluding with an overview of the initiative. The symposium also acted as a closing event for a larger conference co-sponsored by NCI and NIBIB (National Institute of Biomedical Imaging and Bioengineering) on Point of Care Technologies for Cancer held January 8-10, 2014. Through formal presentations and discussions, the conference provided an opportunity for bioengineers to learn about important cancer research topics, and identify potential technologies that could be refined through collaborations. If interested in learning more about this conference, please visit http://ncifrederick.cancer.gov/events/PointOfCare/default.asp. To learn more about the Cancer Detection, Diagnosis and Treatment Technologies for Global Health Initiative and others supported by the NCI Center for Global Health, please visit http://www.cancer.gov/aboutnci/globalhealth.

Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative

Announced by President Barack Obama on April 2, 2013, the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative proposes to bring together nanoscience, engineering, computational science, neurology, and many other research areas to make sense of how the brain works, and an understanding of ways to prevent, treat, and cure diseases of the brain. Initially catalyzed by the Kavli's Foundation's Brain Activity Map Project (outcome of a group meeting involving nanoscientists and neuroscientists), this is an effort launched by the NIH, the Defense Advanced Research Projects Agency (DARPA), and the National Science Foundation (NSF) with a proposal for federal funding of approximately $100 million during fiscal year 2014 (FY14). Private foundation partners, the Allen Institute for Brain Science, the Howard Hughes Medical Institute, the Salk Institute for Biological Studies, and the Kavli Foundation are also investing in this initiative with their own funding opportunities (see BRAIN Initiative Fact Sheet).
To discuss how this new effort should be focused at NIH, the Advisory Committee to the Director (ACD) convened a high level working group, the NIH BRAIN Working Group, to develop an extensive multi-year plan for achieving this scientific vision, which would involve many centers and institutes. The 15-member group was co-chaired by neuroscientists Cornelia Bargmann (Rockefeller University) and William Newsome (Stanford University), and charged with defining the milestones and cost estimates for NIH's investment. To begin meeting this request, the working group reached out to a broad community of scientists through a series of four workshops held across the United States in spring/summer 2013, culminating in an interim report that outlined a list of high-priority areas to be considered for FY14 funding (www.nih.gov/science/brain/11252013-Interim-Report-Final.pdf).

The report was released by the group in September 2013, and included nine high-priority research areas with an overarching goal of combining these approaches to develop an advanced understanding of how neuronal networks interact, ranging from individual genes to complex behaviors. These findings were recommended to the NIH Director by ACD, and used as a guide for the development of the initial BRAIN Initiative RFAs. In December 2013, six NIH funding opportunities for the initiative were announced. NIH intends to commit at least $40 million for projects funded during the next year with contributions from the NIH Blueprint for Neuroscience Research, the NIH Director's Office, and individual institutes. The RFAs will primarily fund U01 research project cooperative agreement awards and include one RFA for R24 resource-related research projects. The funding opportunities are:

- Transformative Approaches for Cell-Type Classification in the Brain (U01) (RFA-MH-14-215)
- Development and Validation of Novel Tools to Analyze Cell-Specific and Circuit Specific Processes in the Brain (U01) (RFA-MH-14-216)
- Planning for Next Generation Human Brain Imaging (R24) (RFA-MH-14-217)
- New Technologies and Novel Approaches for Large-Scale Recording and Modulation in the Nervous System (U01) (RFA-NS-14-007)
- Optimization of Transformative Technologies for Large Scale Recording and Modulation in the Nervous System (U01) (RFA-NS-14-008)
- Integrated Approaches to Understanding Circuit Function in the Nervous System (U01) (RFA-NS-14-009)

There will be one receipt date for each of these opportunities and all awards are expected to be made by September 2014. Applications for RFA-MH-14-215, RFA-MH-14-216, and RFA-MH-14-217 are due by March 13, 2014, with letters of intent due February 13, 2014. Applications for RFA-NS-14-007, RFA-NS-14-008, and RFA-NS-14-009 are due by March 24, 2014, with letters of intent due February 24, 2014. For each of the RFAs, the amount of funding and number of awards varies between $4 million and $10 million, and seven to 10 awards (please check individual announcements). The majority of the funding opportunities focus on feasibility testing and the development of new technologies and approaches to understand how information is stored and processed in neural networks. Because of the innovative nature of the projects, similar to NCI's PQs, preliminary data is not a strict requirement for most of the requested applications. Only one funding opportunity, Optimizing of Transformative Technologies for Large Scale Recording and Modulation in the Nervous System (RFA-NS-14-008), requires preliminary data. For all opportunities, applications that propose integration of multiple approaches and inter-disciplinary collaborations are encouraged. The formation of interdisciplinary teams is required for projects proposed in response to RFA-MH-14-217 and RFA-NS-14-009. In particular, RFA-MH-14-217, Planning for Next Generation Human Brain Imaging, calls for the creation of teams composed of imaging scientists, engineers, material scientists, nanotechnologists, and computer scientists to plan innovative approaches for the development of next generation imaging techniques. This initial round of awards will help determine which requested projects will have the most promise and would benefit from a second round of funding. In parallel with review of the inaugural applications, the NIH BRAIN Initiative Working Group's final report will be delivered to ACD in June 2014, and will include longer term recommendations for the specific goals and milestones needed to guide the progress of the BRAIN Initiative over multiple years.

Websites:

- NIH Common Fund Nanomedicine Initiative
  www.commonfund.nih.gov/nanomedicine
- NCI Provocative Questions
  provocativequestions.nci.nih.gov
- NCI Center for Global Health
  www.cancer.gov/aboutnci/globalhealth
- National Science Foundation (NSF): Understanding the Brain
  www.nsf.gov/news/newsmedia/sfn_brain_factsheet.pdf
- Defense Advanced Research Projects Agency (DARPA)
  http://www.darpa.mil/Opportunities/Solicitations/DARPA_Solicitations.aspx
- Fact Sheet: BRAIN Initiative
  www.whitehouse.gov/the-press-office/2013/04/02/fact-sheet-brain-initiative
- NIH BRAIN Initiative
  www.nih.gov/science/brain
- NIH Blueprint for Neuroscience Research
  neuroscienceblueprint.nih.gov

Participants in the Alliance-hosted TONIC Workshop on Enhanced Permeability and Retention (EPR) Effect, NIH Bethesda Campus October 2012.

Alliance Working Groups Provide their Opinions to the Nanotechnology Community

BY DOROTHY FARRELL AND STEPHANIE A. MORRIS

The Office of Cancer Nanotechnology Research coordinates eight working groups* in areas of scientific and practical importance to Alliance researchers. Each group has its own mission to facilitate the discussion and exchange of ideas, and is chaired by one or two volunteer Alliance members. Levels of participation and output vary across the groups, although most hold regular teleconferences to discuss topics of emerging and shared interest. Working groups, like the Animal Models and Nano-formulation and Nanosynthesis groups, are seeking consensus on appropriate models and minimum information standards for research and publications in the field, with the intention of sharing these standards across the Alliance. The Alliance is also working with NCI's National Cancer Informatics Program Nanotechnology Working group to further these goals and provide resources like the cancer Nanotechnology Laboratory Portal for data sharing (Gaheen et al., 2013, *Computational Science & Discovery*, "caNanoLab: data sharing to expedite the use of nanotechnology in biomedicine"). These efforts are helping the program office to understand and define community needs for research resources and data infrastructure, as well as provide opportunities for participation in other federal initiatives and cross-agency activities.

The most engaged groups, Biotargeting and Imaging, have prepared and published their insights, reflecting the combined experience of their members. Formed to address challenges in

developing targeted cancer nanomedicines, the Biotargeting Working Group authored and published in Nanomedicine the perspective piece "Biotargeted nanomedicines: Six tenets before you begin," in early 2013 (Goldberg et al., 2013). The piece focuses on the biological and translational difficulties that must be navigated for successful market approval of targeted nanomedicines. One of the major biological challenges identified by the working group is the selection of an effective membrane protein to target with an appropriate targeting moiety, the latter of which must be simultaneously specific and internalizing. An additional challenge is in developing a strategy for overcoming the multiple physiological barriers nanomedicines face in transit from circulation to the interstitial tumor space, to the plasma membrane and into the appropriate organelle. The perspective highlights the necessity to choose and design appropriate materials particularly with respect to surface properties and interaction with biological surfaces to maximize success. In keeping with the translational focus of the Alliance program, issues of manufacturing, including quality control and scale-up, regulatory review, and cost-effectiveness were addressed in the working group's analysis.

The Imaging Working Group took on a similar task of reviewing the current status of nanoparticle-based cancer imaging and identified the major challenges that have prevented successful clinical translation of numerous nanoparticle contrast agents (Chapman et al., 2013, Nano Today, "Nanoparticles for cancer imaging: The good, the bad, and the promise"). This paper also addressed regulatory considerations, particularly important for imaging agents, which may face a higher regulatory scrutiny than therapeutics because of the differing risk-benefit calculations for the two uses. The paper highlights opportunities in the area, while acknowledging difficulties that existing nanoparticle contrast agents like Feridex and Combidex have had in securing regulatory approval and market acceptance. The consensus of the group is that the greatest opportunity lies in the multifunctional capabilities of nanoparticle imaging, particularly for multi-modal imaging and the simultaneous collection of complementary images over space and time.

Likewise, members of the Translation Of Nanotechnology In Cancer (TONIC) Consortium, an NCI-initiated public-private partnership involving the Alliance, published a report in *Cancer Research* on an issue of great concern to industry, the Enhanced Permeability and Retention Effect (EPR) (Prabhakar et al., 2013, "Challenges and key considerations of the Enhanced Permeability and Retention Effect for nanomedicine drug delivery in oncology"). The primary goals of TONIC are to accelerate clinical translation of nanotechnology by promoting collaborations between Alliance investigators and industry partners, and providing Alliance researchers insight into industry needs in technology platforms and drug targets. To meet its goals, TONIC has conducted regular meetings through teleconferences and face to face meetings to discuss nanotechnology research gaps that the community has yet to fill and concerns about the efficiency of drug delivery. EPR was identified at one of these meetings as a key concern that must be understood in nanoparticle therapeutics, resulting in a one-day EPR workshop in October 2012. In the published report, members highlighted the key outcomes of this meeting, which included a discussion of the experimental evidence of EPR in animal models and humans, factors influencing EPR, and ways to address gaps in what is known about this phenomenon to advance the development of nanoparticle-based drug delivery technologies. TONIC members also formed a nanodrug clinical working group to discuss clinical protocols that will enable further studies of EPR activity in patients using imaging approaches. The working group has recognized and is addressing the fundamental limitations and gaps in preclinical tumor models in recapitulating characteristics of solid tumors in patients.

*Alliance Working Groups: Biotargeting; Genetic Therapy/RNA Interference; In Vitro Diagnostics and Cancer Detection; Imaging; Nanoformulation and Nanosynthesis; Animal Models; Nanoparticle Biodistribution; and Communication and Integration

Websites:

- National Cancer Informatics Program Nanotechnology Working Group (NCIP Nano WG) https://wiki.nci.nih.gov/display/ICR/Nanotechnology+Working+Group
- NCI cancer Nanotechnology Laboratory (caNanoLab) Portal https://cananolab.nci.nih.gov/caNanoLab

Crowdsourcing and the Dialogue on Nanotechnology in Cancer

BY LYNN HULL

In an effort to seek input about the Alliance program from a wide audience, the Office of Cancer Nanotechnology Research set up a crowdsourcing website, the Dialogue on Nanotechnology in Cancer (https://nanocancer.ideascale.com), in early 2013. Crowdsourcing websites have been used by NIH, as well as other federal government agencies, to gather feedback from the public for a variety of reasons from programmatic direction to website utility.

Traditionally, input on program direction comes from publications in the field, feedback from researchers in the program, and solicited comments from experts outside of the program. However, by using a crowdsourcing platform we were able to allow a broader audience to participate in this information gathering process, including more junior members of the field, as well as international members of our research community. This online platform had the additional benefit of permitting users to comment on one another's ideas, as well as vote for or against ideas. This allowed for an organic sorting to occur with the most popular ideas floating to the top of the group.

During the three months we were actively seeking input on the website, March to May 2013, we had 1,357 unique visits to the site and 4,922 page views. The visits to the site came from 82 countries. The most frequent country represented was the USA, with 65% of the visitors. The next five countries represented were India, the United Kingdom, Spain, Canada, and Indonesia. In total we had 116 registered users of the site with the submission of 28 ideas followed by 39 comments and 154 votes on those ideas.

The topics discussed in the submitted ideas included Targeting, Drug Delivery, Metastasis and Circulating Tumor Cells, Tumor Microenvironment, Pharmacokinetics, Nanoinformatics, Thermal Ablation, Nanocharacterization, Imaging, Biomarkers, Immunotoxicity and Clinic to Lab Translation. In addition to these ideas being taken into consideration by the program office, they were also presented at a Strategic Workshop on Cancer Nanotechnology organized by the office in June 2013.

As a next step for the Dialogue website, we have been soliciting educational videos from the Alliance and the wider cancer nanotechnology community to post on the site. Some videos are meant to educate the research community and general public, while others are meant to share information about innovations and resources available to the field. Currently, videos from the David H. Koch Institute for Integrative Cancer Research at MIT, Northwestern University, University of Kentucky, Case Western Reserve University, and the Nanotechnology Characterization Laboratory are posted. New videos will be posted as we receive them, as well an announcements for upcoming opportunities to refine existing ideas and post new ones.

In addition to the crowdsourcing effort, the office also posted a Request for Information (RFI) on the Directions and Needs for Cancer Nanotechnology (grants.nih.gov/grants/guide/notice-files/NOT-CA-13-017.html), which has provided the program office with insight into what a wide group of individuals of different career levels felt would benefit the field, as well what barriers need to be overcome for successful advancement. Developed and posted by the program office on the NIH Office of Extramural Research's Grants and Funding website on September 12, 2013, the last RFI response was received on December 15, 2013. The purpose of the RFI was to gain feedback from interested members of the cancer nanotechnology community, other relevant scientific communities, and the American public about specified cancer-relevant nanotechnology topics, including its support by NCI. We received 31 separate responses made up of a total of 76 participants. Overall, the respondents had many suggestions for where the field of cancer nanotechnology should progress scientifically, pro-grammatically, in training, and in translation and commercial development. A summary of the RFI responses is available on the Alliance website at http://nano.cancer.gov/about/activities/publications.asp.

NANO in the **NEWS**

2013 GEM4 Bionanotechnology Summer Institute. Faculty, graduate students, and researchers representing 18 international and domestic universities that participated in the 2013 Summer Institute at the University of Illinois at Urbana-Champaign July 29-August 9, 2013. Attendees participated in lectures and hands-on training in engineering and physical science laboratory techniques taught by experts in the field. For more information, go to http://www.nano.illinois.edu/BioNano2013. Courtesy of the Midwest Cancer Nanotechnology Training Center (M-CNTC).

Creating Steam with Gold Nanoparticles

Naomi Halas, PI of the Rice University Platform award "Preclinical Platform for Theranostic Nanoparticles in Pancreatic Cancer," was elected to the National Academy of Sciences in April 2013. Halas is a pioneer in plasmonics, nanophotonics and nano-particle design and is at the leading edge of using the unique properties of engineered nanomaterials to tackle stubborn societal problems. Her inaugural article (Neumann et al., 2013) in the *Proceedings of the National Academy of Sciences* in July 2013 was dedicated to recent work from her lab showing that focused sunlight can create high temperature steam from a mixture of gold or carbon coated silica nanoparticles in water, without an additional power source. The process was used to create a portable autoclave for sterilizing medical equipment and a unit for sanitizing animal or human waste, both potentially suitable for use in low resource settings. The work illustrates intriguing features of nanoparticle mediated heating, as steam forms before the water bath reaches boiling temperature. Light absorption by nanoparticles leads to vaporization of the water immediately surrounding nanoparticles, creating steam "bubbles" that rise and merge with other bubbles before reaching the surface and releasing the steam. The steam bubbles insulate the nanoparticles from the larger mass of water, so comparably little energy is

lost to heating the water bath. The work is supported by the Bill and Melinda Gates Foundation and has been featured in the *Washington Pos*t. You can learn more about the work in the initial ACS Nano publication (Neumann et al., 2013) electronically published in November 2012.

Gold Nanoparticles Move Forward in Biomedicine

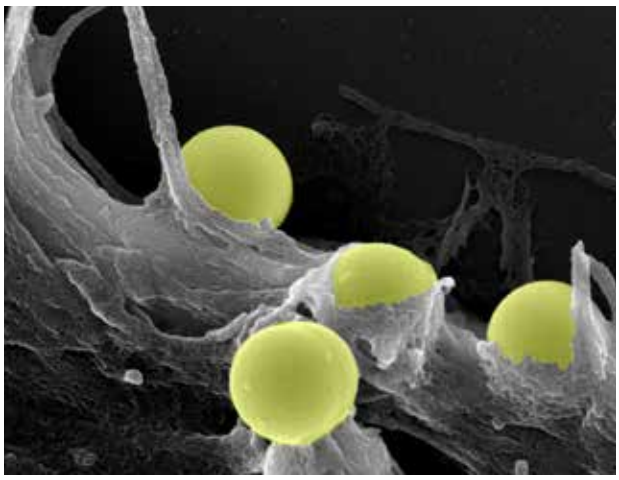
The work of Alliance PI Naomi Halas with gold nanoparticles was featured alongside that of Northwestern University Center PI Chad Mirkin in a March 2013 *Nature Outlook* article "The new gold standard" about the recent growth in biomedical applications for gold nanoparticles. Halas and colleagues have established that laser heating of gold nanoshells can destroy tumors in a highly targeted fashion, research that has led to the initiation of two clinical trials of the technique in head and neck, and lung cancer. Halas has also recently shown that ultraviolet irradiation can trigger release of anti-sense DNA or siRNA from the surface of gold nanoshells, opening another avenue for potential therapeutic application for the nanoshells. Chad Mirkin's research in oligonucleotide coated gold nanoparticles is also leading to multiple applications in biomedicine. Two recent innovations based on these materials, the expansion of the Verigene diagnostic platform for the rapid detection and identification of antibiotic resistant bacteria and the use of spherical nucleic acids (SNAs) for gene delivery in cancer treatment, were spotlighted in the piece. The excellent trans-cytosis properties of the SNAs make them particularly promising for topical treatment of skin diseases like melanoma and for passage through the blood-brain-barrier to deliver therapy to highly lethal brain cancers. The article also captured exciting applications in drug delivery and cellular imaging.

AAAS Spotlights Rashid Bashir

In June 2013, PI Rashid Bashir of the Midwest Cancer Nanotechnology Training Center was the subject of a AAAS Member Spotlight, "Rashid Bashir brings engineering to life." Bashir's research is built on a love of building and a desire to harness and expand on the capabilities of biological systems to create new machines with greater functionalities. Beginning with two undergraduate biology courses, Bashir has charted a career at the intersection of engineering and medicine, leading to his recent appointment as head of the Department of Bioengineering at the University of Illinois Urbana-Champaign. Bashir will lead the department through growth spurred by the Grainger Engineering Breakthoughs Initiative, which began in January 2013 with $100 million in support from the Grainger Foundation. His own research interests are in the area of BioMEMS, lab on a chip and nanopore sequencing devices. His nanopore work in particular has gained recognition for the development of a sensor for methylated DNA in collaboration with colleagues from the Mayo Illinois Alliance for Technology Based Healthcare. The sensor could improve the detection of disease related gene expression in clinical samples, while the researchers are also interested in pursuing nanopore devices for low-cost, fast, reliable and high-accuracy sequencing of whole genomes. Bashir's interest in biomedical nanotechnology extends beyond research and into extensive training and international collaboration efforts. In addition to the training center, Bashir runs an NSF-funded IGERT training program, and Illinois hosts an annual BioNanotechnology Institute that attracts participants from around the world.

Wider Recognition of Nanotechnology Therapeutics for Cancer

In July 2013, OncLive recognized the growing importance of nanotechnology efforts in cancer therapy in an article by Andrew D. Smith, "Big Moment for Nanotech: Oncology Therapeutics Poised for a Leap." With input from Alliance members Mark E. Davis of Cal Tech and Ennio Tasciotti of the Methodist Hospital Research Center and Program Director Piotr Grodzinski, the article outlines the advantages of nanoparticle drug delivery, such as tumor specificity, decreased toxicity and a rapid pace of innovation leading to ever better nanoparticle designs. Promising results from a number of clinical trials, including a Phase 1 clinical trial of Alliance affiliated BIND Therapeutics' lead candidate BIND-014 and trials testing efficacy in additional indications for the FDA approved paclitaxel formulation Abraxane, have provoked new interest in nanoparticle therapeutics from large pharmaceutical companies. The article highlights some of the recent moves by these companies to enter the nanotechnology field, such as the deals struck between BIND and Amgen, AstraZeneca and Pfizer to develop BIND's polymeric nanoparticle platform for delivery of proprietary drugs provided by these pharmaceutical companies. These deals could have a value of greater than $1 billion if all milestones are met, giving an indication of the potential for nanoparticle drug delivery to have a major impact on cancer therapeutics in the next decade. OncLive is the official website of the Oncology Specialty Group and is dedicated to providing oncology professionals with the resources and information they need to provide the best patient care.



One of the winners in the FASEB's 2013 BioArt Competition. Scanning electron micrograph of silica beads (colored yellow), nanospheres used for drug delivery, on the surface of a human fibroblast cell. Courtesy of Matthew Ware and Biana Godin Vilentchouk from the Texas Center for Cancer Nanomedicine.

Cancer Research a Major Presence in Houston

In August 2013, Bayan Raji profiled the significant investment in cancer research in the Houston area for the Houston Business Journal, and spoke to researchers about the outlook for the field in the face of major cuts in federal funding due to the sequester and flat budgets for NCI. Texas is a hub for cancer research, receiving over $100 million from NCI in fiscal year 2013 and home of the Cancer Prevention and Research Institute of Texas (CPRIT), which aims to spend over $3 billion over 10 years. Commercialization is a major goal of CPRIT, underscoring the economic importance cancer research has taken on in the state, which has staked significant funds on cancer research to garner both public health and economic benefits. Texas CCNE PI Mauro Ferrari was quoted in the piece about the extent to which the Houston community, including its many hospitals and academic centers, recognizes the importance of discoveries in cancer research and the value of collaborating to develop new strategies to treat the disease. The state remains committed to CPRIT and its dual research and commercialization focus, and CPRIT recently began awarding grants again following a moratorium brought on by irregularities in funding commercialization awards.

NCL's Efforts to Drive Nanomedicine Towards the Clinic Recognized

In September 2013, the *Chemical & Engineering News* profiled the Nanotechnology Characterization Laboratory (NCL) and its efforts to move nanomedicines into clinical trials. In a story and accompanying video, the process by which NCL evaluates submissions and then characterizes and helps prepare them for clinical testing is outlined. NCL's role in "bridging the gap" between basic research and clinical trials is critical for the nanomedicines they characterize, and the article explains how NCL accomplishes this mission. Rapid testing of the most basic and necessary parameters, such as sterility and reproducible size, allows NCL to halt many compounds early in the process, saving time and money over the long term. NCL also helps diagnose and correct the errors in synthesis and processing that lead to these early failures, bringing the nanomedicines back on track for further evaluation. NCL continues to work to establish standard nanomaterials that researchers can use to benchmark their materials for size, shape, and surface properties. The current absence of standards for nanomaterials is a significant concern to large pharmaceutical companies when considering entering the field, as is uncertainty about the safety of such complicated materials with multiple active ingredients and potentially reactive constituents. NCL's studies of a number of nanomedicines showing safety and non-toxicity are credited by the small companies developing these new therapeutics with providing the reassurances need by large pharmaceutical companies to invest in the field.

Alliance Members among 2013 FASEB BioArt Winners

An image of silica nanobeads on the surface of human fibroblast cells submitted by Mathew Ware and Biana Godin Vilentchouk of the Texas Center was among the winners of the 2013 FASEB BioArt contest. The contest is intended to utilize images and videos produced in scientific investigations as a resource to "engage and educate the general public, as well as policymakers, about biomedical and biological research." Ten images and two videos with accompanying non-technical captions were chosen as winners based on both their visual appeal and their ability to clearly communicate the scientific concept underlying the work that produced the image.

More News from the Alliance can be found on the Alliance website at http://nano.cancer.gov/action/news/alliance_news

Websites:

- Nanotechnology Characterization Laboratory
  ncl.cancer.gov

ALLIANCE Transitions

Steven Rosen, M.D., co-PI of the Northwestern Center of Cancer Nanotechnology Excellence, has been selected to serve as the first provost and scientific director of City of Hope Cancer Center. He will work to develop the scientific direction of City of Hope and will also be responsible for the Comprehensive Cancer Center, the Beckman Research Institute, and the Irell & Manella Graduate School of Biological Sciences. Dr. Rosen will assume this new role on March 1, 2014. At Northwestern, he is the director of the Robert H. Lurie Comprehensive Cancer Center and is a Professor in the Department of Medicine's Division of Hematology/Oncology. He oversees a basic science laboratory and clinical research team that develops technologies and novel therapeutic agents to treat patients with hematologic cancers.

Anirban Maitra, M.D., a project leader in the Center of Cancer Nanotechnology Excellence at Johns Hopkins and former co-director of the Johns Hopkins Training Center, became co-director and scientific director of the Sheikh Ahmed Bin Zayed Al Nahyan Center for Pancreatic Cancer Research at the University of Texas MD Anderson Cancer Center on August 1, 2013. In addition to his leadership at this new center, he is deputy division head for academic science in MD Anderson's Division of Pathology and Laboratory Medicine as well as a Professor in the Departments of Pathology and Translational Molecular Pathology. Dr. Maitra's laboratory investigates developmental molecular networks that are abnormally reactivated in adult cells. He also develops clinically relevant pancreatic cancer animal models that can be used in the analysis of targeted therapies. At Johns Hopkins, Dr. Maitra was a professor of Pathology and Oncology at the Sol Goldman Pancreatic Cancer Research Center, as well as an affiliate faculty member of the McKusick-Nathans Institute of Genetic Medicine. He is succeeded by Dr. Hai-Quan Mao as the co-director of the Johns Hopkins Training Center.

Wadih Arap, M.D., Ph.D. and **Renata Pasqualini, Ph.D.**, project leaders in the Texas Center for Cancer Nanomedicine, recently joined the University of New Mexico (UNM) Health Sciences Center and the UNM Cancer Center. Dr. Arap is the new Deputy Director of the UNM Cancer Center and Chief of the Division of Hematology/Oncology in the Department of Internal Medicine in the School of Medicine. He also holds the Victor and Ruby Hansen Surface Endowed Chair in Cancer Medicine. Dr. Pasqualini joined UNM as the new Associate Director for Translational Research and co-leads the UNM Cancer Center's Program in Experimental Therapeutics and Drug Discovery. She is also a Professor in the Department of Internal Medicine and holds the Maralyn S. Budke Endowed Chair in Cancer Experimental Therapeutics. Prior to their appointments, Drs. Arap and Pasqualini led a joint laboratory at the University of Texas MD Anderson Cancer Center where they used targeting technologies to develop novel cancer therapeutic, imaging, and diagnostic strategies. Dr. Arap was the Stringer Professor of Medicine and Experimental Diagnostic Imaging and Deputy Chair of the Department of Genitourinary Medical Oncology in the Division of Cancer Medicine at MD Anderson Cancer Center, while Dr. Pasqualini was the Helen Buchanan & Stanley Seeger Professor of Medicine and Experimental Diagnostic Imaging.

Wenbin Lin, Ph.D., co-PI of the Platform award "Nanoscale Metal-Organic Frameworks for Imaging and Therapy of Pancreatic Cancer," joined the faculty of the Department of Chemistry at the University of Chicago in July 2013 where he was named the James Franck Professor. He is among six newly appointed faculty members that received named professorships. His group is focused on a variety of projects that include work on metal-organic frameworks, catalysis, renewable energy, and nanomedicine. Prior to his appointment, Dr. Lin was a Kenan Distinguished Professor in the Department of Chemistry and Division of Molecular Pharmaceutics at UNC-Chapel Hill, and was also a member of the UNC Lineberger Comprehensive Cancer Center and Biomedical Research Imaging Center.

Hung-jen Wu, Ph.D., a member of the Texas Center for Cancer Nanomedicine, joined the Artie McFerrin Department of Chemical Engineering at Texas A&M University as an Assistant Professor on September 1, 2013. Prior to this appointment, he was a Research Associate in the Nanomedicine Department at Houston Methodist Research Institute. Dr. Wu's research focuses on the development of nanostructured materials for the diagnosis of diseases, including cancer.

Hui Ding, Ph.D., a research scientist working with Dr. Julia Ljubimova, PI of the Cedars-Sinai Platform award "Nanobioconjugate Based on Polymalic Acid for Brain Tumor Treatment," was appointed Assistant Professor in the Department of Neurosurgery at Cedars-Sinai's Nanomedicine Research Center. Dr. Ding's work includes polymeric drug delivery, anticancer treatment, and nanomedicine. He will continue his research in nanomedicine with a focus on the treatment of brain and breast cancers.

Katie Frato, Ph.D., a postdoctoral faculty fellow in the Boston University Cross-Disciplinary Training in Nanotechnology for Cancer Center, began an Assistant Professor position in the Department of Chemistry at Seattle University in fall 2013. Her research group is focused on the study of the structure and reactivity of metalloproteins, particularly heme-containing enzymes. At the Boston Training Center, Dr. Frato was a postdoctoral fellow in the laboratory of Dr. Sean Elliot in the Department of Chemistry where she investigated redox active enzymes.

Emily Day, Ph.D., a postdoctoral fellow in the Northwestern Center of Cancer Nanotechnology Excellence, began an Assistant Professor position in the Department of Biomedical Engineering at the University of Delaware in September 2013. Her laboratory is focused on engineering nanomaterials to detect and treat cancer. At Northwestern, Dr. Day worked in the Department of Chemistry in the laboratory of Dr. Chad Mirkin where she applied biomedical photonics and nanomedicine to create novel nanoparticle platforms. She did her graduate work at Rice University in the laboratory of Dr. Jennifer West, co-PI of the Texas Center for Cancer Nanomedicine.

Li Tang, a graduate student in the Midwest Cancer Nanotechnology Training Center, recently received his Ph.D. and was awarded a three year Cancer Research Institute Irvington Postdoctoral Fellowship that started in July 2013. This Fellowship Program provides support to fund and train young scientists in cancer immunology at top universities and research centers around the world. Li is carrying out his postdoctoral training in the laboratory of Dr. Darrell Irvine at MIT, which is focused on cancer immunotherapy and the development of an HIV vaccine. As a graduate student, Li worked in the laboratory of Dr. Jianjun Cheng in the Department of Materials Science and Engineering.

Brian Dorvel and **Sean Sivapalan** graduated with their Ph.D.s from the Midwest Cancer Nanotechnology Training Center. Brian joined Dow Chemicals as a Senior Analytical Chemist and Sean is a Process Engineer at Intel Corporation. While graduate students in the Midwest Training Center, Brian was in the Biophysics Department under the supervision of Drs. Rashid Bashir and Susan Clare, and Sean was in the Department of Materials Science and Engineering under the supervision of Drs. Catherine Murphy and Rohit Bhargava.