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Nanoscale Science, Engineering & Technology

University of Minnesota

Nanotechnology News from the University of Minnesota

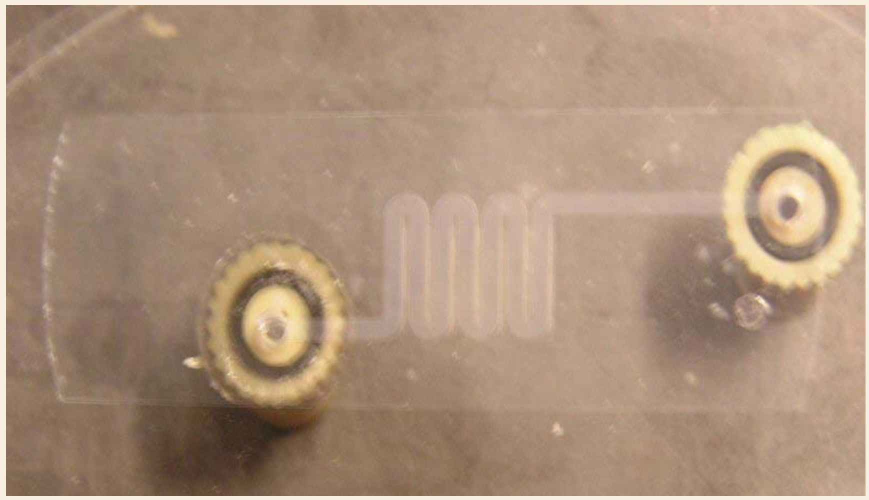
Winter 2008

Welcome to the January 2008 issue of the newsletter. I would like to call your attention to a couple of items. The Center for Nanostructure Applications (CNA) sponsored workshop held in November was a great success. Over 300 registrants participated in sessions that included some of the leading figures in nano in the world. If you missed the event, some of the talks are available on our website at www.nano.umn.edu/conference2007.

This newsletter issue continues our recent format, offering an article about a CNA sponsored group to provide a glimpse into their work. In this issue Professor John Bischof (Mechanical Engineering) discusses the project that he leads. His group's work, which involves faculty from Mechanical Engineering, Chemical Engineering & Materials Science, Radiology, and Urologic Surgery, concerns the development of certain types of polymers for intracellular cargo transport for the detection, localization and treatment of cancer.

Finally I want to point out a current funding opportunity within CNA for seed grants. These interdisciplinary awards will provide two years of support for a student who is coadvised by two faculty members from different areas. Please visit our website for more information including application procedures and deadlines: www.nano.umn.edu/cnaseedgrant08.

Winter 2008 Nano Image



A channel fabricated in PDMS for use in a membrane based counter-current extractor in a microfluidic, flow through DNA purification device. Image courtesy Professor Michael Bowser (Chemistry).

Reminder: If your work uses CharFac, NFC, or PTL, please add the following in the acknowledgements section of any publication: "Parts of this work were carried out in the Minnesota (Characterization Facility, Nanofabrication Center, or Particle Technology Lab) which receives partial support from NSF through the NNIN program."

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Next Generation Nanoparticles for Detection and Treatment of Cancer

John Bischof, PhD, Mechanical Engineering
Joel Slaton, MD, Urologic Surgery
Efrosini Kokkoli, PhD and Frank Bates, PhD, Chemical Engineering & Materials Science
Shalom Michaeli, PhD, Radiology, Center for Magnetic Resonance Research

Image guided therapies are increasingly being used in the detection, diagnosis and treatment of cancer and other diseases [1]. The Thermal Therapies Interest group, a part of the Institute for Engineering in Medicine (www.iem.umn.edu) at the University of Minnesota, has focused on a variety of minimally invasive image guided thermal therapies for cancer treatment. Preclinical testing has shown that molecular adjuvants such as tumor necrosis factor (TNF), can dramatically improve the control and efficacy of these treatments. Unfortunately, systemic delivery of TNF leads to dose-dependent toxicity. Recently, we have shown that ***nanoparticle (NP) delivery*** of TNF does not produce systemic toxicity at doses that significantly enhance the image guidance for cryosurgical treatment of prostate cancer. CYT-6091, a gold nanodrug in a Phase I Clinical Trial is manufactured by Cytimmune Sciences Inc. It is composed of PEG-coated 33 nm gold NP with bound TNF. The PEG coating prevents rapid particle uptake by the reticuloendothelial system (liver and spleen) and thus increases its blood circulation time, allowing it to more effectively target the tumor. Particle uptake in the tumor is facilitated by "leaky" microvasculature (10–200 nm pores), which is enhanced by TNF binding within the tumor. As shown in Figure 1, visually guided cryosurgery of these tumors can completely destroy the cancer with TNF addition [2]. However, the avoidance of TNF systemic toxicity can only be achieved with CYT-6091. Similar enhancement of hyperthermic injury in a breast cancer hindlimb model was also reported with this nanodrug

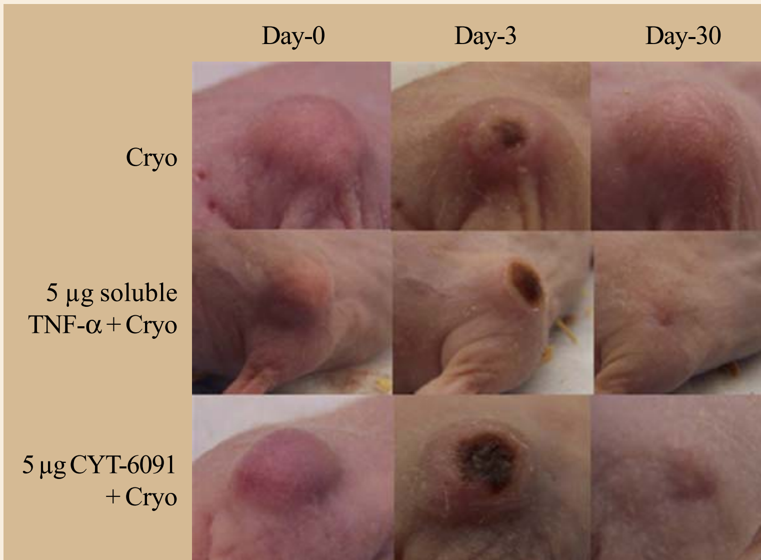

Figure 1: Gross tumor destruction with no toxicity or morbidity using CYT-6091 and cryothermia [2].

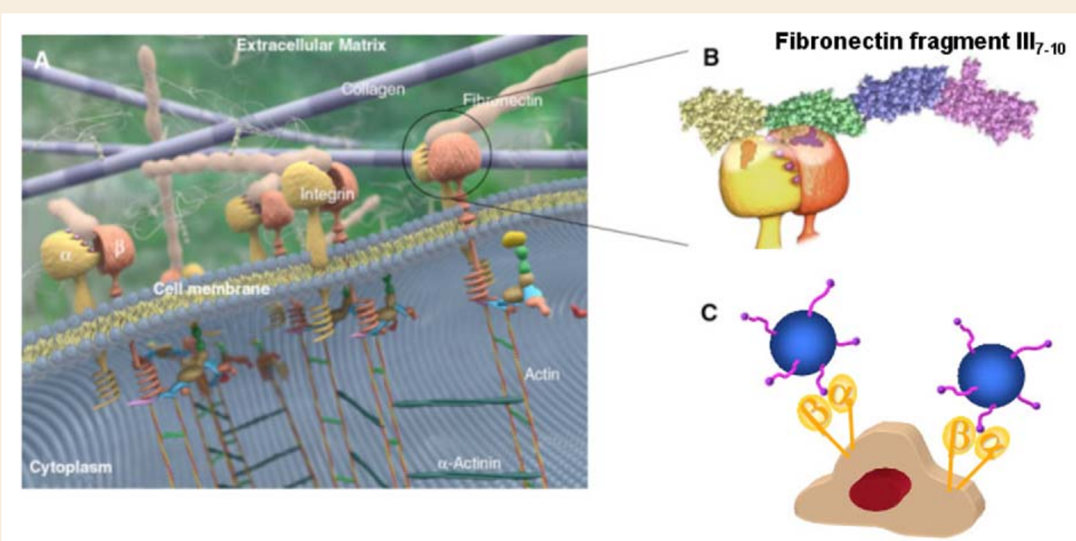

Figure 2: (A) Integrins, cell surface receptors which are linked to the cytoskeleton, hold a cell in place by binding to proteins of the extracellular matrix (ECM). (B) Integrins bind to the adhesion domains (module III7-10) of the ECM proteins, such as fibronectin, by recognizing specific motifs within that domain. (C) Particles functionalized with peptides that mimic part of the ECM proteins are recognized by integrins via "specific interactions" and can be delivered only to cells that over express the integrins of interest. Images A) and B) are adapted from Tirrell et al [5].

by our group [3]. We are currently translating this NP assisted cancer therapy procedure into a large animal model in collaboration with Drs. Joel Slaton and Dr. Kyle Anderson in the Department of Urologic surgery. This exciting result has also stimulated work on developing the next generation NP with improved targeting and imaging capabilities:

Improved targeting: While the TNF nanodrug has shown efficacy in both stand alone and combination therapies, other targeting approaches can be used which may improve tumor specificity thereby expanding detection and treatment options for cancer. Both metal NPs and liposomes have been used in the past, however, a new approach using polymersomes (which have tremendous flexibility in size, shape and stability) is being attempted with the assistance of Drs. Bates and Hillmyer. More efficient targeting of polymersomes and other NPs can be achieved by attachment of a targeting moiety to eliminate non-specific toxicity and side-effects resulting from systemic biodistribution. Selective targeting to the disease site can also reduce the therapeutic payload requirements. The inspiration for the design of targeting molecules often comes from bioadhesion molecules such as integrins (Figure 2). Peptide sequences that mimic binding sites for such proteins have several advantages: 1) the peptide is smaller than a typical protein and is domain specific, and 2) peptide sequences can be used not only for site-directed delivery of NPs but also for studying mechanistic details of binding and delivery. Dr. Efie Kokkoli, a team member, has shown increased adhesion of $\alpha_5\beta_1$ integrin (over expressed in tumor cells) targeted peptide to HUVEC cells [4]. We plan to use this promising peptide to functionalize targeted delivery systems. This approach is being vigorously pursued both *in vitro* and *in vivo* for improved imaging based detection and treatment of several cancers.

Imaging / detection / tracking: Intrinsic properties of NPs determine the applicability of various detection and imaging techniques. Non-invasive imaging of gold NPs by Raman approaches has limited resolution in tissues, hence limiting clinical imaging opportunities. Iron-oxide and other high moment magnetic NPs, such as collaborator Dr. Jianping Wang's, have the advantage of being a natural contrast agents in the magnetic resonance (MR) environment. Working with Dr. Bruce Hammer on cancer phantom models, we have been able to detect levels of iron oxide NPs at 1.5 T MR at a resolution of 10 µg/ml within the phantom [6]. In addition, Dr. Shalom Michaeli of the Center for Magnetic Resonance Research (*www.cmrr.umn.edu*) has also shown that pathologic iron concentrations in the brains of Parkinson's disease (PD) patients can be reproducibly imaged at high field MR in the same concentration range (i.e. 10's of µg/g tissue) [7]. Figure 3 demonstrates the ability of MR to detect such low levels of iron in the brains of PD patients using recently developed $T_{2\rho}$ MRI techniques based on adiabatic pulse sequences [8]. Using state of the art high field MR imaging, we therefore should be able to track and detect magnetically labeled nanoparticles at unprecedented resolutions within tumors and other tissues. Thus, with pre-clinical and translational models of cancer, improved targeting and imaging our team is working to create an improved NP platform for detection and treatment of cancer.

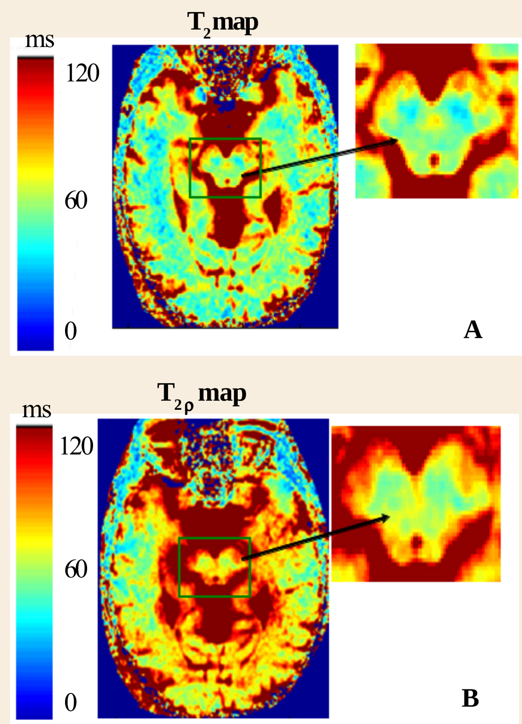

Figure 3: Representative T_2 (A) and $T_{2\rho}$ (B) relaxation maps of the brain of a PD patient. MRI contrast is generated by the tissue variation of longitudinal and transverse relaxation of the ^1H_2O MR signal in the presence of radiofrequency (RF) irradiation, as described by the T_1 and T_2 time constants, respectively. T_2 is highly sensitive compared to conventional T_2 MRI to diffusion and exchange of water protons in environments with different local magnetic susceptibilities, thereby provides better spatial specificity [8].

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UPCOMING NANO EVENTS

Polymer Characterization Tutorial Short Course
March 27 – 29, 2008
Abbott Vascular Corporation, Santa Clara, California
Sponsored by Golden Gate Polymer Forum

This short course will provide an intensive 3-day tutorial with applications from Biomaterials and Medical Devices with major emphasis on the newer techniques involved in surface and morphological characterization. It will include presentations by experts including Greg Haugstad, Director of the University of Minnesota's Characterization Facility; Shaw Ling Hsu, Professor of Polymer Science at the University of Massachusetts; and Dr. Steven Goodman, President of 10H Technology.

This event may be particularly convenient for those attending the 2008 Spring Materials Research Society meeting in San Francisco, March 24 – 28.

For complete information on this short course, visit http://www.ggpf.org/ and click on 'Polymer Characterization Tutorial'.

BioMEMS & Microfluidics Short Course
May 7 – 8, 2008
Nanofabrication Center, University of Minnesota

This hands-on workshop will provide an understandable overview of microfluidics for biomedical applications. It is intended for those who might be interested in becoming involved in the microfluidics field, but need a basic outline of what is possible and how the devices are designed and built. A hands-on component will get the participants in the lab where they will build some basic microfluidic structures. Principles and software will be introduced to familiarize the participants with the design of more complex devices. Also, many of the current technology applications will be reviewed. Look for more details soon at www.nano.umn.edu/biomems08.

Cryo TEM/Tomography Master Class
May 22 – 23, 2008 (*tentatively scheduled*)
Characterization Facility, University of Minnesota

This master class will include lectures and laboratory demonstrations. Look for details to come at the Characterization Facility or Center for Nanostructure Applications websites.
www.charfac.umn.edu/
www.nano.umn.edu/

3rd Annual Minnesota Nanotechnology Conference Recap

On November 13 - 14, 2007 the University of Minnesota hosted the 3rd Annual Minnesota Nanotechnology Conference, which offered presentations and discussions on Nano Energy, Devices, Sensors and Materials.

We were fortunate to have talks by some of the country's leading nano researchers from top institutions.

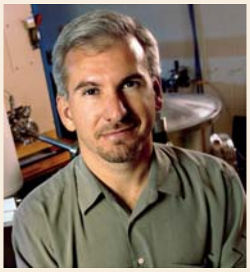
Attendance at this year's conference was over 300 people. We were very pleased that about 100 faculty and students from 27 other educational institutions were able to attend. Almost 90 industry attendees from 45 different companies — from the very small to the very large — also joined us. And faculty, staff and students from more than 20 different University of Minnesota departments attended.

A reception and poster session took place after the first day's talks. The reception was well attended and provided an opportunity to network and view the poster exhibit while talking one-on-one with researchers about their work.

For a complete event recap, including some of the program's presentations, lists of attendees and poster presenters, and pictures, visit www.nano.umn.edu/conference2007/.

CHARACTERIZATION FACILITY NEWS

CHARFAC DIRECTOR'S MESSAGE



CharFac Director,
Greg Haugstad

We are thrilled to announce the addition of a Transmission Electron Microscopy (TEM) specialist, Ozan Ugurlu. Before joining the CharFac, Ozan was a postdoc at the Los Alamos National Laboratory working on microstructural characterization of superconductors. His 6+ years of experience in electron microscopy also includes a period at Iowa State University, working on TEM of rare-earth alloys and alcanate hydrogen storage materials as a member of complex materials group led by Karl Gschneidner and Vitalij Pecharsky. Ozan managed the ISU Materials Science and Engineering Department's SEM laboratory for three years as a side project to his PhD research and received multiple TA awards for his efforts. In 2006 he received the Excellence in Research award. He earned a bachelor's degree in Materials Science and Engineering from METU, Turkey in 2001, a master's degree in Ceramic Engineering from Alfred University in 2003 and a doctorate in Materials Science and Engineering from Iowa State University in 2006. Dr. Ugurlu has nearly 20 peer-reviewed journal articles and more than a dozen presentations at international microscopy and materials related conferences, such as MRS, MSA, TMS etc. He is also an active reviewer for Journal of Materials Research and International Journal of Hydrogen Energy.

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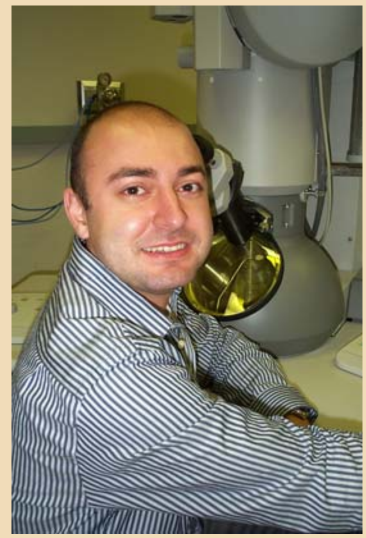
Ozan's principal CharFac activity involves TEM in various modes such as Diffraction, High-Resolution TEM (HRTEM), Scanning TEM (STEM), Energy Dispersive Spectroscopy (EDS), Electron Energy Loss Spectroscopy (EELS) and Energy Filtered TEM (EFTEM), with principal effort on the 300-kV FEG-TEMs in Shepherd Labs and Hasselmo. Additionally he will be working with TEM- and SEM-related sample preparation techniques including the Focused Ion Beam (FIB) system in the Nanofabrication Center. His research interests include TEM characterization of cross-sectional thin and thick films, hard materials, diffraction and crystallography studies, in-situ TEM experiments and high-resolution TEM.



Ozan Ugurlu, CharFac's new TEM specialist.

A second laser was recently configured for the Confocal Raman Microscope. This krypton laser emits at 752.5 nm with maximum power close to 60 mW. A triple grating SpectraPro spectrometer with a deep-depletion CCD detector was installed during the Raman workshop in November. It has enhanced sensitivity to scattered light at this long wavelength. The new capability is intended to reduce fluorescence from the sample. Those interested in using this laser/spectrometer modification should contact staff specialist Dr. Jinping Dong; substantial laser realignment may be required when switching from the usual 514 nm laser.

An nPoint closed loop scanner is now available for the Veeco Multimode AFMs in Shepherd Labs. This provides more linear scans and with no piezocreep effects (e.g., distortion/drift after zooming), as well as a much larger Z range compared to our J scanners. Among other things such a scanner can be used to measure film thickness via a film edge that is laterally broad, say from a masked deposition process. Such nanoscale changes of height, if spread over many microns of lateral distance, can be invisible to conventional scanners, because these changes are superimposed on a curved apparent surface due to scanner nonlinearity.

A spectroscopic ellipsometry workshop in collaboration with J.A.Woollam is being planned for mid to late February.

CHARFAC AT THE UNIVERSITY OF MINNESOTA

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Greg Haugstad, Director

Nanofabrication Center News

NFC Director's Message

NFC Director,
Steve Campbell

The last four months have been very stable in the lab with no new equipment acquisitions. We have had considerable problems with our direct write e-beam system lately and have had manufacturer's representatives in several times to address the issues; it now appears to be resolved. We are also looking at possible new equipment acquisitions. Several groups have expressed interest in acquiring a nanoimprint system. These tools allow one to make a large number of nanoscale patterns much more rapidly than can be done by direct write e-beam. This is of particular interest for research groups that need to make millions or billions of highly repetitive features. As always, if you are interested in providing input on this or any new NFC equipment needs, please let me know. All of our acquisitions are based on the needs of our faculty to the extent that we know them.

Our new accountant, Mr. Assefa Geleta, is now on board. Over the next few months the Institute of Technology will be moving to a cluster approach to financial operation in preparation for the new PeopleSoft financial system. As part of this, many of the functions that are currently done locally will be off loaded to the centrally managed cluster. In preparation for this change we have entered a cooperative agreement with the Characterization Facility to have Assefa support both labs.

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Steve Campbell, Director
Greg Cibuzar, Lab Manager

New NFC Process Staff

In the past few months the Nanofabrication Center has hired two new process staff members to work with NFC researchers in the cleanroom. Paul Kimani and Lage Matzke both joined NFC last summer. With the addition of Paul and Lage, NFC now has a process staff of five full-time employees.

Paul is a graduate of the two year nanoscience program at Dakota County Technical College (DCTC) in Rosemount, MN. At NFC Paul is focusing on two areas of processing - photomask fabrication and photolithography. We are making more photomasks than ever for users around the country, and Paul's assistance will allow us to continue our high level of service.

Lage also comes to us from the DCTC program and is nearly finished with his degree requirements. At NFC Lage primarily works in the deposition and etching process areas. He has been busy learning the various tools we have in these areas, and developing processes to monitor tool operational status.

In addition, both Paul and Lage have been working with NFC customers by performing project processing. Both will be heavily involved in training of new NFC users on equipment operation.

Paul Kimani (right)

Lage Matzke (left)

Safety Training

NFC is offering safety training for new users twice each month. On the first Thursday of every month, the training sessions begin at 1:15PM, and on the third Thursday of the month sessions begin at 10:00AM. The training includes watching our safety video and taking a brief quiz. Also, a NFC staff member provides a tour showing some of the safety related equipment and the gowning process used for the NFC cleanroom. Finally, there is training on using the Coral lab software. The safety training takes about two hours to complete, and must be done before users will be granted access to NFC facilities.

PARTICLE TECHNOLOGY LAB NEWS

PTL DIRECTOR'S MESSAGE

Distinguished McKnight University Professor, David Y.H. Pui

During the past three years, we have developed several unique facilities for nanoparticle research. Under Intel support, we have developed a vacuum test facility that allows us to inject nanoparticles of known size and speed into a chamber evacuated down to 20 mTorr. A second system is designed to operate under atmospheric pressure which allows us to deposit NIST traceable standard nanoparticles on photomasks without haze formation. Under Center for Filtration Research support, we have developed several filter testers that allow us to evaluate sheet filters or panel filters under a wide range of face velocities. Monodisperse nanoparticle aerosols of known size and concentration can be injected into an ASHRAE 52.2 tunnel and their fractional efficiency determined using a condensation particle counter or a nanoparticle surface area monitor. We are now able to offer these unique facilities to internal or external users from academia or industry. Because of the NNIN support, we are able to offer these testing services at substantially reduced cost. During the past three months, we have performed or negotiated contracts with several major companies, including Intel, Sematech, Donaldson Company and DuPont. Please contact us if you have a need in these testing services.

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Also, we have started an international collaboration project with Prof. Amal at the University of New South Wales, Australia. The project "Optical fibre photoreactor for removing airborne molecular contaminants and volatile organic carbons for semiconductor fabrication and fuel cell applications" with PI Rose Amal and Co-PI David Pui is an Australian Research Council Linkage International Project. It will involve setting up facilities at UNSW and UMN to evaluate photocatalytic performance, system integration and airborne molecular contaminants generation. Prof. Amal will visit the PTL in May 2008. She will give presentations at the review meeting of the Center for Filtration Research.

PTL NEWS

The PTL received a generous donation from IBM, Rochester, MN in December 2007. The donation includes over 30 laser particle counters, two multiplexers, two condensation particle counters, and a multi-stage impactor. The instruments will be used to advance our microcontamination research, and to instruct our graduate students in two classes, ME 5133 Aerosol Measurements, and ME 5116 Cleanroom Technology. We thank Steve Nickel, Manager of Dept 5E3, IBM for the donation. And we also thank Paul Pederson for initiating this donation, and Terry Ryks for his meticulous work of preparing the instruments for pick up.

The PTL received a generous donation of a Lindberg Tube Furnace from Donaldson Company in January, 2008. The furnace is similar to model HTF55667C, 6" ID, 32" long, three zones, 1200C, 208/240VAC with controller 58434-P S/N 927459. The furnace is a valuable tool in the generation of nanoparticles and will contribute to our filtration and other studies. We thank Tom Kotz and Kevin Evans for initiating the donation and delivering the furnace.

As part of NNIN activity, our Lab Manager, Dr. Jing Wang, research assistant professor in Mechanical Engineering, will teach a Continuing Education class MT3142 this spring semester to a group of technical college students. These students will be able to systematically learn the particle instrumentation in the PTL, from Scanning Mobility Particle Sizer for nanoparticle size distribution measurement, to Aerosol Time-of-Flight Mass Spectrometer for composition analysis. PTL faculty and staff have developed many aerosol instruments used widely for nanoparticle measurements. It will be a good experience for students taking this class. The course offering is part of the outreach program performed under NNIN.

PARTICLE TECHNOLOGY LAB AT THE UNIVERSITY OF MINNESOTA

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David Y.H. Pui, Director
Jing Wang, Lab Manager

Center for Nanostructure Applications

The primary mission of the Center for Nanostructure Applications is to seed interdisciplinary nano research projects that will go on to attract external support. Active nanostructures include applications of nano as diverse as energy conservation and production, large area displays and lighting, printed electronics, smart fabrics, electronic noses, drug delivery, cancer therapy, and new types of medical imaging.

These applications often require significant participation across traditional disciplines and the Center is designed to foster the cross-disciplinary research necessary to bolster the nano applications area at the University.

The Center also organizes workshops, speaker series, and short courses, as well as serving as a focal point for nano at the University.

For more information, visit http://www.nano.umn.edu/

The Minnesota Nanotechnology Cluster

MiNTeC is an umbrella organization of three labs at the University of Minnesota that support the development of nano technology: the Characterization Facility, Nanofabrication Center, and Particle Technology Lab. As a node in NSF's National Nanotechnology Infrastructure Network (NNIN), MiNTeC provides access to advanced multi-user facilities to both industry and academic researchers, the latter at a subsidized rate. The MiNTeC facilities are at the University of Minnesota's Minneapolis campus.

For more information, visit http://www.mintec.umn.edu/ and www.nnin.org

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and the National Nanotechnology Infrastructure Network.

Comments and suggestions are welcome! Would you like to be added to or removed from our distribution?

Contact: Becky von Dissen at vondi001@umn.edu or 612-625-3069

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