Nanotechnology: Future of Oncotherapy

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Abstract

Recent advances in nanotechnology have established its importance in several areas including medicine. The myriad of applications in oncology range from detection and diagnosis to drug delivery and treatment. Although nanotechnology has attracted a lot of attention, the practical application of nanotechnology to clinical cancer care is still in its infancy. This review summarizes the role that nanotechnology has played in improving cancer therapy, its potential for affecting all aspects of cancer care, and the challenges that must be overcome to realize its full promise.

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doi: 10.1158/1078-0432.CCR-14-1189
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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Editor's Disclosures

The following editor(s) reported relevant financial relationships: J.R. Grandis—none.

CME Staff Planners’ Disclosures

The members of the planning committee have no real or apparent conflicts of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should have a better knowledge about the role of nanotechnology in various aspects of cancer therapy and the challenges that must be overcome to improve its transition to clinical practice.

Acknowledgment of Financial or Other Support

This activity does not receive commercial support.

Introduction

Nanomedicine offers unique opportunities for improving current ways of treating cancer and other diseases (Fig. 1). These stem from the potential of nanoformulations to improve drug delivery and achieve targeted delivery, thereby reducing systemic toxicity (1). Various nanoparticle formulations, such as quantum dots, liposomes, polymeric nanoparticles, carbon nanotubes, metallic nanoparticles, or dendrimers, have been investigated in preclinical and clinical settings for drug or gene delivery, photothermal therapy, immunotherapy, and imaging (Table 1). Although only a few formulations have been approved by the FDA (Table 2), the full potential of nanotechnology in the clinical setting is yet to be realized. Here, we review the successes of nanotechnology in cancer care and provide a critical appraisal of its future applications.

Nanoparticles for Drug Delivery

Small-molecule drug delivery

Chemotherapy drugs are used for many cancer types, but conventional chemotherapy is nonspecific and can lead to intolerable toxicities, compromising patients’ quality of life. Nanotechnology has the potential to overcome such hurdles. Targeted delivery, reduced toxicity, improved pharmacokinetics, and bioavailability are some of the potential advantages offered by nanotechnology.

Among various nanoparticle platforms, liposomes are the most advanced with regard to integration into clinical care. Liposomal incorporation of doxorubicin and daunorubicin increase plasma concentration and reduce clearance rate and volume of distribution, thus increasing bioavailability of the drug (2, 3). Moreover, there is a substantial decrease in cardiac and other toxicities with liposomal doxorubicin as compared with free doxorubicin (4). Further improvement in the safety and pharmacokinetics was achieved by using polyethylene glycol (PEG) to coat liposomes (5–7).
Polymeric nanoparticles have also been instrumental in improving the therapeutic window of conventional drugs. For instance, the use of Cremophor (Sigma-Aldrich) with paclitaxel contributes to hypersensitivity reactions and neuropathy, but albumin nanoparticle-based formulation of paclitaxel facilitates endothelial transcytosis to achieve significant accumulation in the tumor (8). Phase I evaluation established that maximum tolerated dose (MTD) of such nanoparticles was about 70% higher than traditional paclitaxel (9). This formulation is associated with lower neutropenia and hypersensitivity while achieving a higher response rate than standard paclitaxel (10). Paclitaxel poliglumex poly(l-glutamic acid)-paclitaxel is another polymeric formulation with increased water solubility of paclitaxel, increased plasma half-life, tumor uptake, increased antitumor activity, and an improved safety profile compared with free paclitaxel (11, 12).

The nanoparticle platforms discussed above rely predominantly on passive accumulation of nanoparticles at tumor sites based on the enhanced permeability and retention (EPR) effect. Tumor selectivity can be further enhanced by attaching tumor-specific ligands (e.g., folic acid, HER2 antibody, aptamers, and transferrin) to nanoparticles to enhance tumor accumulation, increased cellular internalization and increased antitumor effects (13–17). For example, MCC-465 (PEGylated immunoliposome conjugated with F(ab')2 fragment of GAH and encapsulates doxorubicin) was well tolerated in preclinical and early clinical testing (18). MM-302 is a HER-2–targeted PEGylated liposome containing doxorubicin that has shown an improved cardiac toxicity profile in combination with trastuzumab (19). Phase I testing of cetuximab-conjugated doxorubicin liposome was also well tolerated (20). Additional formulations, such as MBP-426 and SGT53 (p53), are in clinical testing (21).

Several nanoparticle strategies have been developed for targeting stromal populations such as endothelial cells, macrophages, and cancer stem cells. Paclitaxel loaded into poly (lactic-co-glycolic) acid PLGA nanoparticles decorated with CD133 antibody resulted in enhanced survival in preclinical cancer models (22). Combination therapy with epigenetic-targeted decitabine and doxorubicin nanoparticles targeting cancer stem cells was shown to be more beneficial than free decitabine and doxorubicin in chemoresistant breast cancer models (23). Chitosan nanoparticles decorated with RGD peptides localize to the tumor vasculature and exert antiangiogenic effects (24). The next-generation nanoparticles aim to achieve further selectivity by allowing spatiotemporal control over drug release. These nanoparticles are designed to selectively release drugs in response to stimuli such as an alternating magnetic field, UV or near-IR radiation, or low pH in the tumor microenvironment (25–29). However, issues related to tumor heterogeneity, cost considerations and changes in characteristics of a nanoparticle after ligand conjugation will require careful consideration during drug development.

**Nucleotide delivery**

Nucleotide therapies hold an important place in cancer therapy because many of the undruggable genes can be targeted using antisense oligonucleotides (ASO) or siRNAs. Several ASOs are now in clinical trials, but the success has been modest (30). ASOs may be a better alternative to ASOs due to ease of synthesis and ability to achieve greater silencing at lower concentration than ASOs. However, several challenges associated with siRNA (e.g., enzymatic degradation in plasma, inefficient uptake by cells, and immunostimulation) must be overcome. Several nanoparticle platforms have been investigated to overcome these hurdles in siRNA delivery. Although some cationic liposomes are efficacious, these carriers can cause toxicities (e.g., activation of complement system and inflammatory responses) (31–33). Formulations such as AtuPLEX showed that toxicity can be reduced by incorporation of helper neutral lipids and PEGylation (34). The lipoplex Atu027 containing siPKN3 is currently in clinical trials for advanced solid cancers. Although preclinical studies showed antitumor effect, it should be noted that the PKN3 mRNA reduction was more pronounced in liver and lung compared with tumor (35). Stable nucleic acid lipid particle (SNALP) formulations such as ALN-VSP02 (first-generation SNALP containing siVEGF and siKSP) showed moderate gene knockdown (36), and some liver and spleen toxicities were noted. The next-generation SNALP, TKM-080301, was formulated with more stable PEG-lipids in the nanoparticles. The clinical trial with siPK1 showed a better immune profile along with increased drug exposure compared with the earlier generation of SNALPs (37). Neutral nanoliposomes (e.g., DOPC) have shown improved delivery...
(approximately 10-fold) of siRNA and antitumor effects with systemic delivery (38). Moreover, in a hepatocarcinoma mouse model, neutral liposome containing doxorubicin showed a better biodistribution profile and antitumor efficacy compared with its cationic counterparts (39).

Once inside the tumor cells, it is important to overcome barriers such as endosomal uptake (40). Systems such as the polymer-based dynamic polyconjugate (DPC) delivery system, which contains endosomolytic N-acetylgalactosamine–conjugated melittin-like peptide, may allow specific endosomal release of
siRNA from its nanocarrier, thus lowering siRNA the half-maximal effective concentration (37, 41).

**Table 2. Nanoformulations currently in clinical trials**

<table>
<thead>
<tr>
<th>Name</th>
<th>Formulation</th>
<th>Indication</th>
<th>Phase status</th>
<th>Trial number (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug delivery</strong></td>
<td></td>
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</tr>
<tr>
<td>Myocet (Sopherion)</td>
<td>Liposomal doxorubicin</td>
<td>Metastatic breast cancer</td>
<td>Approved</td>
<td></td>
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<tr>
<td>DaunoXome (Galien)</td>
<td>Liposomal daunorubicin</td>
<td>Kaposi sarcoma</td>
<td>Approved</td>
<td></td>
</tr>
<tr>
<td>Doxil (Janssen)</td>
<td>PEGylated liposomal doxorubicin</td>
<td>Kaposi sarcoma</td>
<td>Approved</td>
<td></td>
</tr>
<tr>
<td>Marqibo (Spectrum/Talon)</td>
<td>Liposomal vincristine</td>
<td>Acute lymphoblastic leukemia</td>
<td>Approved</td>
<td></td>
</tr>
<tr>
<td>Abraxane (Celgene)</td>
<td>Albumin-bound paclitaxel</td>
<td>Breast cancer</td>
<td>Approved</td>
<td></td>
</tr>
<tr>
<td>Pacilitaxel poliguimem</td>
<td>Polyamino acid bound paclitaxel</td>
<td>Head and neck cancer</td>
<td>Phase II</td>
<td>NCT00660218</td>
</tr>
<tr>
<td>Zinostatin stimalamer</td>
<td>Neocarzinostatin SMANCS (polymers-protein conjugate)</td>
<td>Hepatocellular carcinoma</td>
<td>Approved</td>
<td>NCT00045682</td>
</tr>
<tr>
<td>Onaspar (Saga-Tau)</td>
<td>PEG--asparaginase</td>
<td>Acute lymphoblastic leukemia</td>
<td>Approved</td>
<td></td>
</tr>
<tr>
<td><strong>siRNA delivery</strong></td>
<td></td>
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</tr>
<tr>
<td>CALAA-01</td>
<td>Transferrin-targeted cyclodextrin nanoparticle with siRRM2</td>
<td>Solid tumor</td>
<td>Phase I</td>
<td>NCT00689065</td>
</tr>
<tr>
<td>Atu027</td>
<td>Catonic liposome-siPRKN3</td>
<td>Solid tumor</td>
<td>Phase I</td>
<td>NCT00938574 NCT01808638</td>
</tr>
<tr>
<td>TKM 080301</td>
<td>SNALP-siPLK1</td>
<td>Solid tumor</td>
<td>Phase I</td>
<td>NCT01262235</td>
</tr>
<tr>
<td>ALN-VSP02</td>
<td>SNALP-siVEGF and siKSP</td>
<td>Solid tumors</td>
<td>Phase I</td>
<td>NCT0158079</td>
</tr>
<tr>
<td>Epharma (unlicensed)</td>
<td>EphA2 siRNA-DOPC</td>
<td>Solid tumor</td>
<td>Phase I</td>
<td>NCT0159356</td>
</tr>
<tr>
<td>CHP-HER2 and CHP-NY-ESO-01</td>
<td>Cholesterol-bearing hydrophobized pullulan HER2 protein 146 (CHP-HER2) and NY-ESO-1 protein (CHP-NY-ESO-1) in combination with OK-432</td>
<td>Esophageal cancer Lung cancer</td>
<td>Phase I</td>
<td>NCT00291473</td>
</tr>
<tr>
<td>CYT004-MelQbG10</td>
<td>Virus-like nanoparticle with antigens Melan-A/MART-1 and adjuvant CpG oligonucleotide (CDN)</td>
<td>Malignant melanoma</td>
<td>Phase II</td>
<td>NCT00651703</td>
</tr>
<tr>
<td><strong>Photothermal (Nanospectra) and radiotherapy application</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AuroLase (Nanospectra)</td>
<td>Silica core with gold metal shell and near IR laser</td>
<td>Head and neck cancer Lung cancer</td>
<td>Phase I</td>
<td>NCT00848042 NCT01679470</td>
</tr>
<tr>
<td>NBTXR3</td>
<td>Hafnium oxide nanocrystals</td>
<td>Soft tissue sarcoma</td>
<td>Phase I</td>
<td>NCT01946867 NCT01433068</td>
</tr>
<tr>
<td><strong>Imaging agents</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SPION MRI</td>
<td>Ultrasmall superparamagnetic iron oxide MRI</td>
<td>Pancreatic cancer</td>
<td>Phase IV</td>
<td>NCT00920023</td>
</tr>
<tr>
<td>Fluorescent cRGDY-PEG-Cy5.5-C dots</td>
<td>RGD-labeled silica nanoparticle with Cy5.5 dye Carbon nanoparticles</td>
<td>Solid tumor</td>
<td>Phase 0</td>
<td>NCT02106598</td>
</tr>
<tr>
<td>Carbon nanoparticles</td>
<td></td>
<td>Advanced gastric cancer</td>
<td>Phase III</td>
<td>NCT02123407</td>
</tr>
</tbody>
</table>

**Novel Agents for Immunotherapy**

One of the unmet needs in the field of immunotherapy is the lack of efficient delivery systems for cytokines and antigens. Success of systemic administration of cytokines has been limited because of their early degradation, nonspecific binding to proteins, quick excretion, and undesired toxic effects. Gold nanoparticles conjugated with TNFα are currently being investigated in clinical trials (42). Early results suggest that such a formulation may be safer with higher MTD than free recombinant TNFα (43). In addition, studies with IL2 and IL12 have also shown that nanoparticle incorporation increased plasma retention time (44, 45).

Successful antigen vaccination can be achieved by ensuring (i) sufficient concentration of antigen in antigen-presenting cells (APC); (ii) sustained release of antigen for prolonged exposure to APCs; and (iii) cytoplasmic delivery of antigen for MHC class I processing. Incorporation of an antigen into target-specific nanoparticles can increase the concentration of antigens in dendritic cells (DC; refs. 46–48). Nanoparticles can also incorporate adjuvants and antigens in the same vehicle (46, 47, 49). For example, conjugation of polyribocytidylic acid (adjuvant) with DOTAP containing a tumor lysate (antigen) not only increased Toll-like receptor signaling, but also led to increased DC maturation and...
Nanoparticle as an Individual Active Agent for Therapy and Imaging

Photothermal ablation for tumoricidal effect

Photothermal ablation involves exposure of tissues to high temperature for membrane lysis and subsequent cell death (57). Increased susceptibility of cancer cells to hyperthermia is due to their higher metabolic rates than normal cells (58); however, this selectivity is minimal. The main concern with photothermal therapy (PTT) is the nonspecific effect on surrounding normal tissues. Localized heating, enabled with the use of nanoparticles, can avoid toxicity to normal cells. Blood and tissues are relatively transmissive in near-infrared (NIR) range. NIR has thus been effective for PTT as it achieves optimal tissue penetration to reach deeply localized tumor tissues. Initial preclinical studies were conducted using FDA-approved NIR-free dyes (e.g., indocyanine green). Although this strategy showed an antitumor effect, the strategy mainly suffered because of the low circulation time of indocyanine green (ICG) (3 minutes) and damage to normal tissues (59). Incorporation of these dyes into polymeric nanoparticles improved solubility and stability and increased photothermal ablation while keeping toxicity at a minimum (60–62).

Gold nanoparticles are widely used for PTT (57, 63, 64). Nanoshells with silica core coated with a thin gold layer have been investigated extensively in preclinical studies and are currently in clinical trials for head and neck and metastatic lung cancer (65, 66). The temperatures achieved by these nanoparticles ($\Delta T = 37.4 \pm 6.6^\circ C$) were significantly higher than those achieved by laser treatment alone ($\Delta T < 10^\circ C$, ref. 63). In the treatment arm, tumor growth was significantly lower and survival was significantly higher. Further studies demonstrated that malignant cells required less than half of the laser density ($\sim 20 \text{ W/cm}^2$) for ablation compared with normal cells ($57 \text{ W/cm}^2$) when incubated with EGFR conjugated gold nanoshells (67, 68). Smaller hollow gold nanospheres have also been developed for simultaneous laser triggered drug delivery of doxorubicin, with significantly better antitumor effects compared with PTT alone (69), and have a favorable safety profile (70). Copper sulfide (CuS) nanoparticles are also being investigated for PTT. PEG-CuS nanoparticles plus laser treatment resulted in significantly higher tumor tissue necrosis ($\sim 65\%$) compared with saline plus laser treatment ($\sim 5\%$, ref. 71). Several attractive features [smaller size ($<15 \text{ nm}$), better renal clearance, ease of synthesis, and low cost] make them promising candidates for PTT (71, 72).

Clinical applicability of a nanoparticle can be further improved if it can also be used as an imaging agent for MRI and spatiotemporal monitoring of the nanoparticles (73). Similar to previously discussed nanoparticles, gold and iron oxide nanoparticles also have certain toxicity issues (74–77) that will require additional work.

Tumor imaging

The limitations of current imaging modalities, such as iodine and gadolinium based CT, X-ray, and MRI scans, are lack of sensitivity in detecting small tumor nodules, lack of specificity, short imaging time, and toxic effects. Novel nanoparticle platforms may help to overcome these limitations. For example, ferumoxtran-10, an iron oxide nanoparticle, showed significantly higher sensitivity (90.5% vs. 35.4%) in detecting lymph node metastasis as compared with conventional MRI scans (78, 79). Iron oxide nanoparticles, when compared with gadolinium chelates, showed lower diffusion from tumor site, increased internalization by cancer cells, and enhanced detection of lesions in the brain (80). Polymeric dendrimers used as nanocarriers for gadolinium proved to be a better tool for detecting lymph nodes compared with free gadolinium chelates; such sensitivity was achieved at 1/2,500th of the molar concentration of the clinical gadolinium dose (81). Owing to the high atomic number and electron density, gold nanoparticles have a higher absorption coefficient than conventional iodine and are better contrast agents for PET scans and X-rays (82). Ability to coat them with PEG and functionalize the surface with targeting ligands makes it possible to increase circulation time and achieve high tumor cell specificity (83, 84). Nanoparticle formulations have also been used to reduce the toxicity of conventional contrast agents. Gadolinium-containing agents can cause nephrogenic systemic fibrosis, which can be prevented with nanoparticle incorporation (85, 86). Certain nanoparticles, such as self-assembled nanocages, facilitate interaction between water molecules and Gd, allowing a higher magnetic resonance signal at a much lower gadolinium concentration (87). This was also the case with free NIR dyes, where nonspecific accumulation of dyes in lungs and testicles had raised concerns, but nanoparticle formulations improved biodistribution and significantly reduced toxicity (88). Carbon nanotubes are being investigated for X-ray imaging, but may be limited by potential carcinogenic effects (89).

Oncolytic Viruses

Oncolytic viruses are natural or genetically modified viruses that specifically kill cancer cells either by intensive cytopathic effect or inducing a strong immune response in the tumor microenvironment. JX-594 poxivirus, genetically modified to express GM-CSF, has been shown to increase antitumor immune response. The intratumoral injections had limited side effects and resulted in partial remission or stable disease in patients with liver cancer (90). Talimogene laherparevvec (T-vec) is a Herpes simplex virus expressing GM-CSF that has shown promising results in patients with advanced melanoma. ONX-015, an adenovirus specifically targeting tumors with inactivated p53 has also shown promising results in phase I and II clinical trials (91). A similar virus (H101) has already gained approval for the treatment of head and neck cancer in China. Systemic administration can lead to the production of neutralizing antibodies, which may require
immunosuppressive treatments prior to viral therapy (92). Combination of oncolytic viral therapy with chemotherapy or radiation may further enhance its activity (91).

**Challenges and Future Perspectives**

Nanotechnology has transformed the field of medicine by crafting promising avenues in therapeutics and diagnosis (Fig. 2), but there is clearly room for further improvement. Considering the heterogeneity of tumor, extent of hypoxia or expression of specific enzymes required for drug release may not be the same at all metastatic sites, potentially making drug release unpredictable. A possible solution to increase tumor specificity is to use dual stimuli-responsive triggers (93–96), but particular attention must be given to characterizing these systems further and improving the scalability of the formulations. Regarding the multidrug-carrying nanoparticles, optimized ratiometric loading and compatibility of their efficacy and toxicity profiles are important aspects to be considered. For theranostic nanoparticles, care must be taken to avoid compromising imaging quality or therapeutic efficacy. Pharmacokinetic (PK) and pharmacodynamic (PD) requirements are also different for imaging and drug delivery vehicles. For example, long circulation times that are ideal for effective drug delivery may not be suitable for imaging purposes and will give high background signal (97, 98). Collectively, several factors must be considered to improve the translation of nanomedicines from bench to bedside. Here, we discuss key issues and ways to accelerate the development of clinically feasible nanosystems.

**Use of relevant preclinical models to predict EPR effect**

Most nanoparticles are thought to rely on the EPR effect to accumulate in tumors. Reliable methods for assessing delivery are needed. A recent study with near-infrared fluorescence–labeled polymeric nanoparticles showed that tumors with high vascular permeability accumulated a greater density of nanoparticles (99). Although the study used fairly small nanoparticles (10 nm), the concept of predicting EPR effects by simple ultrasound imaging of vasculature should be explored further in relevant preclinical and clinical models.

**Discrepancies between preclinical studies and clinical trials**

It is now recognized that in vitro models may not reliably predict the utility of nanoparticles. For example, a dual targeted (Tf and mAb 2C5) nanoparticle system failed to reproduce the in vitro effectiveness when tested in mouse models (100). Whether 3D biomimetic tumor models can help bridge this gap to some extent is not fully understood (101). The current 3D systems could potentially be improved by incorporating relevant stromal cells, extravascular matrix proteins, or even relevant mechanical forces. These factors will help to closely simulate the tumor microenvironment and will make 3D systems a reliable platform for designing subsequent preclinical studies.

Testing the biodistribution and efficacy of nanoparticles in relevant animal models is crucial to move the therapy into the clinic. Ideally, animal models that are reflective of human disease should be used for such studies. Subcutaneous models are likely to be the least reliable due to aberrant stromal and vascular biology compared with the orthotopic sites (102). Design of preclinical trials is crucial for predicting the efficacy and safety of the nanoparticles. Moreover, it is also important to assess immunologic parameters (e.g., changes in cytokine levels or number of immune cells) during preclinical testing. Such comprehensive analysis will help in predicting the efficacy and toxicity profile of an individual nanotherapy in patients. In addition, phase 0 studies should be used to improve clinical translatability of nanoparticles. PK profile and...
tumor localization potential of a given nanocarrier in humans can be assessed in a timely manner in phase 0 trials. They are much less expensive to conduct compared with phase I trials and researchers can also obtain feedback on the clinical feasibility of a given nanosystem much more quickly.

Selection of a clinically relevant route of administration

Nanodrugs should ideally be administered the same way in the preclinical models as it is expected to be delivered in patients. For instance, preclinical studies with oncolytic viral therapy typically use intratumoral injections (103). Many other studies using nonviral nanocarriers also try to prove better efficacy using intratumoral injections (104, 105). However, this would have limited utility in patients with widely metastatic disease. Unlike intratumoral injections; i.v. injections can expose the particles to various biologic barriers, and thus will not be as effective as intratumoral route.

Choosing the right ligand for targeted delivery

Ligand-targeted therapies have been shown to be superior in terms of tumor specificity and low off-target effects. (106–108). In preclinical studies, greater accumulation of nanoparticles can be achieved by choosing a tumor model overexpressing the specific receptor (105). However, there is heterogeneity in receptor expression in tumors (109, 110), and a single ligand could ultimately lead to selection of cells that lack target expression. A multiligand approach has been shown to be more specific and leads to better uptake of nanoparticles (111–113). With increased specificity, multiligand nanoparticles are less likely to be taken up by normal cells, and thus have fewer toxicity issues (112, 114).

In summary, the versatility of formulations, targeted delivery, and biocompatibility have garnered a lot of interest in nanotechnology. However, we must first address several practical issues. Every new nanomaterial and added complexities require additional controls and toxicity checks, making FDA approval potentially more difficult. Batch-to-batch variations in these cases further complicate scaling up the production. Thus, the clinical benefit and toxicity profile must be far superior compared with the conventional drugs to justify the cost. Moreover, it is important to understand the intricacies of nanotechnology in vivo and predict the behavior, distribution, and kinetics with certainty. Then, we can develop strategies for scaling up production and distribution with the ultimate goal of direct clinical translation and patient benefit.

Grant Support

K.M. Chaturvedi is supported by the Altman Goldstein Discovery Fellowship. S.Y. Wu is supported by the Ovarian Cancer Research Fund, Foundation for Women’s Cancer, and Cancer Prevention Research Institute of Texas (CPRIT) training grants (RP101502, RP101489, and RP101595). C. Li and A. K. Sood are supported by the NIH under award number U54CA151668. A.K. Sood is supported by the NIH under award numbers P50CA083639, CA101928, P50CA098258, U54TR000943, CA106672, U54CA96300, and U54CA96297; CPRIT grants (RP101595 and RP120214); an Ovarian Cancer Research Fund Program Project Development Grant; U.S. Department of Defense grants (OC120547 and OC120541); the Betty Ann Asche Murray Distinguished Professorship; the RGK Foundation, the Gilder Foundation; the Judi A. Rees Ovarian Cancer Research Fund; the Chapman Foundation; the Meyer and Ida Gordon Foundation; and the Blanton–Davis Ovarian Cancer Research Program.

Received January 9, 2015; revised March 26, 2015; accepted April 1, 2015; published online July 15, 2015.

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