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Nanotechnology: Is the Magic Bullet Becoming Reality?

Researchers at a recent New York conference discuss what the future of nanomedicine may hold.

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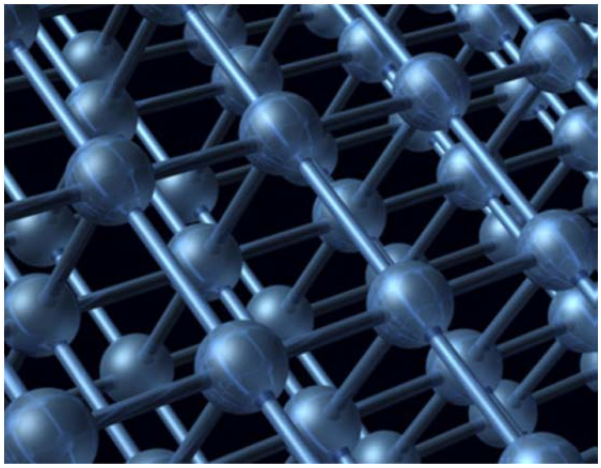


Nanotech seems promising, but regulatory and patent issues remain. [© Anterovium - Fotolia.com]

Slightly over a century ago, Paul Ehrlich coined the term “magic bullet” to refer to therapeutic compounds designed to selectively target a pathogen without affecting the host. Subsequently, this idea flourished not only for infectious diseases but also for other fields, such as cancer therapy. At the recent “Nanomedicines: Addressing the Scientific and Regulatory Gap” conference held at the New York Academy of Sciences in late November, investigators discussed key concepts shaping a vibrant field that promises to bring this concept closer to the clinic.

- ## Liposomes

“When we entered this field, from the few systems that existed, we chose to work on liposomes,” said Yechezkel Barenholz, Ph.D., professor of biochemistry at the Hebrew University – Hadassah Medical School in Jerusalem. Liposomes presented the advantage that relatively more knowledge existed about their pharmacokinetic properties. The compound that Dr. Barenholz and colleagues started to work on, doxorubicin, is one of the most effective first-line anticancer therapeutics ever developed, but one of its disadvantages is that adverse effects occur in many organs upon systemic administration. Work by Dr. Barenholz and colleagues on a liposome-based doxorubicin formulation culminated with the development of Doxil (doxorubicin), the first nanodrug approved by the FDA in 1995. “In a way, the success of this project started from a failure,” Dr. Barenholz said. Investigators in his lab initially developed a liposome-based doxorubicin formulation to reach the liver and treat hepatocellular carcinoma, and even though this worked well

in an animal model, the pharmacokinetics was not favorable in humans. “As a result we became more determined, and in a new approach, we decided to first determine what kind of performance we need from liposomes, and then we used a materials science approach,” he added.

A key concept in developing the doxorubicin-loaded liposomes was the enhanced permeability and retention effect. This phenomenon, which results from differences in vasculature between normal and inflamed tissue, refers to the ability of the poorly aligned, fenestrated endothelial cells from the malignant tumor neovasculature to allow 10–300 nm diameter nanoparticles to cross and become selectively enriched in the tumor. “This is not the case in normal tissues, and it represents the Achilles’ heel of the tumor,” said Dr. Barenholz. The defective lymphatic drainage of malignant tissues further facilitates the accumulation of nanoparticles.

To load the liposomes with doxorubicin, Dr. Barenholz and colleagues relied on a transmembrane ammonium sulfate gradient that acted as the driving force for the loading process. As a result, doxorubicin reached 100-fold higher concentrations in the intraliposomal aqueous phase as compared to the loading medium. The circulation time of liposomes was extended by stabilizing them with a formulation composed of phospholipids with high melting temperature, cholesterol, and a pegylated lipopolymer. Clinical studies in humans revealed that the nanoparticles accumulated in tumors, and doxorubicin reached higher concentrations in the tumor than what could what could be achieved with systemic administration. “This formulation improves patient compliance and the quality of life,” Dr. Barenholz said.

- ***TNF***

“We wanted to use nanotechnology in cancer therapy and change the way we treat this disease,” said Lawrence Tamarkin, Ph.D., president and CEO of CytImmune. The approach that Dr. Tamarkin and colleagues developed relies on 27 nm gold nanoparticles that have been used since the 1930s to treat psoriatic arthritis and present an established history of safety.

The surface of the colloidal gold nanoparticles was simultaneously bound to covalently linked thiolyated PEG, to avoid immune detection, and recombinant human tumor necrosis factor (TNF). Clinically, TNF has been successfully used in Europe to treat tumors of the extremities, in a procedure known as isolated limb perfusion. Infusing high-dose TNF prior to chemotherapy can achieve 15–25-fold higher concentrations as compared to systemic administration, without the same risks of adverse effects. With this strategy, several studies found up to 95% response rates after one treatment in patients with melanoma and sarcoma. “We wanted to mimic this clinical experience systemically,” said Dr. Tamarkin.

The 27 nm-diameter gold nanoparticles are small enough to travel through the blood vessels, and the 2–4 nm gaps between endothelial cells in healthy blood vessels are too small to allow them to cross into tissues, due to the presence of the tight junctions. “But at the site of the tumor, where the neovasculature fenestrations are 200–400 nm, the blood pressure forces them into the tumor bed, where TNF molecules bind to TNF receptors on the endothelial cells and start

causing vascular disruption," he added. In a Phase I clinical trial, CYT-6091, the nanotherapeutic that Dr. Tamarkin and colleagues developed, delivered up to 1.2 mg TNF, as compared to 0.4 mg, which is the maximum tolerated human dose, without any signs of dose-limiting toxicity. "The promise of nanotechnology is that we can reduce or eliminate toxicity and improve the therapeutic index," he said. Moreover, the drug accumulated at tumor sites, and very few gold nanoparticles were seen in healthy tissues. "We intended not simply to reformulate an already approved drug, but to create a safe and effective therapeutic by using nanotechnology," he said. Two patients, one with inoperable breast cancer and another one with pancreatic cancer, neither of them having previously undergone surgical treatment, showed the most nanoparticles accumulating in the tumor, as compared to the adjacent healthy tissue. "This indicated that perhaps treating patients surgically so quickly might not be a good idea, because it tears up the roadway that nanoparticles use to reach their targets," he commented.

Gold nanoparticles accumulated in malignant tissues even at the lowest doses, but accumulation was not increasing in a dose-dependent manner. Reducing the tumor burden in situ offers the possibility to reduce the need for sophisticated surgery and the hospitalization time. "We have the promise to dramatically improve healthcare because of decreased treatment costs," he concluded.

- ## *Generic Nanotech*

The concept of generic substitution, which guides the replacement of a prescribed brand of a drug with an identical formulation of the same active compound made by a different manufacturer, appears to open uncharted territory when applied to nanomedicine. Generic medicinal products are normally therapeutically equivalent and therefore interchangeable and substitutable to the reference (innovator) product because they are pharmaceutically comparable and bioequivalent, and they do not require additional clinical efficacy or safety studies.

"But it has to be ensured that the drug can be fully characterized," said Stefan Mühlebach, Ph.D., professor of pharmacology at the University of Basel and scientific director at Vifor Pharma. The generic paradigm was successful in the past for small molecules such as aspirin, but it is more problematic for the more complex biological drugs, which are much larger and more difficult to characterize. A third category of medicinal products, the nonbiological complex drugs, is distinct from both the small molecules and the biological therapeutics by the presence of multiple different large molecular structures, some of which may be nanoparticulate, and by not being a biological.

In nonbiological complex drugs, the entire product represents the active pharmaceutical ingredient, all the components contribute to the characteristics of the final product, and the properties cannot be fully characterized by physicochemical means, which is a prerequisite to show pharmaceutical comparability to a reference listed drug (RLD) and requested for generics. "The characterization of nonbiological complex drugs is seriously limited by the fact that we do not always know what to look for when characterizing clinical meaningful differences," said Dr. Mühlebach. Additionally, the characteristics of nonbiological complex drugs are highly dependent on the elaborate, multistep synthetic manufacturing process.

Examples of nonbiological complex drugs are the iron carbohydrates, such as iron sucrose used for intravenous iron treatment, liposomal drugs, and some polymeric polypeptides like the glatiramoids. Iron sucrose, a colloidal solution, was introduced into therapy almost 50 years ago and used safely without knowing its nanomedicine character. “A challenge for some of these products is that the first generation of compounds started to be even replaced by competitors (similars) in the absence of the awareness on their nano properties and a lack of established or appropriate regulatory evaluation tools,” he added.

The example of an iron sucrose similar that was used to substitute for the original compound is revealing. A retrospective analysis that investigated adverse effects in 600–700 postpartum gynecology patients from South Korea showed that the original product always caused fewer adverse effects compared to the new formulation. When diluted and administered over a longer time, classically used to improve the tolerance for a parenteral drug, even more adverse effects were reported with the new formulation, contrary to the predictions, but understandable from the complexity and the fragile stability of the products. As these results indicate, the conventional generic paradigm is not reliable any longer in the case of nanosimilars, and concluding that two products could be interchangeable, substitutable, or therapeutically equivalent may be wrong. “What we know about nanosimilars is that we need to go into the details of understanding the complexity of the manufacturing process, not only starting with the materials, but also regarding the final product, because these aspects are of highest importance for pharmaceutical equivalence, bioequivalence or the fate of the product in the body and finally efficacy and safety of the therapeutic product for the patient,” Dr. Mühlebach said.

- ## Regulatory Issues

“Nanotechnology, along with the promise and benefits that it brings, may also raise some questions and concerns over safety and effectiveness,” says Ritu Nalubola, Ph.D, senior policy advisor at the Food and Drug Administration. Some of the most significant regulatory considerations revolve around unveiling the properties of nanomaterials and understanding the relevance of those properties to the regulatory status of the specific products. To provide a framework for the regulatory oversight of emerging technologies in general and of nanotechnology products in particular, in 2011 the Emerging Technologies Policy Coordination Committee prepared two strategic documents. “Building on these U.S. government policy principles, the FDA developed its own agency-specific regulatory approach, and these emphasize our mission to protect and promote public health, adopt risk-based regulatory approaches based on sound science, and develop transparent and predictable regulatory pathways that are grounded in the best available science,” says Dr. Nalubola.

The definition of nanoparticles—including their size, which has commonly been placed in the 1-100 nm range—continues to present ample interest for regulatory purposes. “There are challenges in deciding how to address aggregates, agglomerates, and some other complex structures, and whether, in addition, we should also take into account novel engineering properties for regulatory purposes”, Dr. Nalubola commented.

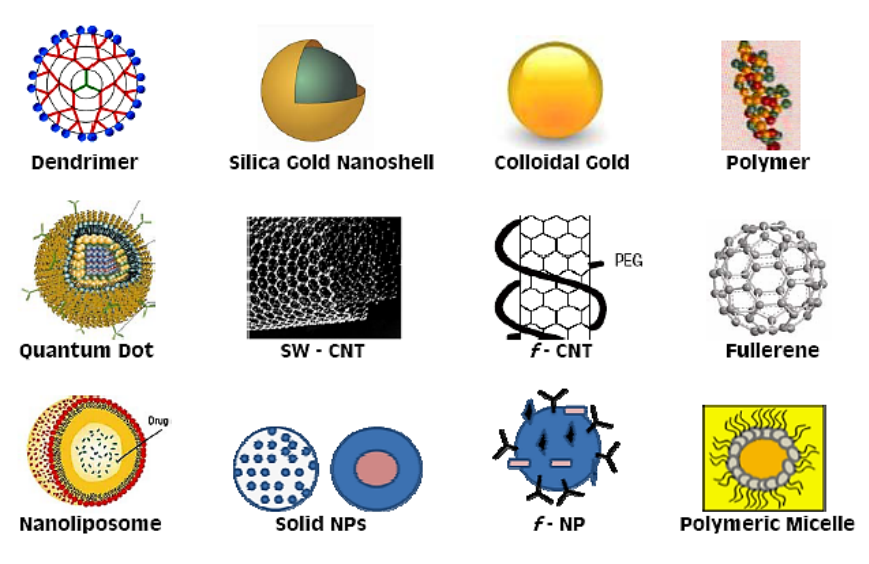
In 2011, the FDA issued a draft guidance that provides a broad screening tool for regulatory processes. “The FDA draft guidance recognizes our interests in size, but also that our interest extends beyond size, and that other properties are also relevant for safety and efficacy reviews,” she said. The guidance document encourages industry to seek FDA consultation early during product development, to ensure that any questions related to safety, effectiveness, and regulatory status can be adequately and timely identified and addressed. “We also articulated our general position, which is that we do not categorically judge all nanotechnology products as being inherently benign or harmful but, rather, that we are looking at products and their characteristics on a case-by-case basis,” she added. This ensures that the current regulatory framework is sufficiently robust and flexible enough to consider a variety of nanomaterials, and to concomitantly identify existing regulatory gaps.

The FDA is actively engaged in the national nanotechnology initiative and participates in some of its research activities. “On the policy side, and in context of the Emerging Technologies Interagency Policy Coordination Committee, we have ongoing dialogues on developing policy approaches and policy-related coordination, and we also participate in the international arena with our regulatory counterparts,” Dr. Nalubola said. From more than 80,000 articles on nanoparticles that were available on PubMed in January 2014, over half were published after 2010, revealing the interest and progress that are marking this area. As a multidisciplinary field, nanotechnology impacted diverse disciplines including agriculture, engineering, energy production, communications, information technology, cosmetics, and biomedicine. Among these, the diverse biomedical applications provide a clear indication that Ehrlich’s era of the “magic bullet” is becoming reality.

- ## *Fool’s Gold in the Nanotech Patent Rush*

“The past few years, especially the past decade, have witnessed a nanotechnology patent boom, a sort of patent ‘land grab’ by ‘patent prospectors’ who have captured upstream, foundational nanotechnology-related technologies,” says Raj Bawa, Ph.D., patent agent at Bawa Biotech LLC in Ashburn, VA, and adjunct professor at Rensselaer Polytechnic Institute, Troy, NY.

At the recently concluded New York Academy of Sciences meeting, Dr. Bawa discussed some of the main considerations with respect to nanotechnology and nanopharma patents. According to information obtained from the U.S. Patent and Trademark Office (PTO), as of December 2012 over 8,000 U.S. nanopatents have been issued by various PTO technology centers and classified under Class 977. However, Dr. Bawa does not put too much stake into these numbers and even considers the classification strategy inadequate. “These data simply reflects an upward trend, a sort of ‘nano-explosion’ and nothing more,” he commented. “It is based on the ill-conceived National Nanotechnology Initiative (NNI) definition of nanotechnology that limits all nanostructures and nanoproducts to a subnanometer range. Obviously, such a narrow (1-100 nm) and arbitrary classification scheme by the PTO misses many, if not most U.S. nanopatents and the actual numbers are meaningless to a researcher, policy-maker, or patent practitioner.”



A lack of a universal nanonomenclature is one factor complicating the patenting of nanotechnologies. [© Raj Bawa]

Another significant conundrum pertaining to nanotechnology patenting is the lack of a universal nanonomenclature whereby researchers and policy-makers often use distinct terms to refer to the same or similar nanostructure. Furthermore, the late 1980s and early 1990s have witnessed issuance of more than one U.S. nanopatent for the same invention. "This is contrary to the foundation of U.S. patent law where only one U.S. patent may be issued per invention," Dr. Bawa added. "Partly, this situation developed because the search tools and commercial databases that were being used by patent examiners at the PTO, while well-suited to search patents on established technologies, were not well scaled to search most of the early scientific literature residing in scientific publications, as opposed to U.S. patents. Also, the U.S. patent examiners generally lacked expertise and training with respect to the emerging field of nanotechnology."

The classic example of these limitations is the issuance of multiple U.S. patents on carbon nanotubes. In a study on carbon nanotubes, Dr. Bawa and colleagues analyzed the claims from approximately 200 existing patents. "We discovered many foundational patents on carbon nanotubes recited overlapping or 'legally identical' patent claims," he said. "A classical patent thicket exists today with respect to carbon nanotube patents."

One of the reasons that major conflicts have not emerged in this area is that not too many products have been commercialized yet. "The hope is that such U.S. patents will expire prior to widespread commercialization so that there is little or no need for litigation. However, some have proposed that the government employ provisions under the Bayh-Dole Act of 1980 by imposing compulsory licensing while others have even urged creation of an open-source type process to rectify the erroneous issuance of some of these basic, foundational U.S. nanopatents so that downstream development of nanotechnologies are not stifled," Dr. Bawa said.