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ABSTRACT

Nanotechnology – the science and engineering of manipulating matter at the molecular scale to create devices with novel chemical, physical and biological properties – has the potential to radically change oncology. Research sponsored by the NCI Alliance for Nanotechnology in Cancer has led to the development of nanomaterials as platforms of increasing complexity and devices of superior sensitivity, speed and multiplexing capability. Input from clinicians has guided researchers in the design of technologies to address specific needs in the areas of cancer therapy and therapeutic monitoring, \textit{in vivo} imaging, and \textit{in vitro} diagnostics. The promising output from the Alliance has led to many new companies being founded to commercialize their nanomedical product line. Furthermore, several of these technologies, which are discussed in this paper, have advanced to clinically testing.

Keywords: nanotechnology, oncology, imaging, diagnostic, treatment, multidisciplinary research team

1. INTRODUCTION

Nanotechnology offers an untapped resource to study and interact with biology in real time, at the molecular, cellular and system levels, enabling therapeutic action at the earliest stages of the disease process. With cancer, nanotechnology offers the capability to open new avenues for developing therapies and devices to reduce toxicity, enhance the efficacy and delivery of treatments, and also increase sensitivity for cancer imaging and detection. As a result, nanotechnology strives to be a critical tool to meet the National Cancer Institute's (NCI) mission of reducing the burden of cancer.

To advance oncological nanotechnology, the NCI established the Alliance for Nanotechnology in Cancer (Alliance) in September 2004. The Alliance is a comprehensive, systematized effort encompassing the public and private sectors in multidisciplinary research designed to advance basic scientific discoveries and translate them into viable cancer applications.

In its first five years (2005-2010), the Alliance involved funding a group of eight Centers for Cancer Nanotechnology Excellence (Centers) and twelve Cancer Nanotechnology Platform Partnerships (Platforms), together with eleven Multi-disciplinary Research Training and Team Development awards. Center teams are multidisciplinary and focused on discovery and tool development for clinical application. The Platforms are designed to support individual research projects that address major barriers and fundamental questions in cancer. The Multi-disciplinary Research Training and Team Development program was dedicated to training graduate students and post-doctoral fellows across scientific genres. The Alliance also formed an intramural laboratory, the Nanotechnology Characterization Laboratory (NCL), to
serve as serve as a national resource where analytical techniques are developed and vetted to describe the nature of biologically applied nanotechnology through preclinical evaluation of efficacy and toxicity. Collectively, these diverse groups established a thriving platform of technological advancement that put cancer nanotechnology on the map, driving new clinical efforts.

The success of the Alliance led to the program's renewal for a second five-year cycle. New awards were made in response to an open call for applications that welcomed many new institutions into the fold, as described on the Alliance website [1]. Phase II seeks to build on the accomplishments of its predecessor with greater focus on training and clinical translation, particularly regarding cancers with poor outcomes, including Central Nervous System (CNS), lung, pancreatic, and ovarian cancers. To this end the Alliance is again composed of Centers (nine) and Platforms (12). NCI believes that achieving the envisioned progress in cancer nanotechnology also requires systematic efforts to train a cadre of researchers who are skilled in both nanotechnology and biology and oncology and therefore, the Centers and Platforms are complimented by six Cancer Nanotechnology Training Centers (Training Centers) and seven investigators who received Pathway to Independence Awards in Cancer Nanotechnology. The goal of the Training Centers is to educate and train researchers from diverse fields in the development and use of nanotechnology-based approaches to study cancer biology. The Path to Independence Award assists the transition of post-doctoral scientists working on cancer nanotechnology from mentored environments to becoming principal investigators. The NCL continues to be a part of the Alliance and will continue the standardization of preclinical characterization of nanomaterials intended for cancer therapeutics and diagnostics for the public and private sectors.

2. DEVELOPMENT OF TRANSLATIONAL TECHNOLOGIES

Since its inception, the Alliance has made important advances through its multidisciplinary collaborative effort that has led to the development of point-of-care diagnostics and multifunctional agents for imaging and therapy. Over the last five years, the Alliance program has not only produced strong scientific results (over 1300 peer-reviewed publications), but also helped in establishing the field of cancer nanotechnology. By forming the NCL, the NCI established a hub for nanomaterial characterization and standardization which supports the research community while aiding and moving technologies through the translational pipeline toward commercialization. The ultimate measure of successful research and development lies in new clinical solutions. To this end, the Alliance has been structured to include researchers from several disciplines including oncology, cancer biology, engineering, chemistry, and physics. Each Center is also affiliated with an NCI Cancer Center and industrial entities involved in technology commercialization. Through the formation of this multi-faceted network, the Alliance has been able to create multiple pipelines ranging from technology discovery through technology proof-of-concept to prototype and product development. The Alliance also places a premium on collaborations with the private sector and encourages the movement of promising laboratory discoveries into the clinic. In the last five years, Alliance investigators developed an intellectual property (IP) portfolio of over 250 disclosures and patents. Alliance investigators have used this strong IP either founded or played key technological roles in the creation of over fifty companies over the last five years (Fig. 1).
As stated above, a major goal for the Alliance is to catalyze discovery and development efforts that offer the greatest opportunity for advances in the shortest possible timeframe and to lower the barriers to commercialize these advances for the benefit of cancer patients. To this end, several nanotechnology-enabled diagnostic, imaging tools and therapeutic agents developed by Alliance investigators have reached the clinical trial stage, and several others are nearing that goal. A few examples of promising diagnostic, imaging, therapeutic technologies as well as novel nano-platforms developed by Alliance researchers are discussed in the following section. For additional highlights, please visit the Alliance website [1].

2.1 Therapies: Cancer therapies are currently limited to surgery, radiation, and chemotherapy. All three methods involve significant risk of damage to normal tissues, resulting in many debilitating side-effects, and incomplete eradication of the cancer. The unique and diverse properties of nanomaterials benefit oncological applications by enabling selective drug delivery to tumors, increasing the therapeutic index of drugs by decreasing patient toxicity associated with an effective dose, or by protectively encapsulating drugs that under normal conditions could not be administered due to solubility and/or stability issues.

Cyclodextrin for delivering siRNA: Since its discovery, RNA interference (RNAi) has been a tantalizing possibility for a major new class of cancer drugs owing to the in vitro ability of small interfering RNA (siRNA) to specifically silence oncogenes essential for tumor growth. The major challenge to using these therapies in vivo is the difficulty of delivering siRNA to specific cells in high therapeutic concentration as siRNA is rapidly degraded in the bloodstream or cleared from blood via kidneys. In order to overcome this difficulty, Dr. Mark Davis’ group from the Caltech-UCLA Center has developed a complex targeted nanoparticle delivery system, which contains: (1) a linear, cyclodextrin-based polymer (CDP), (2) a human transferrin protein (TF) targeting ligand displayed on the exterior of the nanoparticle to engage TF receptors (TFR) found on the surface of many cancer cells, (3) a hydrophilic polymer [polyethylene glycol (PEG)] used to promote nanoparticle stability in biological fluids, and (4) siRNA designed to silence the expression of the RRM2 gene (M2 subunit of ribonucleotide reductase, a protein critical for the rapid cell
division seen in cancer) (Fig. 2A). In collaboration with Dr. Antoni Ribas from UCLA, Dr. Davis is testing these nanoparticles in a Phase I clinical trial in patients with solid tumors. So far, clinical data have provided the first in vivo proof that a nanoparticle can reach a tumor and silence a target gene using RNAi. Tumor biopsies from melanoma patients obtained after treatment show the presence of intracellularly localized nanoparticles in amounts that correlate with dose levels of the nanoparticles administered (a first for systemically delivered nanoparticles of any kind). A reduction was found in both the specific messenger RNA (mRNA) and expression levels of the RRM2 protein when compared to pre-dosing tissue (Fig. 2B). Most notably, Davis et al. detected the presence of an mRNA fragment that demonstrates that siRNA-mediated mRNA cleavage occurs specifically at the predicted site in a patient who received the highest dose of the nanoparticles. Together, the data demonstrates that siRNA administered systemically can produce a specific gene inhibition (reduction in mRNA and protein) by an RNAi mechanism [2]. This technology is being developed and commercialized by Calando Pharmaceuticals, Inc.

Figure 2. A. Schematic representation of targeted nanoparticles. B-C: RRM2 mRNA and protein expression in tumour tissue. B. qRT–PCR analysis of RRM2 mRNA levels in samples from patients A and B before and after dosing. RRM2 mRNA levels are normalized to TATA box binding protein (TBP) mRNA levels. Results are presented as the percentage of the pre-dosing RRM2/TBP mRNA levels for each patient. C. qRT–PCR and western blot analysis of RRM2 protein expression from patient samples C2pre and C2post. (Adopted with permission from [2] Copyright © 2010 Nature Publishing Group)

Polymeric nanoparticles for targeted anticancer drug delivery: Polymeric nanoparticles for targeted delivery and controlled drug release may improve the therapeutic index of cancer drugs. This is particularly important when administering strong chemotherapeutics that are so toxic, systemic dosing presents a significant danger to the patient such necessitating reduced dosages resulting in suboptimal efficacy. Scientists have been working to develop nanoparticles to deliver drugs specifically to tumors enabling a high-local dose while protecting normal tissues. However, it remains challenging to reproducibly formulate targeted nanoparticles with the complex optimal interplay of parameters that confer molecular targeting, immune evasion, and drug release to overcome physiological barriers in vivo. To overcome this challenge, Dr. Robert Langer’s group from the MIT-Harvard Center formulated drug-encapsulating targeted nanoparticles using self-assembly of an amphiphilic triblock copolymer composed of (1) end-to-end linkage of poly(lactic-co-glycolic-acid) (PLGA, a controlled released polymer), (2) polyethyleneglycol
(PEG, which protects against systemic clearance as well as improves pharmacokinetics), and (3) aptamers (DNA or RNA oligonucleotides) which bind specifically to proteins expressed on the surface of cancer cells [3]. Aptamers have the benefits over antibodies as they are nonimmunogenic and stable in a wide range of pH (4-9), temperature, and organic solvents. This formulation enables controlled drug release and cell-specific targeting. The construct was used to encapsulate the drug docetaxel and deliver it to prostate cancer cells by using an aptamer that recognizes the extracellular domain of the prostate-specific membrane antigen (PSMA). This nanoparticle binds to the PSMA protein expressed on the surface of LNCaP cells (a prostate epithelial cancer cell line) where it gets taken up resulting in significantly enhanced in vitro cellular toxicity as compared to nontargeted nanoparticles that lack the PSMA aptamer. This construct also exhibited efficacy and reduced toxicity as measured by mean body weight loss in vivo using mice. Moreover, after a single intratumoral injection of this construct containing docetaxel, complete tumor reduction was observed in LNCaP xenograft nude mice and 100% of these animals survived the 109-day study. In contrast, docetaxel alone had a survival rate of only 14%. [4] This technology is being developed by BIND Biosciences, Inc, a company founded by Drs. Langer and Farokhzad. Currently, the company, together with the Virginia G. Piper Cancer Center at Scottsdale Healthcare in Scottsdale, Arizona, the Translational Genomics Research Institute (TGen), and the Scottsdale Healthcare Research Institute, is conducting a clinical trial to determine the maximum tolerated dose and to assess preliminary evidence of its antitumor activity.

**Systemic nanocurcumin for pancreatic cancer therapy:** Curcumin, an extract from the rhizome of turmeric, has already demonstrated anticancer and chemopreventive properties in preclinical models. Nevertheless, adopting curcumin to clinical practice is challenging due to its hydrophobicity and poor oral bioavailability. Even in cases of large doses of daily oral curcumin, uptake is generally limited to the colonic mucosa, and only minimal amounts of the active compound reach the bloodstream. This barrier can be overcome by engineering polymeric nanoparticles that encapsulate curcumin. Dr. Anirban Maitra from Johns Hopkins Center has generated polymeric nanoparticles that are capable of solubilizing a broad range of poorly water-soluble drugs, including curcumin [5]. Administration of nanocurcumin in mice results in strikingly higher plasma levels of curcumin, when compared to the equivalent dose of the free curcumin. Together with industry partners, Dr. Maitra is currently testing nanocurcumin in preclinical settings to treat pancreatic cancer.

2.2. *In vitro* diagnostic devices: Screening for biomarkers in patient tissues and fluids for diagnosis could also be enhanced by nanotechnology as early detection is highly correlated to survival. Individual cancers differ from each other and from normal cells by changes in the expression and distribution of tens to hundreds of often very dilute molecules. As therapeutics advance, it may require the simultaneous detection of several biomarkers to identify a cancer for treatment selection.

**Blood protein profiling of glioblastoma patients:** Dr. James Heath’s group from the Caltech-UCLA Center has engineered an integrated microfluidic system – the integrated blood barcode chip (IBBC) – that can sample a large panel of protein biomarkers from whole blood over broad concentration ranges (~10^5) within 10 minutes of sample collection. A microfluidic network on the IBBC enables ~15% of the plasma (with over 99% purity) to be skimmed from whole blood for detection of plasma proteins without pre-processing (Fig. 3A). These proteins are then detected using DNA Encoded Antibody Library (DEAL) technology also developed at the CalTech-UCLA Center. The DEAL barcodes in the plasma channels consist of spots of single-stranded DNA hybridized to antibodies that are labeled with complementary ssDNA oligomers (Fig. 3B). The antibodies recognize specific plasma proteins. The DNA, unlike antibodies, is stable to the processing used to create the elastomeric microfluidics chips and resists biofouling. Each complementary DNA pair is chosen, via computational and empirical methods to limit cross-reactivity [6]. IBBC protein assays exhibit a sensitivity that matches or betters conventional assays, but the concentration range of IBBC assays is significantly increased through control over the surface chemistry of the glass substrate and the DNA loading on a given spot. Furthermore this system provides this diverse and sensitive analysis in a low-cost, platform that is minimally invasive and takes only ten
minutes. Working with Dr. Paul Mischel of UCLA, Dr. Heath is currently using the IBBC for molecular and functional analysis of clinical glioblastoma tumor samples, to identify patients with the greatest potential for positive response to Avastin® therapy.

![Diagram of plasma separation from a finger prick of blood](image)

**Figure 3.** Scheme depicting plasma separation from a finger prick of blood by harnessing the Zweifach-Fung effect. A. Multiple DNA-encoded antibody barcode arrays are patterned within the plasma-skimming channels for **in situ** protein measurements. B. DEAL barcode arrays patterned in plasma channels for **in situ** protein measurement. A, B, C indicate different DNA codes. (1)–(5) denote DNA-antibody conjugate, plasma protein, biotin-labeled detection antibody, streptavidin-Cy5 fluorescence probe and complementary DNA-Cy3 reference probe, respectively. The inset represents a barcode of protein biomarkers, which is read out using fluorescence detection. The green bar represents an alignment marker. (Reprinted with permission from [6] Copyright © 2008 Nature Publishing Group).

**Biobarcode assay for measuring undetectable levels of Prostate Specific Antigen (PSA):** Although several diagnostic procedures for the detection and measurement of biological analytes exist, the major methods of choice for quantifying proteins are typically ELISA or immunoblots. These assays, however, are limited with respect to sensitivity and multiplexing capabilities and furthermore do not compare with the sensitivity that PCR affords in the nucleic acid field. Certain nanostructured materials are ideal for high sensitivity multiplexed analyte detection because their physical properties can be systematically varied to produce specific emissive, absorptive and light scattering properties that offer advantages over conventional molecular probe technology. Dr. Chad Mirkin from the Northwestern University Center has developed an ultra-sensitive bio-barcode assay, which is used for the detection of PSA. This assay uses antibody-oligonucleotide gold nanoparticle (AuNP) conjugates for PSA detection and AuNP initiated gold or silver deposition for signal amplification and assay readout. Signal readout and quantification is done by measuring AuNP-mediated light scattering. This test is currently clinically validated for monitoring PSA levels in patients following radical prostatectomy and assesses response to adjuvant and salvage therapy [7]. Specifically, Dr. Mirkin and the group of Dr. C. Shad Thaxton, also from the Northwestern University Center, were able to reliably and accurately quantify PSA values at far less than 0.1 nanograms per milliliter, the clinical limit of detection for commercial assays. The lower limit of PSA detection using the bio-barcode assay is approximately 300 times lower than the lower limit of detection for commercial tests. The PSA measurements were used to classify the patients as either having no evidence of disease or having a relapse of disease generating the possibility for this system to be used to categorize patients after prostatectomy to know who to monitor most closely [7]. The Northwestern University Center team, in collaboration with Dr. William Catalona, M.D. and Nanosphere, Inc. is now conducting a similar retrospective study of over 400 patients and eventually plans to do a large prospective study.

**2.3. Imaging:** Current imaging methods can only detect cancers once they have made a visible change to a tissue, by which time millions of cells will have proliferated and perhaps metastasized, limiting treatment effectiveness. And even when visible, the pathology of the tumor and the characteristics that might make it sensitive to a particular treatment must be assessed through biopsy. Nanotechnology can enable the
visualization of cancer cells that are orders of magnitude smaller than those detected with current technologies, offering earlier tumor detection and consequently improved prognosis.

Carbon nanotube X-ray source: X-rays are indispensable in many medical applications including cancer detection, characterization, and treatment. The basic design of the X-ray tube however has not changed significantly in the past 100 years: a thermionic cathode is used to produce electrons, which strike on a metal target to generate X-rays. It has several intrinsic drawbacks that have limited the effectiveness and advancements of X-ray technologies. These include a high cathode operating temperature (~1000°C), which prevents miniaturization and novel source configurations that can increase imaging speed and accuracy; high imaging dose which causes radiation damage; and low temporal and spatial resolution which affects the size and accuracy of the features that can be detected. Carbon nanotube (CNT) based field emission X-ray sources have the potential to not only overcome these limitations but also enable new imaging modalities [8]. Dr. Otto Zhou’s team at the University of North Carolina Center has demonstrated that the CNT X-ray technology can generate programmable pulsed X-ray waveform, at room temperature, with high temporal resolution which readily enables synchronized/gated imaging and temporal Fourier processing to increase signal/noise ratio and miniaturize X-ray source while allowing novel source configurations such as scanning multi-beam X-ray sources for dynamic and high-speed imaging. Dr. Zhou’s team uses CNT X-ray technologies for improving cancer imaging methods and radiotherapy and has recently employed tomosynthesis to perform in vivo imaging of breast cancer in a quicker manner with less patient radiation exposure. The system is composed of a 25-pixel X-ray source array, a flat panel detector for full-field mammography, a control unit for X-ray sources, and a computer work station. It can acquire 25 projection images in 11 seconds at 0.2-mm resolution [9]. By contrast, an available Siemens system at the same dose requires 20 seconds to take 25 images with 0.3-mm focal spot size. The imaging system with the multi-beam field emission X-ray source and an area digital detector can increase the imaging speed, reduce the size and cost of the equipment and enable experiments on new imaging configurations which can give better quality images not feasible with the conventional step-and-shoot method. Furthermore, the CNT X-ray system’s low operating temperature enables multiple emissive sources to placed around the target enabling simultaneous multi-angle image capture. Digital tomosynthesis is an innovative technique merging digital image capture with conventional radiographic tomography. This technology is manufactured and commercialized by Xintek, Inc, a company, which was founded by Dr. Zhou.

Surface enhanced Raman spectrometry gold-based nanoparticles for colorectal cancer detection: Molecular imaging of cellular and molecular processes within living subjects has the potential to impact many facets of biomedical research and clinical patient management. Imaging is currently possible by using positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), computed tomography (CT), optical bioluminescence and fluorescence, high frequency ultrasound (HFUS), and several other emerging modalities. However, no single modality currently combines high sensitivity, high spatial and temporal resolution, and high multiplexing capacity with low cost and high-throughput capability. Dr. Sanjiv Sam Gambhir and his colleagues at the Stanford University Center have attempted to develop new imaging strategies incorporating all of these capabilities. Their approach has been to use Raman spectroscopy, a well-established bioanalytical tool with many instrumental advantages including excellent sensitivity to small structural and chemical changes, minimal sample preparation, and high spatial resolution. Raman spectroscopy can also differentiate the spectral fingerprint of many molecules, resulting in very high multiplexing capabilities. Since Raman is a scattering phenomenon, not absorption/emission, narrow spectral features are separable from background broadband autofluorescence. In addition, Raman-active molecules are more photostable than most fluorophores, which are rapidly photobleached. While Raman scattering is a very inefficient process (only one in ten million photons is inelastically scattered), the use of surface enhancers such as gold or silver nanoparticles effectively increases the process by several orders of magnitude, thus enabling picomolar sensitivity. This effect is known as surface enhanced Raman scattering (SERS) and is a result of a plasmonic phenomenon where molecules absorbed onto nano-roughened noble metal surfaces experience a dramatic increase in the incident electromagnetic field
producing high Raman intensity. For years, scientists have reported the use of SERS to image biological processes within living cell cultures and excised tissues. Dr. Gambhir’s team has harnessed this SERS phenomenon using gold nanoparticles for \textit{in vivo} diagnostic applications. His team has developed ten different Raman nanoparticles consisting of a 50-nm gold core with a unique Raman active layer absorbed onto the gold surface and coated with glass, for a total diameter of 120 nm. Each of these ten nanoparticles has a unique Raman spectral fingerprint, which allows for multiplexed imaging. So far, Dr. Gambhir’s team has demonstrated that an optimized Raman microscope has the potential to non-invasively image deep tissues as well as multiplex 10 spectrally-unique batches of SERS nanoparticles in living mice (Fig. 4) [10]. At present, Dr. Gambhir is in the process of using this technology in a clinical trial for detection of colorectal cancer.

Figure 4. Demonstration of deep-tissue multiplexed imaging 24 h after i.v. injection of five unique SERS nanoparticle batches simultaneously. (A) Graph depicting five unique Raman spectra, each associated with its own SERS batch: S420 (red), S421 (green), S440 (blue), S466 (yellow), and S470 (orange). It is noteworthy that their peaks have very little spectral overlap, allowing easier spectral unmixing and resulting in better deep-tissue detection. (B) Raman image of liver overlaid on digital photo of mouse, showing accumulation of all five SERS batches accumulating in the liver after 24 h post i.v. injection. Panels below depict separate channels associated with each of the injected SERS nanoparticle batches. Individual colors have been assigned to each channel, and the resulting mixture shows a purple color that represents a mixture of the five SERS nanoparticle batches accumulating simultaneously. It should be noted that all channels show accumulation in the liver; however the channels are not all homogenous in their distribution throughout the liver. (Reprinted with permission from [10] Copyright© 2009 National Academy of Sciences USA).
2.4. Technology platforms: Nanotechnology offers a wide range of tools for research community, which could enable biologists and physicians to study, monitor, and treat every aspect of the cancer progress. It also offers new materials and devices for cancer applications.

PRINT® technology for cancer therapy and imaging: The exploration and utilization of nanocarriers for the delivery of therapeutics in vivo has led to dramatic improvements in the preclinical efficacy of various therapies. Clinically, the success of these carriers has been limited by the lack of control over size, chemical composition, uniformity, cell targeting, and ability to consistently load and release known amounts of cargo. A particle fabrication technology, called PRINT® (Particle Replication In Non-wetting Templates), developed by Dr. Joseph DeSimone of the University of North Carolina Center takes advantage of the unique properties of elastomeric molds comprised of a low surface energy perfluoropolyether to produce monodispersed, shape-specific particles from an extensive array of organic precursors. PRINT® allows for the elucidation of mechanisms by which organic particles of controlled size, shape, site-specific surface chemistry, and tunable particle matrix composition undergo endocytosis. Studies into the endocytic pathway using PRINT® particles should lead to information crucial not only for enhancing specific cellular internalization, but also manipulating the intracellular location of particles, and minimizing cytotoxic effects [11]. Once the mechanisms of internalization are established, it will then be possible to use these findings to better engineer the intracellular release of specific cargos. This information, in combination with ongoing efforts to understand the biodistribution of shape controlled particles, will help to establish rules toward the rational design of nanocarriers for effective in vivo delivery of various cargos, especially those cargos that need to be internalized into cells such as siRNA and antisense oligonucleotides. The PRINT® platform was licensed-out to Liquidia Technologies, Inc, which manufactures this technology for a wide range of life sciences and materials science applications.

RNA nanotechnology: Beyond the aforementioned RNAi, RNA molecules' diversities in function and structure make it particularly attractive as a building block for bottom-up assembly in nanotechnology and nanomedicine. Dr. Peixuan Guo from the University of Cincinnati Platform has engineered this new nanotechnology platform, which is based on the RNA-skeleton of the bacteriophage phi29’s DNA packaging nanomotor. This motor is central to translocating the bacteriophage DNA genome and is built from stable dimers and trimers of packaging RNA known as pRNA [12]. Currently, Dr. Guo’s team together with its commercial partner Kylin Therapeutics, Inc. is elucidating the principles underlying the RNA/RNA interactions in RNA nanoparticle assembly using phi29 motor pRNA system and RNA junction motifs to build polyvalent RNA oligomers containing combinations of aptamers, siRNA, ribozymes, ligands, imaging markers or drugs for cancer cell recognition. This new approach should be able to screen for stable and high affinity RNA aptamers that target and enter cancer cells specifically [12,13]. Additionally, RNA is notoriously instable in biological systems making its implementation as a therapeutic platform untenable. Recent work from this Platform with Kylin has created modified RNA nucleotides, fluorinated at the 2’ position [14]. pRNA made from these modified ribonucleotides was shown to be highly resistant to degradation while maintaining their biological activity. Progress such as this keeps the door open for this innovative platform for future nanomedical applications.

3. FUTURE PROSPECTS

Since 2005, the Alliance has demonstrated that the field of cancer nanotechnology has the potential to transform oncology. This comes in the form of improved methods for therapy as well as monitoring of therapeutic efficacy, and developing innovative ways to diagnose the disease at its early stages, using both in vitro assays and novel imaging methods. It is expected that, in the future, nanotechnology will become a core component of research and translational programs making it a significant part of comprehensive cancer care.

There are, however, various barriers that need to be overcome to ensure efficient translation of such laboratory discoveries to clinical trials and, ultimately, to clinical practice. Currently, there is a lack of available standards, publicly available datasets of fully characterized (e.g., in terms of their physical,
chemical, and physiochemical properties) nanoscale materials and devices, and a lack of a consolidated strategy for performing such characterizations in an integrated manner. The Alliance continues lead the process of standardizing bio-nanomaterials as well as promote widespread acceptance of NCL-established protocols within the research and development community. In addition, good manufacturing procedures (GMPs) such as scale-up process, purity and batch-to-batch consistency have to be established for nanomaterials. This is one of the major challenges facing the next stage of the Alliance.

Furthermore, commercialization of nanotechnology-based diagnostics and therapeutics often poses a challenge. The Alliance is working to educate its investigators about regulatory guidelines for drug and device approval to accelerate implementation and adoption. Regardless, a majority of the nanomedical commercial efforts are carried out by small start-up companies formed through licensing of the early stage technologies from university laboratories. These companies face the ‘valley-of-death’ scenario during the phase of technology scale-up and early stage clinical trials [15]. Therefore, it is important to establish partnerships with industry counterparts to provide an outlet for technology translation to the marketplace.

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REFERENCE


