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REPORT

The Unither Conference—Recent Advances in Nanomedical Structures and Devices

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1. INTRODUCTION

New paradigms are shrinking our world and a classic technological revolution in medicine is unfolding. The agents of this revolution are microscopically small, products of a relatively nascent interdisciplinary field known as nanomedicine—the application of nanotechnology to healthcare. Nanomedicine, with all its excitement and expectation, is already influencing the pharmaceutical industry, especially in the design, formulation and delivery of therapeutics. Based on this broad theme, the 2nd Annual Unither Nanomedical and Telemedical Technology Conference was held in Orford, Quebec, Canada from February 24–27, 2009.

United Therapeutics Corporation (www.unither.com/UnitherHome.aspx), a biotechnology company headquartered in Silver Spring, Maryland, USA, sponsored this conference. The company focuses on the development and commercialization of unique products that address the unmet medical needs of patients with chronic and life-threatening cardiovascular disease, various infectious diseases and certain cancers. Martine Rothblatt, Ph.D., J.D. (Chairman and CEO of United Therapeutics Corporation) and Nobel Laureate Baruch S. Blumberg, M.D., Ph.D. (Distinguished Scientist at NASA Ames Research Center, California, US), chaired the conference. This year's conference highlighted numerous cutting-edge presentations broken up into various sessions that focused on innovations in nanomedicine, telemedicine, and the applications of nanotechnology to the pharmaceutical, device and biotechnology industries. Approximately hundred researchers, engineers, physicians, ethicists, lawyers, business professionals, policy makers and venture capitalists were in attendance.

2. NANOMEDICINE SESSIONS

Selected topics discussed at the conference pertaining to nanomedicine that are currently transforming medicine, the device industry, big pharma as well as the biotechnology industry, are highlighted below:

Nanomedicine and Drug Delivery—Size Does Matter

Size can have a major impact in drug delivery. Therapeutic-containing nanomaterials (also known as "nanotherapeutics" or "nanopharmaceuticals") often have unique "nanoproperties" (i.e., physiochemical properties) due to

(a) their small size compared with their bulk-phase counterparts;
(b) a high surface-to-volume ratio; and
(c) the ability to modulate their properties.

Specifically, as a particle's size decreases, a greater proportion of its atoms are located on the surface relative to its core, often rendering the particle more reactive and/or more soluble in water. Therapeutic-containing nanomaterials are, in essence, nanoparticles intended for a broad spectrum of clinical therapeutic applications. They are colloidal particles of 10 to 1,000 nanometers that are diverse in size, shape and composition and have the potential to target a particular organ or tissue site either passively or actively.

Raj Bawa, Ph.D. (Adjunct Associate Professor, Rensselaer Polytechnic Institute, Troy, New York, USA; Senior Scientist, SynerGene Therapeutics Inc., Potomac, Maryland, USA and Patent Agent, Bawa Biotechnology Consulting LLC, Ashburn, Virginia, USA) highlighted some of the fascinating and innovative nanotherapeutics/nanodevices that cleverly integrate biological, information technology and material sciences. In his talk, Dr. Bawa highlighted commercially promising nanomedicine-related drugs, medical devices and drug delivery technologies, such as:

(a) miniaturized nanofluidic devices and systems that more efficiently transport fluids to the site of delivery preventing turbulence and mixing (because fluids generally move with laminar flow through micro/nanochannels);

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(b) more efficient site-specific or precision targeting via nanodrugs (functionalized nanoparticles or nanoencapusulated/nanocoated drugs) with reduced systemic side effects and better patient compliance;
(c) close-looped drug delivery nanodevices/nanoimplants (also known as "smart pills") containing sensors (to monitor biomolecules) and drug reservoirs (for precise delivery) located on the same chip; and
(d) futuristic microsurgical devices, molecular motors or nanobots that are capable of navigating throughout the body to carry out targeted healing procedures such as repairing damaged sites, destroying tumors or viruses, and even performing gene therapy or vaccination.

Topics such as personalized nanomedicine, drug patents, the role of the US Food & Drug Administration (FDA) and the US Patent & Trademark Office (PTO) and nanomedicine's impact on the future soldier were also emphasized. Dr. Bawa predicted that, in the future, novel "multifunctional" nanopharmaceuticals will be designed and delivered to the human body via a variety of routes. However, he emphasized that it will be imperative that nanotherapeutics be evaluated on a case-by-case basis in an effort to correlate their physiochemical property with *in vivo* biological behavior as well as therapeutic outcome. In this regard, any research strategy must involve adsorption, distribution, metabolism and excretion (ADME) testing, toxicology tests and physiochemical characterization.

The Emergence of Nanopharmaceuticals

It is widely recognized that big pharma faces serious financial challenges. The pipeline of new drugs is too limited and many new products are higher-priced biologics with much narrower target patient populations. Furthermore, in recent years patent expirations on blockbusters and various market forces (emergence of generics, expanded FDA oversight, etc.) are dictating a change in pharma's quest for discovering, developing and delivering novel therapeutics. All of this is driving big pharma to search for new technologies and competitive business strategies. Clearly, new ground rules are in order in the post-blockbuster world. In fact, big pharma views novel drug delivery approaches as representing a strategic tool for expanding existing drug markets.

In this regard, drug delivery via nanopharmaceuticals presents novel reformulation opportunities for active agents (e.g., small-molecule drugs, proteins, nucleic acids, etc.) that were previously unsuitable for traditional oral or injectable drug formulations. Specifically, nanopharmaceuticals have enormous potential to address the failures of traditional drugs that could not be effectively formulated due to factors such as poor water solubility or a lack of target specificity. Nanopharmaceuticals allow active agents to be delivered efficaciously while minimizing side effects, thereby enhancing patient compliance. Although there are only a few FDA-approved nanopharmaceuticals on the market today, they are already influencing the practice of medicine.

Nanopharmaceuticals are selected for characteristics such as biodegradability, biocompatibility, conjugation, complexation or encapsulation as well as their ability to be functionalized. For simplicity, they can be divided into two groups:
(1) those where the active agent possesses intrinsic therapeutic properties and acts as its own polymeric carrier (examples include multivalent dendrimers, cerium oxide and platinum nanoparticles); and
(2) those where the active agent is directly coupled (functionalized, entrapped or coated) to a distinct polymeric carrier.

In the ideal situation, these polymeric (or lipid) carriers will be able to transport the active agent to a specific desired target site (ligand, receptor, active site, etc.) to impart maximum therapeutic activity with maximum safety (i.e., protecting body tissues from adverse reactions while preventing the degradation/denaturation/inactivation of the active agent during delivery/transit).

Jamboor K. Vishwanatha, Ph.D. (Dean and Professor, University of North Texas Health Science Center, Fort Worth, Texas, USA) presented on his research focusing on elucidating the molecular changes during progression of prostate and breast cancers, and utilizing nanobased drug delivery for therapy. Utilizing various molecular, immunological and imaging technologies, his lab is investigating the role of annexin A2, STAT-6 and C17orf37 genes in breast and prostate cancer progression. Sustained release nanoparticle formulations are being designed that can target specific diseased tissues. The ultimate goal is to formulate multifunctional nanoparticles for both acute and sustained therapy of diseases such as cancer, glaucoma, chronic obstructive pulmonary disease (COPD) and sickle cell anemia. Dr. Vishwanatha also presented on delivery of anticancer drugs through biodegradable nanoparticles for target-specific drug therapy. He presented a method for the efficient encapsulation of various anticancer drugs in poly(lacticco-glycolic acid) nanospheres using the multiple-emulsion solvent evaporation technique. Biodegradable polymers are preferred because surgical removal of the spent device, as in the case of implants, is not required. Furthermore, biodegradable nanoparticles are less likely to cause toxicological problems and their release rates can be tailored. They also degrade in biological fluids to generally produce biocompatible or non-toxic products in the body which can be removed via normal physiological pathways.

Simon Benita, Ph.D. (Professor of Pharmaceutics, Hebrew University of Jerusalem, Israel) presented on "Antibody-Nanocarrier Conjugates for Drug Targeting and Improved Cancer Therapy." His research pertains to nanodrug delivery systems aimed at improving oral bioavailability and the strategy of covalently linking monoclonal

antibodies to nano-carriers for drug targeting. Specifically, he described the conjugation of Trastuzumab to pegylated polylactic nanoparticles containing the chemotherapeutic agent, paclitaxel-palmitate. Cell culture binding/uptake, surface plasmon resonance and pharmacokinetic experiments showed that the conjugation process did not alter the original affinity and intrinsic binding properties of the monoclonal antibody. The findings revealed that these immunonanoparticles enhanced drug internalization into the desired cells. This was further confirmed in a pharmacological model of metastatic prostate cancer in SCID/Bg mice where pcpl-loaded immunonanoparticles inhibited the tumor growth much more than the pcpl nanoparticles in solution. Therefore, these immunonanoparticles can be considered a promising modality for an efficient targeted treatment of various malignancies.

Mark Kester, Ph.D. (Thomas Passananti Professor of Pharmacology, Penn State Hershey College of Medicine, Hershey, Pennsylvania, USA) presented on "Calcium Phosphate Nanoparticles as Nano 'Solutions' for Drug Delivery and Bioimaging." Dr. Kester's research interests include the evaluation of nanoliposomes, nanodendrimers and nanocolloids as effective drug delivery vehicles for pharmacological and molecular agents. His recent work involves nontoxic nanoscale systemic delivery systems for hydrophobic pro-apoptotic lipids as well as siRNAs that target mutated tumorigenic proteins. According to Dr. Kester, paradigm-shifting modalities that more efficiently deliver drugs to cancerous lesions require the following attributes: nanoscale-size, targetability and stability under physiological conditions. Often, these nanoscale drug delivery vehicles are limited due to agglomeration, poor solubility or cytotoxicity. Therefore researchers in his lab have designed a methodology to encapsulate hydrophobic chemotherapeutics (20–30 nm diameter) in a pH-responsive, non-agglomerating and non-toxic calcium phosphate matrix. These calcium phosphate nanoparticles (CPNP) can encapsulate both fluorophores and chemotherapeutics and are colloidally stable in physiological solution at 37 °C. They can also efficaciously deliver hydrophobic antineoplastic agents *in vitro* and *in vivo*. In addition, indocyanine green (ICG)-encapsulated CPNPs exhibit significantly greater intensity at the maximum emission wavelength relative to the free constituent fluorophore, which is consistent with the multiple molecules encapsulated per particle and an increased quantum efficiency and photostability. Optical near infrared bioimaging reveals that PEGylated ICG-CPNPs accumulate in solid, 5 mm diameter xenograft breast adenocarcinoma tumors via the enhanced retention and permeability (EPR) effect within 24 hours after systematic tail vein injection in a nude mouse model. These studies demonstrate that CPNPs can be considered as nano "solutions" for efficient bioimaging and drug delivery for certain cancers.

Modifying the Function of DNA Repair Nanomachines for Therapeutic Benefit

Shuyi Li, M.D., Ph.D. (Research Scientist, Institute of Molecular Medicine and Genetics, and Medical College of Georgia, Augusta, Georgia, USA) described strategies for understanding and manipulating DNA double strand break (DSB) repair responses in mammalian cells. He explained that the occurrence of site-specific DSBs initiates a complex series of events, including chromatin modification and protein complex assembly. He described strategies for introducing bright, stable fluorescent tags to track assembly of single repair complexes *in situ* and discussed the use of engineered antibody fragments to modulate activity of DSB repair machines as a mechanism-based strategy for increasing efficacy of radiotherapy. Specifically, he discussed adaptation of DSB repair machinery for gene correction in stem cells as a way to provide genetic cures for common human diseases.

Nanoporous Silicon—Platform for Personalized Medicine?

Ennio Tasciotti, Ph.D. (Assistant Professor, University of Texas Health Sciences Center, Houston, Texas, USA) has been leading research efforts in demonstrating the multistage delivery of nanoparticles from a non-toxic, biodegradable mesoporous silicon first stage carrier. To overcome current limitations in the detection and treatment of cancer, researchers in his lab have developed nanoporous silicon chips ("nanochips") for identification of protein signatures in biological fluids and, in tandem, have designed injectable silicon nanoporous particles (NPs) that provide multi-stage, multi-functional platforms for targeted delivery of therapeutic and contrast agents. These two silicon nanotechnology platforms offer significant advantages in their ability to fine-tune their surfaces by biochemical modifications. Nanochips provide clinical diagnostic tools for early detection of human diseases and for tracking an individual patient's responses to treatment regimens. NPs can be designed with specific size, shape, pore size and density, and their surfaces can be functionalized to allow for their selective targeting. Furthermore, NPs can be loaded with multiple agents including therapeutics, genes, small interfering (si)RNAs and imaging agents such as iron oxide or gadolinium. According to Dr. Tasciotti, the development of these silicon nanoporous platforms represents a significant contribution to realizing the goals of personalized medicine.

Improvements in Dosimeters for Radiation Oncology Applications

John T. W. Yeow, Ph.D. (Assistant Professor, Department of Systems Design Engineering, University of Waterloo, Ontario, Canada) presented on a nanotechnology-based

flexible and transparent dosimeter that provides conformity to body structures while providing real-time radiation dose measurement. According to Dr. Yeow, the significance of improvements in dosimeter design and functionality is evident given the fact that thirty-five percent and forty-five percent of Canadian women and men respectively will develop cancer during their lifetimes. In fact, about 50% of cancer patients will receive radiation therapy as part of their treatments and dosimeters will be routinely used to calibrate and monitor their radiation treatment units (e.g., linear accelerators for external beam therapy) as well as their exposure to treatment beams.

NanoXray™—A Novel Nanodevice for Radiotherapy

Laurent Levy, Ph.D. (President and CEO, Nanobiotrix SA, Paris, France) presented on NanoXray™, a technology platform that can be turned 'on' and 'off' outside the body to selectively treat a variety of cancers safely and noninvasively. NanoXray™ consists of non-drug nanoparticles that specifically target and bind cancer cells when delivered to a patient. After accumulation in targeted cancer cells, the core of the nanoparticles is activated by applying an external energy source (e.g., X-rays) triggering the nanoparticles to destroy the cancer cells. Dr. Levy summarized preclinical and regulatory development of the NanoXray™ platform while discussing potential clinical applications.

Micro- and Nanotopography for Controlled Cellular Response

Morten Foss, Ph.D. (Senior Scientist, Nanoscience Center, Aarhus University, Denmark) presented on his research that focuses on the interaction of artificial materials with biological systems. He emphasized that control of cellular behavior is critical in regenerative medicine. With this backdrop, he briefly discussed two techniques for identifying biosurfaces that control cellular behavior:
(a) a newly developed large-scale screening of topographic microstructures called BioStructure Surface Arrays (BSSA); and
(b) Glancing Angle Deposition (GLAD), which can generate varying morphological characteristics and well-controlled surface nano-roughness.

According to Dr. Foss, by employing these techniques it is possible to identify specific micro (and possibly nano) structures for cellular systems of technological importance. Identification of such structures would enable designing "smart" Petri dishes or implants that could have various applications, including an expansion of embryonic stem cells, control of stem cell differentiation and inhibition of proliferation of primary human fibroblasts.

Merging Biology and Nano-Electronics for Biomolecule Detection/Manipulation

Jean-Pierre Leburton, Ph.D. (Professor of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, Illinois, USA) discussed his research pertaining to solid-state nanopores as a new tool for DNA and RNA characterization and possible sequencing. Among solid-state nanoporous membranes, the use of semiconductor materials is particularly attractive because of their electric versatility and physical robustness. In his talk, Dr. Leburton presented a scenario that integrates biology with MOS nano-electronics for probing the electrical activity of DNA molecules during their translocation through a semiconductor membrane nanopore, thereby providing a means to manipulate them and possibly electronically identify their molecular sequences. Multiscale simulation of DNA molecule translocation through silicon membrane nanopores (based on the integration of molecular dynamics with device electronics) indicates the electrical resolution of individual base pairs by the semiconductor membrane.

Bioengineering with (Only) DNA

David Yu Zhang, Ph.D. (Professor, California Institute of Technology, Pasadena, California, USA) uses a unique approach to diagnose and reprogram cells for therapeutic purposes involving the *de novo* engineering of similar nanoscale reaction chambers using olignucleotides. According to him, nucleic acids are desirable materials because of their well-understood thermodynamic, kinetic and physical properties. Nucleic acids have been used to engineer biochemical sensors, motors, logic gates, addressable structures and amplification elements. By integrating these elements, a generalized framework for protein analogs can be designed from DNA because of its predictable Watson-Crick binding that renders it a suitable material for rational design. Dr. Zhang discussed the construction of *de novo* DNA logic gates and catalysts—two essential tools for nanoscale molecular therapeutics. He explained that Boolean logic gates allow the DNA circuit to "determine" the disease status of cells by comparing the relative concentrations of various mRNA and microRNA markers. Catalysis allows molecular gain, amplifying low copy-number nucleic acids to facilitate detection and expedite response. Dr. Zhang's logic gates have an ON/OFF ratio of more than 1,000 and the catalysts exhibit a turnover of over 100.

Nanoplatforms for Nanomedicine

Srinivas Sridhar, Ph.D. (Arts and Sciences Distinguished Professor and Chair of Physics and Director, Electronic Materials Research Institute, Northeastern University, Boston, Massachusetts, USA) presented research showing

the impact of nanoplatforms that have resulted in dramatic developments in imaging, early diagnosis and targeted delivery of therapeutics. Several varieties of nanoplatforms (metal, semiconducting polymeric and magnetic nanoparticles, liposomes, micelles and nanoassemblies) have been developed in his lab that can potentially enable efficacious delivery of drugs, DNA or energy to localized sites such as tumors. These nanoplatforms use targeted agents such as antibodies or guided navigation via magnetic fields. The optical properties of these nanoparticles offer an attractive alternative to the fluorophore-based staining and labeling of biological samples, and have potential use in a wide range of biological and physical applications. Also presented were magnetic nanoplatforms for theranostics that combine multiple functionalities including imaging, magnetic guidance to the disease site and delivery of the drug payload through sustained as well as triggered drug release. Nanoporous coatings were presented that were developed for implants, cardiovascular stents and fiducials used in image-guided radiotherapy. The nonerodable coatings show sustained release profiles that are comparable to those from erodible polymer platforms, but without the problems of delamination.

Functional Protocells for Nanomedicine

Eric Jakobsson, Ph.D. (Director, National Center for Design of Biomimetic Nanoconductors, University of Illinois at Urbana-Champaign, Illinois, USA) presented on the functional protocell, as developed by his consortium. A protocell is a nanoporous silica core and a biomimetic membrane coating. Its size can range from a few tens of nanometers to approximately a micron. The interior of the protocell can be loaded with an aqueous concentration of a desired solute, including biological macromolecules. The membrane can contain any set of components that can be assembled into a vesicle.

Dr. Jakobsson's Center has so far created two varieties of functional protocells: (a) one type is adapted to enter cells and deliver bioactive materials to the cell's interior. Entry into specific cells is achieved by coating the surface membrane with peptides derived from phage display. Killer protocells, specific for liver cancer cells, have been demonstrated by the team of Jeff Brinker, Juewen Liu and Carlee Ashley (University of New Mexico/Sandia National Laboratories, Albuquerque, New Mexico, USA). In a mixed culture of liver cancer cells and normal liver cells, the protocells loaded with doxorubicin selectively kill the cancer cells without harming the normal cells; and (b) a second type of functional protocell is called the "decoy cell." The decoy cell mimics the human cell by displaying human receptors of the type that facilitate cell entry by pathogens. One version of the decoy cell, developed by Anne Moscona and Matteo Porotto (Weil College of Medicine of Cornell University, New York, New York, USA) and David LaVan (National Institute of Standards and Technology, Gaithersburg, Maryland, USA), has been shown in cell culture to prevent viral infection by prematurely triggering the viral fusion protein that penetrates the human cell membrane as the initial step in entry following recognition. In addition to providing a possible new approach for antiviral and anticancer therapy, the interactions of protocells with membranes of living cells may provide important information about the fundamental mechanisms of membrane–membrane interactions.

3. CONCLUSIONS—POTENTIAL, CHALLENGES AND FUTURE PROSPECTS

Several variables will determine whether advances in nanomedicine in the laboratory will translate into a wide range of opportunities for the consumer. Although early forecasts for commercialization are encouraging, currently there are several challenges and risks that beset nanocommercialization. These include legal, environmental, safety, ethical and regulatory questions as well as emerging thickets of overlapping patent claims. The emerging thicket of nanomedical patent claims has resulted from patent proliferation and continued issuance of surprisingly broad and/or overlapping patents by the PTO. In fact, patent systems in general are under greater scrutiny and strain, with patent offices around the world continuing to struggle with evaluating the swarm of nanotechnology-related patent applications. As nanomedical products move out of the laboratory and into the clinic, US federal agencies like the FDA and the PTO will continue to struggle to encourage their development while imposing some sort of order. At present, both these critical agencies are in flux, and their credibility has sunk to an all-time low. It is hoped that desperately needed reforms to overhaul the PTO and the decades old US patent system along with clearer regulatory/safety guidelines from the FDA regarding nanomedical products will be forthcoming. To make matters more confusing, the US National Nanotechnology Initiative's (NNI) widely cited definition of nanotechnology is inaccurate and irrelevant in relation to nanopharmaceuticals.

Given this backdrop, it is hard to predict the exact course nanomedicine will take. Will this relatively nascent area make small yet valuable contributions to medicine, or will it become a driving force that catalyzes a vast technological and healthcare revolution? Many believe that "nano" is here to stay and, in the future, it will generate both evolutionary as well as revolutionary drug and medical products ("nanomedical products"). As evidence, one can look beyond current challenges and point to governments around the world that continue to be impressed by nanotechnology's potential and are staking their claims and doling out billions of dollars, euros and yen for R&D. From a business point-of-view, nanomedical products offer

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the ability to extend the economic life of proprietary drugs and create additional revenue streams, thereby significantly affecting the drug commercialization landscape.

Given this backdrop, investors have been cautious as to what route, if any, the FDA will take in regulating these products in the future. Undoubtedly, regulating nanomedical products will require greater cooperation between drug companies, policymakers and the FDA. Although the FDA has previously downplayed safety issues and the need for modification of the current regulatory regime with respect to nanoscale products, it is starting to recognize that there are knowledge gaps and a lack of scientific expertise in these area. The FDA is encountering problems in applying its current regulations to nanomedical products as well as placing these products into its present classification scheme. These issues are compounded by the fact that this agency is confronted with inadequate resources, budgetary constraints, an inefficient regulatory structure, lack of expertise and growing reviewer case loads. However, proper planning and efforts by the FDA now to mitigate foreseeable problems will insure that scientific, ethical, commercialization and legal obstacles are overcome in future. In light of these challenges, a multidisciplinary team of experienced regulators from the drug, biologic and device areas of the FDA (working with a scientific panel of experts), should:

(a) identify unique safety issues associated with nanomedical products;

(b) review/revise existing methodologies but also develop new paradigms for evaluating data pertaining to their safety and efficacy;

(c) assist in developing unique tools and techniques to characterize nanoscale materials (with an eye on quality, safety, product liability and effectiveness); and

(d) Reevaluate the current FDA classification scheme, e.g., develop classification based on (i) function or (ii) risk of potential harm.

As "nano" begins to appear in a wide variety of products, their safety and effectiveness will warrant careful review. Size changes within the nanoscale and the potential unpredictability therefrom are likely to add additional complexity to the FDA review process.

It is difficult to predict to predict how the field will be regulated. It is possible that the FDA will view most nanomedical products as technologically overlapping (miniaturization will blur distinctions between different categories) from a review perspective, and therefore, consider them as "combination products." Many consider that current laws for regulating nanomedical products may not be adequate to regulate the manufacturing and distribution of all such products. Therefore, the FDA should carefully consider whether to operate under the current regulations or write new laws that address certain unique size-related issues. To date, no formal regulations for nanotechnology have been drafted.

Whether the FDA eventually creates new regulations or establishes a new center to handle its regulation, at the moment it should at least look at nanomedical products on a case-by-case basis. The FDA should not attempt regulation of nanomedicine by applying existing statutes; incorporating them into the current regulatory scheme is a poor idea.

Eventually, all these undertakings should expand the burgeoning field of nanomedicine. This is likely if nanomedical products offer novel properties that address unmet medical needs, especially if their development costs and risks are low. It is hoped that this will result in big pharma and biotech further embracing nanomedicine so that it can enter into mainstream society.

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STATEMENT OF DISCLOSURE/CONFLICTS OF INTEREST

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