SUMMARY REPORT

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NanoUtah 2008 focuses on cancer, builds bridges between nanotechnology fabrication experts and biomedical researchers

Nano Institute Established at meeting kick-off

NanoUtah 2008, Utah's fourth statewide nanotechnology conference, held this year at the University of Utah Oct. 16-17, 2008 at the Huntsman Cancer Institute on the university campus (www.nanofab.utah.edu/nanoutah08), focused on 'Bridging the Gap" between nanotechnology fabrication and developing nano-sized applications for biomedical use.

"This year's conference was particularly exciting because nanomedicine holds much promise for health care and making people's lives better," said conference organizer Hamid Ghandehari, Ph.D., USTAR professor of pharmaceutics and bioengineering. "With the discoveries, devices and techniques offered by nanomedicine, the hope for targeted cancer therapies, localized drug delivery, tissue engineering and gene therapy can become everyday realities. With *NanoUtah2008*, I think we have taken a significant step in that direction."

The Keynote Speakers

Conference keynote speakers emphasized the promise of nanotechnology for cancer diagnosis, prognosis and treatment and discussed nanotechnology’s potential for “resurrecting” some cancer treatment modalities once abandoned because of their cytotoxic properties. Those treatments, they said, may have new potential when targeted locally and delivered more safely to tumors with the help of nanotechnologies.

Wallace Akerley, MD, professor in the Department of Internal Medicine, Division of Medical Oncology at the University of Utah School of Medicine, said that oncologists need revolutionary nanotechnologies to improve screening and imaging tools for making better diagnoses and prognoses. He also called for new nanotechnologies to target anti-cancer agents directly to tumors.

“My nanotechnology wish list includes developing better imaging techniques using nanotechnology with the same kind of aggressiveness that we use to develop new drugs,” concluded Akerley.

Keynote speaker **Lawrence Tamarkin, Ph.D**, CEO and founder of Cytimmune Sciences, Inc. (www.cytimmune.com) in Rockville, Maryland, offered a new tool. Tamarkin co-invented a colloidal (suspended in water) gold-based, tumor-targeting nanomedicine platform technology that successfully carries the potent recombinant human tumor necrosis factor alpha (rhTNF) directly to tumors.

“The successful use of nanosized drug delivery systems to target potent but toxic anti-cancer therapies to solid tumors must first and foremost avoid uptake by the immune system,” Tamarkin told conference attendees. “Our 27nm colloidal gold particle limits the biodistribution of the drug to the tumor, where rhTNF binds to receptors in and around the tumor and disrupts the tumor’s blood supply.”

Historically, rhTNF’s toxicity was so severe that its use was greatly limited, said Tamarkin. Hoping that the new technology would make the drug safer, he sent the new rhTNF nano delivery system to the National Cancer Institute’s Nanotechnology Characterization Laboratory for evaluation. Their tests in animal models found that the drug ‘trafficked to tumors,’ but was not picked up by the immune system because the colloidal gold nano vehicle was encased in water, so the lab gave it a ‘thumbs up’ in terms of its activity.

“We were thrilled to be involved,” said keynote speaker **Scott McNeil, Ph.D.**, director of the NCI lab (http://ncl.cancer.gov).

According to McNeil, the characterization lab, initiated in late 2004, is a joint effort between NCI, the U.S. Food and Drug Administration (FDA) and the National Institute for Standards and Technology (NIST). Their mission is to test *in vitro* and *in vivo* using animal models promising nanotechnologies for their physical characteristics, such as toxicity and cell uptake. According to McNeil, in an effort to speed technologies to the market and to the bedside, the lab also helps explain and defend successful technologies to both the FDA and to venture capitalists.

The NCI lab's services are free, McNeil stressed to conference goers, urging they send their promising projects. He added that, to date, no researchers have submitted carbon nanotube technologies for evaluation.

Also from the NCI, keynote speaker **Piotr Grodzinski, Ph.D**., director of NCI's Alliance for Nanotechnology in Cancer (http://nano.cancer.gov), stressed the need to get more oncologists involved in the nanotechnology community's efforts to develop diagnostic, imaging, staging and treatment technologies for combating cancer. Grodzinski cited the potential for using nano particles as "tags" for targeting specific proteins, as well as developing magnetic nano particles for ultra sensitive imaging.

"We not only need to develop new cancer drugs that would benefit from nanotechnology, but also take another look at compounds that failed because of high toxicity, drugs that may be made safer and more effective using nanotechnology devices to deliver them."

The design of those nano-sized devices, said Session Two (materials and characterization) keynote speaker **Joseph DeSimone, Ph.D**., of the University of North Carolina Chapel Hill, is critical, as they must be fabricated precisely, allowing for control over nanoparticle size, shape, deformability and surface chemistry. To accomplish that, DeSimone's laboratory has developed a high resolution molding technique called PRINT (Particle Replication in Non-wetting Templates) that can produce nano particles ranging in varying sizes, from 20nm to greater than 100 microns, and in a variety of shapes, including spheres, cylinders, discs and toroidal. The nanoparticles can be made of organic or inorganic materials and with solid or porous characteristics for a variety of cargoes.

"We can steal Trojan horse design strategies from bacteria," said DeSimone. "This approach can help resurrect drugs the NCI has abandoned because of solubility issues."

Keynote speaker **Henry Kopecek, Ph.D**., of the University of Utah's Departments of Pharmaceutics, Pharmaceutical Chemistry and Bioengineering, who attendees described as a pioneer in nanotechnologies for targeted drug delivery, said that clinical trials of nanomedicines have "demonstrated reduced side effects, increased therapeutic efficacy and improved patient compliance." Noting that translation to the clinic has not been fast enough, Kopocek added that the next step required drugs with longer intravascular half-lives and the potential for double targeting to tumor cells as well as subcellular organelles, especially the mitochondria.

Research Briefs

In addition to keynote speakers, researchers, faculty members and post-doctoral students from across the University of Utah campus, Utah State University and Brigham Young University shared the results of their nanotechnology research through brief presentations, poster sessions and pre-meeting workshops.

Timothy E. Doyle, Utah State University presented “Simulation of wave propagation in cells and tissues at the microscopic level” and discussed evaluating models that can be used to better understand and predict transport and activation mechanisms for nano particles in heterogeneous tissues and at the plasma membrane.

“We have used a multipole approach to numerically model the propagation of ultrasonic and electromagnetic waves through spherical, nucleated cells and 3D tissues with random, ordered and hierarchical microstructures,” said Doyle of their computer simulations of noninvasive models for cancer detection. “We want to get a realistic histology.”

“A Pluronic ® micelle formulation increases the ant-leukemic activity of the novel anti-cancer nitric oxide prodrug JS-K,” was presented, **Paul J. Shami** of the Huntsman Cancer Institute. According to Shami, nitrous oxide (NO) induces cell differentiation and apoptosis in human myeloid leukemia cells *in vitro* and inhibits their growth *in vivo*. “We developed a class of 02-arylated diazeniumdiolate NO generators that release NO upon activation by the glutathione S-transferases (GST),” explained Shami. “This drug design exploits the upregulation of GST in malignant cells. The JS-K compound induces apoptosis and differentiation. We studied the anti-leukemic activity of JS-K formulated in micelles implanted in mice.”

Shami and colleagues, who were able to deliver NO directly to cancer cells, concluded that JS-K established a new class of cancer chemotherapeutic agents.

In presenting “Directed evolution of an engineered intracellular nanocompartment,” speaker, **Kenneth J. Woycechowsky**, University of Utah, discussed confining an enzyme in capsid to control catalytic activity.

“In principle, encapsulation can be used to sequester a toxic enzyme away from its substrate targets to abolish its deadly effects,” said Woycechowsky. “We have shown that a rationally designed protein capsid can exert a protective effect. Such a system could provide useful as a method for the production of toxic proteins in their active forms, for protein folding or for drug delivery.”

Furong Ye, University of Utah presented “A targeted polymeric contrast agent specific to fibrin-fibronectin complexes for cancer molecular imaging with MRI” and explained the incorporation of novel targeting moieties into polymeric MR contrast agents to facilitate active targeting of the polymer conjugates in diseased tissues, thereby improving contrast enhancement in MR images.

“Our preliminary results showed that the targeted polymeric contrast agent can specifically bind to the fibrin-fibronectin complex in cancer tissues, which allows for a potential for cancer molecular imaging with MRI,” said Ye.

Sun Hwa Kim, University of Utah, presented research entitled “Cardio-myocyte-targeted siRNA delivery by prostaglandin E2-Fas siRNA polyplexes formulated with reducible poly(amido amine) for preventing cardiomyocyte apoptosis.” According to Kim, she and colleagues developed a cardiomyocyte-targeted delivery system to inhibit cardiomyocyte apoptosis. PGE2 was used as a specific ligand for cardiomyocytes in a complex that included Fas siRNA. In rat models, once delivered, significantly increased Fas gene silencing, resulting in inhibition of cardiomyocyte apoptosis.

"Toxicity and cellular uptake of gold nanoparticles in human prostate and colon carcinoma cells," was discussed by speaker, **Arnida**, University of Utah.

"We evaluated the cytotoxicity and cellular uptake of gold nanoparticles on prostate and colon cancer cells using gold spheres and rods of different size, shape and charge," explained Arnida. "The toxicity of rods, in both cell lines using a variety of evaluation methods, was much higher than the spheres." The group found that the presence of cetyltrimethylammonium bromide (CTAB) on the rods was implicated as the primary reason for the observed toxicity.

"*In vitro* selection and engineering of highly specific DNAzymes for toxic metal biosensor applications," presented by **Kevin E. Nelson**, University of Utah, explored practical applications of new sensors constructed with DNAzymes.

"Our lab has developed a group of RNA-cleaving DNAzymes that are highly specific for transition metal ions," explained Nelson. "These highly selective DNAzymes have yielded many potential applications in metal ion sensors."

For example, Nelson pointed to their development of highly sensitive and selective fluorescent and colormetric biosensors with detection limits as low as 45pM or 11 ppt and selection in excess of 106-fold, making the sensors especially suitable for the development of biosensors for metal ions and small molecules of interest in clinical toxicology, environmental monitoring or anti-terrorist applications.

Michael H. Bartl, University of Utah, presented “Post-synthesis size tuning and spectroscopic studies of colloidal semiconductor nanocrystals.”

“The unique size and shape-related tunable functionalities of nanometer-sized semiconductors have dramatically altered our perceptions of fundamental properties,” said Bartl. “Our new equilibrium-chemistry based technique enables us to adjust and control the size, and therefore also the properties of before-hand-synthesized nanocrystals.”

The research team, said Bartl, used optical spectroscopy to show that their technique created highly luminescent nanocrystals with predictable and precisely tunable emission colors, promising for biological labeling and imaging.

Work with “Hyperpolarized silicon for biological imaging” was discussed by **Dane R. McCarney**, University of Utah, as a way to increase the sensitivity of MRI.

“The ability of MRI to image materials depends on the polarization of the spins in the material,” said McCarney. “Hyperpolarization has been proposed as a way to increase sensitivity.”

While most work in this area has been aimed at polarizing gasses, according to McCarney, their group worked at polarizing a solid material – phosphorus doped silicon. McCarney discussed the physical mechanisms at-play and outlined the future of their research.

Matthew Linford, Brigham Young University, discussed “Micropatterning by silicon subsurface oxidation (M-SiSO) and recent studies on silane deposition.”

“Surface patterning on silicon is critically important in research and industry and central to microchip fabrication,” said Linford. “We offer a straightforward tool to pattern silicon based on plasma oxidation through a stencil mask.”

According to Linford, the technique can be used in any normal chemistry lab with a plasma generator and oxidation is performed near room temperature.

Presenting “Stable non-accumulation nanospheres for nonionic mesomechanical use in biological systems,” speaker **William Niedermeyer** of NLC Laboratories, Inc., said that their development of production methods for turning out spherical nano particles with controllable sizes from six to 35 nanometers, with high zeta potentials for stability, proved successful. Their methods, he said, were scaled to provide large quantities for use in collaborative research and industry.

“A collaborative program at NLC Laboratories, Inc., provides these materials free of cost to legitimate research programs,” said Niedermeyer.

Rostislav Bukasov, University of Utah, presented “Application of nanocrescents’ tunable IR plasmonic properties in IR spectroscopy.” Bukasov told attendees that tuning the localized plasmon resonance (LSPR) wavelength, as well as the localized field enhancements of plasmonic materials, is especially important for spectroscopy applications such as Surface Enhanced Raman Spectroscopy (SERS) and Surface Enhanced Infrared Absorption Spectroscopy (SEIRA). There have been a lack of tunable substrates for the IR spectral region, he added.

“Good control over gold and silver nanocrescent (NC) size, shape and orientation is largely responsible for the broad tunability and strength of the structure’s LSPR,” said Bukasov. “We applied this unique tunability to maximize signal enhancements in Surface Enhanced Infrared Absorption Spectroscopy (SEIRA) and found that the tunability of nanocrescents makes them a very promising sensing platform for both SEIRA and LSPR spectroscopy."

"Mass selecting ion beam-line for the creation of size selected metal particle covered surfaces," was the subject for speaker **William E. Kaden**, University of Utah.

"The catalytic properties of model surfaces consisting of metal clusters on well-defined ceramic substrates were of interest to us," said Kaden, explaining that metal-ion clusters are formed via laser vaporization and helium impact induced condensation before passing through an atomically resolved quadrapole mass filter and colliding with a surface of interest in ultra-high vacuum conditions to result in mono-disperse surfaces of size selected MN clusters.

"Cluster sizes are limited to 2000 amu in mass and surfaces must be somewhat conductive," said Kaden.

Beginning the third session, devoted to devices and sensors, speaker **Richard A. Normann**, University of Utah, discussed "Neuroprosthetics restoration of function via neuronal scale communication systems," by explaining the 'Utah Electrode Array," a silicon-based interface to the nervous system's neurons.

"This technology allows an unprecedented and highly selective means for bi-directional communication to these cells," said Normann, who explained examples of how the Utah Electrode Array could offer potential solutions to nervous system disorders that include blindness and limb paralysis when coupled with recent advances in micro-electronic machines (MEMS).

Speaking on the "Challenges and opportunities for nanotechnologies in neuroscience and neural engineering," **John White**, University of Utah, also presented revolutionary nanotechnology that could aid stimulating neurons with "cell type specificity." For White, the 'vexing problems' of memory and vision loss, for example, may be solved by nanotechnologies revolutionary contributions that could include improving neural activities in the hippocampus and Broca's area of the brain.

In discussing "Facial prosthetic and artificial eye," speaker **Ian R. Harvey**, University of Utah, presented data on creating 'artificial vision' through the use of micro-optics using a neural interface between an artificial eye and the brain.

"Neural stimulation will be the means of supplying image data from the camera unit to the visual cortex, ideally and ultimately through the optic nerve," said Harvey. "Neural feedback will be necessary to drive the accommodating lens for near and far focal response."

"Optoelectronic gas sensing with organic nanowires," was the topic for speaker **Ling Zang**, University of Utah, who said that organic nanowires had gained increasing interest in the past few years, largely due to their potential applications in various nanodevices.

"Nanowires fabricated from rigid, planar, aromatic molecules have one-dimensional optical and electronic properties along the long-axis of nanowire," reported Zang. "Such properties are highly favorable for long-range charge transport and exciton migration, making nanowires unique building blocks for optoelectronic devices."

In his talk, Zang discussed recent progress in nanowire fabrication from various organic materials and their potential applications.

Agnes Ostafin, University of Utah, spoke on "Functional nanoparticles for sensing medical applications."

"Our team develops functional nanoparticles for specific chemical sensing/delivery of biomedical applications," Ostafin told attendees. "We are interested in establishing collaborative opportunities for further research and commercialization."

Ostafin pointed to a number of their nanoparticles with specific capabilities built in, such as restiveness to environmental contaminants, improved durability and better performance. Examples include nanoparticles for pH/oxidant detection in complex environments, for gas absorption, drug delivery and infrared imaging and detection.

“Pumpless, micron-scale, self-contained, microinjector with high success rates,” was the focus of speaker **Quentin Aten**, Brigham Young University.

“We have developed and tested a pumpless, self-contained MEMS microinjector fabricated using polyMUMPS (a MEMS multiproject wafer service),” explained Aten. “Microinjection is an important tool for generating transgenic model organisms used in the study of transplant rejection, tumor suppression and immune response. We anticipate that our MEMS microinjector will have much greater overall success that traditional microinjectors.”

The big difference in their microinjector, said Aten, is the use of electrostatic charges to attract suspended DNA onto the micro needle and, once inside the zygote, repel the DNA from the needle surface.

Gregory M Dittami, University of Utah, spoke on “Stimulus-controlled neurotransmitter release and quantal detection on a microchip.”

His research team fabricated a microchip using surface micromachining and thick film technologies that facilitates electrical and electrochemical measurements of individual cells and cell clusters.

“We anticipate that such a chip could provide a semi-automatic alternative to the conventional, labor intensive carbon fiber electrode approach to neurotransmitter measurement," said Dittami.

“Enhancing the sensitivity of immunoassays through plasmonics optimization of surface enhanced raman scattering of gold nanoparticle labels,” was the topic for speaker **Eric J. Dufek**, University of Utah. According to Dufek, the emergence of Surface Enhanced Raman Scattering (SERS) has ‘driven the limit of detection for a wide range of immunoassays to remarkably low levels.’ The use of gold capture substrates and gold nanoparticles has played a significant role in this, he said. Dufek presented data that looked at enhancements factors on a ‘per particle basis’ as evaluated by using SERS and atomic force microscopy.

“Giant magetoresistive (GMR) sensors as a chip-scale detection platform for multiplexed immunoassay,” speaker **Michael Granger**, University of Utah. Granger explained that microfabricated devices are becoming more integrated into the bioanalytical sciences as chip-scale readout tools and their use in high-data density storage drives.

“Our lab has attempted to extend these attributes into the immunoassay area,” said Granger. “Our recent work focused on the multiplexed detection of immunoglobin (IgG) proteins.”

He discussed responses from sampling the sample coupon with the GMR, images from scanning electron microscopy for particle enumeration, and preliminary assessments of the sensitivity of this novel readout platform.

“Comparative SERS activity of Rhoamine 6G absorbed on different nanoparticle substrates,” was presented by speaker **Analia G. Dali’Asen**, University of Utah. Dali’Asen outlined comparative studies analyzing the capability of new tunable plasmonic approaches for SERS nanosensors in order to improve spectroscopy sensitivity.

He presented data from SERS of quartz substrates and Rhodamine 6G analyte by solid-state gold nanoparticle assemblies and gold nanoparticle colloids examined across a range of analyte and nanoparticle concentrations.

Nano Institute establishment announced at NanoUtah 2008

At NanoUtah 2008, officials at the University of Utah announced the establishment of the *Nano Institute of Utah,* representing a significant and decisive step in the state’s quest to bring together the university’s and the state’s nano science experts in diverse areas of chemistry, physics, biology, engineering, medicine and pharmacy.

“Our mission is to develop and implement a comprehensive program to advance nanoscience and technology across the university and the State of Utah,” said Nano Institute director Marc Porter, Ph.D, USTAR professor in the departments of chemistry and chemical engineering told attendees. “The Institute will drive research partnerships with academia, the private sector and government agencies.”

The Institute, said Porter, would help Utah enhance its position in nanotechnology research and development and also facilitate commercialization of new nanoscience discoveries.

“The Institute formalizes and strengthens the work and the partnerships in place,” explained Porter. “By establishing the institute, we begin bringing together the pieces and players to take nanoscience in Utah from the scientist’s bench to commercialization and beyond -- where innovation begins affecting peoples’ lives.”

Institute framers identified five important nanoscience areas of focus for the Institute: nanomaterials (thin films, coatings); interfacial sciences dealing with the behavior of fine particles and thin films that interact (molecular structuring, ion transport); nanobiosensors (diagnostics, chemical detection); nanomedicine (localized drug delivery, diagnostic imaging, scaffolds for tissue engineering); and micro and nano systems integration and reliability (building nano systems and devices).

According to institute co-director, Hamid Ghandehari, Ph.D., USTAR professor of pharmaceutics and bioengineering, Utah State officially recognized the importance of nanotechnology in 2005 when its Office of Economic Development hosted the first meeting to plan the State of Utah Nanotechnology Initiative.

In 2006 the Utah Science Technology and Research initiative (USTAR) was established, which is investing $15 million annually in a range of research projects, including some focused on nanotechnology. USTAR's intent is to recruit world class nanotechnology researchers and enable research and development of nanotechnology development and commercialization among other advanced scientific fields. The Nano Institute of Utah, he said, is further evidence of the state's commitment.

Florian Solzbacher, Ph.D, professor in the departments of electrical engineering, materials science and bioengineering, and Co-Director of Nano Institute added that the institute will identify and promote entrepreneurial opportunities and help launch new high tech companies to commercialize nanoscience discoveries.

USTAR nanotechnology director Darwin Cheney, Ph.D. agreed, saying that “ the institute should prove to be a magnet for industry-sponsored research and other collaborative efforts with leading life science business. It will be in a unique position to capitalize on state-of-the-art nanofrabrication facilities the University is adding as part of the USTAR building project.”

According to University of Utah Vice President for Research Thomas N. Parks, Ph.D., the creation of the Nano Institute was the best vehicle for providing a nucleus of administration and science that could bring together the disparate elements necessary to build competitive research programs in nanotechnology.

“The goal is to have the highest quality research team who will be major players in the multidisciplinary area of nanotechnology,” suggested Parks. “The Institute will attract like-minded engineers and scientists who can as quickly as possible take us to the forefront of nanoscience and also provide a foundation for training the next generation of nanoscientists.”

Parks also noted that the Institute effectively brings together the University’s ‘upper campus,’ home to medicine and pharmacy, and the ‘lower campus,’ home to engineering, chemistry and physics.

Training is an important mission for the Institute, confirmed Ghandehari.

"Faculty at the Institute will be fully involved with teaching nanotechnology topics at the undergraduate, graduate and professional levels," promised Ghandehari. "These efforts will be integrated with existing educational outreach programs initiated by USTAR."

Newly formed at the University of Utah, the Center for Nanomedicine will be a critical part of the new Institute as researchers at the Center work toward developing methods to target therapeutics and diagnostics at the cellular level, revolutionizing imaging and drug delivery for treating cancer and neurological diseases.

For more information about the University of Utah's Nano Institute, go to (www.nanoinstitute.utah.edu).

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