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Executive Summary of Testimony

The benefits of treating human disease with nanoparticle therapeutics far exceed the potential safety risks. In particular, there is great anticipation that these new medicines will be able to revolutionize the diagnosis and treatment of metastatic cancer.

Nanoscaled materials typically have properties not manifested either in larger particles with the same composition or in individual molecules, a distinguishing feature of great significance. While this motivation has driven nanoscience and technology in physics and engineering, it is not the main reason that nanoparticles are useful for systemic applications in the human body. Nanoparticles in the body behave differently compared with larger particles, not because of any fundamental difference in physical or chemical properties, but instead because the small size of a nanoparticle allows access to locations that are either denied to larger particles or difficult to reach in significant quantities with smaller molecular drugs.

Nanoparticles used for the treatment of systemic cancer in humans will likely be in the size range of 10-100 nm. Control over size and surface properties allow nanoparticle therapeutics to target tumors and give safety profiles that are superior to small molecule chemotherapeutic drugs. Additionally, nanoparticles can be engineered so that they enter cells. Nanoparticles internalize into cells in ways that bypass the mechanisms that make existing molecular therapies ineffective. Therefore, nanoparticles containing these drugs can facilitate new therapies that increase effectiveness and lower the toxicity of these existing drugs. This capability of nanoparticles may provide whole new treatment methodologies for cancer patients.

Not all nanoparticles are the same, and those created for the purpose of injection into humans for therapeutic purposes are well designed and rigorously tested for safety, unlike nanoparticles that enter the body from environmental exposure. While nanoparticle medicines have been used safely in humans for several decades, further investigation into the biocompatibility of nanoparticles in humans is merited. At this time, additional statutory authority to complement the FDA approval process is not necessary given the high benefit to risk ratio for cancer patients.

Newer nanoparticles will be more uniform in their size and surface properties than current versions, and this uniformity should translate into more effective medicines and imaging agents with better definable biocompatibilities. Additionally, nanoparticles will become “smart” in the sense that they will be able to take cues from their local environment to activate functions at specified times and locations. These complex, multifunctional nanoparticles will be expensive to produce, and issues regarding scale-up and manufacturing for human use will be rate limiting factors to commercialization. Additionally, the multicomponent nature of the nanoparticles makes IP issues around freedom to operate and regulatory approval processes capital intensive. However, the potential therapeutic benefits of these nanoparticles are so high that there is no doubt that new nanoparticle medicines will reach the public in the near future. If the true benefits of advanced nanomedicines are to reach the public within the next decade, there must be a significant effort underway in their discovery and development *today* because of lengthy approval processes.

Testimony

Mr. Chairman and members of the Committee, thank you for the opportunity to testify at this hearing. Since the early 1980's, I have been working in areas of science and technology that are now classified as nanoscience/nanotechnology. My objective today is to present the potential of nanoparticles for use as therapeutics to treat human disease. In particular, I wish to convey the excitement over what these new medicines could mean to the diagnosis and treatment of metastatic cancer. Additionally, I want to emphasize that not all nanoparticles are the same: those created for the purpose of injection into humans for therapeutic purposes are well designed and rigorously tested for safety offer a tremendous benefit to risk ratio for the treatment of cancer, unlike nanoparticles that enter the body from environmental exposure.

Numerous diseases occur throughout the human body, and systemic imaging and therapy are necessary to treat and eradicate them. Metastatic cancer, for one, is a particularly important disseminated disease requiring such an approach, because treatment-resistant metastases (tumors located throughout the body that are not the primary tumor or site of the cancer) ultimately are the cause of death in most cancer patients. Detection and treatment of systemic diseases present numerous challenges, since humans possess a variety of defense mechanisms against the foreign agents that must be inserted into the body for imaging and therapy. Additionally, systemically delivered agents need to reach all their intended tissue and cellular targets to be effective. These features and many others make the creation of systemic imaging and therapeutic agents a daunting task.

Nanoscaled materials typically have properties not manifested either in larger particles with the same composition or in individual molecules, a distinguishing feature of great significance. While this motivation has driven nanoscience and technology in physics and engineering, it is not the main reason that nanoparticles are useful for systemic applications in the human body. Nanoparticles in the body behave differently compared with larger particles, not because of any fundamental difference in physical or chemical properties, but instead because the small size of a nanoparticle allows it access to sites that larger particles cannot reach.

To achieve systemic localization, medicines must at some point enter the circulatory system for dissemination throughout the body. Molecular medicines that are typically 1 nm in size are quickly removed from the body by the kidneys. In order to stop this fast elimination, nanoparticles must be larger than 10 nm in diameter. Thus, an advantage of nanoparticle medicines over molecular medicines is that they can remain in circulation for longer times and provide for extended length of therapy (in addition to the enhanced localizations). Through careful experimentation, we and others have shown that nanoparticles can access tumors from the circulatory system and move throughout them if they are "well designed" and have sizes in the 50-100 nm range (Hu-Lieskovan *et al.*, 2005 and Kim *et al.*, 2006). By "well designed", I mean the surface of the particles are carefully controlled as the surface properties of the nanoparticles can greatly influence their behavior in humans (Chen *et al.*, 2005). It is the purposeful control of size and surface properties of nanoparticle medicines that distinguishes them from other types of nanoparticles.

Nanoparticles for imaging and therapy will be of size 10 – 100 nm and are composites of polymers and other organic materials and the therapeutic/image agents. These particles are typically spherical and they are seven orders of magnitude smaller than a soccer ball. That is, the increase in size from the nanoparticles to the size of a soccer ball is the same increase in size as going from the size of a soccer ball to the size of the earth. While these nanoparticles are small compared to other particles, they are large compared to molecules. For example, the size of a molecule (ca. 1 nm) to the size of a 100 nm nanoparticle is analogous to the size relationship between a soccer ball and the Goodyear blimp (think about how many soccer balls could be held in the blimp). This size allows nanoparticles to have a variety of features and functions that are not possible with molecules. It is precisely these features and functions that can be exploited to create nanoparticle medicines.

What particular features will be exploited when nanoparticles are used for systemic imaging and therapy? First, control over size and surface properties allows access to locations that are either denied to larger entities or difficult to reach in significant quantities with smaller entities such as molecule therapeutics because of rapid loss from the body (renal clearance). Additionally, if the drug or imaging agent needs entrance into the cell, nanoparticles can be engineered so that they can be internalized. There are at least two important consequences of this feature. Nanoparticles can be used to attack intracellular disease targets. Many of these intracellular targets have been known for some time but have been considered undruggable. Also, nanoparticles can be designed to release a significant portion of their “payload” when they enter cells, and this feature can be very advantageous. For example, many anticancer drugs lose their effectiveness when tumors become resistant owing to surface proteins that deny entrance to the drug molecules. Nanoparticles internalize into cells in ways that bypass the surface proteins, and can thus facilitate new therapies using existing drugs that, administered alone, would be ineffective. This capability of nanoparticles may provide whole new treatment methodologies for cancer patients.

These attributes lead to a second feature of nanoparticles that makes them useful for systemic imaging and therapy: their ability to perform multiple functions, since the particles are large enough to accommodate numerous components within the same particle. Multiple agents can be assembled into individual nanoparticles (multiple therapeutic agents, multiple imaging agents, and their combinations), making it possible, for example, to combine small molecular chemotherapeutic agents with other types of agents to simultaneously attack cancer at multiple pathways.

A third feature important for systemic imaging and therapy is the large number of atoms contained in a nanoparticle relative to that contained in a molecule (think of the soccer balls in the blimp). The nanoparticle thus delivers a greater “package” of material, and this increased payload size can help enhance the signal for imaging or provide a localized “bolus” of drug. One can imagine nanoparticle imaging agents that provide information on intracellular targets. The molecular target of the disease could be verified to exist in a patient prior to treatment, and since the observation was made via a nanoparticle with the same size and surface properties as the therapeutic particle, the therapy would be expected to reach the target. This combination will allow personalized medicine in the sense that treatment does not have to be administered until the target is known actually to be present in the patient. Also, follow-up imaging can be performed to verify that the target has been reached and that the therapy is working.

While there is tremendous excitement over the potential of nanoparticles for cancer imaging and therapy, there are also words of caution about their safety appearing in the literature. Concerns about nanoparticle toxicity are legitimate since not much is known about how these entities behave in humans. The size and surface properties of nanoparticles give them access to locations that were not previously available with larger particles, and the size of properly designed nanoparticles can affect their localization. Studies in this area suggest that more investigation is needed in order to define the biocompatibility of nanoparticles in humans. On the one hand, there are examples where nanoparticles have no detrimental effects (silica coated magnetic 50 nm particles: Kim *et al.*, 2006), and, on the other hand, examples where they do (carbon nanotubes: Salvador-Morales *et al.*, 2006). As expected, the size and surface properties of nanoparticles dictate their behavior, and much more data are necessary to develop a fundamental understanding of the structure-property relationships. However, one must consider the benefit to risk ratio for the intended application when assessing the biocompatibility of nanoparticles. In cancer, this ratio is very high and therapeutic agents in current use are not without their own safety risk profile. In fact, current nanoparticle medicines have superior safety profiles to the drugs that they are carrying. Also, in order to use a nanoparticle in humans, they must pass rigorous and lengthy regulatory processes prior to approval.

Nanoparticle medicines and imaging agents already have a history of use in humans. Commercial therapeutics and imaging agents such as AmBisome (liposomal amphotericin B), SMANCS (synthetic polymer–drug conjugate), Abraxane (albumin–paclitaxel nanoparticle), and Feridex (dextran–iron oxide nanoparticle for MRI) are just a few of the nanoparticulate drugs and imaging agents currently available for human use. Some of these nanoparticles are in the 10–100 nm range (AmBisome has an average size of 60–90 nm, Feridex an average size of approximately 30 nm), while others are not (Abraxane has an average size of 130 nm). Other nanoparticulate materials such as the polymer–drug conjugate XYOTAX (polyglutamate–paclitaxel) are in late stage clinical trials. Thus there is at least a 25-year history of using nanoparticles in medicine (AmBisome being the first and used in clinical trials in the 1980’s). These commercial nanoparticles have gone through rigorous toxicity testing for regulatory approvals and have years of experience in humans. This increasing store of information provides an initial understanding of how nanoparticles can exist and function in the body. Although each new nanostructure will need to be tested individually, there is reason to believe that nanoparticles can be used as effective systemic medicines and imaging agents. As more biocompatibility data become available, a further understanding of how to tune size and surface properties to provide safety will permit the creation of new, more effective nanomedicines for systemic use.

Since nanoparticles already exist as commercial medicines and imaging agents, what might be expected in the future? To begin, control over the size distribution and surface properties will see great improvements. Although *average* sizes of commercial nanoparticulate medicines and imaging agents fall within the range 10–150 nm, the distribution in size (that is, the spread of values about the average) and the consequent variation of surface properties are quite large for each product. Newer nanoparticles will be much more uniform in their size and surface properties than current ones, and this uniformity should translate into more effective medicines and imaging agents with better definable biocompatibilities. Additionally, nanoparticles will become “smart” in the sense that they will be able to take cues from their local environment to activate functions at specified times and locations. Early examples of this phenomenon already exist for nanoparticles designed to sense their entrance into cells and trigger the release of therapeutic agents (Davis *et al.*, 2004).

There is no doubt that these types of nanoparticles will exist in the future. Current nanoparticle medicines and imaging agents provide initial support for low toxicity with properly designed nanoparticles, and significant advancements in nanoparticle uniformity will further improve this situation. As newer and more complex nanoparticle systems appear, better methodologies to define biocompatibility will need to be developed, especially those that can assess intracellular biocompatibility. A significant remaining question is whether complex nanoparticle agents for imaging and therapy will be commercially viable in the face of numerous impediments to their development and implementation. These complex, multifunctional nanoparticles will be expensive to produce, and issues regarding scale-up and cGMP production are not often discussed. The multicomponent nature of the nanoparticles also renders their manufacture and regulatory approval very difficult. Beyond the cost of development itself, intellectual property costs can be very high as well, because each of the many components needed to create the nanoparticle might require multiple licenses. Given these high barriers to commercialization, some excellent medical nanoscience will doubtless never attain clinical or commercial status, and those products that do win approval will likely be expensive. Finally, we must recognize that the time frame for regulatory approval is sufficiently long that new nanomedicines of the next 10 to 15 years—if they are to be realized—must already exist and be in some stage of research or development, or else be invented within the next few years. If advanced nanomedicines are to reach the public within 10 or 15 years, there must be a significant effort underway in their discovery and development *today* because of lengthy approval processes.

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BIOGRAPHY OF MARK E. DAVIS

Mark E. Davis is the Warren and Katharine Schlinger Professor of Chemical Engineering at the California Institute of Technology and a member of the Experimental Therapeutics Program of the Comprehensive Cancer Center at the City of Hope. He has over 325 scientific publications, two textbooks and over 40 patents. Professor Davis is a founding editor of CaTTech and has been an associate editor of Chemistry of Materials and the AIChE Journal. He is the recipient of numerous awards including the Colburn and Professional Progress Awards from the AIChE and the Ipatieff, Langmuir and Murphree Prizes from the ACS. Professor Davis was the first engineer to win the NSF Alan T. Waterman Award. He was elected in the National Academy of Engineering in 1997. Professor Davis' research efforts involve materials synthesis in two general areas; namely, zeolites and other solids that can be used for molecular recognition and catalysis, and polymers for the delivery of macromolecular therapeutics such as nucleic acids. He is the founder of Insert Therapeutics Inc., a company based in Pasadena, CA USA, focused on the use of cyclodextrin-containing polymers for drug delivery applications (www.insertt.com) and Calando Pharmaceuticals, Inc. (www.calandopharma.com) a company based in Duarte, CA USA that creates RNAi therapeutics. He is currently or has been a member of the scientific advisory boards of Symyx (Nasdaq: SMMX), Alnylam (Nasdaq: ALNY) and NovoDynamics.