Preface: Nanotechnology in Imaging and Cancer Therapy

One major obstacle to developing new therapies is a lack of routinely used non-invasive methodologies allowing us to monitor treatment efficacy. Molecular imaging has important implications assisting in monitoring disease course and in the assessment and prediction of treatment efficacy. To date, responders and non-responders to therapies are often identified on the basis of a reduction in tumor size, or by evaluating indirect tumor markers weeks or months after initiation of treatment. The development of nanotechnology enables *in vivo* cell-tracking methods to monitor instantly, noninvasively, and in real time the presence, distribution, quantity, and viability of therapeutically administered drugs in target tumors or elsewhere in the body. Furthermore, *in vivo* cell-tracking methods are used to determine the fate and metastatic potential of tumor cells in animal models and to design clinical trials that ultimately help to monitor therapies in clinical practice.

Targeted nanoparticles (TNPs) have the potential to overcome the toxicity and efficacy limitations associated with traditional cytotoxic agents and newer-generation molecularly targeted drugs by directing a greater fraction of the administered drug directly to cancer cells in a controllable and tunable manner. Nanomedicines hold great promise for addressing some of the most challenging problems in nearly every medical specialty, and this nascent field has the potential to generate many new opportunities for improving human health. This special issue by experienced contributors provides an up-to-date overview of nanotechnology used in both imaging and in theranostic applications and addresses additional aspects in this developing field.

Dr. Grimm and colleagues extensively review the nanotechnology in cancer imaging in the first part of their article. This article includes the description of a wide variety of organic as well as inorganic materials, including particles, dendrimers, wires, and tubes, but also proteins and viruses and much more, that have been developed for use in different imaging modalities. The authors discuss the use of nanoparticles in different optical imaging methods, such as fluorescence imaging, surface-enhanced Raman spectroscopy and photoacoustic tomography (PAT). Next, they address the use of nanoparticles in magnetic resonance imaging (MRI) and lastly in nuclear imaging such as PET and SPECT. In this section, an emphasis is made in the selection of the nanoparticle used according to the different architectures, chemical properties, and material properties that are best suited to computed tomography (CT), the specific imaging procedure. In the second part of their article, the focus is on exploiting properties of nanoparticles for therapeutic applications. Objectives include how to transform them into supramolecular drug-delivery systems that will be <100nm in diameter, avoid the innate and adaptive immune responses, target only the tumor and allow imaging to monitor both drug-delivery and tumor response. In addition, they discuss the development of polymeric nanoparticles that are the most versatile platforms for drug-delivery and imaging, evolving since the 1970s. Recently, hybrid polymeric drug-delivery vehicles have been developed that target multiple oncogenic mechanisms, achieving complete tumor responses in mice. Regarding liposomes and micelles, original delivery issues were addressed, which resulted in the FDA-approved liposomal formulation Doxil® (PEGylated liposomes loaded with doxorubicin), used in the clinic to minimize the cardiotoxicity associated with the conventional delivery of this drug.

Liposomes provide a nature-inspired approach to deliver therapeutics to cells that was introduced as early as 1965 using phospholipids, and was later refined in the form of lipid-based drug-delivery vesicles capable of retaining drugs. Dr. Sofou and his colleagues review liposome-based delivery approaches that aim to address toxicities and to improve the therapeutic efficacy of mainstream chemotherapeutics, namely doxorubicin, paclitaxel, and

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cisplatin. In addition, the molecular mechanism(s) of action of these agents is followed by description of characteristic examples of therapeutic approaches and of liposome membrane designs. Short reports on clinical studies are also included where applicable. The more technical issues of different loading/encapsulation methods of these drugs into liposomes are also discussed in terms of the physico-chemical properties of both the drugs themselves and of the lipid-based self-assemblies. Although liposome-based approaches for chemotherapeutics have offered therapies that have already proven their promise in the clinic, from the drug-delivery point of view, however, there are still several challenges that need to be addressed to improve outcome in cancer patients.

A significant body of evidence indicates that metal nanoparticles, in particular gold nanoparticles, can amplify the dose of delivered radiation by enhancement of the photoelectric effect. In their review, Dr. Nadeau and his colleagues discuss the properties and advantages of these nanoparticles. Gold nanoparticles as an x-ray contrast agent were first reported in 2006 to have high x-ray attenuation because of their high atomic number, high density, and high absorptivity due to their favorable K-edge energy in the range of clinical CT operating voltage, making them suitable for imaging. Further advantages of gold nanoparticles are their relative ease of synthesis, numerous methods of surface modification and functionalization, as well as good biocompatibility and nontoxicity. PEGylated gold nanoparticles conjugated to anti-EGFR antibodies have been shown to target A341 human head and neck tumor cells in mice and to be detected by clinical CT. The drawbacks of gold nanoparticles are its high price and the need for high doses to achieve sufficient contrast. Nevertheless, on-going clinical trials of gold-nanoparticle-assisted radiation therapy and other possible nanoparticles to be used for nanodiagnostics and theranostics are discussed, including hybrid radio/photodynamic therapy.

Dr. Heldman and his colleagues compare the lipid-based nanoparticles, in particular bolalipid vesicles they have developed, to other types of nanoparticles. Bolalipid vesicles, or bolaamphiphilic vesicles, are made from bolaamphiphiles, compounds composed of two hydrophilic head groups connected to the two ends of a hydrophobic alkyl chain. The high stability of bolalipid membranes makes bolalipids excellent building blocks for vesicles used as drug-delivery systems. In spite of their stability, bolaamphiphilic vesicles switch rapidly from vesicular structure to other nanostructures, such as fibers, cylinders, and lamellar sheets, upon structural changes in their hydrophilic head groups, a property that can be used to provide bolalipid vesicles with controlled-release mechanisms. These investigators had generated bolaamphiphiles monolayer membrane vesicles, delivering efficiently high drug concentrations. In addition, these bolalipid vesicles were shown to be effective in gene delivery and in the delivery of peptides and proteins across biological barriers. The use of bolaamphiphilic vesicles for drug-delivery with an emphasis on cancer therapy, as well as imaging, is addressed in their article.

The work of Drs. McDevitt and Scheinberg focuses on carbon nanotubes (CNT) that have been demonstrated to transit cell membranes, deliver siRNA, and silence genes *in vitro* and *in vivo* when locally administered to tissues. The fibrilar pharmacology of CNT is now better understood, as is the chemical identity and stoichiometric composition of functionalized CNT (f-CNT) constructs laden with oligonucleic acid sequences. In addition, functionalization of carbon nanotubes for use *in vivo* will be discussed. Next, they address pharmacokinetic (PK) studies including, distribution, excretion, absorption and metabolism. PK analyses of siRNA/f-CNT in murine models demonstrated the essential role that the f-CNT platforms have in specific tissue accumulation and protection of the cargo from degradation. Improving PK performance of CNT is discussed.

An attractive explanation for the differential accumulation of the nanoparticles within tumors versus normal tissue is that it is due to the phenomenon of enhanced permeation retention (EPR) effect. In their review, Drs. Geary and Salem address the EPR effect and physicochemical properties of submicron carriers that determine rate of clearance of nanoparticles from circulation, such as size, surface characteristics and molecular composition. They focus on liposomes and alternative carrier systems such as those made from

the biodegradable polymer poly (lactic-co-glycolic) acid (PLGA), investigated in preclinical settings with promising outcomes. In addition, they review the principle behind biodegradable submicron carriers (e.g. liposomes and PLGA-based carriers) as drug-delivery vehicles for solid tumors, and highlight the strengths and weaknesses of each system.

Dr. Bergkvist and his colleagues review nanotechnology-based approaches in order to address chemoresistance developing in ovarian cancer, one of the deadliest of all gynecological cancers and the fifth leading cause of death due to cancer in women. The successful clinical use of Doxil®, a PEGylated liposomal nanoencapsulated doxorubicin, on recurrent ovarian cancer, has paved the way for the current wave of nanoparticle formulations in drug discovery and clinical trials. In their review, they summarize new nanoformulations that are currently moving into clinical trials and highlight novel nanotherapeutic strategies that have shown promising results in preclinical studies. In addition, they discuss the potential for nanoparticles in diagnostic imaging techniques and the ability to leverage nanotechnology for early detection of ovarian cancer.

In summary, the reviews in this issue emphasize that nanotechnology is ushering in new strategies for both imaging and theranostics so as to improve targeting and delivery of chemotherapeutic drugs, drug efficacy, and toxicity profiles. More clinical trials are necessary to have a better idea of whether these nanoparticles are truly effective at seeking out and killing cancer cells. However, there are also concerns that the fundamentally different properties of nanoparticles compared with bulk materials may pose significant safety issues and, therefore, require additional regulatory scrutiny. Thus, current US and international regulatory frameworks for nanomedicines should address safety and toxicity issues to determine the unknown properties of nanomaterials *in vivo* before these materials are incorporated into routine clinical practice.

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