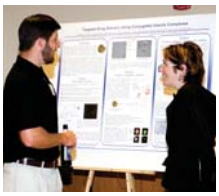
NHLBI Inter-PEN Quarterly

Program of Excellence in Nanotechnology

National Heart, Lung & Blood Institute

PEN members in attendance at the 1st Annual Inter-PEN Conference, on the campus of Washington University in Saint Louis, October 6-8, 2006.



IN THIS ISSUE

The First Annual Inter-PEN Conference October 6-8, 2006 Washington University Saint Louis, Missouri

By Karen L. Wooley
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Approximately one year after the four Programs of Excellence in Nanotechnology (PENs) were launched, a meeting was held to assemble researchers from across the PENs and further advance the broad mission that had been set forth with the establishment of this unique program, to explore nanoscience within the context of medically-relevant nanotechnologies of importance to the NHLBI. Throughout this two-day event, the four PENs, represented by a total of *ca*. eighty participants, presented their accomplishments, techniques, expertise and strategies through a series of oral presentations. Poster sessions provided opportunities for in-depth discussions. The concluding session involved discussions that built from the exchange of information that had occurred, with the intention of identifying plans for the coming year, especially in relation to opportunities for inter-PEN collaborations in research, skills development, dissemination of knowledge generated, and outreach to the community. The conference was considered to be hugely successful in the transfer of information and building of bridges between the PENs. The 2nd Annual Inter-PEN Conference has been scheduled for October 19-21, 2007 in Santa Barbara, CA.

For more information about the PENs and public viewing of slides presented during this 1st Annual Conference, please visit http://www.nhlbi-pen.net.

A word from our Program Official

National **Heart Lung and Blood** Institute

Nanotechnology at NHLBI

By Denis Buxton
Chief of the Advanced
Technologies and Surgery Branch
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The exciting and rapidly growing field of nanotechnology takes advantage of novel mechanical, electrical, chemical and optical properties of materials at the nanoscale, 1-100nm in size. The NHLBI Programs of Excellence in Nanotechnology (PENs) represent the first major NIH program applying nanotechnology to disease. This ground-breaking program grew out of a working group held in 2003 to assess how NHLBI could harness the potential of nanotechnology to diagnose and treat heart, lung, blood, and sleep diseases. The biggest barrier to the use of nanotechnology for clinically relevant problems was felt to be a lack of interdisciplinary interactions, so that disease-oriented investigators had insufficient understanding of nanotechnology while those with nanotechnology expertise lacked understanding of the relevant diseases.

In response, NHLBI released a Request for Applications in 2004 inviting proposals for multidisciplinary programs to apply nanotechnology to cardiovascular, pulmonary, hematopoietic and sleep disorders. After a highly competitive review of many excellent applications, the four PENs were funded in 2005, with NHLBI committing approximately $54 million over 5 years. The Washington University PEN, led by Karen Wooley, was selected as the administrative center. With coordination from the administrative center, the first 18 months have seen a rapid growth in interactions both within and between PENs, particularly in the development of trans-institute training activities and meetings. As the PENs mature, we expect these interactions to develop further into collaborative research activities, helping to move the field forward.

The Four PENs and their Principal Investigators

Nanotechnology: Detection & Analysis of Plaque Formation
Emory University
Georgia Institute of Technology
P.I. - Gang Bao, Ph.D.
Director , Emory-GT, Program of Excellence in Nanotechnology
CoE Distinguished Professor
The Wallace H. Coulter Department of Biomedical Engineering
Georgia Institute of Technology
Emory University

Nanotherapy for Vulnerable Plaque
The Burnham Institute
University of California - Santa Barbara
The Scripps Institute
P.I. - Jeffrey W. Smith, Ph.D.
Professor
Director, Center on Proteolytic Pathways
Director, Program of Excellence in Nanotechnology
Burnham Institute for Medical Research

Translational Program of Excellence in Nanotechnology
Harvard University
Massachusetts General Hospital
P.I. - Ralph Weissleder, M.D., Ph.D.
Director, Center for Molecular Imaging Research
Professor of Radiology, Harvard Medical School
Massachusetts General Hospital

Integrated Nanosystem for Diagnosis and Therapy
Washington University in Saint Louis
University of California - Santa Barbara
University of California - Berkeley
P.I. - Karen L. Wooley, Ph.D.
James S. McDonnell Distinguished University Professor in Arts & Sciences
Professor, School of Arts & Sciences, Department of Chemistry
Professor, School of Medicine, Department of Radiology
Faculty member in the Center for Materials Innovation

NHLBI Inter-PEN Quarterly

MASSACHUSETTES GENERAL HOSPITAL
HARVARD UNIVERSITY

Noninvasive imaging of atherosclerotic VCAM-1 expression using targeted Nanoparticles

By Matthias Nahrendorf,
Ralph Weissleder
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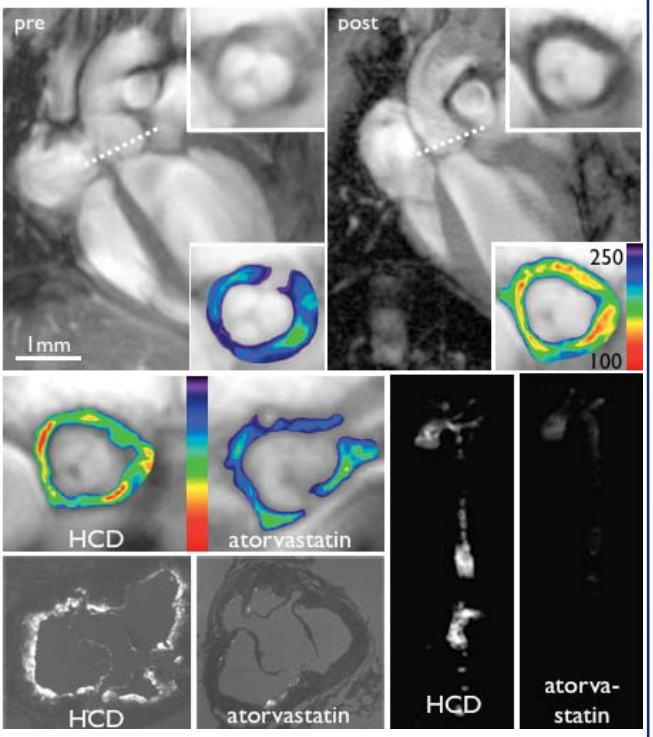
Since vascular adhesion molecule-1 (VCAM-1) is a critical component of the leukocyte–endothelial adhesion cascade and participates in a number of inflammatory diseases, including atherogenesis, we have synthesized a second generation imaging agent targeted to VCAM-1 with enhanced sensitivity due to improved agent design. This was accomplished by first utilizing *in vivo* phage screening with a linear peptide library to identify sequences of interest. The resulting peptide hit (VHPKQHR)[1] was employed to synthesize a novel agent, termed VINP-28 (for VCAM-1 Internalizing NanoParticle, phage clone #28). Improved linker chemistry and the linear peptide allowed us to now attach up to 12 targeting peptides onto one nanoparticle versus the previous cyclic agent, which contained only 2-4 peptides. By FITC-immunoassay, the new multivalent agent showed a 10-fold higher uptake into cultured endothelial cells.[1] Preincubation of VINP-28 with soluble VCAM-1 was also shown to inhibited cell uptake, establishing the specificity of the agent. VINP-28 was then employed to image VCAM-1 expression in atherosclerotic plaques of apoE$^{-/-}$ mice. Initially, we established an *in vivo* imaging protocol including optimized timing and dosage of agent injection, and implemented a highly sensitive MRI protocol on a high field scanner, using a cardiac murine surface coil and cardiac and respiratory gating. Imaging of cross sections of the aortic root, an area with high plaque prevalence in apoE$^{-/-}$ mice, was identified as the most promising approach. Using T2* weighted gradient echo cine imaging, we detected a VCAM-1 mediated contrast enhancement in the aortic root 48h after injection of VLIN-28 (Figure).[2] Lipid lowering therapy with atorvastatin was shown to reduce VLIN-28 uptake concomitant with reduction VCAM-1 protein levels, as demonstrated by Western blots. *Ex vivo* fluorescence reflectance imaging and fluorescence and immunoreactive microscopy further validated the *in vivo* findings and demonstrated VLIN-28 uptake into endothelial cells, fibroblasts and macrophages within atherosclerotic plaques depending on their VCAM-1 expression levels.[2]



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2. Nahrendorf, M.; Jaffer, F.A.; Kelly, K.A.; Sosnovik, D.E.; Aikawa, E.; Libby, P.; Weissleder, R. "Noninvasive Vascular Cell Adhesion Molecule-1 Imaging Identifies Inflammatory Activation of Cells in Atherosclerosis", *Circulation,* **2006**, Oct. 3; *114*(14), 1504-11.

Photodynamic Therapy Agent for the Treatment of Atherosclerosis

By Jason R. McCarthy,
Ralph Weissleder
(rweissleder@partners.org)

The macrophage has emerged as a key component of atherosclerotic lesions, and as such has become the target of a number of imaging and therapeutic strategies. The use of photodynamic therapy to control the macrophage content of atheromata has recently received attention, due to the ability to localize therapy and decrease plaque burden. We have therefore designed a photodynamic therapy agent based upon the conjugation of a photosensitizer to a fluorescently labeled (AlexaFluor 750) iron oxide nanoparticle.[1] The photosensitizer, 5-(4-carboxyphenyl)-10,15,20-triphenyl-2,3-dihydroxychlorin (TPC), has a singlet-oxygen quantum yield of 0.65 when excited at 646 nm. It has also proven more efficacious than the commonly used chlorin e6.[2] The resulting particles had previously displayed high affinity for atherosclerotic lesions and are actively phogocytosed by macrophages. One of the main advantages of the particles is that the wavelengths of excitation for the fluorophore and the photosensitizer are spectrally distinct, thus allowing for fluorescence imaging or therapy without excitation of the other chromophore. Localization of the nanoagent can also be determined by magnetic resonance imaging. The conjugate showed excellent, time-dependent uptake in both murine and human activated macrophages *in vitro* as determined by flow cytometry and fluorescence microscopy (Figure A and B). This uptake also corresponded to an increase in phototoxicity. Complete ablation of macrophages was demonstrated by treatment of the cells *in vitro* for 1 hour with the particles at a concentration of 0.2 mg Fe/mL, followed by light treatment (42 mW/cm^2, 7.5 J, Figure C and D). Control cells incubated with the nanoagent, but not treated with light exhibited no dark toxicity. Currently, we are exploring the utility of these particles *in vivo*, in the murine apoE -/- model. Whereas preliminary evidence has, thus far, demonstrated uptake of the PDT nanoagent within atherosclerotic lesions, photodynamic efficacy has yet to be determined and is the focus of our ongoing research.

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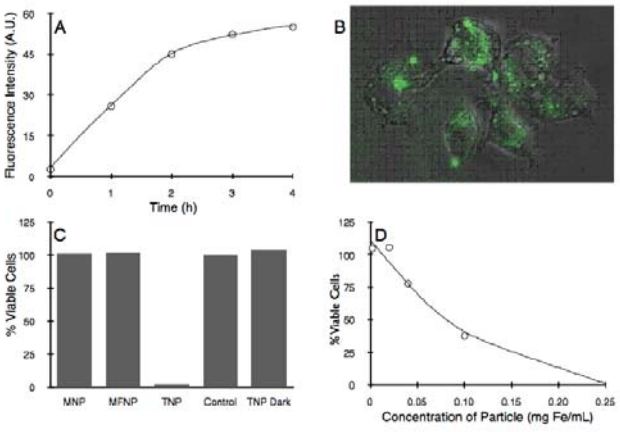

Upcoming Events

Second Annual Nanotechnology & the Life Sciences Workshop
March 30-31, 2007
Saint Louis, Missouri
www.sccne.wustl.edu

Second Annual Inter-PEN Conference
October 19-21, 2007
Santa Barbara, California

Executive Committee Meetings

March 9	September 7
June 1	December 7

NHLBI Inter-PEN Quarterly

EMORY UNIVERSITY
GEORGIA INSTITUTE OF TECHNOLOGY

Correlation between Hemodynamic Shear Stress and VCAM-1 Expression in Mouse Aorta

By Gang Bao
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The hemodynamic environment is a determinant of susceptibility to atherosclerosis in the vasculature. Although mouse models are commonly used in atherosclerosis studies, little is known about local variations in wall shear stress (WSS) in the mouse and if the levels of WSS are comparable to those in humans. We have carried out studies to determine WSS values in the mouse aorta and to relate these to expression of gene products associated with atherosclerosis[1].

Utilizing micro-CT and ultrasound methodologies we developed a computational fluid dynamics model of the mouse aorta and found values of WSS to be much larger than those for humans. We have shown that the magnitude of WSS present in the normal mouse aorta is overall much higher than in humans, consistent with concepts of allometric scaling. Indeed, peak, mean and low shear stresses are approximately an order of magnitude higher in the mouse aorta, and at the peak levels WSS can be well above values reported to cause endothelial cell disruption in acute studies in dogs and significantly larger than those computed for healthy human arteries.

We also used a quantum dot-based approach to study VCAM-1 and ICAM-1 expression on the aortic intima and demonstrated that increased expression for these molecules occurs where WSS was relatively low for the mouse. As shown for a representative mouse aorta in Figure 1, regions with enhanced VCAM-1 expression can be observed along the inner curvature of the aortic arch and at the orifices of the arch branches. This distribution correlates with the lower values of mean WSS. The lateral walls of the ascending aorta are areas where there is less VCAM-1 expression, which coincides with a relatively high mean WSS in the computational model. Conversely, the inner curvature in the aortic arch is an area of higher VCAM-1 expression and where WSS is, for the mouse, relatively low. Similar results were found for ICAM-1, another surface protein known to be regulated by shear stress.

Since the magnitude of WSS in the mouse is much larger than that observed in humans, our findings suggest that the absolute magnitude of WSS may not be the primary determinant of atherogenic gene expression and subsequent atherosclerosis. We found that, despite large differences in WSS in mouse and human, the

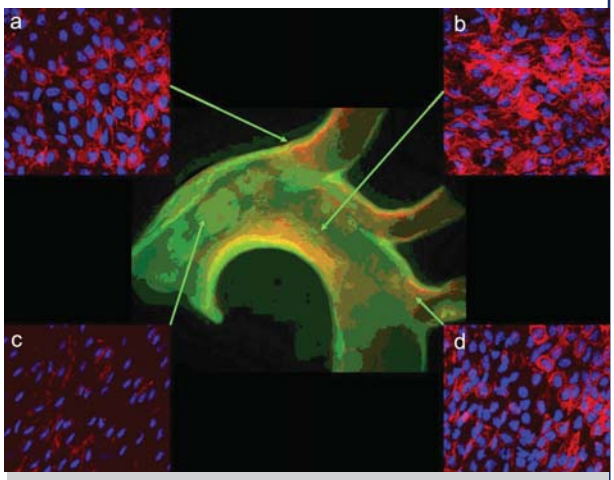

Figure 1. The differential localization of VCAM-1 protein expression is evident in the epifluorescence image of a whole aortic mount (center). Note the intense distribution of the signal from fluorophore along the inner curvature of the arch and in the orifices of the arch vessels, areas that correspond to relatively lower values of mean WSS in the CFD results. The central image corresponds to a mouse treated with lipopolysaccharide (LPS) in order to achieve fluorescence enhancement. However, the peripheral confocal pictures (a-d) were taken from specific areas of a non-LPS treated mouse using quantum dot bioconjugates targeting VCAM-1.

spatial distributions of atherogenic molecules in the mouse aorta are similar to atherosclerotic plaque localization found in human aortas. These results suggest that *relative* differences in WSS or in the direction of WSS, as opposed to the absolute magnitude, may be relevant determinants of flow-mediated inflammatory responses.

References

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WASHINGTON UNIVERSITY
UNIVERSITY OF CALIFORNIA - SANTA BARBARA
UNIVERSITY OF CALIFORNIA - BERKELEY

In vivo evaluation of new ^{64}Cu-labeled nano-structured materials

R. Rossin (rossinr@mir.wustl.edu), E.D. Pressly, K. Fukukawa, B.W. Messmore, A. Hagooly, K.L. Wooley, C.J. Hawker, M.J. Welch

The multi-disciplinary nature of nanotechnology has allowed molecular, material and medical scientists to form strong collaborative groups in order to study grand challenges and opportunities in medicine. One specific target is the development of nano-devices engineered to optimize targeting, control the uptake and release of drugs, achieve a temporal and site-specific degradation, and to decrease *in vivo* toxicity. Within this field, the goal of the NHLBI-PEN "Integrated nanosystems for diagnosis and therapy" (HL080729) is to develop nano-sized scaffolds with multivalent functionalities for diagnosis and intervention of acute pulmonary and cardiovascular injury. However, our first challenge is to optimize the pharmacokinetics of these systems to avoid the rapid clearance from the bloodstream by the mononuclear phagocytic system (MPS) upon intravenous administration. Despite considerable effort in the area of stealth drug delivery, there are no absolute rules or methods to avoid nanoparticle (NP) elimination from the circulation. NP size, composition, surface charge and polymer coating are among the parameters that can be finely tuned in order to change blood retention and clearance [1,2].

Recently, ^{64}Cu and small animal PET imaging were used to detect NPs in living tissues [3,4]. Because of its optimal nuclear properties (β^+: 0.653 MeV, 17.4%; β^-: 0.578 MeV; 39%), this versatile radionuclide produces high spatial resolution images (Figure 1) and is a promising candidate for molecular imaging and radiotherapy [5]. Furthermore, the convenient half-life (12.7 h) allows *in vivo* tracking of medium- to long-circulating macromolecules up to 48 hours post-administration.

In order to compare the bioavailability of a range of nanostructures synthesized within this NHLBI-PEN, we have developed a variety of methods to conjugate DOTA-based chelators to NPs [6]. The obtained nanoconjugates are easily radiolabeled with ^{64}Cu in high yields (30-300 μCi/μg) under

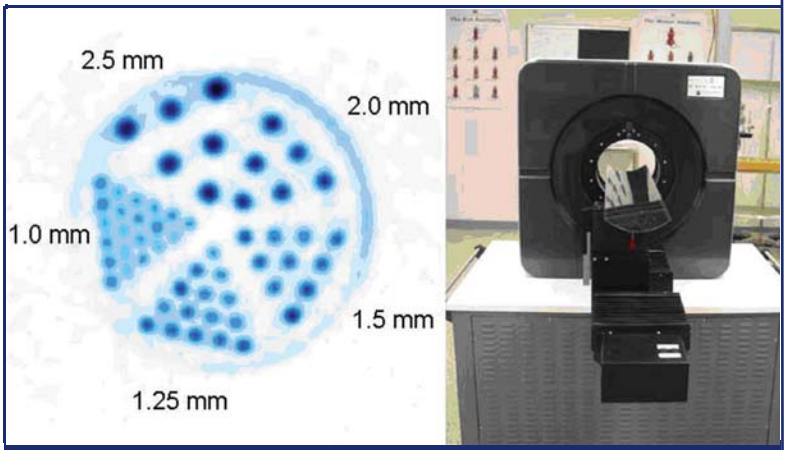

Figure 1: Mini-Derenzo phantom of ^{64}Cu (left) imaged on the microPET Focus 220 (right), CTI-Concorde Microsystems Inc

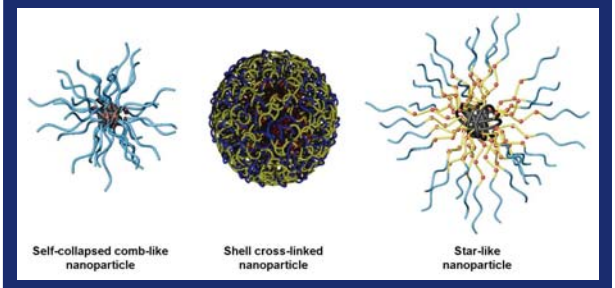

Figure 2: Representative structures of comb-like NP, shell cross-linked NP, and star-like NP

mild reaction conditions. A short comparative evaluation of three different nanostructures (Figure 2) in normal rodents was presented recently [7]. Since surface PEGylation is the preferred method to "hide" particles from macrophages *in vivo* [1,2], the three NPs were functionalized with PEG_{2000}. Interestingly, the three different systems exhibited a different hepatic clearance, reasonably due to different size and composition. Similarly, a markedly different splenic uptake and release were also observed and the star-like NP showed the highest blood retention up to 4 hours post-injection, suggesting its possible use as a drug delivery system. Prolonged blood circulation was also confirmed by small animal PET imaging (Figure 3). In fact, the heart was

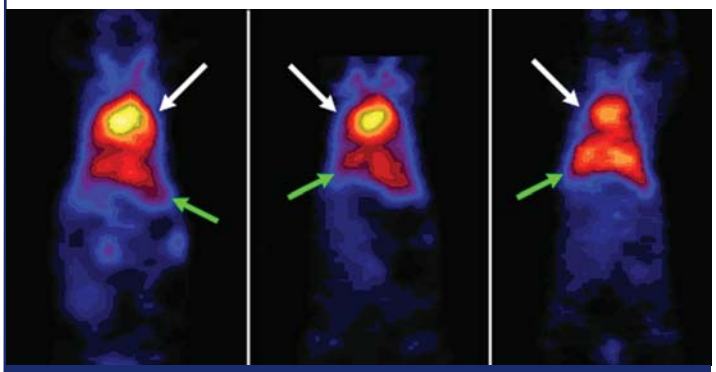

Figure 3: MicroPET images (coronal slices) of a Balb/C mouse administered with ^{64}Cu-labeled star-like NP at 1h (left), 4h (center), and 24 h (left) post-injection. White and green arrows indicate heart and liver, respectively.

clearly imaged up to 24 h post-injection due to radioactive particles in the bloodstream [6]. These data confirm the need for a detailed *in vivo* evaluation of NPs, as bioavailability and pharmacokinetics cannot be predicted by physico-chemical properties such as size, charge, surface chemistry. To this aim, ^{64}Cu-labeling and imaging/biodistribution techniques are powerful tools, as they allow the tracking of NPs in living tissues. Our next step will be the evaluation of these sophisticated materials for multivalent detection, diagnosis, and intervention of disease states.

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THE BURNHAM INSTITUTE
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Engineering Shape of Polymeric Microparticles for Drug Delivery

By Julie Champion, Samir Mitragotri, Jeffrey W. Smith
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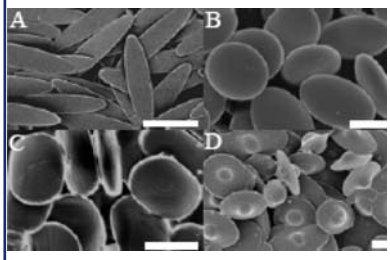
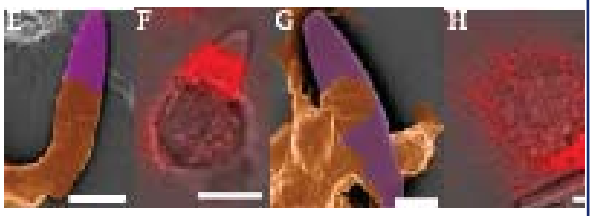
Encapsulation of therapeutic drugs in polymeric particles offers significant advantages over conventional formulations such as sustained release, drug protection, and increased bioavailability. Particles can be targeted to specific tissues for local drug delivery, making them ideal for delivery to atherosclerotic plaques. Several properties of particles, including shape, size, and surface chemistry, influence their performance in drug delivery applications. Previous research has focused on particle surface chemistry and size. The role of particle shape has not been determined for these processes due to difficulty in fabricating non-spherical particles. We successfully fabricated particles with over 20 distinct geometries (Figs. A-D, scale 5μm). Shapes are formed by stretching polystyrene spheres embedded in a polymer film combined with heat or solvent treatment. Particle dimensions and aspect ratio are tuned by initial sphere diameter and degree of stretching.

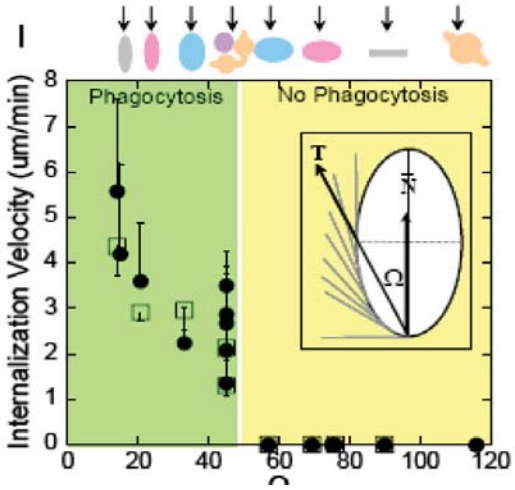


Particle shape could affect a variety of drug delivery properties including circulation time, targeting ability, drug release, and susceptibility to phagocytosis. Phagocytosis is an actin-dependent process of the innate immune system in which macrophages internalize large (> 0.5μm) particulate targets. It is one of the primary obstacles of particulate drug delivery systems. We investigated the effect of particle shape on phagocytosis using timelapse video microscopy, scanning electron microscopy and actin staining. Internalization of particles exhibited a strong dependence on local particle shape from the perspective of the phagocyte. For example, macrophages that attached to elliptical disk particles (EDs) at the narrow end, internalized them very quickly, in several minutes, and exhibited actin structures characteristic of phagocytosis (Figs. E, F,



scale 10 μm). Alternately, cells that attached to the same EDs along the flat side did not internalize them or show coordinated actin structures, even after 12 hours (Figs. G, scale 10 μm, H, scale 5 μm). Similar results are seen for all shapes and sizes clearly showing that the local particle shape at the point of initial contact, not overall size, determined their phagocytic fate.

To quantify the role of shape in phagocytosis, we defined Ω as the angle between the membrane normal at the point of initial



contact, $\overline{N}$, and a vector $\overline{T}$ (Fig. I inset). The angle of $\overline{T}$ represents the mean direction of tangents drawn to the target contour from the point of initial contact to the center line of the target. Internalization velocity (distance traveled by cell membrane to complete

phagocytosis divided by elapsed time) of both IgG opsonized (□) and non-opsonized (●) particles decreased with increasing Ω (Fig. I, arrows and shapes indicate point of attachment for each Ω). At Ω ~ 45° there is an abrupt transition in internalization velocity to zero, indicating phagocytosis was not attempted. Particle size only impacts completion of phagocytosis when particle volume exceeds cell volume.

Particle shape plays a crucial role in phagocytosis and is expected to affect other aspects of drug delivery as well. In collaboration with the PEN team, future work involves targeting these particles to activated platelets to study the effect of shape on targeting and attachment. Particle shape presents a new dimension in drug delivery particle design to treat atherosclerosis and a variety of other diseases.

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Making a difference

COMMUNITY OUTREACH

NanoKids 2006

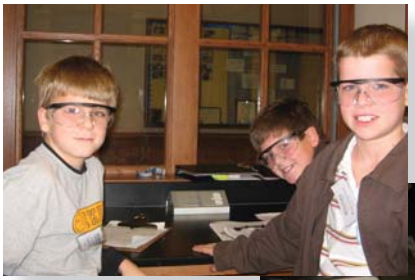
SCIENCE EDUCATION AND OUTREACH: WASHINGTON UNIVERSITY AND BEYOND

By Kenya T. Powell (ktpowell@artsci.wustl.edu), Karen L. Wooley

November 2006

Washington University Chemistry Department

Students from several local schools were given an overview of nanotechnology and polymer chemistry. All equipment, materials and supplies were provided to the students, as well the experiment procedure and notebook.



FIRST LEGO League

This outreach activity was conducted to facilitate the student's understanding of nanotechnology through a hands-on, legitimate research experience in cooperation with participants of FIRST LEGO League of St. Louis, MO.

The activity was provided for 20 students with strong participation by LEGO League organizers and parents. The students were provided with a nanotechnology/Polymer Chemistry Workbook (which included introductions on nanotechnology, polymer chemistry, and a laboratory notebook pages), goggles, and a take-home science-starter kit.

Outreach works! The students who participated in Nanokids 2006 advanced to win the Research division of the FIRST LEGO League's tournament held in December of 2006. They credited their win with the experience of working hands-on in the laboratory.

WASHINGTON UNIVERSITY IN SAINT LOUIS
SKILLS DEVELOPMENT

Program of Excellence in Nanotechnology (PEN): *Skills Development Component*

By Monica Shokeen,
Carolyn J. Anderson
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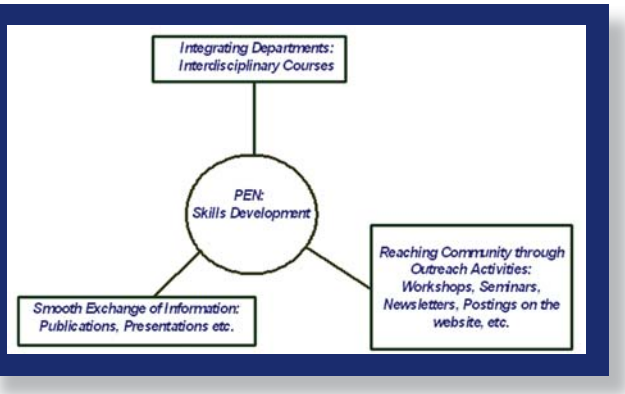
The broad aim of the Skills Development Component of the WU PEN is to promote cross disciplinary education and training of medical and materials scientists. This goal is currently being realized by development of a formal curriculum in the areas of nanotechnology and imaging sciences. Through new and existing courses, together with cross-disciplinary research experiences, the next generation of scientists and clinicians are being mentored and trained to use nanotechnology in the treatment of disease. These individuals are taught to integrate nanoscience, nanotechnology, biology and medicine creatively and proficiently.



The Skills Development Component also involves rigorous dissemination and translation of nanotechnology developments to the scientific and general community *via* publications, workshops, talks and web-based formats.

Through new and existing courses, together with cross-disciplinary research experiences, the next generation of scientists and clinicians are being mentored and trained to use nanotechnology in the treatment of disease.

Accomplishments:

The Skills Development Component is making steadfast progress in accomplishing the aforesaid goals. New courses based on nanoscience are being designed and offered. The structure and content of the courses appeal to both graduates and undergraduates from different fields of science. The diversity of the curriculum is an invaluable addition to the graduate/undergraduate course profile. In addition to the courses offered, the Skills Development Component is making solid efforts to reach out to the scientific and general community *via* outreach programs. Some of the strides made in since May, 2005 are as follows:

1) Nanomedicine course: Special Topics in Organic Chemistry: Nanomedicine (Chemistry 555; Fall, 2006). Course Master: Karen L. Wooley

♦ This course focused on recent advances made in the field of nanotechnology, from fundamental principles to designs for medical applications.

♦ The course was taught in a survey fashion with lectures given by several professors who highlighted the recent progress made in their areas of expertise such as PET imaging, MRI, Optical Imaging, *etc*.

♦ The course received encouraging participation from both undergraduates and graduates. There were total of 24 students enrolled (22 credit, 2 audit). The class was truly interdisciplinary in nature with students from Biomedical Engineering, Anthropology, Chemistry, Biology, French, Energy, Environmental and Chemical Engineering, and Biochemistry.

♦ **Distance learning component:** One of the highlights of the course was that it was available to all the students participating in the NHLBI PEN initiative. Students from UCSB and Georgia Tech/Emory attended the lectures

live *via* teleconferencing. All the lectures were videotaped and made available to participating students and professors *via* WebCT (web based resource). The PowerPoint presentations and readings were also made available through Washington University's Telesis.

♦ **Student participation**: The style of the course encouraged active student participation. The students were divided into groups of their interests and the teams made presentations on current literature during the class. The quality of the presentations was above par!

2) **Imaging curriculum:** A series of courses are also being offered through the imaging sciences curriculum. These courses focus on the principles and applications of biological imaging and complement the nanomedicine based courses.

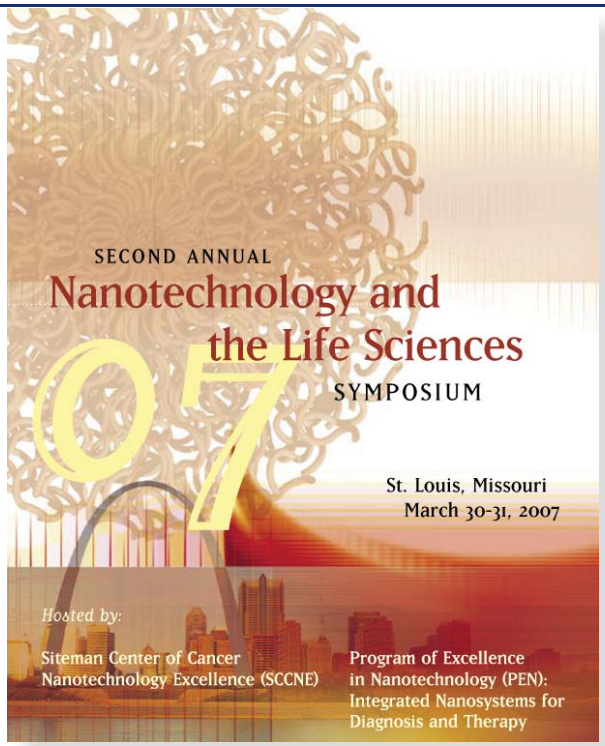
♦ The first course was taught in Spring, 2006 (Biology 5146: Principles and Applications of Biological Imaging). **Course Master: Carolyn J. Anderson.**

♦ Two new courses are being offered in Spring, 2007: Contrast Agents in Biological Imaging (Biology 5147; Chemistry 5147), **Course Master: Carolyn J. Anderson**; and Biological Imaging Technology (ESE 489/589), **Course Master: Joe Culver**.

3) **Nanomedicine Workshop: An outreach initiative!**

The Skills Development Component is working vigorously toward the knowledge dissemination to the community as a whole. One significant step in this direction is a scientific symposium organized in collaboration with the Siteman Center of Cancer Nanotechnology Excellence (SCCNE) to review progress in the application of nanotechnology for the diagnosis, treatment and prevention of cardiovascular disease and cancer.

Two new courses are being offered in Spring 2007:
Contrast Agents in Biological Imaging
and
Biological Imaging Technology



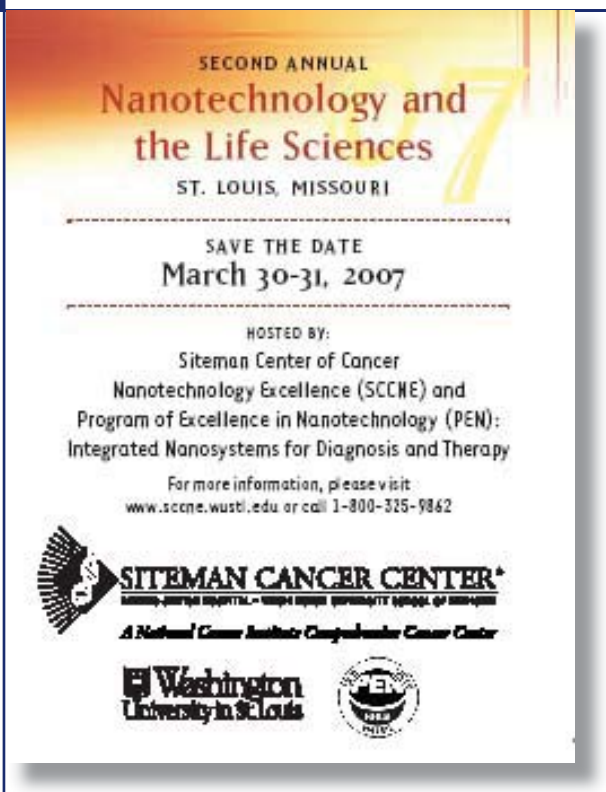
The key features of the workshop are as follows:

♦ This will be a one and a half day intensive program to educate participants in the current science in nanotechnologies. Oral and poster presentations will be made by leading experts, local university faculty, and students.

♦ The symposium is designed to raise awareness and increase the knowledge level of individuals for nanotechnology and to encourage dialogue between the nanotechnology and clinical scientists.

♦ The workshop will highlight the current state-of-the-art on the field of study to develop nanoscale materials to impact the life sciences.

♦ The workshop should be of interest to professionals working in the applied fields of medicine, radiology, pharmacology, chemistry, chemical engineering, materials science, polymer engineering, biochemistry, bioengineering, biomedical engineering and physics.



Invited speakers -

Jan E. Schnitzer, M.D. Sidney Kimmel Cancer Center, San Diego, California "Proteomic Profiling of Endothelium & its Caveolai to Target Organs and Solid Tumors: Overcoming *In Vivo* Barriers to Nanoparticle Delivery"

Eric Jakobsson, Ph.D. Beckman Institute for Advanced Science and Technology, University of Illinois "Self-Assembled Membranes on Nanoporous Substrates"

Rudy Juliano, Ph.D. Department of Pharmacology, School of Medicine, University of North Carolina "Nanotechnology and Nucleic Acid Based Therapeutics: The Perfect Marriage"

Gang Bao, Ph.D. Department for Biomedical Engineering, Georgia Institute of Technology and Emory University "Nanostructured Probes for Live Cell Gene Detection"

Jeff Bulte, Ph.D. Institute for Cell Engineering, Johns Hopkins University of Medicine "The Use of Nanoprobes and Nanopores in MRI Cell Tracking"

Stanley Shaw, M.D., Ph.D. Cardiology Division, Chemical Biology, Harvard and MIT "Cell-based Phenotypes Based on Response to Systemic Perturbation: Nanoparticle Toxicity Profiling"

Dennis Discher, Ph.D. Biophysical & Polymer Engineering, University of Pennsylvania "Polymersomes and Filomicelles - Imitation of Viral Morphologies for Controlled Release Drug Delivery"

M. Fredrick Hawthorne, Ph.D. International Institute of Nano and Molecular Medicine University of Missouri -Columbia, MO "Applications of Polyhedral Boranes in Nano and Molecular Medicine"

Speakers from the PENs

(Gang Bao, Ph.D. - see above)

Adah Alumaitari, Ph.D. University of California - Berkeley "Designing Nanoscale Delivery Vehicles for Bioactive Agents"

Jungie Chen, D.Sc. Washington University, St. Louis, MO "Targeting Stem Cell with Nanoparticles for Medical Imaging"

Raffaella Rossin, Ph.D. Washington University in Saint Louis "Nanotechnology for Imaging and Imaging for Nantechnology: *In vivo* evaluation of new radiolabeled stealth nanocarriers"

John-Stephen Taylor, Ph.D. Washington University in Saint Louis "PNA-based Agents for Imaging Gene Expression"

NHLBI Inter-PEN Quarterly

JOB OPPORTUNITIES

Within the four PENs

Center for Molecular Imaging Research

Position: Postdoctoral Fellow

Research Area: Chemistry

Labs: Dr. McCarthy and Dr. Hilderbrand

Description: The Center for Molecular Imaging Research (http://cmir.mgh.harvard.edu) at the Massachusetts General Hospital and Harvard Medical School is recruiting a post-doctoral fellow for research in the synthesis and development of nanoparticulate delivery systems for the imaging and therapy of numerous disease states. We are expanding our chemistry facilities and are looking for scientists with experience in polymer and/or organic chemistry who will be interested in the development of biologically applicable nanoagents. CMIR is a diverse facility; therefore, we offer excellent training opportunities in a collaborative research environment including biology, chemistry, and imaging disciplines.

Requirements: The candidate (PhD or equivalent) should have experience in polymer and/or organic chemistry, familiarity with peptides, and an understanding of nanotechnology.

Position: Postdoctoral Fellow

Research Area: Implication Of Monocyte/Macrophage Subsets in Tumorigenesis

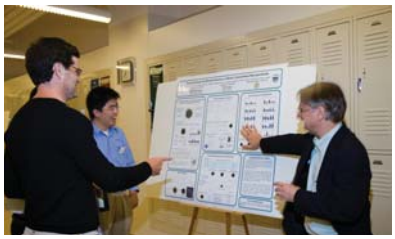
Lab: Dr. Pittet

Description: The research projects are focused on understanding the recruitment, fate and activity of monocytes (*i.e.*, macrophage precursors) in a mouse model of local and metastic lung cancer, and to determine the effects of monocyte/tumor-associated macrophage depletion on tumor progression and metastases. The discovery effort will utilize novel cell tagging probes and recently developed three-dimensional non-invasive in vivo imaging approaches. The research projects are part of the Cellular Imaging Program at CMIR.

Requirements: The candidate (PhD or MD) should have experience in cell and molecular biological techniques, as well as publications in the field of immunology. We offer excellent training opportunities in a collaborative research environment including immunology, chemistry and imaging disciplines. Salary is provided for 2 years.

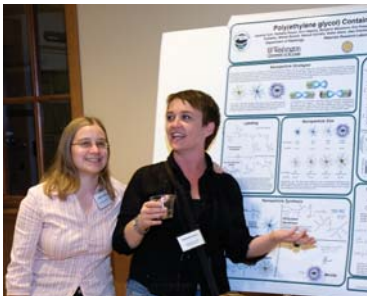
Further information and several other positions can be found at http:/cmir.mgh.harvard.edu/

Please send your application to (please specify position): Serena Laft, sdlaft@PARTNERS.ORG
CMIR, MGH, 149 13th Street, Room 5407; Charlestown, MA 02129-2060.



LOOKING BACK ... OCTOBER 2006

Thanks to all who participated in this weekend of knowledge sharing. Many excellent suggestions for improving the PENs were discussed and are now being implemented, namely: more research collaborations within the PENs, multi-lab co-authorship as well as between the PENs, and also this new quarterly newsletter. Please remember to forward all published manuscripts to Eileen Cler at (eacler@wustl.edu) so they can be added to the Inter-PEN website.



Slides from the First Annual Inter-PEN can be viewed by PEN members at http://cmir.mgh.harvard.edu. Contact Eileen Cler for userid and password.

MARK YOUR CALENDARS
FOR THE
SECOND ANNUAL INTER-PEN CONFERENCE
IN
SANTA BARBARA, CALIFORNIA
OCTOBER 19-21, 2007

The Second Annual Inter-PEN Conference will be hosted by Principal Investigator, Jeffrey W. Smith, of The Burnham Institute for Medical Research - University of California in Santa Barbara. We hope to see all PEN researchers there, so please be sure to "Save the Date" for **October 19-21, 2007** on your calendar now. We look forward to hearing about the latest research with each of the four PENs.

NHLBI Inter-PEN Quarterly
www.nhlbi-pen.net

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