

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Insights Into Drug Development Using Nanotechnology



Jan Grimm, MD, PhD
Member, Molecular Pharmacology Program
Professor, Gerstner School of Biomedical Sciences
Attending, Department of Radiology
Memorial Sloan Kettering Cancer Center
Professor of Pharmacology
Weill Cornell Medical College
New York, New York

H&O What is the objective of your laboratory?

JG Overall, the objective is to improve therapy and imaging for patients with cancer through clinically translatable methods. Our current research on nanotechnology aims to evaluate and expand the use and effects of clinically approved nanoparticles. We evaluate how to utilize the biology behind nanotechnology. We provide some labeling of the nanoparticles with a targeting moiety, if needed, in a way that does not alter the particle chemically. We use imaging methods to create novel agents based on clinically approved particles. Predominantly, our research has focused on the clinically approved iron oxide particle ferumoxytol (Feraheme, AMAG Pharmaceuticals).

We currently have ceased to generate novel, multi-functional, complex nanoparticle systems, which usually have a limited chance of being successfully translated.

H&O Could you please define nanotechnology?

JG Nanotechnology is the study and use of particles up to 100 nm in diameter. These particles are 10,000 times smaller than the width of a hair. In oncology drug development, these particles often have a total hydrodynamic size of less than 100 nm. Nanoparticles are used in many other environments, such as paint and personal care products, often unbeknownst to the user. A recent study showed that the heat process involved in baking a pizza can create fluorescent nanoparticles on the surface. Unfortunately, nanoplastics are now found in the oceans. Nanoparticles are essentially everywhere. At my

By bringing drugs directly to tumors, nanoparticles can decrease the amount of the drug needed to be effective and thereby reduce toxicity.

laboratory, we are interested in the beneficial biomedical application of these particles for new avenues, particularly drug delivery and therapy, as well as biologic interactions and diagnostic imaging.

H&O Are there unique characteristics of nanomaterials used in drug development?

JG In general, nanomaterials have properties that are distinct from larger materials and from small molecules. Nanoparticles have unique properties that occur at the nanoscale size that can be exploited in medical imaging or for drug delivery. For example, nanoparticles sometimes have a preferential uptake into tumors or areas of inflammation, allowing delivery of drugs or imaging agents. That being said, the characteristics of nanomaterials vary greatly in size, shape, and surface charges. Their composition can be different. For example, 2 particles might have

the same size and the same charge, but one might consist of iron oxide and the other of a polymer. Although these nanoparticles share the same size and charge, they have very different biologic effects. These differences render it possible to make very specific use of the particles, but they also create new challenges.

A prime example of a nanoparticle is a quantum dot. Quantum dots can be sized to produce certain colors. Quantum dots also classically contain heavy metals, such as selenium or cadmium. Cadmium is of course too toxic for use in patients. There are efforts to synthesize quantum dots so that they are small enough for rapid excretion in the urine to remove most of them from the body, reducing toxicities. It is also possible to shape some biocompatible nanoparticles so that they are more easily drawn into cells. For example, researchers have found that particles that are more elongated—and therefore similar in shape to some bacteria—penetrate cells better than round particles. It is therefore possible to gear the characteristics of a particle to suit a particular objective, such as rapid removal from the body to alleviate toxicity concerns or rapid entry into cells to release a drug.

H&O What are the advantages and disadvantages to developing drugs with nanotechnology?

JG There are many potential advantages. Nanoparticles are versatile. It is possible to create an application-specific design with a functionalization that allows a nanoparticle to be personalized for an individual patient. Basically, nanoparticles can be used as a scaffold, which can be modified on the surface so that they target a specific antigen on the tumor cells. The particles can act in a therapeutic capacity by transporting a drug, as a diagnostic by carrying an imaging agent, or as a theranostic, carrying both. By bringing drugs directly to tumors, nanoparticles can decrease the amount of the drug needed to be effective and thereby reduce toxicity. It is thought that tumors can retain nanoparticles owing to increased vascular permeability, a concept known as the enhanced permeability and retention (EPR) effect. It is not clear, however, whether observations in animal studies are translatable to humans.

A disadvantage to nanoparticle technology is that we still lack a good understanding of how nanomaterials act in biologic systems, including which biologic switches they hit and how they might impact the body. In addition, we do not know if this effect differs among the nanoparticles. The advantage of having multiple different nanoparticles also complicates their use. As an example, it was previously thought that iron oxide nanoparticles were biologically inert and that when they degrade, they enter into the iron metabolism with no further effects. It turns

out, however, that iron oxide nanoparticles exert some interesting biologic effects, particularly on macrophages. Nanoparticles also have a disproportionately high uptake in the liver, spleen, and lymph nodes. This property can provide an advantage if these organs are being targeted, but it is a disadvantage if the target is a tumor situated elsewhere.

Compared with standard doxorubicin, the liposomal nanoparticle formulation has improved efficacy and less systemic toxicity.

H&O Are there any recent insights concerning nanotechnology and drug development?

JG A 2016 meta-analysis suggested that nanoparticle drug delivery is less effective than anticipated, and that this method does not bring a substantial amount of the drug to the tumor. At my laboratory, however, we somewhat disagree with this observation because we see higher drug delivery with our particles. Another advance from some laboratories, including ours, concerns the direct biologic effects of nanoparticles. We showed, for example, that it is possible to use nanoparticles as therapy for some leukemias. An article from colleagues at Stanford University and Oregon Health and Science University showed that nanoparticles have immunologic effects by switching the function of a tumor-resident macrophage from tumor-promoting to tumor-inhibiting. More advances in this field are likely, as researchers embrace an integrated view of the nanoparticle's activity in biologic environments.

H&O What are some examples of hematology/oncology drugs developed through nanotechnology?

JG The prime example of a clinical nanoparticle is doxorubicin in a liposomal nanoparticle encapsulation. Compared with standard doxorubicin, the liposomal nanoparticle formulation has improved efficacy and less systemic toxicity. Less cardiac toxicity was shown in breast and ovarian cancer mouse models. Simple radiolabeling of the nanoparticle showed that more of the drug was brought to the tumor. Similar drugs have been used to treat Kaposi sarcoma.

As mentioned above, a study from my laboratory showed that the clinically approved iron oxide nanoparticle ferumoxytol could be used as therapy for acute myeloid leukemia. This drug is already approved to treat anemia. Animal models showed that ferumoxytol significantly extended survival. The dose was the same as that used in patients with anemia. This observation provides an example of how to find additional applications for approved drugs.

H&O What are some areas of future research in nanotechnology for drug development?

JG An important area is to study how nanoparticles modulate their surrounding biologic environment. It is necessary to know what is happening in the body to the nanoparticles, how the nanoparticles interact with the biologic system they entered, and how to use these effects to benefit the patient. We also need to learn how to improve the safety profile.

Another area of research is how to further increase delivery accuracy to ensure that most of the drug reaches the tumor and not the liver. There is debate concerning whether nanoparticles must be targeted specifically to a tumor or whether a nontargeted particle might still efficiently reach a tumor based on the EPR effect. This question would need to be addressed for each individual particle, which is challenging. This need will vary based on factors such as the nanoparticle's size and charge.

Researchers are evaluating so-called smart nanoparticles, which can sense environmental conditions and adapt to them. For example, a smart nanoparticle could sense a low pH level—a characteristic of tumors—and then release the drug directly into the tumor and nowhere else.

H&O Are there other opportunities for nanotechnology in the management of malignancies?

JG The immunomodulatory effect of nanoparticles can be used to activate the immune system and steer it to act against the cancer. Nanoparticles can impact reactive oxygen species generation and the oxidation-reduction

(redox) potential of cells, reactions that convey important messages among cells. Nanoparticles can modulate vascular permeability by opening blood vessels. The blood vessels then leak drugs into the tumor, facilitating drug delivery. Nanoparticles can enhance the effects of radiation therapy or provide additional radiation effects. They can also improve photodynamic therapy. In the field of iron oxide nanoparticles, researchers are exploring whether, once these particles are delivered to the tumor, it would be possible to apply alternative oscillating magnetic fields to move them. The resulting friction and heat could provide thermal ablation. Research is evaluating nanoparticles as diagnostic agents that can also deliver therapy.

It is expected that nanoparticles will be used in the management of malignancies. A challenge with clinical translation is that approval—and reimbursement—will need to be sought for each nanoparticle.

Disclosure

Dr Grimm and his team have two patents pending for iron oxide nanoparticles.

Suggested Readings

Cong S, Wang N, Wang K, et al. Fluorescent nanoparticles in the popular pizza: properties, biodistribution and cytotoxicity. *Food Funct.* 2019;10(5):2408-2416.

Greish K. Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting. *Methods Mol Biol.* 2010;624:25-37.

Grimm J. Cancer nanomedicine: therapy from within. *Nat Nanotechnol.* 2015;10(4):299-300.

Hadla M, Palazzolo S, Corona G, et al. Exosomes increase the therapeutic index of doxorubicin in breast and ovarian cancer mouse models. *Nanomedicine (Lond).* 2016;11(18):2431-2441.

Kaittanis C, Bolaender A, Yoo B, Shah N, Ouerfelli O, Grimm J. Targetable clinical nanoparticles for precision cancer therapy based on disease-specific molecular inflection points. *Nano Lett.* 2017;17(11):7160-7168.

Pratt EC, Shaffer TM, Zhang Q, Drain CM, Grimm J. Nanoparticles as multimodal photon transducers of ionizing radiation. *Nat Nanotechnol.* 2018;13(5):418-426.

Trujillo-Alonso V, Pratt EC, Zong H, et al. FDA-approved ferumoxytol displays anti-leukaemia efficacy against cells with low ferroportin levels. *Nat Nanotechnol.* 2019;14(6):616-622.

Wilhelm S, Tavares AJ, Dai Q, et al. Analysis of nanoparticle delivery to tumours. *Nat Rev Mater.* 2016;1(5):16014.

Zanganeh S, Hutter G, Spitler R, et al. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. *Nat Nanotechnol.* 2016;11(11):986-994.