EMSL Quarterly Highlights Report

3rd Quarter, Fiscal Year 2009

(April 1, 2009, through June 30, 2009)

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EMSL Quarterly Highlights Report, 3rd Quarter, Fiscal Year 2009

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July 2009

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Richland, Washington 99352

EMSL—the Environmental Molecular Sciences Laboratory—is a U.S. Department of Energy (DOE) national scientific user facility located at Pacific Northwest National Laboratory (PNNL) in Richland, Washington. EMSL is operated by PNNL for the DOE Office of Biological and Environmental Research. At one location, EMSL offers a comprehensive array of leading-edge resources and expertise.

Access to the instrumentation and expertise is obtained on a peer-reviewed proposal basis. Users are participants on accepted proposals. Staff members work with users to expedite access. The EMSL Quarterly Highlights Report documents research and activities of EMSL staff and users.

Research Highlights

Biological Interactions and Dynamics

Global Systems-Level Analysis of Hfq and SmpB Deletion Mutants in *Salmonella*: Implications for Virulence and Global Protein Translation

C Ansong[a], H Yoon[b], S Porwollik[c], H Mottaz-Brewer[d], BO Petritis[a], N Jaitly[a], JN Adkins[a], M McClelland[c], F Heffron[b], and RD Smith[a]

(a) *Pacific Northwest National Laboratory, Richland, Washington*
(b) *Oregon Health and Sciences University, Portland, Oregon*
(c) *The Sidney Kimmel Cancer Center, San Diego, California*
(d) *EMSL, Richland, Washington*

One of the most complete analyses of global post-transcriptional regulatory mechanisms in any organism indicates that post-transcriptional regulation plays an unexpectedly prominent role in the bacteria Salmonella's *ability to infect its host. Post-transcriptional regulation is the control of protein synthesis by genes after RNA synthesis has begun.*

The analyses, performed by scientists from Pacific Northwest National Laboratory, Oregon Health Sciences University and The Sidney Kimmel Cancer Center were described in the online journal *PLoS One*. The team investigated the proteome of *Salmonella* Typhimurium mutant strains lacking specific RNA-binding proteins that mediate the translation of RNA into protein (post-transcriptional control) and the parent strain. Specifically, the team investigated the *Salmonella* RNA-binding virulence proteins Hfq and SmpB. The team then compared the proteomics data to sample-matched transcriptomics data to characterize the global control of gene expression at the post-transcriptional level (Figure 1). "Sample-matched" means that RNA for transcriptomics analysis and protein for proteomics analysis were prepared from the same sample.

The comparison revealed that a relatively high percentage of all the annotated *Salmonella* genes (≥20%) are regulated post-transcriptionally. The extent of post-transcriptional regulation observed is much greater than previously thought with profound effects in all stages of *Salmonella's* life cycle. These include known and novel virulence factors.

Hfq and SmpB are proteins essential for virulence in a wide range of pathogenic bacteria including *Salmonella*, a leading cause of foodborne illness. *Salmonella* Typhimurium was the bacterium of interest in the recall of peanut butter crackers in 2008 and 2009. Understanding how Hfq and SmpB impact *Salmonella's* virulence is important for protecting human health and agriculture.

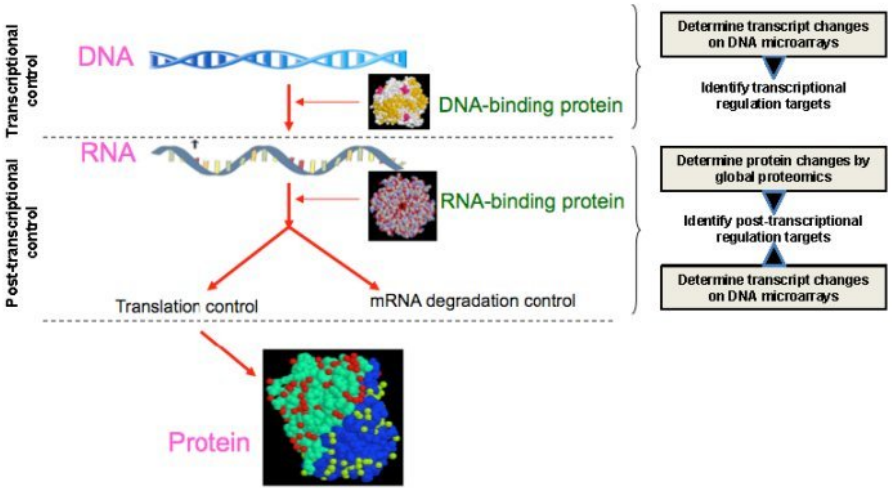

Figure 1. *Sample matched proteomics-transcriptomics measurement capabilities now make it possible to quantitatively characterize global post-transcriptional control mechanisms. RNA-binding proteins mediate post-transcriptional control. Quantitative global proteomics measurements determine the protein-dependent changes in protein expression and sample-matched transcriptomics analysis reveals if the change in protein expression is mediated post-transcriptionally.*

While the role that DNA-binding proteins play in regulating gene expression at the transcriptional level is well studied, how RNA-binding proteins control gene expression at the post-transcriptional level is less clear. The team's work provides one of the first quantitative global analyses of the role RNA-binding proteins play in regulating gene expression and makes a significant contribution to knowledge of this regulatory process.

The researchers used capillary liquid chromatography-mass spectrometry analyses to analyze the proteomes of *Salmonella* mutant strains lacking specific RNA-binding proteins that mediate the translation of RNA into protein (post-transcriptional control) and the parent strain grown under four different conditions. They then applied the accurate mass and time tag strategy developed at PNNL to quantitate proteins in the samples. They employed whole genome microarray analysis to perform sample-matched transcriptome analyses. Bioinformatics approaches were then used to compare the proteomics data to sample-matched transcriptomics data to identify targets of post-transcriptional control and provide quantitative information on changes in the expression pattern of targets at the level of translation.

The genomes of most living organisms including all animals, plants and bacteria encode a large number of RNA-binding proteins with increasing evidence pointing to their extensive involvement in post-transcriptional regulatory events. The work described here has established the framework for the future systematic characterization of the global program and molecular mechanisms of post-transcriptional regulation of gene expression in any genetically tractable organism.

This research was supported by the National Institute of Allergy and Infectious Diseases, and the National Center for Research Resources.

Citation

Ansong C, H Yoon, S Porwollik, H Mottaz-Brewer, BO Petritis, N Jaitly, JN Adkins, M McClelland, F Heffron, and RD Smith. 2009. "Global Systems-Level Analysis of Hfq and SmpB Deletion Mutants in *Salmonella*: Implications for Virulence and Global Protein Translation." *PLoS ONE* 4(3):e4809.

A Targeted Releasable Affinity Probe (TRAP) for *in vivo* Photo-Crosslinking

P Yan[a], T Wang[b], GJ Newton[c], TV Knyushko[d], Y Xiong[b], DJ Bigelow[b], TC Squier[b], and M Uljana Mayer[b]

(a) *Novozymes, Inc., Davis, California*
(b) *Pacific Northwest National Laboratory, Richland, Washington*
(c) *The University of Tokyo, Tokyo, Japan*
(d) *Harris IT Services, Bethesda, Maryland*

DNA might be the blueprint for living things, but proteins are the builders. Researchers trying to understand how and which proteins work together have developed a new cross-linking tool that is small and unobtrusive enough to use in live cells. Using the new tool, the scientists have discovered new details about a well-studied complex of proteins known as RNA polymerase. The results suggest the method might uncover collaborations between proteins that are too brief for other techniques to pinpoint.

Proteins are the workhorses in an organism's cells. Whole fields of research are dedicated to teasing out which proteins work together to make cells function. For example, drug researchers seek chemicals that disrupt or otherwise change how proteins interact to combat diseases; environmental scientists need to understand how proteins collaborate in ecosystems to make them thrive or fail.

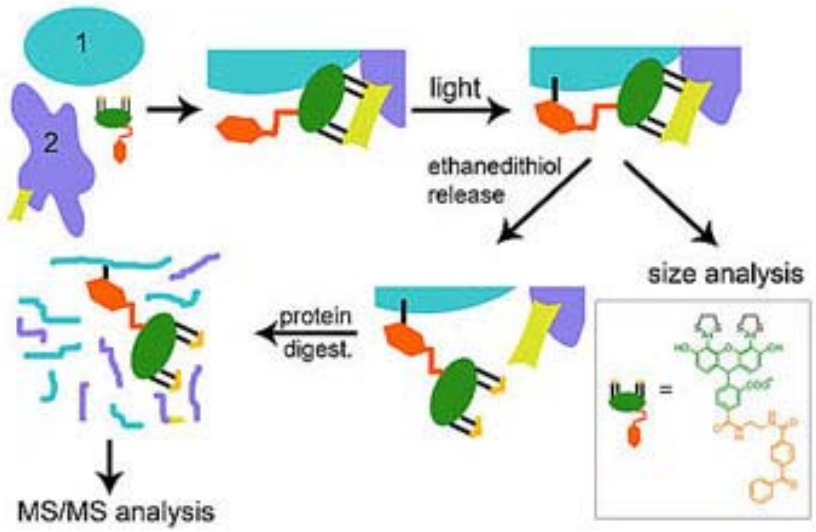

Figure 1. *TRAP (in green, orange and yellow) binds to a tag on known protein (#2). Light crosslinks TRAP's benzophenone to mystery protein (#1). Subsequent biochemical analysis reveals clues to unknown protein (#1).*

To learn about protein networks, scientists start with a familiar one and use it as bait to find others that work alongside it. To pin down the collaborators, researchers make physical connections between old and new proteins with chemicals called crosslinkers. The sticky crosslinkers will only connect proteins close enough to work together, the thinking goes. But most crosslinkers are too large to squeeze into living cells, are harmful to cells, or link proteins that are neighbors but not coworkers.

To address these issues, the research team developed a crosslinking method that uses small crosslinkers whose stickiness can be carefully controlled. To find coworkers of a protein of interest, they built a tiny molecule called a tag into the initial protein. They then add a small molecule called TRAP to the living cell, which finds and fits into the tag like two pieces in a puzzle. TRAP waves around, bumping into nearby proteins. The scientists control TRAP with a flash of light, causing it to stick to coworkers it bumps into. The researchers then identify the new "TRAPped" proteins in subsequent analyses (Figure 1).

To demonstrate how well this method works, the team tested it out on RNA polymerase, a well-studied machine in cells. The polymerase is made up of many proteins that cooperate to translate DNA. One of the polymerase proteins has a tail that is known to touch the DNA and some helper proteins just before the polymerase starts translating. No one knew if this tail -- also known as the C-terminus of the alpha subunit -- touches anything else in the core of the RNA polymerase complex.

The team engineered a tag in the C-terminus and cultured bacteria with the tagged RNA polymerase. After adding TRAP to the cells and giving it time to find the C-terminus tag, the team shined a light on the cultures.

The team then identified the proteins marked with TRAP using instruments in EMSL. They found that the tagged protein, as expected, interacts with many other proteins, for example previously identified helper proteins, so-called transcription factors. But they also found it on another core protein called the beta subunit, suggesting the tail of the alpha subunit makes contact with the beta subunit as it plugs along. This interaction had never been seen before.

The team reported their results in the journal *ChemBioChem*. The tag in their unique method is made up of a "tetracysteine motif" -- two pairs of the amino acid cysteine separated by two other amino acids that doesn't interfere with the normal function of the protein of interest. TRAP includes a small "biarsenical" probe, which fluoresces so the team can find the proteins to which it has become attached. TRAP can also be easily unlinked from the tag with a simple biochemical treatment, allowing researchers to piece out the coworker from their original protein of interest.

The team also tested the method on other proteins, such as those found in young muscle cells. Mayer said they will use the method in the future to understand how environmental conditions affect how proteins work together in large networks.

The research is funded by DOE's Office of Biological and Environmental Research.

Citation

Yan P, T Wang, GJ Newton, TV Knyushko, Y Xiong, DJ Bigelow, TC Squier, and MU Mayer. 2009. "A Targeted Releasable Affinity Probe (TRAP) for *in vivo* Photo-Crosslinking." *ChemBioChem* 10:1507 –1518.

An Integrated Top-Down and Bottom-Up Strategy for Broadly Characterizing Protein Isoforms and Modifications

S Wu[a], NM Lourette,[a] N Tolic,[b] R Zhao,[b] EW Robinson,[b] AV Tolmachev,[a] RD Smith,[a] and L Pasa-Tolic[b]

(a) *Pacific Northwest National Laboratory, Richland, Washington*

(b) *EMSL, Richland, Washington*

An integrated top-down bottom-up proteomics strategy, as developed by a team of EMSL users and researchers, could play a critical role in identifying and characterizing biomarkers of cancer, cardiovascular disease, neurological disease, diabetes, and autism.

Researchers at Pacific Northwest National Laboratory and EMSL used EMSL resources to develop an innovative approach that integrates two fundamental proteomic strategies for protein identification and characterization by mass spectrometry (Figure 1). The approach overcomes the limitations of the traditional

top-down and bottom-up strategies, allowing for high-throughput analysis of protein isoforms and genetic variance through amino acid modifications, such as acetylation and phosphorylation.

Bottom-up sequencing is the analysis of trypsin-digested proteins and is the basis for contemporary proteomics. However, researchers are limited by the bottom-up approach because complete sequence coverage of proteins is rarely achieved. Top-down analysis involves direct analysis of intact proteins without digestion. But it suffers from limited throughput and has a low success rate when used with online liquid chromatography-tandem mass spectrometry and online fraction collection. By combining top-down and bottom-up approaches, scientists can achieve more precise identification and characterization of protein isoforms and combinatorial post-translational modifications.

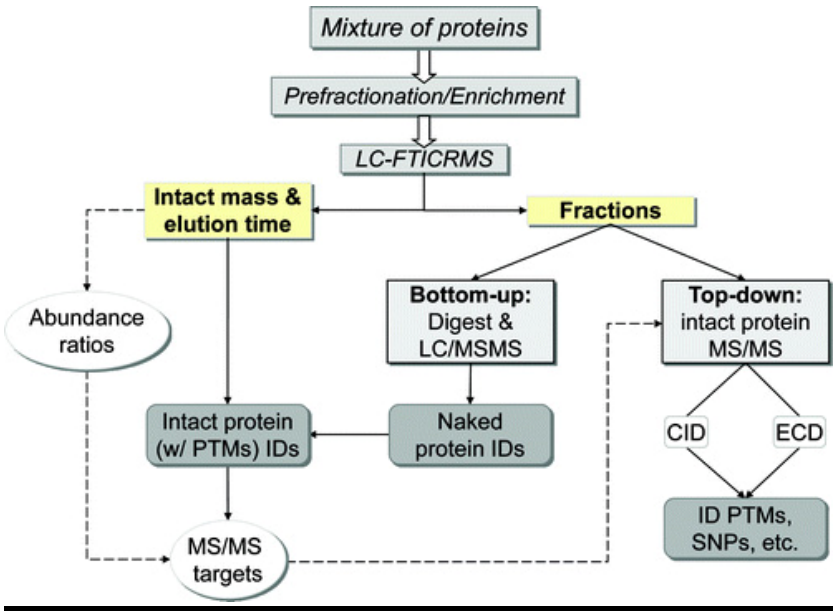

Figure 1. *Integrated top-down and bottom-up strategy for characterizing protein isoforms and modifications*

The researchers demonstrated their integrated strategy by coupling reversed-phase liquid chromatography with a 12-Tesla Fourier transform ion cyclotron resonance mass spectrometer and online fraction collection. They identified modified proteins by applying intact protein masses with "bare" proteins from the bottom-up analysis of the collected fractions. Integrated proteomics opens up new areas in the profiling of potential biomarkers that may be used to diagnose disease and is a more comprehensive approach to protein identification and profiling, allowing for high-throughput characterization of intact proteins and their modifications.

This work was supported by the National Center for Research Resources, the National Institute of Allergy and Infectious Diseases, the National Institute of General Medical Sciences, and DOE's Office of Biological and Environmental Research. It was featured *in Journal of Proteome Research.*

Citation

Wu Si, M Lourette, N Tolic, R Zhao, E Robinson, AV Tolmachev, RD Smith, and L Pasa-Tolic. 2009. "An Integrated Top-Down and Bottom-Up Strategy for Broadly Characterizing Protein Isoforms and Modifications." *Journal of Proteome Research* 8(3):1347-1357. DOI: 10.1021/pr800720d

Platelet Proteome Changes Associated with Diabetes and during Platelet Storage for Transfusion

DL Springer,[a] JH Miller,[b] SL Spinelli,[c] L Pasa-Tolic,[d] SO Purvine,[d] DS Daly,[a] RC Zangar,[a] S Jin,[b] N Blumberg,[c] CW Francis,[c] MB Taubman,[c] AE Casey,[c] SD Wittlin,[c] and RP Phipps[c]

(a) *Pacific Northwest National Laboratory, Richland, Washington*
(b) *Washington State University-Tri-Cities, Richland, Washington*
(c) *University of Rochester School of Medicine and Dentistry, Rochester, New York*
(d) *EMSL, Richland, Washington*

About 18 million people in the United States have type 2 diabetes, and the disease is spreading with the epidemic of obesity. Amid emerging concerns that blood platelets donated for transfusion by individuals with Type 2 diabetes may be unsafe, scientists are reporting the first detailed identification and quantification of proteins in the platelets from diabetic donors. The study could lead to screening tests to detect and monitor these "high risk platelet preparations," say EMSL users from Pacific Northwest National Laboratory, Washington State University-Tri-Cities, and the University of Rochester. Their study appeared in the May issue of the Journal of Proteome Research.

Thousands of patients receive potentially lifesaving transfusions of platelets each year to treat bleeding from trauma and for a wide range of medical conditions. Scientists have known that activated platelets in the blood of diabetics may predispose these individuals to heart disease. This led to the concern that platelets from these individuals stored for transfusion may be less effective and even unsafe. However, scientists know little about how diabetic platelets differ from those of healthy people.

In this study, Dr. David Springer, a biochemist at PNNL, and colleagues identified 122 proteins whose abundances differ in the platelets of individuals with diabetes compared to the platelets of non-diabetics. They also found that freshly collected platelets from diabetics show almost as many changes (more than 100) in protein abundance as healthy donor platelets stored for up to 5 days. These findings could lead to new tests for detecting and monitoring abnormal platelets to improve the outcome of blood transfusions from both diabetic and healthy individuals.

The researchers used EMSL mass spectrometry-based proteomics on platelets from healthy and type 2 diabetics collected at the University of Rochester Blood Bank. They also investigated the role of transfusion storage, including diabetes effects on the platelet proteome. Their approach enabled highly sensitive detection of a variety of molecular species in platelets from diabetics.

This work was supported by the National Institutes of Health.

Citation

Springer DL, JH Miller, SL Spinelli, L Paša-Tolic, SO Purvine, DS Daly, RC Zangar, S Jin, N Blumberg, CW Francis, MB Taubman, AE Casey, SD Wittlin, and RP Phipps. 2009. "Platelet Proteome Changes Associated with Diabetes and during Platelet Storage for Transfusion" *Journal of Proteome Research* 8(5):2261-2272.

Engineering an Ultra-Stable Affinity Reagent Based on Top7

CB Boschek,[a] DO Apiyo,[a] TA Soares,[a] HE Engelmann,[a] NB Pefaur,[a] TP Straatsma,[a] and CL Baird[a]

(a) *Pacific Northwest National Laboratory, Richland, Washington*

$Top7_{CB1}$, designed by EMSL users from the Pacific Northwest National Laboratory, is a synthetic protein that can specifically bind a protein targeted by the human immunodeficiency virus, or HIV, that can lead to AIDS. $Top7_{CB1}$ can also be used as an inexpensive and effective alternative to antibodies. The work is the cover story in the May 2009 issue of Protein Engineering Design & Selection *(Figure 1).*

Antibodies are one of the weapons used to fight disease or detect harmful substances. These proteins are one of the most commonly used reagents in the laboratory because they can be used to bind, recognize and quantify specific targets, such as toxins or proteins that specify different disease states.

Antibodies can be generated against virtually any target by immunization or by *in vitro* selection. However, they are large and frequently unstable, which makes them difficult to use for many practical applications. As a result, scientists are working to engineer smaller antibody fragments that remain specific and stable while being easy to produce. But again, designing these engineered fragments to be structurally robust while retaining their binding specificity has been difficult.

An emerging alternative is the use of intrinsically stable proteins as scaffolds for the generation of novel binding agents instead of generating natural or engineered antibodies. In fact, these novel scaffolds could be used in adverse environments such as those found in parts of the human body or in industry, where antibodies fail.

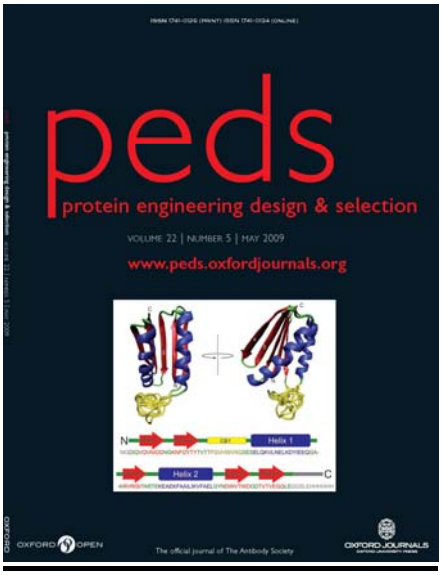

Figure 1. *This research was featured on the cover of the May 2009 issue of* Protein Engineering Design & Selection.

The aim of the study was to design a highly stable affinity reagent—a specific binding molecule—based on the synthetic protein Top7 to assess its viability as a general affinity scaffold. Top7 is a small protein computationally designed by University of Washington scientists to be extremely stable. Its small size, known structure and very stable configuration make it an ideal scaffold for an affinity reagent.

The researchers selected a site in Top7 to insert CB1, a peptide constructed from a well-characterized peptide, PDP-CB1, that comes from a region of an anti-CD4 antibody. CD4 is a protein on the surface of immune cells that helps protect against infections such as HIV. Inserting this peptide resulted in the variant called $Top7_{CB1}$. Team members then evaluated the structural effect of the variant using molecular dynamics simulations that suggested that $Top7_{CB1}$ retains conformational stability at temperatures greater than 100°C—hotter than boiling water.

The modified Top7 also bound CD4 and, consistent with simulations, was extremely resistant to thermal and chemical structural change—retaining its secondary structure up to at least 95°C. This CD4-specific protein

demonstrates the functionality of Top7 as a viable scaffold for use as a general affinity reagent that could serve as a robust and inexpensive alternative to antibodies.

The PNNL team is currently using complementary determining region loops harvested from antibody libraries at PNNL as diversity elements for building libraries of Top7 variants for selection through yeast surface display. Based on suggestions that the destabilization effects of multiple loop addition are not synergistic, they are also exploring the use of multiple binding sequences at other regions within Top7 to further increase specificity and affinity.

This work was supported by the U.S. Department of Energy with Laboratory Directed Research and Development funding through the Biomolecular Systems Initiative.

Citation

Boschek CB, DO Apiyo, TA Soares, HE Engelmann, N Pefaur, TP Straatsma, and CL Baird. 2009. "Engineering an ultra-stable affinity reagent based on Top7." *Protein Engineering, Design & Selection* 22(5):1-8, doi:10.1093/protein/gzp007.

Identification of a Putative Protein Profile Associating with Tamoxifen Therapy Resistance in Breast Cancer

A Umar,[a] H Kang,[b] AM Timmermans,[a] MP Look,[a] ME Meijer-van Gelder,[a] MA den Bakker,[a] N Jaitly, [b] JWM Martens,[a] TM Luider,[a] JA Foekens,[a] and L Pasa-Tolic[b]

(a) *Erasmus Medical Center, Rotterdam, The Netherlands*
(b) *EMSL, Richland, Washington*

The drug tamoxifen is used to treat breast cancer; however only about 50 in 100 people taking tamoxifen respond. Of those that respond, the majority eventually develop a resistance to the drug. This study provides data that could aid in isolating a protein or set of proteins that would predict if a patient will respond to the drug or if a different treatment is needed.

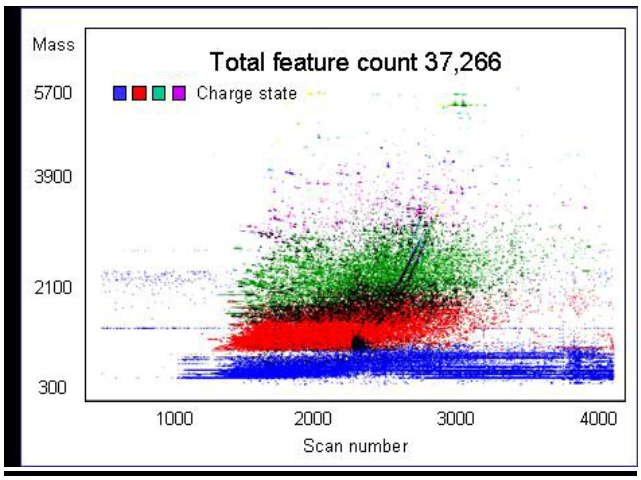

Figure 1. *EMSL users determined the relative abundance of thousands of peptides, which led to the identification of 55 proteins that were different in abundance between the patients that responded to the drug and those that did not.*

At EMSL, researchers from Erasmus Medical Center Rotterdam and EMSL studied cancerous cells and identified 55 proteins that vary in abundance between patients responsive to the breast cancer treatment tamoxifen and those that are not. The cells were microdissected from larger tumors. This exacting process, done by scientists at the Rotterdam center, results in pure samples of cancerous cells. The samples, constituting only about 3000 cells, were then packed by experts at EMSL into small inner-diameter capillaries and processed through EMSL's liquid

chromatography/Fourier transform mass spectrometer. The data were analyzed using the accurate mass and tag approach. Using this process, the team identified 2000 proteins from each sample procured by laser microdissection.

Of these proteins, 55 were different in abundance between those that responded to tamoxifen and those that did not, indicating that a biomarker for resistance to this drug might exist (Figure 1).

This study shows the effectiveness of using the accurate mass and tag approach with relatively small clinical samples. With this approach, 2000 proteins were identified that differed between tumors extracted from patients resistant to tamoxifen and those that were not. Previous studies that employed a small number of cells (<10,000 cells) typically identified 20 times fewer proteins.
This research, funded by the National Institutes of Health's National Center for Research, was featured in *Molecular & Cellular Proteomics. MCP.*

Citation

Umar AN, H Kang, AM Timmermans, MP Look, ME Meijer-van Gelder, MA den Bakker, N Jaitly, JW Martens, TM Luider, JA Foekens, and L Pasa-Tolic. 2009. "Identification of a Putative Protein Profile Associating with Tamoxifen Therapyresistance in Breast Cancer." *Molecular & Cellular Proteomics. MCP.* doi:10.1074/mcp.M800493-MCP200

Syndecan-1 Mediates the Coupling of Positively Charged Submicrometer Amorphous Silica Particles with Actin Filaments across the Alveolar Epithelial Cell Membrane

G Orr,[a] DJ Panther,[a] KJ Cassens,[a] JL Phillips,[a] BJ Tarasevich,[a] and JG Pounds[a]

(a) *Pacific Northwest National Laboratory, Richland, Washington*

By combining single-molecule microscopy and nanoparticle engineering at EMSL, scientists from Pacific Northwest National Laboratory showed how nano-sized particles interact with lung cells. Their results, which were published on the cover of Toxicology and Applied Pharmacology*, provide insights about the mechanisms underlying of inhaled nanomaterials.*

Dr. Galya Orr and her colleagues found that some positively charged nanomaterials seek out a specific cellular protein that gives them a free pass into alveolar type II epithelial cells in the lungs. The protein, known as syndican-1, is an integral plasma membrane protein that participates in cell proliferation, migration and organization.

Alveoli are tiny air sacs within the lungs where oxygen and carbon dioxide are exchanged. The alveolar type II cell regulates surfactant (wetting agent) metabolism, ion transport and alveolar repair in the lung. These cells are a potential target for inhaled engineered nanoparticles, which can cause inflammation and lead to respiratory diseases.

The researchers showed that positively charged nanomaterials attach to syndican-1 on the plasma membrane of cells. This specific attachment is critical to internalizing nanoparticles in alveolar cells, which do not accumulate larger particles. The consequence of this interaction may be inflammation and, eventually, disease or migration of the nanoparticles into the bloodstream.

Sand-like synthetic amorphous silica particles at the submicron scale (<10^{-6} or 1 millionth of a meter) and nanoscale (<10^{-9} or 1 billionth of a meter) are being explored for drug delivery and medical imaging and sensing. These particles have been also used in a wide array of industrial applications, such as the food, cosmetic and paint industries, creating a significant source of potential human exposure through inhalation.

Much is already known about how microscale particles such as bacteria or combustion byproducts get into and affect cells. And, in fact, the human body has evolved cells and molecular processes to deal with these larger particles.

According to Orr, "Knowing more about the cellular interactions and fate of the particles, which drive the cellular response, and ultimately determine the impact on human heath, will help us to understand what makes a particle toxic or biocompatible."

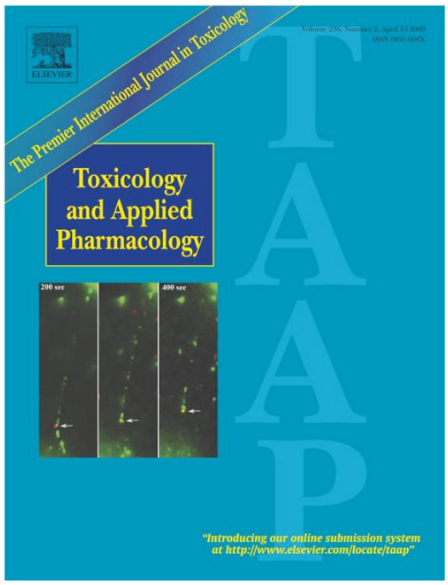

Figure 1. *This research was featured on the cover of the April 15, 2009, issue of* Toxicology and Applied Pharmacology.

The scientists used time-lapse fluorescence imaging at EMSL and materials science capabilities at PNNL to follow one particle at a time as it interacts with the living cell. This approach allowed them to identify cellular processes and molecular interactions that could not be otherwise observed.

Because nanomaterials come in many sizes, shapes, and physical properties, more research is needed to understand how cells process materials with other properties, and the intracellular fate. Because it is impossible to study each and every particle, the PNNL team is working to develop prediction approaches for nanotoxicity.

This work was supported by an Environmental Protection Agency STAR grant and the Air Force Research Laboratory through the Oregon Nanoscience and Microtechnologies Institute-Safer Nanomaterials and Nanomanufacturing Initiative and the Environmental Biomarkers Initiative at PNNL.

Citation

Orr G, DJ Panther, KJ Cassens, JL Phillips, BJ Tarasevich, and JG Pounds. 2009. "Syndecan-1 Mediates the Coupling of Positively Charged Submicrometer Amorphous Silica Particles with Actin Filaments across the Alveolar Epithelial Cell Membrane." *Toxicology and Applied Pharmacology* 236(2):210-220.

Calmodulin Mediates DNA Repair Pathways Involving H2AX in Response to Low-Dose Radiation Exposure of RAW 264.7 Macrophages

HS Smallwood,[a] D Lopez-Ferrer,[b] PE Eberlein,[a] DJ Watson,[a] and TC Squier[b]

(a) *Washington State University-Tri-Cities, Richland, Washington*

(b) *Pacific Northwest National Laboratory, Richland, Washington*

Students taught by Dr. Heather Smallwood at Washington State University working side-by-side with scientists at Pacific Northwest National Laboratory identified a new pathway that cells take when exposed to low levels of radiation, such as those used to shrink tumors. The newly identified cellular pathway upregulates, or increases the cellular components of, DNA repair pathways in response to low-dose radiological exposures. Cell survival is enhanced through pathways involving phosphorylated histone H2AX—the addition of phosphorous to the chief protein components of the complex combination of DNA, RNA, and protein that makes up chromosomes. These DNA repair pathways are distinct from other protein complex pathways tested that enhance cell death in an attempt to remove damaged cells in response to radiation. Such removal systems prevent the damaged cells from sapping further nutrients from an organism and act to halt further spread of infection.

As part of the mammalian immune system, macrophages, or white blood cells, normally recognize and remove dead cells and pathogens while further stimulating an immune response. This capability makes them a first line of defense against disease. Identifying a dose-dependent increase in the expression level of the calcium signaling protein, calmodulin (CaM), in irradiated mouse macrophage cells indicates that such increases are part of a specific radiation-dependent cellular response that can help expedite DNA damage repair (Figure 1).

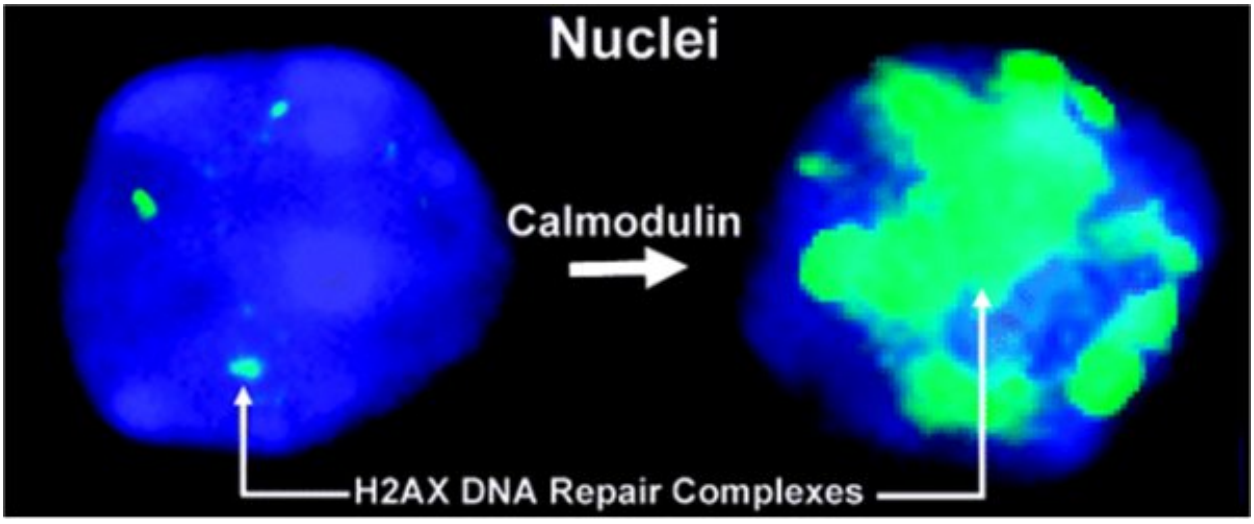

Figure 1. *Visualization of DNA repair complexes (green) within DAPI-stained nucleus (blue) of macrophage cell, demonstrating augmentation of repair pathways associated with the upregulation of the regulatory protein calmodulin.*

Understanding the molecular mechanisms that modulate macrophage resistance to radiation is necessary for developing effective radiation therapies, because tumor-associated macrophages promote processes that enhance the spread of cancer. The increases in CaM abundance in response to the lower radiation doses used in the study suggest a possible role of CaM in mediating cellular response pathways to clinically relevant doses in radiation therapy. Because phosphorylated histone H2AX acts as a universal organizing center that both anchors chromosomal ends and mediates DNA repair, these results are broadly significant for understanding the radioresistance mechanisms of macrophages and other blood-generating cell types in response to radiation exposure.

The results suggest that therapeutic treatments that target CaM in conjunction with traditional radiotherapies may help kill tumor-associated macrophages, thereby restricting cancer cell proliferation and tumor metastisis. Such treatments are likely to have other beneficial effects because CaM antagonists are known to prevent cancer invasiveness.

To better understand the molecular basis for the sensitivity of macrophages to low therapeutic doses of ionizing radiation, the research team investigated the possible role of CaM in modulating double-stranded DNA damage. CaM is suggested to be a principal mechanism of radiation-induced cellular death and transformation. They grew and irradiated mouse macrophage leukemia cells (i.e., RAW 264.7), then assayed cell survival to identify cells undergoing programmed death, or apoptosis, and to assess DNA damage and repair pathways, changes in the expression level of CaM, and total protein content.

After macrophage irradiation, increases in CaM abundance resulted in an increase in the number of phosphorylated histone H2AX foci, associated with DNA repair, with no change in the extent of double-stranded DNA damage. Measurement of the radiation sensitivity of RAW 264.7 macrophages, using a well-established survival assay for studying the effectiveness of specific agents on the survival and proliferation of cells, showed that macrophages are more resistant to high radiation doses than low. Altering CaM levels and protein complex NFκB-dependent pathways was found to have multiple effects, some of which may disrupt DNA damage response pathways and cellular apoptosis. CaM overexpression reduced radiation-dependent cell killing and disrupted the adaptive cellular response to low-dose radiation, while radiation-induced DNA damage was shown to be insensitive to CaM. Upregulation of CaM abundance enhanced DNA repair pathways after irradiation. Hence, Laboratory Fellow Thomas Squier emphasized that "the medical significance of the finding is that specifically inhibiting repair mechanisms in tumor cells and tumor associated macrophages before radiation damage occurs will enable more rapid and targeted killing of these cells upon treatment, which is the main challenge in successful radiation therapies."

Future measurements will need to identify the components of the CaM-dependent pathway that leads to histone H2AX phosphorylation, thereby activating DNA repair and enhancing macrophage survival following radiation exposure.

This work was completed as part of the student radiobiology laboratory associated with Washington State University Tri-Cites, Richland. A portion of the research was performed using an LTQ-Orbitrap mass spectrometer and a custom-built liquid chromatography system at EMSL. Results were published in *Chemical Research in Toxicology*.

Citation

Smallwood HS, D Lopez-Ferrer, PE Eberlein, DJ Watson, and TC Squier. 2009. "Calmodulin Mediates DNA Repair Pathways Involving H2AX in Response to Low-Dose Radiation Exposure of RAW 264.7 Macrophages." *Chemical Research in Toxicology* 22(3):460-470. doi:DOI: 10.1021/tx800236r

Geochemistry/Biogeochemistry and Subsurface Science

Antibody Recognition Force Microscopy Shows that Outer Membrane Cytochromes OmcA and MtrC are Expressed on the Exterior Surface of Shewanella oneidensis MR-1

BH Lower,[a] R Yongsunthon,[b] L Shi, [c] L Wildling,[d] HG Gruber,[d] NS Wigginton,[e] CL Reardon,[c] GE Pinchuk,[c] TC Droubay,[c] JF Boiley,[f] and SK Lower[a]

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(b) *Corning, Inc., Corning, New York*
(c) *Pacific Northwest National Laboratory, Richland, Washington*
(d) *Johannes Kepler University of Linz, Linz, Austria*
(e) *Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland*
(f) *Umea University, Umea, Sweden*

Electron exchange is a basic function carried out by bacteria such as Shewanella. Understanding the mechanism of this exchange is of fundamental importance and may lead to advanced bioremediation strategies.

An international team used EMSL surface science and imaging capabilities to determine the location, with nanoscale resolution, of MtrC and OmcA – two *Shewanella oneidensis* MR-1 surface proteins that can affect environmental quality. Bacteria such as *Shewanella* exchange electrons with minerals, yielding effects such as changes in the migration of environmental contaminants and water purity. MtrC and OmcA are cytochromes, or surface-bound iron-containing proteins that facilitate this exchange between *Shewanella* and iron. Carried out, in part, as a contribution to EMSL's Biogeochemistry Grand Challenge, the team's imaging studies offer a deeper understanding of the role MtrC and OmcA play in electron exchange and may lead to enhanced bioremediation methods.

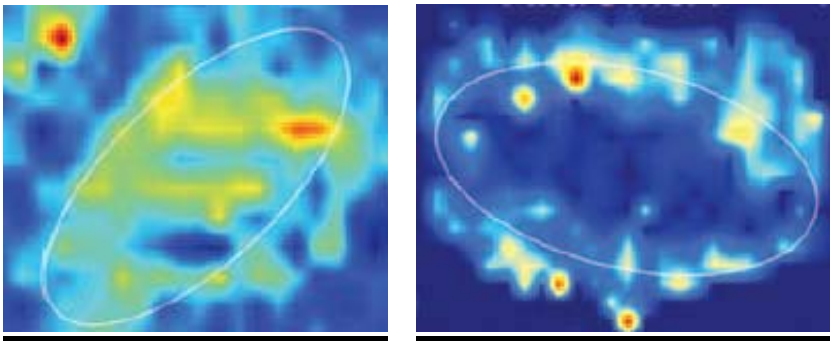

Figure 1. *Ig-RFM showed that MtrC is distributed across the Shewanella surface (left). OmcA is localized to the cell-hematite interface (right). Both MtrC and OmcA are in the EPS (white lines indicate the bacterium boundary).*

Comprised of participants from The Ohio State University; Pacific Northwest National Laboratory; Corning Incorporated, Johannes Kepler University of Linz, Austria; Ecole Polytechnique Fédérale de Lausanne, Switzerland; and Umeå University, Sweden, the research team used EMSL's oxygen plasma-assisted molecular

beam epitaxy capability to grow hematite (Fe_2O_3) thin films. *Shewanella* cells were allowed to attach to the thin films; the iron in the hematite serves as an electron acceptor. EMSL's dynamic force-scanning probe microscope for single-molecule force spectroscopy as well as antibody-recognition force microscopy (Ig-RFM) were then used to map the locations of MtrC and OmcA on the live *Shewanella* surface (Figure 1). A relatively new technique, Ig-RFM uses a nanometer-scale, flexible antibody-coated tip that is moved across a sample surface. When the antibody, in this case anti-MtrC or anti-OmcA, comes in contact with its binding partner, a measurable force is required to separate the two. Force measurements indicate that MtrC is distributed rather uniformly on the bacterial surface, and OmcA is localized at the cell-mineral interface. Both cytochromes locate to the extracellular polymeric substance, which is made up of the secretions that help bacteria bind to surfaces.

Understanding microbe-mineral electron exchange is important to developing enhanced bioremediation methods for contaminated environments, such as the DOE's Hanford Site in Richland, Washington.

This work was supported by DOE's Office of Basic Energy Sciences' Geosciences Research Program, EMSL's Biogeochemistry Grand Challenge, DOE Office of Biological and Environmental Research's Genomics-Genomes to Life Program, and the National Science Foundation. It was featured on the cover of the May 1, 2009, issue of *Applied and Environmental Microbiology*.

Citation

Lower BH, R Yongsunthon, L Shi, L Wildling, HJ Gruber, NS Wigginton, CL Reardon, GE Pinchuk, TC Droubay, JF Boily, and SK Lower. 2009. "Antibody Recognition Force Microscopy Shows that Outer Membrane Cytochromes OmcA and MtrC Are Expressed on the Exterior Surface of *Shewanella oneidensis* MR-1." *Applied and Environmental Microbiology* 75(9)2931-2935. DOI:10.1128/AEM.02108-08.

Surface and Interfacial Properties of Nonaqueous-Phase Liquid Mixtures Released to the Subsurface at the Hanford Site

SR Nellis,[a] H Yoon,[a] CJ Werth,[a] M Oostrom,[b] and AJ Valocchi[a]

(a) *University of Illinois, Urbana, Illinois*

(b) *Pacific Northwest National Laboratory, Richland, Washington*

Models developed by EMSL users that incorporate data from real-world scenarios will predict the fate and transport of environmental contaminants more accurately, enabling the development of better remediation techniques and the protection of human health and the environment.

New results afforded by use of EMSL resources demonstrate the importance of accounting for complex organic liquid mixtures in flow and transport models. Basing its experiments on a real-world scenario, a research team led by Professor Charlie Werth from the University of Illinois and involving participants from the Pacific Northwest National Laboratory measured the surface and interfacial tensions of carbon tetrachloride (CCl_4) based nonaqueous-phase liquids and a wastewater solution both composed of chemicals known to have been discharged at the DOE's Hanford Site in Richland, Washington (Figure 1). The surface and interfacial tensions of liquids contaminating the environment are of particular importance because they affect the ability of those solutions to migrate in the subsurface.

For their experiments, the team prepared six CCl_4-based mixtures primarily containing tributyl phosphate, dibutyl butyl phosphonate, and lard oil as well as a representative wastewater solution containing nitrates and metals. In comparison to pure CCl_4, the CCl_4-based mixtures had a significantly lower interfacial tension upon interacting with wastewater; the surface tensions of the CCl_4-based mixtures compared to pure CCl_4 were minimally affected. The chemicals added to CCl_4 in solution also increased the mixtures' spreading coefficients such that if the mixtures were released to an uncontaminated area, they would spread quickly and contaminate larger areas of the subsurface than would pure CCl_4. Adding another complication, the mixtures change over time; for example, CCl_4 will volatize more quickly than the other components, leaving those components more concentrated in the mixture, thus lowering the mixture's interfacial tension. Per these results, the properties and behavior of chemical mixtures need to be accounted for in flow and transport models to provide accurate predictions and be most effectively used for remediation studies.

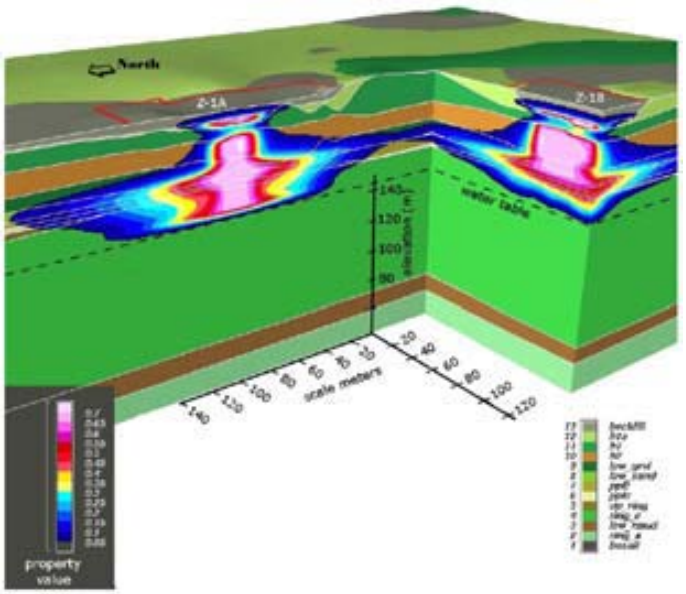

Figure 1. *Modeling studies conducted by co-author Mart Oostrom to predict gaseous CCl_4 concentrations for two Hanford Site disposal areas show that simulations using the Werth team's data (above, pink indicates highest CCl_4 levels) yield larger contaminant plumes than simulations using single-component fluid properties.*

Real-world-based experiments such as these will lead to more enhanced fate and transport models for use by the remediation sciences and geochemistry communities. This work, primarily supported by DOE's Office of Biological & Environmental Research's Environmental Remediation Sciences Program, was featured in *Vadose Zone Journal.*

Citation

Nellis SR, H Yoon, CJ Werth, M Oostrom, and AJ Valocchi. 2009. "Surface and Interfacial Properties of Nonaqueous-Phase Liquid Mixtures Released to the Subsurface at the Hanford Site" *Vadose Zone Journal* 8(2):343–351.

Electron Donor–Dependent Radionuclide Reduction and Nanoparticle Formation by *Anaeromyxobacter dehalogenans* Strain 2CP-C

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(a) *Pacific Northwest National Laboratory, Richland, Washington*
(b) *EMSL, Richland, Washington*
(c) *Georgia Institute of Technology, Atlanta, Georgia*
(d) *University of Illinois, Urbana, Illinois*

Recent scientific findings show that the bacterium Anaeromyxobacter dehalogenans *can efficiently use either organic carbon or hydrogen as an electron donor—or energy source—to reduce the solubility of uranium. This could benefit cleanup efforts at the U.S. Department of Energy's Hanford Site, where subsurface sediments have electron donor variability that may work with versatile bacteria such as* Anaeromyxobacter *to make uranium less risky to the environment.*

A research team led by EMSL users from Pacific Northwest National Laboratory investigated mechanisms involved in reducing radionuclide contaminants by *A. dehalogenans*. At the Hanford Site, uranium and technetium are contaminants whose migrations in the subsurface are anticipated being a major risk factor to the Columbia River in the future. Biotransformation of uranium and technetium can reduce their mobility in the subsurface by converting them to less soluble forms, thus decreasing their eventual threat to the river.

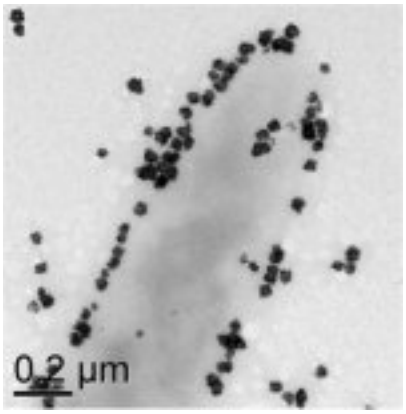

Figure 1. *Transmission electron micrograph image of A. dehalogenans 2CP-C.*

Previously, scientists showed that *A. dehalogenans* coupled cellular growth with uranium reduction; however, they knew little about the biotransformation product of this reaction or the interaction of this bacterium with other radionuclides. In this study, scientists observed that the electron donor source provided for uranium reduction influenced the reduction rates and the extent of aggregation of extracellular uraninite, a solid form of uranium resulting from microbial reduction. They saw that when *Anaeromyxobacter* cells were provided with an organic electron donor source, distinct nanoparticle aggregates formed that were ten times larger in diameter than individual nanoparticles produced during hydrogen oxidation. Similarly, individual extracellular technetium dioxide nanoparticles aggregated in clusters greater than 50 nm in diameter, although this was not linked to the electron donor source.

Using high-resolution electron microscopy (Figure 1), the scientists determined the localization, size and degree of aggregation of the nascent nanoparticles. These findings provide a better understanding of the importance of electron donor type on radionuclide reduction by *Anaeromyxobacter* and the nature of the insoluble oxide precipitates. They then used kinetic studies and transmission electron microscopy to determine the localization, size and degree of aggregation of the less-soluble technetium and uraninite nanoparticles.

The results of this work provide the scientific community important insights into *Anaeromyxobacter* electron transfer to contaminants found at DOE sites that will aid in finding remediation solutions. Recent findings indicate that members of the *Anaeromyxobacter* genus contribute to metal and radionuclide reduction in contaminated groundwater and sediments at DOE's Oak Ridge Field Research Center in Tennessee. They may also be present at other contaminated DOE sites, including Hanford.

The results produced in this study suggest that *Anaeromyxobacter* uses biomolecular mechanisms similar to other model metal-reducing bacteria such as *Geobacter* and *Shewanella* to transform radionuclide contaminants. Further investigations will be needed to consider the biomolecular mechanisms contributing to metal reduction by *Anaeromyxobacter* and the physiochemical properties of the nanoparticulate end products and their long-term behavior in porous subsurface such as that at the Hanford Site.

This work, supported by DOE's Environmental Remediation Sciences Program, was featured in *Environmental Microbiology*.

Citation

Marshall MJ, AC Dohnalkova, DW Kennedy, AE Plymale, SH Thomas, FE Löffler, RA Sanford, JM Zachara, JK Fredrickson, and AS Beliaev. 2009. "Electron donor-Dependent Radionuclide Reduction and Nanoparticle Formation by *Anaeromyxobacter dehalogenans* Strain 2CP-C." *Environmental Microbiology* 11:534-543 (doi:10.1111/j.1462-2920.2008.01795.x).

Science of Interfacial Phenomena

Self-Assembled TiO_2-Graphene Hybrid Nanostructures for Enhanced Li-Ion Insertion

D Wang,[a] D Choi,[a] J Li,[a] Z Yang,[a] Z Nie,[a] R Kou,[a] D Hu,[a] C Wang,[b] LV Saraf,[b] J Zhang,[a] IA Aksay,[c] and J Liu[a]

(a) *Pacific Northwest National Laboratory, Richland, Washington*
(b) *EMSL, Richland, Washington*
(c) *Princeton University, Princeton, New Jersey*

Many ideas to reduce the nation's oil addiction require an effective battery. For example, plug-in hybrid electrical vehicles need better batteries to drive longer distances. Solar farms only produce electricity when the sun shines. Rechargeable batteries are needed to capture electricity for use on cloudy days. Lithium ion batteries, used in camcorders and other devices, are a popular option, because pound for pound, they are some of the most energetic rechargeable batteries available. However, these batteries need to store more energy. New titanium oxide structures on carbon sheets devised by EMSL users and researchers could help the batteries hold more energy.

High capacity, safe batteries are needed for efficient hybrid or electrical vehicles and for storing and releasing electricity from intermittent power sources like wind turbines and solar panels. That's where an innovation by scientists at Pacific Northwest National Laboratory, EMSL, and Princeton University comes in. The researchers devised a method for building tiny titanium oxide and carbon structures that greatly improve the performance of lithium ion batteries. This new material stores twice as much electricity at high charge/discharge rates as batteries that don't use it.

Rechargeable lithium ion batteries, popular in cell phones, camcorders, and other devices, are based on the movement of a lithium ion—a lithium atom minus an electron. The lithium ion begins its journey attached to a metal cylinder or sheet, known as an electrode. The ion pushes off the electrode, moves through a liquid, and attaches itself to an electrode on the other side. The ion's movement generates electricity, powering the battery. The researchers' new material, titanium dioxide crystals attached to a thin carbon sheet called graphene, is incorporated into the battery's negative electrode. The carbon/titanium material greatly improves the ion's ability to move in the electrode to provide a high capacity at high charge/discharge rate.

The challenge in designing this material was water. The researchers used water to reduce the cost of manufacturing. The precursors for the titanium dioxide crystals mixed well in water, easily dispersing. However, the graphene is hydrophobic or water fearing. Like oil or grease, it does not mix in water. The solution? The active ingredient in many types of detergents: sodium dodecyl sulfate. This long, chain-like molecule contains a cluster of chemicals, or a head at one end, that mixes well with water. It has a long tail that grabs hold of hydrophobic materials. So, adding sodium dodecyl sulfate allows the graphene to evenly mix in the water with the precursors for the oxide crystals.

Figure 1. *This research was featured on the April 2009 cover of* ACS Nano.

The sodium dodecyl sulfate not only solves the hydrophobic/hydrophilic incompatibility problem, it also provides a molecular template for the crystals to form and grow. Using the template, the titanium oxides form tiny crystals on the graphene sheets.

The researchers studied the resulting materials using EMSL's transmission electron microscopy. The resulting images showed the desired titanium dioxide crystals formed on the graphene sheets. This process is being used by PNNL researchers in the Transformational Materials Science Initiative to precisely design other materials to further increase the capacity and stability of batteries.

This research was funded by Laboratory-Directed Research and Development Program at PNNL and by DOE's Office of Basic Energy Sciences. In addition support was given from the Defense Advanced Research Projects Agency and Army Research Office/Multidisciplinary University of Research Initiative. The research was featured on the cover of *ACS Nano* (Figure 1).

Citation

Wang D, D Choi, J Li, Z Yang, Z Nie, R Kou, D Hu, C Wang, LV Saraf, J Zhang, IA Aksay, and J Liu. 2009. "Self-Assembled TiO_2-Graphene Hybrid Nanostructures for Enhanced Li-Ion Insertion." *ACS Nano* 3(4):907-914.

Molecular Characterization of Nitrogen Containing Organic Compounds in Biomass Burning Aerosols Using High Resolution Mass Spectrometry

A Laskin,[a] JS Smith,[b] and J Laskin[b]

(a) *EMSL, Richland, Washington*

(b) *Pacific Northwest National Laboratory, Richland, Washington*

Every year, ponderosa wildfires occur along the nation's West Coast. While some fires are accidental, others are prescribed land management events. Using EMSL resources, researchers found that smoldering fires such as those in controlled burns produce more alkaloids than blazing fires. Because some plant alkaloids might be harmful, the result could affect planned fires upwind of human populations.

Smoke from burning ponderosa pines contains previously undetected alkaloids, according to a study published by scientists working at EMSL (Figure 1). The alkaloids are potent mutagens that can affect human health and ecosystems in areas near or downwind of the fires. Researchers have long suspected the presence of alkaloids in smoke particles produced in forest fires, but no direct measurements had been made.

Figure 1. *Previously undetected compounds were detected in smoke from a smoldering fire with a new method devised at EMSL.*

With the help of the Forest Service Fire Sciences Laboratory, a team from Pacific Northwest National Laboratory and EMSL sampled the smoke from smoldering fires of ponderosa pine and underbrush. Then, they devised a method that provides highly detailed information about the smoke's composition. This method included using EMSL's LTQ-OrbitrapTM high-resolution mass spectrometer to characterize the smoke. Compared to other studies, the team found that 70% of the molecules detected in the smoke had not been previously reported. More than 30% of newly detected species were alkaloids.

This and earlier studies by the team will aid in understanding the possible effects of smoke particles emitted during forest fires on the environment and human health. The results suggest that smoke might carry biologically useful nitrogen in the form of alkaloids. In addition, alkaloids may present a considerable source of basic compounds in smoke particles, which can impact cloud formation processes important to agriculture and water supplies.

The DOE Office of Basic Energy Science and Office of Biological and Environmental Research as well as the Science Undergraduate Laboratory Internship program funded the research. Results of this research were published in *Environmental Science and Technology* and *Analytical Chemistry*.

Citations

Smith JS, A Laskin, and J Laskin. 2009. "Molecular Characterization of Biomass Burning Aerosols Using High Resolution Mass Spectrometry." *Analytical Chemistry* 81:1512-1521. doi: 10.1021/ac8020664

Laskin A, J Smith, and J Laskin. 2009. "Molecular Characterization of Nitrogen Containing Organic Compounds in Biomass Burning Aerosols Using High Resolution Mass Spectrometry." *Environmental Science and Technology*. doi: 10.1021/es803456n

Symmetry-Driven Spontaneous Self-Assembly of Nanoscale Ceria Building Blocks to Fractal Superoctahedra

SVNT Kuchibhatla,[a] AS Karakoti,[b] DC Sayle,[c] H Heinrich,[b] and S Seal[b]

(a) *EMSL, Richland, Washington*

(b) *University of Central Florida, Orlando, Florida*

(c) *Defence Academy of the United Kingdom, Swindon, United Kingdom*

The evolution of a self-assembled, oxide superoctahedral structure has been elucidated for the first time, and this unique finding was featured on the cover of Crystal Growth and Design – a journal ranked first in the field based on impact factor. Through this research, the ability to understand and tailor nanomaterials with better properties can lead to sustainable, greener energy prospects; environmental protection; and the detection, treatment, and prevention of diseases using nanomedicine.

Researchers at EMSL and their collaborators from the University of Central Florida and the Defence Academy of the United Kingdom used a combination of experimental tools at UCF and EMSL as well as theoretical tools at the Cambridge-Cranfield HPC facility to study cerium oxide. Because cerium oxide is crucial for solid oxide fuel cells, solar cells, catalysis, and biomedicine, understanding its nanostructures is vital to improve their performance in those applications.

To characterize the superstructures, the research team applied high-resolution transmission electron microscopy and fast-Fourier transform analysis. HRTEM yielded structural and morphological information (Figure 1). FFT analysis allowed the researchers to study a specific sample area of interest such that crystallographic information from even single nanoparticles could be derived. Integrating the team's experimental data with atomistic modeling revealed a stepwise process for superstructure formation. Importantly, the process occurred naturally – at room temperature and pressure and without surfactants. First, cerium oxide molecules form individual octahedral nanoparticles that are shaped like two pyramids stuck together at their bases. This step was successfully predicted by molecular dynamics simulations, and that prediction was confirmed experimentally. Next, the octahedra stack tightly together via fractal self-assembly to yield superoctahedral structures. Understanding the orientation of the interfaces between two adjoining octahedral nanoparticles is particularly important. These interfaces may have a low or high energy conformation – in other words, the surfaces of the nanoparticles may lie against one another more or less comfortably. A high-

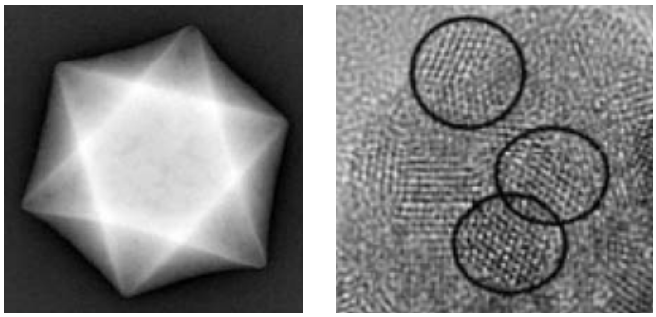

Figure 1. *Ceria oxide forms octohedral superstructures (TEM image at left) composed of octahedral nanoparticles (HRTEM image at right; circles indicate individual nanoparticles).*

energy interface is prone to defects that may act as potential reaction sites, making the defects favorable for improved performance.

Understanding the factors that control oxide nanostructure size, shape, and self-assembly enable the design of new materials with improved properties for energy, catalytic, or biomedical applications. The types of information obtained in these studies demonstrate the importance of EMSL's capability development to enable the design and growth of increasingly complex materials and their characterization with unprecedented (atomic level) resolution.

This work was supported by the National Science Foundation and the Cambridge-Cranfield HPC facility.

Citation

Kuchibhatla SVNT, AS Karakoti, DC Sayle, H Heinrich, and S Seal. 2009. "Symmetry-Driven Spontaneous Self-Assembly of Nanoscale Ceria Building Blocks to Fractal Superoctahedra." *Crystal Growth & Design* 9(3)1614-1620. DOE:10.1021/cg801358z

Clay Nanoparticles-Supported Single-Molecule Fluorescence Spectroelectrochemistry

C Lei,[a] D Hu,[a] and EJ Ackerman[a]

(a) *Pacific Northwest National Laboratory, Richland, Washington*

Scientists at Pacific Northwest National Laboratory devised a method to hold certain types of molecules still and measure if they blink; that is, gain or lose electrons. Mother Nature is very good at making catalysts: proteins that quickly add and remove electrons to create the desired products. Scientists would like to design molecules that mimic Mother Nature's catalysts, but do not yet know how. This research provides an important tool to learn if, when and why single molecules transfer electrons. By understanding electron transfers, scientists can gain the insights needed to design, atom by atom, catalysts that effectively turn water into hydrogen fuel or other reactions.

The scientists combined two existing methods to study immobilized individual molecules of the dye cresyl violet. The first technique is electrochemistry, which allows scientists to add and remove electrons to molecules at specific intervals. The second method is to use a single-molecule fluorescence microscope to record the light emission of the molecules. It uses a dye that gives off light under specific conditions. For example, when cresyl violet loses an electron, it gives off a red glow. When it gains an electron, it goes dark.

So, the researchers built an electrochemical cell that can measure electron movement on a type of conductive glass surface. Then, they placed a few drops of a clay solution on the glass. The liquid dried onto the glass, forming a transparent clay film. Then, they added cresyl violet. The dye attached to the clay film, holding the dye in place. This left the scientists with a piece of glass with a few dye molecules securely attached to it.

Next, they added to and removed electrons from the molecules at regular intervals by changing the electrochemical voltages. Simultaneously, they recorded the light flashes using a single-molecule fluorescence microscope at EMSL.

The method worked well, providing information about single-molecule effectiveness; that is, single molecules regularly gained and lost electrons while the molecules underwent cycles of blinking, dark and then bright.

The researchers plan to use this method to interrogate other molecules and gain the knowledge necessary to design catalysts that mimic Mother Nature's most effective molecules.

DOE's Office of Basic Energy Sciences funded this research, which was featured in *Nano Letters*.

Citation

Lei C, D Hu, and EJ Ackerman. 2009. "Clay Nanoparticles-Supported Single-Molecule Fluorescence Spectroelectrochemistry." *Nano Letters* 9(2):655-658.

Line Intensities for the v_1, v_3, and $v_1 + v_3$ Bands of $^{34}SO_2$

JM Flaud,[a] WJ Lafferty,[b] and RL Sams[c]

(a) *Laboratoire Inter-Universitaire des Systemes Atmospheriques, Paris, France*
(b) *National Institute for Standards and Technology, Gaithersburg, Maryland*
(c) *Pacific Northwest National Laboratory, Richland, Washington*

Acid rain and respiratory problems are related to sulfur dioxide emissions from coal-fired power plants, volcanic eruptions, and other sources. To design cost-effective sulfur dioxide remediation tools and to effectively regulate emissions, scientists must be able to monitor sulfur dioxide at specific sources and in the atmosphere. The infrared crosssection values of $^{34}S16O_2$ determined at EMSL allow field measurements to be done with greater accuracy and source discernment.

Using EMSL resources, an international team completed a detailed infrared spectral analysis of $^{34}S^{16}O_2$. This analysis of this lesser studied sulfur isotope allows researchers to more accurately quantify the total amount of sulfur dioxide in the atmosphere. Measuring the ratio $^{34}SO_2$.and $^{32}SO_2$ may provide insights into discerning between specific natural and human-made sources of sulfur dioxide that contributes to, for example, acid rain (Figure 1). With infrared spectroscopy, atmospheric sensing can be done over meters to many kilometers, from the ground, a balloon, aircraft, or a satellite.

The team began by studying the isotopic sample using EMSL's high-resolution Fourier transform infrared spectrometer. After a preliminary analysis, additional analysis was done at the National Institute for Standards and Technology. The analysis revealed new information about the structure of the molecule, the rotational and vibrational energies of the molecule, and the interactions of these energies within the molecule.

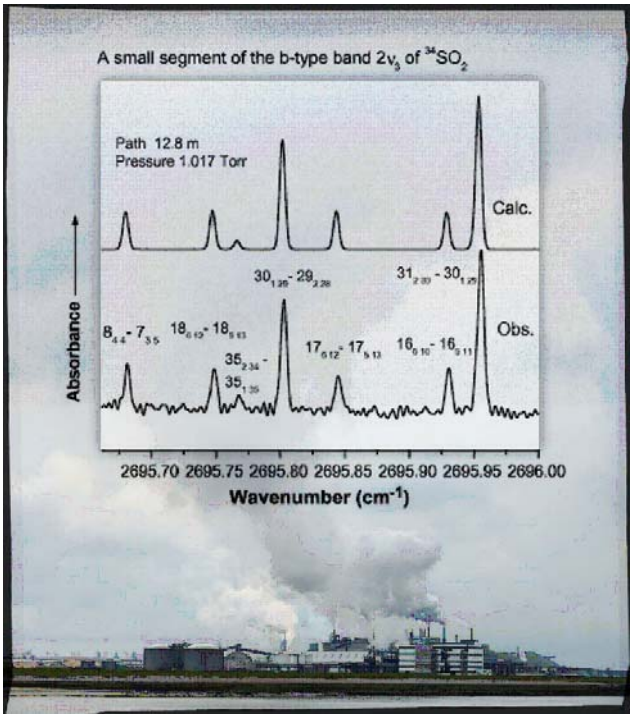

Figure 1. *EMSL users obtained detailed data on the industrial pollutant $^{34}SO_2$.*

This work also measured, for the first time, the infrared absorption cross-sections for individual rotational-vibrational transitions of $^{34}S^{16}O_2$., vital for eco-monitoring.

This study provides a more accurate experimental view of the structure, bonding, and vibrational and rotational energy patterns of $^{34}S^{16}O_2$. The results provide detailed information about the potential energy surface of a molecule with a modest number of electrons. The National Aeronautics and Space Administration's Upper Atmosphere Research Program; DOE's Office of Basic Energy Sciences; and DOE's EMSL Operations funded this research. It was featured in the *Journal of Quantitative Spectroscopy and Radiative Transfer*

Citation

Lafferty W, JM Flaud, and RL Sams. 2009. "Line intensities for the ν1, ν3, and ν1 + ν3 Bands of $^{34}SO_2$." *Journal of Quantitative Spectroscopy and Radiative Transfer* 110:669-674.

Awards and Recognition

Baer receives prestigious AVS award. Don Baer, Lead Scientist for Interfacial Chemistry at the Department of Energy's EMSL, has received the 2009 Albert Nerken Award from the AVS. The award recognizes individuals who have made outstanding contributions to the solution of technological problems in areas of interest to AVS. Baer was cited "for seminal contributions towards advancing the application of surface-sensitive techniques to understand environmentally important materials and interfacial processes." Baer largely attributes the award to Pacific Northwest National Laboratory's rich history of multidisciplinary, team-oriented research that enables significant progress on complex problems. "Although the award is presented to an individual, much of my research has involved participating on and leading teams," he says. "These teams have made important advances in understanding stress corrosion cracking, oxide and mineral surface chemistry, and dynamic behaviors of nanoparticles, as well as in developing and applying interfacial tools in EMSL that facilitate such advances." The award was established in 1984 by Veeco Instruments, Inc., in recognition of Albert Nerken for his role as a founding member of AVS, his early work in the area of high vacuum and leak detection, and his contributions to the commercial development of that instrumentation. Presentation of the award takes place at the AVS International Symposium, which this year is in San Jose, California, in November.

Don Baer

Yanwen Zhang

Zhang invited as guest professor. EMSL researcher Yanwen Zhang has accepted an invitation to serve a two-year term as Guest Professor of Peking University. In this capacity, she will monitor Ph.D. students at EMSL who are mainly supported by the Chinese government and help strengthen materials research at the university, until March 2011. Zhang will visit Peking University approximately twice yearly, and the university professors, researchers and students will also visit EMSL as part of the collaboration. The invitation was extended by Professor J. F. Zhou, the President of Peking University.

Three users named to Visiting Scientist Program. Three longtime EMSL users have been appointed as participants of the Wiley Visiting Scientist Program, which is designed to recognize, reward, and encourage distinguished scientists to come to EMSL for extended periods of time and make significant contributions to the EMSL user program by providing input to and recommendations on the path forward for EMSL.

- **Walter Ermler** is professor of chemistry at the University of Texas at San Antonio. At EMSL, he will work to integrate his CRENB spin-orbit operators with EMSL's NWChem software suite basis set and the EMSL Basis Set Exchange Library for the entire periodic system. The availability of these spin-orbit potentials in NWChem will directly support geochemistry and subsurface science research by enabling calculations that can provide more accurate results for those studying the structures and reaction mechanisms of heavy-element contaminants at various interfaces at the molecular scale. He will also develop collaborations in the area of modeling the electronic structure and spectroscopic properties of trans-uranium molecules and clusters using highly accurate relativistic methodologies.

Walter Ermler

- **Ian Farnan** is on the faculty of the Department of Earth Sciences at University of Cambridge. During his fellowship, Farnan will work to develop the next stage of radiological magic-angle spinning nuclear magnetic resonance capability at EMSL, encompassing higher sample rotation speeds and variable temperature operation. He has been instrumental in past collaborations with EMSL to develop the technology and sample handling protocol for high-resolution, solid-state NMR experiments on plutonium, and his work has led to notable findings in the area of radiation damage produced in zircon ceramics.

Ian Farnan

- **Alex Shluger** is on the Department of Physics and Astronomy faculty at University College London. At EMSL, he will expand on his work in laser desorption from metal oxides to include new opportunities for connecting topographic surface features on oxides to their spectroscopic and chemical properties and, therefore, develop an understanding of photo-induced and chemical processes for sculpting nanoscale metal oxide surfaces. Such surfaces could be beneficial for catalytic and energy applications. Part of this research will involve exchange and implementation of *ab initio* codes developed by Shluger's research team and EMSL's NWChem code.

Alex Shluger

Applications for the Wiley Visiting Scientist Program are accepted quarterly, and appointments include a stipend for travel and per diem. For more information, see http://www.emsl.pnl.gov/news/awards/visiting_scientist.jsp.

Dick Smith

Smith named PNNL Inventor of the Year, Editor in Chief of Journal of Proteomics & Bioinformatics. EMSL user Richard D. Smith (Pacific Northwest National Laboratory) was named the PNNL Inventor of the Year for Fiscal Year 2008. At EMSL, Smith has taken part in developing and applying advanced analytical methods and instrumentation, with an emphasis on high-resolution separations and mass spectrometry, to environmental, biological and biomedical research. Current applications include studies related to carbon sequestration, as well as the development of biomarkers for breast and brain cancer, neurological diseases, and diabetes and kidney diseases, among others. In addition, Smith has accepted an invitation to become Editor-in Chief of the *Journal of Proteomics & Bioinformatics*. Smith sets the direction for the open-access journal and gives final approval for each issue. Founded in 2008, the *Journal of Proteomics & Bioinformatics* strives to provide rapid review and publishing of research in the proteomics and bioinformatics fields. The journal disseminates its articles freely for research, teaching and reference purposes.

Bill Weber named Distinguished Alumnus by University of Wisconsin Oshkosh. EMSL user Bill Weber (Pacific Northwest National Laboratory) was selected for the Distinguished Alumni Award, the highest University of Wisconsin Oshkosh alumni honor given. Weber and eight others will be honored for their professional and civic achievements during homecoming weekend, October 16-17, 2009. Weber is an internationally recognized expert in defects and radiation effects in materials. His research, often done at EMSL, is essential for advanced electronic devices that operate in extreme conditions, developing radiation-tolerant materials for nuclear power, as well as for space exploration and research.

Bill Weber

Julia Laskin honored with special issue of Prestigious Spectroscopy Journal. EMSL user Julia Laskin (Pacific Northwest National Laboratory) was honored with a special issue of the *Journal of the American Society of Mass Spectrometry* in June 2009, now available online. The issue, containing invited articles by several experts, recognizes the 2008 Biemann Medal for her early career work in mass spectrometry. In the scientific community, Laskin is internationally known for her work on gas-phase ion chemistry and mass spectrometry of large, complex molecules. With her colleagues from around the world, she is designing techniques to better characterize complex molecules in biological samples, atmospheric aerosols, and biofuels, work critical for a secure energy future.

Julia Laskin

Lai-Sheng Wang

Wang accepts faculty position at Brown University. Lai-Sheng Wang (Washington State University/Pacific Northwest National Laboratory), a long-time EMSL user, has accepted a faculty position in Chemistry at Brown University. In his role at Brown University, Wang will be teaching physical chemistry and mentoring undergraduate and graduate students. Wang was selected for the faculty position based on his distinguished and innovative contributions to the field of chemistry, specifically his work on atomic clusters and gaseous multiply charged anions.

News Coverage

EMSL's supercomputer featured in *SciDAC Review*. EMSL's new supercomputer, Chinook, was featured in the Summer 2009 issue of *SciDAC Review* (http://www.scidacreview.org/0903/html/hardware.html).

EMSL receives Recovery Act funding. DOE is investing in Pacific Northwest National Laboratory through the American Recovery and Reinvestment Act. EMSL has been awarded $60M. Receipt of these funds will allow EMSL to accelerate existing plans to enhance its user program, obtaining systems and capability that maintain EMSL's position as a state-of-the-art user facility. Purchases will enable high-end scientific capabilities, including nuclear magnetic resonance spectrometry, mass spectrometry, and high-powered microscopy. An article was published in the Tri-City Herald at http://www.tri-cityherald.com/kennewick_pasco_richland/story/519807.html.

Visitors and Users

Year to date in Fiscal Year 2009, a total of 409 users benefited from EMSL capabilities and expertise. This total included 271 onsite users and 138 remote users.

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