



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Conference Summary

## New technology and clinical applications of nanomedicine: Highlights of the second annual meeting of the American Academy of Nanomedicine (Part I)

Chiming Wei, MD, PhD,<sup>a,\*</sup> Yuri L. Lyubchenko, PhD,<sup>b</sup> Hamid Ghandehari, PhD,<sup>c</sup>  
Justin Hanes, PhD,<sup>a</sup> Kathleen J. Stebe, PhD,<sup>a</sup> Hai-Quan Mao, PhD,<sup>a</sup> Donald T. Haynie, PhD,<sup>d</sup>  
Donald A. Tomalia, PhD,<sup>e</sup> Marianna Foldvari, PhD,<sup>f</sup> Nancy Monteiro-Riviere, PhD,<sup>g</sup>  
Petia Simeonova, MD, PhD,<sup>h</sup> Shuming Nie, PhD,<sup>i</sup> Hidezo Mori, MD, PhD,<sup>j</sup>  
Susan P. Gilbert, PhD,<sup>k</sup> David Needham, PhD<sup>l</sup>

<sup>a</sup>Johns Hopkins University, Baltimore, Maryland, USA

<sup>b</sup>University of Nebraska Medical Center, Omaha, Nebraska, USA

<sup>c</sup>University of Maryland, Baltimore, Maryland, USA

<sup>d</sup>Artificial Cell Technologies, Inc., New Haven, Connecticut, USA

<sup>e</sup>Dendritic Nanotechnologies Inc. and Central Michigan University, Mt. Pleasant, Michigan, USA

<sup>f</sup>University of Waterloo, Saskatoon, Saskatchewan, Canada

<sup>g</sup>North Carolina State University, Raleigh, NC, USA

<sup>h</sup>National Institute for Occupational Safety and Health, Morgantown, West Virginia, USA

<sup>i</sup>Emory University and Georgia Institute of Technology, Atlanta, Georgia, USA

<sup>j</sup>National Cardiovascular Center Research Institute, Suita, Osaka, Japan

<sup>k</sup>University of Pittsburgh, Pittsburgh, Pennsylvania, USA

<sup>l</sup>Duke University, Durham, North Carolina, USA

Received 28 October 2006

### Abstract

The Second Annual Meeting of the American Academy of Nanomedicine (AANM) was held at the National Academy of Science Building in Washington, DC, September 9–10, 2006. The program included two Nobel Prize Laureate Lectures, two Keynote Lectures, and 123 invited outstanding State-in-Art lectures presenting in 23 special concurrent symposia. In addition, there were 22 poster presentations in the meeting addressing different areas in nanomedicine research. All of the presenters at the meeting are outstanding investigators and researchers in the field. The Second Annual Meeting of the AANM was a great success. The meeting provides investigators from different world areas a forum and an opportunity for discussion. We believe that nanomedicine research will develop rapidly in the future. The AANM invites basic and clinical researchers from the world to join this exciting research.

**Key words:** Nanomedicine; Nanotechnology; Molecular imaging; Biosensor; Dendrimer-based nanomedicine; Drug delivery; Gene delivery

The Second Annual Meeting of the American Academy of Nanomedicine (AANM) was held at the National Academy of Science Building in Washington, DC, September 9–10,

2006. The program included two Nobel Prize Laureate Lectures, two Keynote Lectures, and 123 invited outstanding State-in-Art lectures presenting in 23 special concurrent symposia. In addition, 22 poster presentations highlighted different areas in nanomedicine research. All of the presenters at the meeting are outstanding investigators and researchers in the field.

\* Corresponding author. Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

E-mail address: [cmwei@jhmi.edu](mailto:cmwei@jhmi.edu) (C. Wei).



Fig 1. President of AANM and Editor-in-Chief, Chiming Wei, MD, PhD, commencing the Second Annual American Academy of Nanomedicine meeting during the opening ceremony.

The opening ceremony was held in the morning of September 9, 2006. AANM President Chiming Wei, MD, PhD, welcomed all the attendees and extended his deep appreciation and thanks to all presenters and attendees for contributing to the meeting (Figure 1). Mr. Joe Mok, Chair of the Governor's Committee of Maryland, gave a wonderful message welcoming everybody who came to Maryland to attend this very important meeting. Tachung Yih, PhD, the Vice President of AANM, gave a thoughtful address encouraging attendees to continue their efforts in advancing nanomedicine research. Donald A. Tomelia, PhD, the Vice Chair of the 2006 AANM Organizing and Program Committee, summarized the AANM program and provided attendees information and presentations in AANM symposia. James Castracane, PhD, Member of the Board of Directors of AANM, summarized the AANM membership and fellowship development and future strategy. Marianna Foldvari, PhD, the Co-Chair of the AANM International Committee, summarized the AANM international collaboration research projects and international research activities and developments.

During the Presidential Lecture, Chiming Wei, MD, PhD, of Johns Hopkins University, summarized new published and unpublished findings and results in each nanomedicine research area, and also reviewed the new nanotechnologies and clinical applications in nanomedicine development. During the past year many important research results were published in nanomedicine research areas. The significance of these investigations lies in the development of platform technologies including nanoscale molecular imaging, drug delivery, gene delivery, and diagnostic approaches. Dendrimer-based nanomedicine was developed for protein mimicry research, nanopharmaceuticals, diagnostic imaging with contrast agents, and targeted drug delivery in cancer cells. Biosensors with nanoscale materials provide unique and powerful technology for detection of biological and chemical species to aid in disease diagnosis and in the discovery and screening of new drug molecules. The development of a cancer therapy and monitoring with diagnostic nanotechnology include cancer-related genotyping



Fig 2. **A**, The Nobel Lecture, “Aquaporin Water Channels: from Atomic Structure to Clinical Medicine” being given by Peter Agre, MD, from the Duke University School of Medicine. **B**, Dr. Agre received the Honor Fellowship from President Chiming Wei, American Academy of Nanomedicine.

detection, gene expression, and immunochemical analysis, as well as nearly real-time monitoring of patient blood for cancer cells. Nanotechnologies were developed for clinical applications in cardiovascular, neurological, pulmonary, skin, and renal diseases.

In the First Nobel Prize Laureate Lecture, “Aquaporin Water Channels: from Atomic Structure to Clinical Medicine”, Peter Agre, MD (2003 Nobel Prize Laureate for Chemistry), from Duke University School of Medicine, summarized the aquaporin (AQP) water channel structure and applications to clinical medicine (Figure 2, A). AQP water channel proteins permit high water permeability of certain biological membranes. In people with no AQP1, lack of water causes defective urine concentration and reduced fluid exchange between capillary and interstitium in lung. Mutations in the gene encoding AQP0, expressed in lens fiber cells, result in familial cataracts. Mutations in the gene encoding AQP2, expressed in renal collecting duct principal cells, result in nephrogenic diabetes insipidus. Mistargeting of AQP5, normally expressed in the apical membranes of salivary and lacrimal gland acini, can occur in Sjogren's syndrome. Aquaporins also are implicated in brain edema and muscular dystrophy (AQP4), anhidrosis (AQP5), renal tubular acidosis (AQP6), conversion of glycerol to glucose



Fig 3. **A**, The Nobel Lecture, “Nanotechnology, Biology and Business” being given by Ivar Giaever, PhD, from Applied BioPhysics, Inc. **B**, Dr. Giaever received the Honor Fellowship from President Chiming Wei, American Academy of Nanomedicine.

during starvation (AQP7 and AQP9), and cystic fibrosis (several). Dr. Agre received the Honor Fellowship from the AANM (Figure 2, B).

In the Second Nobel Prize Laureate Lecture, “Nanotechnology, Biology and Business”, Ivar Giaever, PhD (1973 Nobel Prize Laureate for Physics), from Applied BioPhysics, Inc., indicated that nanotechnology holds much future promise to make things both cheaper and better (Figure 3, A). In particular, Dr. Giaever discussed a general immunology detector that utilizes small indium particles to detect antibodies. He also described a whole-cell biosensor using electrical fields to obtain information about the morphology of cells in tissue culture. Finally, Dr. Giaever discussed means to bring nanotechnology to the market with many important examples and experiments. Dr. Giaever received the Honor Fellowship from the AANM (Figure 3, B).

In the Keynote Lecture, “Electron Cryomicroscopy of Biological NanoMachines”, Wah Chiu, PhD, from Baylor Medical College, demonstrated the applications of electron cryomicroscopy in determination of multiple molecular components and performance of specific biological functions (Figure 4, A). Image reconstruction methods can be used to reconstruct three-dimensional (3-D structures from single nanomachine images at sub-nanometer resolution. Mining of



Fig 4. **A**, The Keynote Lecture, “Electron Cryomicroscopy of Biological Nanomachines” being given by Wah Chiu, PhD, from Baylor Medical College. **B**, Dr. Chiu received the Presidential Award from President Chiming Wei, American Academy of Nanomedicine.

salient structural features within the molecular components of a large nanomachine is a daunting task. Computational and visualization tools have been developed to extract features such as  $\alpha$ -helices and  $\beta$ -sheets of protein subunits with a high degree of reliability. 3-D structure at sub-nanometer resolution can be combined with sequence-based structure prediction methods to derive pseudo atomic models of molecular components of a nanomachine. Dr. Chiu received the Presidential Award from AANM (Figure 4, B).

There were 23 Concurrent Symposia in the Second AANM Annual Meeting. Each symposium focused on a different nanomedicine research area, covering topics from basic nanomedicine to clinical nanomedicine. Following are the summaries for each symposium. Because of the journal’s page limitations we can only publish summaries for several symposia in this issue of *Nanomedicine: Nanotechnology, Biology, and Medicine*. We will publish The summaries for other symposia that remain will appear in the next issue.

### Symposium I: clinical nanomedicine

This symposium focused on the nanoscale analysis of the protein misfolding and aggregation phenomena critically

associated with such neurodegenerative disorders as Alzheimer, Parkinson, and Huntington diseases, to mention a few [1,2]. The field of medicine can be dramatically advanced by establishing a fundamental understanding of key events leading to the misfolding and self-aggregation of proteins involved in the various protein-folding pathologies. There were four speakers at the symposium.

Dr. Yuri Lyubchenko outlined approaches for detection and analysis of protein misfolded states. Protein misfolding is a complex phenomenon that can be facilitated, impeded, or prevented by interactions with various intracellular metabolites and interprotein interaction with intracellular nanomachines controlling protein folding. A fundamental understanding of molecular processes leading to misfolding and self-aggregation of proteins will provide critical information to help identify appropriate therapeutic routes to control these processes. Protein misfolding is the very first link in this long chain of events eventually leading to neurodegeneration. Therefore, availability of methods capable of detecting the pathological protein conformations facilitates the development of novel tools for diagnostic and treating the diseases at very early stages of development. Single-molecule force spectroscopy atomic force microscope was proposed to measure the strength of the interprotein interactions before aggregation [3,4]. The capability of the atomic force microscope to manipulate with the tip in the nanometer scale was used for development of the nanotweezers approach capable of single-molecule selecting of antibodies for a certain type of protein aggregates.

The role of oxidative stress in protein misfolding and aggregation of  $\alpha$ -synuclein was a topic of Dr. Jean-Christophe Rochet. To investigate the link between complex I impairment and sequence-specific, post-translational modifications of  $\alpha$ -synuclein, the protein was isolated from rotenone-treated PC12 cells and analyzed by tandem mass spectrometry [5]. It was found that rotenone induced various modifications in the C-terminal region of  $\alpha$ -synuclein, including oxidation of methionine, nitration and amination of tyrosine, and phosphorylation of tyrosine and serine. These modifications correlated with an increase in the levels of membrane-bound, oligomeric  $\alpha$ -synuclein detectable by fluorescence lifetime imaging microscopy and lipid flotation. In parallel, it was found that  $\alpha$ -synuclein aggregation and toxicity were suppressed by DJ-1, an antioxidant protein that is dysfunctional in some cases of familial Parkinson disease. A current goal in nanomedicine is to determine how the conformational behavior of  $\alpha$ -synuclein is influenced by sequence-specific modifications using single-molecule approaches.

The presentation of Dr. Boris Akhremitchev focused on analysis of thermodynamics of  $\alpha$ -synuclein fragments critically involved in protein misfolding and aggregation. Interactions between individual molecules were studied using a scanning force microscopy-based technique [6,7]. The reported energy landscape parameters of interactions,

including the barrier width and dissociation rate, were obtained, illustrating the possibility for direct measurements of the molecular-level parameters for investigating the molecular origin of the misfolding-based protein aggregation and effects of chemical agents that prevent or hinder the aggregation.

Dr. Robert Tycko reviewed the advances in high-resolution studies of fibrillated aggregates achieved with the use of solid-state nuclear magnetic resonance. This technique is capable of providing site-specific constraints on the secondary, tertiary, and quaternary structures of amyloid fibrils, as demonstrated by recent works on fibrils formed by the full-length  $\beta$ -amyloid peptide associated with Alzheimer disease [8] and fragments thereof [9]. The recent results focused in the following areas [10]: (1) development of a structural models for  $\beta$ -amyloid fibrils grown under either agitated or quiescent conditions; (2) development of a structural model for fibrils formed by the 37-residue amylin peptide, which is associated with type 2 diabetes; (3) constraints on the molecular structures of fibrils formed by the Ure2p and Sup35 yeast prion proteins.

### Symposia III and XXIII: drug delivery nanomedicine I and II

Dr. Justin Hanes from the Johns Hopkins University started the first session by describing a new biomaterial platform for targeted and intracellular drug delivery, the poly(ether-anhydrides). These polymers incorporate poly(ethylene glycol) (PEG) into their backbone structure and are polymerized with one to several other monomers, such as sebacic acid (SA), that are also known to be safe in humans. The addition of PEG to the polymer backbone allows classical poly(anhydrides) to be formulated into nanoparticles that are readily resuspended in liquids for injection or inhalation, or into dry powder microparticles that are easily aerosolized for inhalation. PEG coats the surface of the particles naturally during particle preparation, allowing the linkage of targeting agents to the free end of PEG (i.e., end not attached to the rest of the polymer). Highly selective targeting of poly(PEG-SA) particles to inflamed blood vessels was demonstrated following the attachment of antibodies against molecules that are upregulated on the luminal side of inflamed endothelial cells in a collaboration with Prof. Doug Goetz from the Ohio University. Poly(PEG-SA) nanoparticles (with transferrin attached to the free end of PEG) were also able to penetrate targeted cancer cells and rapidly transit within the cell to the perinuclear region; these particles were more toxic to cancer cells at relevant doses than the free drug.

Dr. Richard Price from the University of Virginia next discussed the use of ultrasound-assisted local permeation of blood vessels by microbubble destruction as a method to enhance the targeting of drugs, including those contained within nano- and microparticles. Microbubbles (hollow microspheres with a shell composed of albumin) are

currently used clinically as a contrast agent in diagnostic ultrasound. Dr. Price showed that ultrasound can be used at low frequencies to cause bubbles in targeted regions to explode (by cavitation), which causes a significant increase in the local permeability of the endothelium to drugs and even large particles. Highly targeted delivery of polymer nanoparticles to muscle tissue was clearly demonstrated in an animal model. Control over particle penetration depth was achieved by simply applying ultrasound without microbubbles, in which case particles penetrated only the endothelium and not into the interstitium, whereas the application of ultrasound with microbubbles led to particle delivery to both the endothelium and the interstitium. The results suggest that this technique may provide an alternative to molecular targeting for a variety of diseases.

Dr. Lawrence Tamarkin from CytImmune Sciences, Inc., next spoke about his company's colloidal gold-based system for targeted drug delivery to tumors (Aurimmune). Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) is bound to the surface of colloidal gold nanoparticles with an average diameter of 30 nm. The nanoparticles are PEGylated to reduce clearance by the reticuloendothelial system; evidence that liver and spleen uptake of the nanoparticles was minimal as compared with uptake by tumors in mice was provided. Aurimmune was administered to two dogs with naturally occurring tumors and to rabbits; in each case its administration caused fever but did not cause hypotension. Hypotension has historically been dose limiting in the treatment of cancer with TNF- $\alpha$ . Based on promising preclinical results, Aurimmune production was scaled up and certified by GMP it is currently being studied in a National Cancer Institute-sponsored phase I trial in patients with advanced-stage cancer.

Dr. Esther Chang from Georgetown University next provided provocative results with targeted cationic liposomes for both the treatment and improved imaging of various tumor types. Noting that tumors need iron to grow and that they therefore typically express high levels of transferrin receptor on their surfaces, Dr. Chang's group uses an anti-transferrin receptor single-chain antibody fragment as the targeting ligand for their liposomal delivery platform. Dr. Chang gave an overview of her laboratory's extensive experience with these liposomal drug carriers in a variety of tumor types, including head and neck, breast, prostate, kidney, and pancreatic, demonstrating antitumor effectiveness of several drugs and drug types, including DNA, small interfering RNA, and small molecules. Dr. Chang reported that the technology is now entering clinical trials in the United States. Finally, Dr. Chang also showed that contrast agents for magnetic resonance imaging could be encapsulated into the liposomes, leading to improved sensitivity and resolution in detecting metastatic lesions.

Dr. Hamid Ghandehari from the University of Maryland, Baltimore, capped the first Drug Delivery session with an overview of ways that nanoscale medicines might be improved by controlling particle structure using specialized

chemistries and fabrication methods. He noted that carriers used for the controlled temporal or spatial delivery of bioactive agents are typically made of polymers, liposomes, or inorganic particles with polydisperse size distributions that can make prediction of biodistribution or subcellular fate challenging. He also pointed out that most of the polymers being studied for drug delivery are made by random copolymerization techniques, which limits control over monomer sequence, polymer molecular weight, and molecular weight distribution that may affect the performance of a given nanomedicine platform technology. Dr. Ghandehari then described several means by which polymers and nanosystems could be made with better definition of structure and dimensions, including his laboratory's experience with *N*-(2-hydroxypropyl)methacrylamide copolymers, poly(amido amine) dendrimers, recombinant polymeric gene carriers, and silica nanotubes, and discussed the relationship of carrier structure at the nanoscale and function in targeted drug delivery.

The second session of the Drug Delivery Nanomedicine Symposium began with a talk by Dr. Kathleen J. Stebe from the Johns Hopkins University on the importance of controlling interfacial phenomena in the production of nanoparticles to enhance particle stability and functionality. Dr. Stebe discussed how the interfacial properties of nanoparticles could be controlled during fabrication to influence the properties and performance of nanomedicine products. The final surface properties of nanoparticles dictate everything, from whether they will aggregate in vivo to how effectively they will circulate and find their target. Understanding the complex kinetics and thermodynamics of nanoparticle systems during their synthesis and formulation is a critical and yet underappreciated science that can improve the performance of nanomedicine platforms.

Dr. Jimmy Yun from Singapore Nanomaterials Technology next discussed his company's efforts in developing an effective process for the large-scale production of pharmaceutical nanoparticles with excellent control over size, size distribution, and morphology by a high-gravity precipitation method. These formulation methods may be valuable in enhancing the performance of drugs used in aerosol and solid dosage forms.

Dr. Tsuneya Ikezu from the University of Nebraska Medical Center discussed his group's findings that amyloid- $\beta$  aggregation and  $\tau$ -tubulin kinase-1 induces  $\tau$  phosphorylation and reduces microtubule extension. This study has important implications in understanding a potential molecular mechanism underlying impaired neuronal plasticity in the brains of Alzheimer patients and may provide a potential therapeutic target for treating Alzheimer disease.

Dr. Hai-Quan Mao from the Johns Hopkins University capped the second Drug Delivery session by discussing a new polyphosphoester block copolymer system that self-assembles into micelles with an average diameter of 80 to 150 nm. Improved gene expression in the liver using this new polymer nanoparticle platform technology

Table  
Length scale of the cell and representative components

Structure	Length scale
Tissue	$> 10^5$ nm
Cell	$10^4$ nm
Mitochondrion	$10^3$ nm
Nuclear pore	$10^2$ nm
Ribosome	$10^1$ nm
Protein	$10^0$ nm

was demonstrated. Polyphosphoester micelles have potential in treating liver-associated diseases by gene medicine approaches.

### Symposium V: cellular nanomedicine

The cell is the basic unit of animate matter, but the cell consists of an astonishing collection of different individual inanimate nanostructures and ordered aggregates of nanostructures (Table 1). Three of the five talks in the symposium had a basic biological bent; the others were more technological in character. One of the technological talks was from a start-up company that has spun out of a university; the others were from academia.

Dr. Anja Nohe (Chemical and Biological Engineering, University of Maine) spoke on mouse genetic models of bone stem cells and nanoscale receptor dynamics. Methods in imaging and microscopy—in particular Fourier imaging correlation spectroscopy, and fluorescence resonance energy transfer—allow assessment of receptor protein dynamics within microdomains of the plasma membrane.

Dr Ari Requicha (Laboratory for Molecular Robotics, University of Southern California) described how “instrumented” cellular systems could be developed with sensor/actuator networks and distributed robotics to open new directions in biomedical research. The eventual realization of multiple nanosensors providing continuous streams of real-time, multimodal, and complementary data on the behavior of groups of cells or single cells will increase human understanding of life processes at the tissue, cellular, and molecular levels.

Dr You Han Bae (Pharmaceutics and Pharmaceutical Chemistry, University of Utah) spoke on the use of pH-sensitive polymeric mixed micelles constructed from the block copolymers poly(L-histidine)- $\beta$ -PEG and poly(L-lactide)- $\beta$ -PEG for targeting tumors and overcoming multiple-drug resistance. The approach could result in a paradigm shift for treatment of solid tumors from monoclonal antibody/receptor-based targeting to pH shift-based targeting.

Dr Don Haynie (Bionanosystems Engineering Laboratory, Artificial Cell Technologies, Inc.) explained how the same polypeptide multilayer nanofilm platform technology is being adapted to the development of different biomedical applications: Artificial extracellular matrixes for tissue regeneration, artificial red blood cells for oxygen therapeutics, and artificial viruses for synthetic vaccine development. In each case peptide design and nanofilm architecture is

tailored to the specific purpose, mimicking key properties of cells, viruses, and biomacromolecules at the microscale and the nanoscale.

Dr Denis Wirtz (Chemical and Biomolecular Engineering, Johns Hopkins University) showed how to probe cytoskeletal dynamics in ovarian cancer progression with multiple particle tracking “nanorheology”. Cells corresponding to the two known pathways of ovarian cancer progression vary distinctly in their cytoplasmic viscosity. Further progress in medicine will require a deeper understanding of how cell, tissue, and system behavior depends on the properties of subcellular nanostructures and nanostructured components of molecular assemblies.

### Symposium XIII: pharmacological nanomedicine

In the Pharmacological Nanomedicine Symposium, four talks were presented with the latest advancements in drug discovery and delivery.

In the first talk, Dr. Jeanne Hardy (University of Massachusetts–Amherst) presented a site-directed approach called “tethering” in which allosteric sites on key proteins are exploited for drug discovery. These sites are on the surface of proteins and can be redesigned to be controlled by a small molecule of choice. Recent advances with the caspase family of cysteine proteases were presented, which revealed the pathway of inhibition for caspase regulation of apoptosis.

Dr. Wafik S. El-Deiry (University of Pennsylvania School of Medicine) presented novel optical imaging approaches to monitor the molecular events relevant to tumor progression and therapeutic response. The approach is to introduce genetic alteration into human cells along with bioluminescent reporter genes to determine the role of specific oncogenes and tumor suppressor genes in controlling tumor progression and therapeutic response. These molecular beacons are then used in high-throughput screens for small molecules that can modulate signaling leading to tumor cell death. Other approaches included evaluation of bioluminescent tumors in animals for drug-target validation and therapeutic efficacy. The overall goal presented by Dr. El-Deiry is to develop new approaches in drug screening and target validation to accelerate the preclinical phase of anticancer drug development to bring new agents into clinical trials.

Dr. Scott L. Diamond (University of Pennsylvania), Director of the Penn Center for Molecular Discovery, reported on their breakthrough in microarray design and screening where nanoliter-scale biochemical reactions can be analyzed by matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry with 10-fmol sensitivity. Dr. Diamond described a multiplex screen across numerous proteases that identified a nanomolar inhibitor of human cathepsin L that was a potent inhibitor of severe acute respiratory syndrome coronavirus entry.

Dr. David Needham (Duke University) described the temperature-sensitive liposome approach for drug delivery that his group introduced in 1996 and is now in phase 1

human clinical trials. The pharmacological agent is packaged in these 100-nm-diameter nanocapsules that can circulate to the tumor endothelia via the bloodstream. However, drug release does not occur until application of heat at the site of the tumor. Dr. Needham described their preclinical studies with doxorubicin to optimize drug delivery, drug action on the vasculature, drug targeting to microregions of tumors where the drugs act most effectively, and drug clearance from the bloodstream and body. Dr. Needham has coined the term “nano-soccerball” liposomes for antitumor drug delivery!

### **Symposium XVI: international nanomedicine development**

The AANM is rapidly expanding into an international organization with membership from all over the world. Symposium XVI was an exciting representation of the international scope of nanomedicine and bionanotechnology research. In addition to the United States, eight other countries' leading researchers gave an overview of the current state of research in nanomedicine in their respective countries.

The following countries were represented: Canada (Dr. Marianna Foldvari, University of Waterloo), China (Dr. Xiaojun Zhao, Sichuan University), Hong Kong (Dr. Ken Wong, Hong Kong University), India (Dr. N.K. Jain, Dr H.S. Gour University), Japan (Dr. Tsuneo Urisu, Institute for Molecular Science, Myodaiji), Korea (Dr. Yoon-Sik Lee, Seoul National University), Russia (Dr. Igor Yaminsky, Lomonosov Moscow State University), Singapore (Dr. Jimmy Yun, Nanomaterials Technology Ltd.), Switzerland (Dr. Patrick Hunziker, University Hospital of Basel), and the United States (Dr. Donald Tomalia, Dendritic Nanotechnologies Inc. and Central Michigan University).

Nanomedicine presents an explosive number of opportunities to improve people's lives. A great diversity of research areas is being developed worldwide, with the United States being the leader. In Canada some of the important nanomedicine research areas include intelligent drug delivery systems; vaccine and gene delivery nanosystems; polymeric systems and devices; biochips; lab-on-a-chip; artificial cells; anti-cancer, immune-, neural- and musculoskeletal systems; nanoscale targeting; tissue and cellular engineering; novel biomaterials; and molecular imaging. In Hong Kong DNA electronics, microfluidic devices, metallic nanoparticles, nanofibers, and biopolymeric materials are being investigated for diagnostic and tissue engineering applications. In India the nanomedicine research includes drug delivery with dendrimer-based nanoarchitecture for the controlled and targeted delivery of anticancer bioactives; mitochondrial drug targeting; gene therapy of genetic disorders like diabetes and cancer using dendrimer-based nano carriers; developing a DNA vaccine against *Leishmania donovani*; and stem cell research. Korea is active in the design of intelligent microsystems and

biomedical devices, whereas in Japan imaging, drug delivery, and the application of nanoscience in medical treatments are already strong. The Second International Conference of America-Japan Nanomedicine Society will be held in Japan during April 2007. The nanotechnology program in Russia has recently been launched and includes nanomedicine research across the country. In Singapore the biomedical sciences are a leading area of nanotechnology and supported by a strong economy.

The panel discussion after the presentations concluded with the future vision of a true international effort in the development of nanomedicine-related technologies and discoveries, with regular updates to be presented at the annual AANM meetings.

### **Symposium XIX: toxicological nanomedicine**

This symposium dealt with highlights relating to the toxicology of skin, eye, respiratory, and cardiovascular effects as well as the interpretation of polymer toxicology.

Dr. Nancy Monteiro-Riviere discussed the effects of multiwalled carbon nanotubes, fullerenes, derivatized fullerenes, and quantum-dot effects in human epidermal keratinocytes and penetration through skin. Some of these nanomaterials depicted inflammatory effects, altered gene expression proteins, ultrastructural localization within skin cells, and irritation profiles. Quantum dots of different sizes and surface chemistries depicted unique profiles in penetration through the skin.

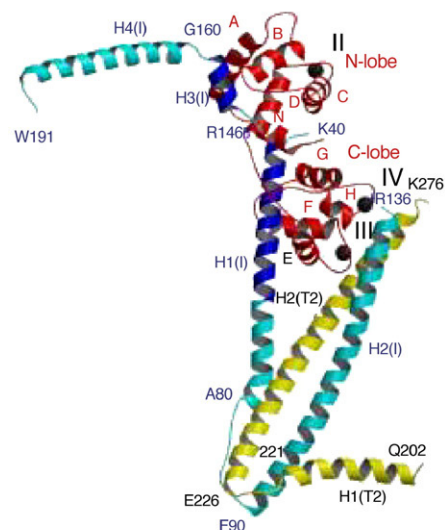
Dr. Gerard Luty talked about the use of different types of injected nanoparticles to deliver genes in rabbit eyes. Chitosan, PCEP, and magnetic nanoparticles did not show toxicity in vitro but demonstrated toxicity in vivo. All of these nanoparticles were capable of transfecting cells with chitosan, causing inflammation in the eyes. Magnetic nanoparticles were the least toxic and can be transfected to specific cell types in the eye.

Dr. Randall Schneider discussed the consideration that must be taken into account when using polymer nanoparticles for biomedical applications. He emphasized the complexity of nanoparticles and that the predictive models currently used may not be suitable for nanoparticles. Therefore, it is important to study the behavior of different types of nanoparticles in the biological environment and to fully characterize these materials before full interpretations can be made.

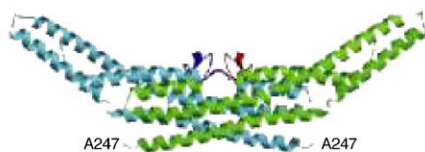
Dr. Petia Simeonova discussed her research with single-walled carbon nanotubes instilled into the lung of mice. She demonstrated a dose-dependent increase in oxidative vascular damage. Her studies also demonstrated that single-walled carbon nanotubes did not modify the lipid profiles but did generate an accelerated plaque formation in a mouse model of arteriosclerosis. These findings not only demonstrated lung toxicity but also depicted cardiovascular effects.

All of these studies presented in the Toxicological Nanomedicine Symposium showed how nanomaterials may be

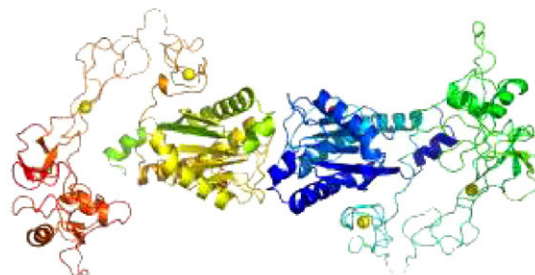




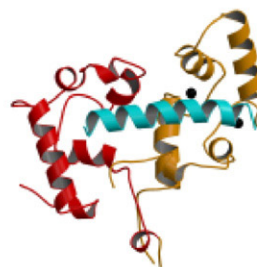
**Human cardiac troponin core domain**  
Takeda et al. *Nature* (2003)



**Human endophilin BAR domain**  
Masuda et al. *EMBO Journal* (2006)



**Snake venom vascular apoptosis-inducing protein-1**  
Takeda et al. *EMBO Journal* (2006)



**Human calcineurin B homologous protein  
in complex with its binding domain  
in Na<sup>+</sup>-H<sup>+</sup> Exchanger-1**  
Ben Ammar et al. *EMBO Journal* (2006)

Fig 5. The protein structure of selected complexes of cardiac troponin and a calcium sensitizer, vascular apoptosis-inducing protein 1, and calcineurin homologous protein 2.

toxic under specific conditions and that extensive studies on interactions of these materials in the body are essential before full interpretations can be made. Nanotechnology product development cycles should incorporate an evaluation of potential risk reduction from the earliest stages.

### Symposium XX: nanotechnology in biomedical and clinical applications

Hidezo Mori, MD, PhD summarized his group's national project in Japan named nanolevel imaging of molecular structure and function. In this project Mori and his group analyzed structures of fundamental protein in human diseases. They selected complexes of cardiac troponin and a calcium sensitizer, vascular apoptosis-inducing protein 1, and calcineurin homologous protein 2 as targets (Figure 5). Proteins expressed in *Escherichia coli* or isolated from crude snake venom are purified and finally crystallized by hanging-drop method. All the x-ray diffraction data were collected at SPring-8 for the structural determination. Such sub-nanolevel structural imaging will be useful for structure-based drug design to treat cardiovascular disease or cancer.

Shuming Nie, PhD talked about semiconductor quantum dots. When linked with biotargeting or biorecognition ligands such as monoclonal antibodies, peptides, or small molecules, these nanoparticles can be used to target tumor antigens (biomarkers) as well as tumor vasculatures with high affinity and specificity. In the "mesoscopic" size range of 10 to 100 nm (diameter), quantum dots and polymeric nanoparticles also have more surface areas and functional groups that can be linked to multiple diagnostic (e.g., optical, radiosotopic, or magnetic) and therapeutic (e.g., anticancer) agents.

Kenneth Wong, PhD reported that topical delivery of silver nanoparticles reduces systemic inflammation of burns and promotes wound healing. His team investigated the wound healing properties of silver nanoparticles in an animal model and found rapid healing and better cosmetic appearance in a dose-dependent manner. Furthermore, through quantitative polymerase chain reaction, immunohistochemistry, and proteomic studies the team showed that silver nanoparticles exerted positive effects through their antimicrobial properties, reduction in wound inflammation, and modulation of fibrogenetic cytokines. These results have given an insight into the actions of silver and



Fig 6. During the welcome reception, researchers and investigators had the opportunity to discuss the day's lectures and presentations.



Fig 7. Wenchi Wei (Chiming Wei's daughter) performed on the Chinese music instrument gu-zheng during the reception.

provided a novel therapeutic direction for wound treatment in clinical practice.

Yoshinobu Bana, PhD described nanofabrication, molecular nanotechnology, and nanomaterials for bioanalysis and biomedical application. Arrays of nanopillars, which are 200 nm wide and 4,000 nm tall, are successfully applicable to fast separation of DNA within 10 to 25 seconds. Nanoball, with a diameter of 50 nm, has been developed and successfully applied for fast separation of DNA fragments from 100 base pairs to 15 kilobase pairs. Bacteria cellulose, a biofiber with a diameter of 50 nm, has been found to be useful in highly sensitive detection of biomolecules based on the optical confined effect. The nanobiodevice is useful for fast separation of protein samples from several kilodaltons to 200 kDa within 15 seconds.

Joe Kao, PhD, reported the possibility of controlling biology with light. A "phototrigger" or "caged molecule" is a biologically inactive but photosensitive precursor that is rapidly transformed into a fully bioactive molecule upon exposure to a flash of light. The bioactive molecule that is thus generated acts as a biochemical trigger; it can be a hormone, a neurotransmitter, a second messenger, or an enzyme modulator. Therefore, in combination with focused light pulses, caged molecules represent a simple methodology for manipulating biology in living cells or tissues with excellent temporal and spatial resolution. Specific applications of the technology to manipulate neurotransmission at single synapses and to stimulate single nerve terminals were discussed.

### Young investigator award competition

This year there were nine finalists for the Young Investigator Award (YIA). The nine finalists each gave a 10-minute platform presentation on topics representing the most novel and exciting areas of nanomedicine. Awards were presented in two categories: those scientists who were more senior and the junior scientists who were graduate students, postdoctoral fellows, or new investigators.



Fig 8. Dr. Ling Xu, the Senior Coordinator of the AANM Staff Team, received the AANM Service Award during the reception.

For the junior YIA scientists, Jean-Christophe Rochet of Purdue University received first place for his work to develop nanoimaging-based approaches for detection and analysis of protein misfolding states. Gengfeng Zheng of Harvard University received second place for his development of nanowire transistor arrays for large-scale, label-free, real-time, parallel electrical detection of a variety of biomolecules ranging from small molecules to proteins and viruses. Third place was awarded to Winston Timp of the Massachusetts Institute of Technology for his development of living-cell microarrays in which arrays of optical traps are able to manipulate hundreds of bacteria or tens of mammalian cells into 3-D arrays. These living-cell microarrays can be observed over time to assay gene expression and cell viability.

In the senior YIA group, the first place award went to Justin Hanes of Johns Hopkins University. His group is developing a new family of polymers, poly(ether-anhydride) nanoparticles, designed to be selectively adhesive to desired cell types, and nonadhesive to obstacles in the body that might prevent their targeted delivery. Second place went to Xiaohua Huang of the University of California–San Diego



Fig 9. The partial conference attendees in the National Academy of Science Building during the Second Annual Meeting of AANM.

for his efforts in developing a technology that is capability of rapidly sequencing a human genome for as little as \$1,000. The third place recipient was Susan L. Beamis Rempe of Sandia National Laboratories for her contributions in understanding ion transport between aqueous and biological environments for the purpose of designing new transporter devices relevant to medical and environmental applications.

### The poster session, reception, and fellowship

There was the poster session in the Second Annual Meeting of AANM. The presentations in these posters covered basic, biosensors, cellular, dendrimer-based, diagnostics, engineering, experimental, genetics, neurology, oncology, policy, and toxicology nanomedicine. The presentations in each poster were excellent, and the discussions were a positive step in building future pathways in various research areas. The First Place of Best Poster Award went to Rutledge G. Ellis-Behnke of the Massachusetts Institute of Technology. The Second Place of Best Poster Award went to Lajos P. Balogh of NanoBiotechnology Center, Roswell Park Cancer Institute. The Third Place of Best Poster Award went to Winston Timp of the Massachusetts Institute of Technology.

During the welcome reception, researchers and investigators had the opportunity to discuss the day's lectures and presentations (Figure 6). Wenchi Wei (Chiming Wei's daughter) performed the Chinese music instrument Gu-Zheng during the reception (Figure 7). This year the AANM Volunteer Staff Team worked very hard and provided the wonderful service for the conference. We greatly appreciate the AANM staff team's excellent work. Dr. Ling Xu, the Senior Coordinator of AANM Staff Team, received the AANM Service Award during the reception (Figure 8). The AANM announced the YIA winners and Best Poster Award winners. The National Foundation for Cancer Research sponsored this year's YIA award. There were a total of nine applications selected as YIA finalists. Each YIA finalist

presented an abstract and answered questions. Reviewers carefully evaluated each presentation of YIA and Best Poster Award, and the AANM Award Committee selected the following recipients:

#### *Senior YIA Group:*

- First Place: Justin Hanes, Johns Hopkins University
- Second Place: Xiaohua Huang, University of California–San Diego
- Third Place: Susan L. Beamis Rempe, Sandia National Laboratories

#### *Junior YIA Group:*

- First Place: Jean-Christophe Rochet, Purdue University
- Second Place: Gengfeng Zheng, Harvard University
- Third Place: Winston Timp, Massachusetts Institute of Technology

#### *Best Poster Award:*

- First Place: Rutledge G. Ellis-Behnke, Massachusetts Institute of Technology
- Second Place: Lajos P. Balogh, NanoBiotechnology Center, Roswell Park Cancer Institute
- Third Place: Winston Timp, Massachusetts Institute of Technology

Because the AANM will guide academic activities, provide leadership, and lead research in the field, the AANM Fellowship Committee approved and elected the 48 new fellows to join the Academy. We would like to invite more qualified scientists and investigators to apply for the AANM Fellowship and join us in the development of nanomedicine research.

In conclusion, the Second Annual Meeting of the AANM was a great success (Figure 9). The meeting provides investigators from different world areas a forum and an opportunity for discussion. We believe that nanomedicine research will develop rapidly in the future. The AANM invites basic and clinical researchers from the world to join this exciting research. We sincerely appreciate everyone who

contributed to this conference, and we are looking forward to seeing everyone next year at the Third Annual Meeting of the AANM, September 8–9, 2007, in San Diego, California.

## References

- [1] Lyubchenko YL, Sherman S, Shlyakhtenko LS, Uversky VN. Nanoimaging for protein misfolding and related diseases. *J Cell Biochem* 2006;99:53-70.
- [2] Uversky VN, Kabanov AV, Lyubchenko YL. Nanotools for mega-problems: probing protein misfolding diseases using nanomedicine modus operandi. *J Proteome Res* 2006 [in press].
- [3] Kransnoslobodtsev AV, Shlyakhtenko LS, Ukrantsev E, Zaikova TO, Keana JF, Lyubchenko YL. Nanomedicine and protein misfolding diseases. *Nanomedicine* 2005;1:300-5.
- [4] McAllister C, et al. Protein interactions and misfolding analyzed by AFM force spectroscopy. *J Mol Biol* 2005;354:1028-42.
- [5] Mirzaei H, Schieler JL, Rochet JC, Regnier F. Identification of rotenone-induced modifications in  $\alpha$ -synuclein using affinity pull-down and tandem mass spectrometry. *Anal Chem* 2006;78:2422-3431.
- [6] Guo S, Akhremitchev BB. Packing density and structural heterogeneity of insulin amyloid fibrils measured by AFM nanoindentation. *Biomacromolecules* 2006;7:1630-6.
- [7] Ray C, Brown JR, Akhremitchev BB. Single-molecule force spectroscopy measurements of “hydrophobic bond” between tethered hexadecane molecules. *J Phys Chem B* 2006;110:17578-83.
- [8] Petkova AT, Yau WM, Tycko R. Experimental constraints on quaternary structure in Alzheimer’s  $\beta$ -amyloid fibrils. *Biochemistry* 2006;45:498-512.
- [9] Paravastu AK, Petkova AT, Tycko R. Polymorphic fibril formation by residues 10–40 of the Alzheimer’s  $\beta$ -amyloid peptide. *Biophys J* 2006;90:4618-29.
- [10] Tycko R. Molecular structure of amyloid fibrils: insights from solid-state NMR. *Q Rev Biophys* 2006;39:1-55.