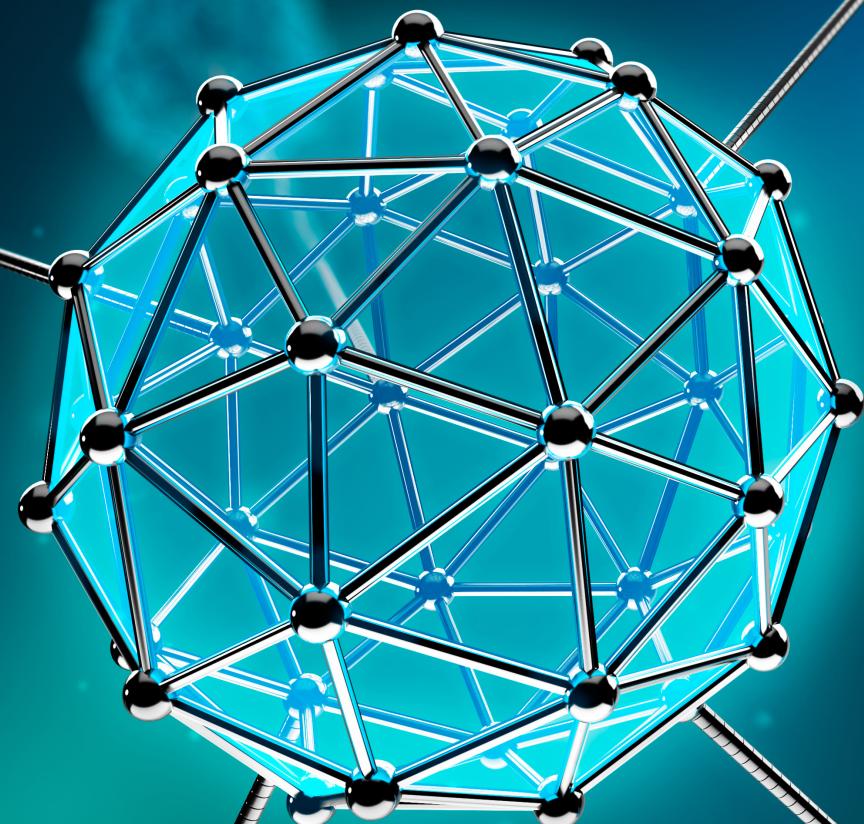


**SUNY** POLYTECHNIC  
INSTITUTE

**COLLEGE OF  
NANOSCALE SCIENCES**



Faculty Research Report  
**2016**

# SUNY POLYTECHNIC INSTITUTE



**Alain Diebold**  
**Interim Dean of the College of Nanoscale Science**

## Overview

The College of Nanoscale Sciences is divided into two Constellations. Although each constellation has a unique research portfolio, there are strong collaborations between constellations.

The **Nanobioscience Constellation** provides world class educational and research opportunities in the area of cancer, neuroscience, biomedical engineering, biophysics, biochemistry, electrophysiology, pharmacology/toxicology, cardiovascular disease and environmental health that tightly integrate diverse aspects of nanotechnology. In addition, a nanoelectronics memristor program is run out of this constellation.

The **Nanoscale Science Constellation** provides world class educational and research opportunities in the areas of materials science and systems whose structures and components exhibit novel and significantly improved physical, chemical and biological properties, phenomena and processes using measurement science (metrology) and thin film fabrication science all at the nanoscale.

The Semiconductor Research Corporation's Institute for Nanoelectronics Discovery and Exploration is part of this college. The INDEX Center includes 18 faculty members across 10 universities. The INDEX program's graphene pn junction effort was awarded a top 10 designation by Physics World in 2016 for proof of the Negative Refraction of electrons in graphene PN junctions.

## **Vision and Mission**

### **Vision**

The College of Nanoscale Sciences will become the premier nanoscale focused academic institution providing world-class educational and research opportunities for undergraduate, graduate and post-doctoral students through the synergistic actions of the Nanobioscience and Nanoscience Constellations.

### **Mission**

The mission of the College of Nanoscale Science is to conduct scholarship and teaching in both physical and biological sciences at the nanoscale. The advancement of nanoscale science and technology is carried out through research, outreach and accelerated deployment of technological innovations to practical applications.

## Faculty Members

1. **Nanobioscience** – 13 tenure track  
Thomas Begley, Ben Boivin, Sara Brenner, Nate Cady, Jim Castracane (Constellation Head), Andres Melendez (Associate Constellation Head), Xinxin Ding, Mike Fasullo, Jan Paluh, Susan Sharfstein, Scott Tenenbaum, Dan White, Yubing Xie
2. **NanoScience** – 12 tenure track, one recurring appointment, 3 instructors, and 1 adjunct  
Hassaram Bakhru (Constellation Head), Robert Brainard, Alain Diebold (Interim Dean), Kathleen Dunn (Associate Constellation Head), Eric Eisenbraun, Robert Geer, Mengbing Huang, Vince LaBella, Eric Lifshin, Jim Lloyd, Serge Oktyabrsky, Carl Ventrice, Alex Xue  
Ernie Levine (non-tenure track), Rodriguez, Miguel (Instructor), Yakimov, Michael (adjunct faculty-RF), Murray, Thomas (Instructor- RF), Tokranov, Vadim (Instructor-RF)

## Research

**2016-2017 Active Funding:** \$14. 8M + \$8.2M INDEX

2016-17 Ave. active funding per tenure track faculty: ~\$570K w/o INDEX

**2016-17 Expenditures (7/1/16- 6/30/17)** ~\$9.8M w/o INDEX

Average research expenditures per tenure track faculty: ~\$376K w/o INDEX

**2016-2017 Publications, presentations, patents (See Appendix B for details)**

Publications: 101

Presentations: 52

Patents & Technology disclosures: 2

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## Begley Lab

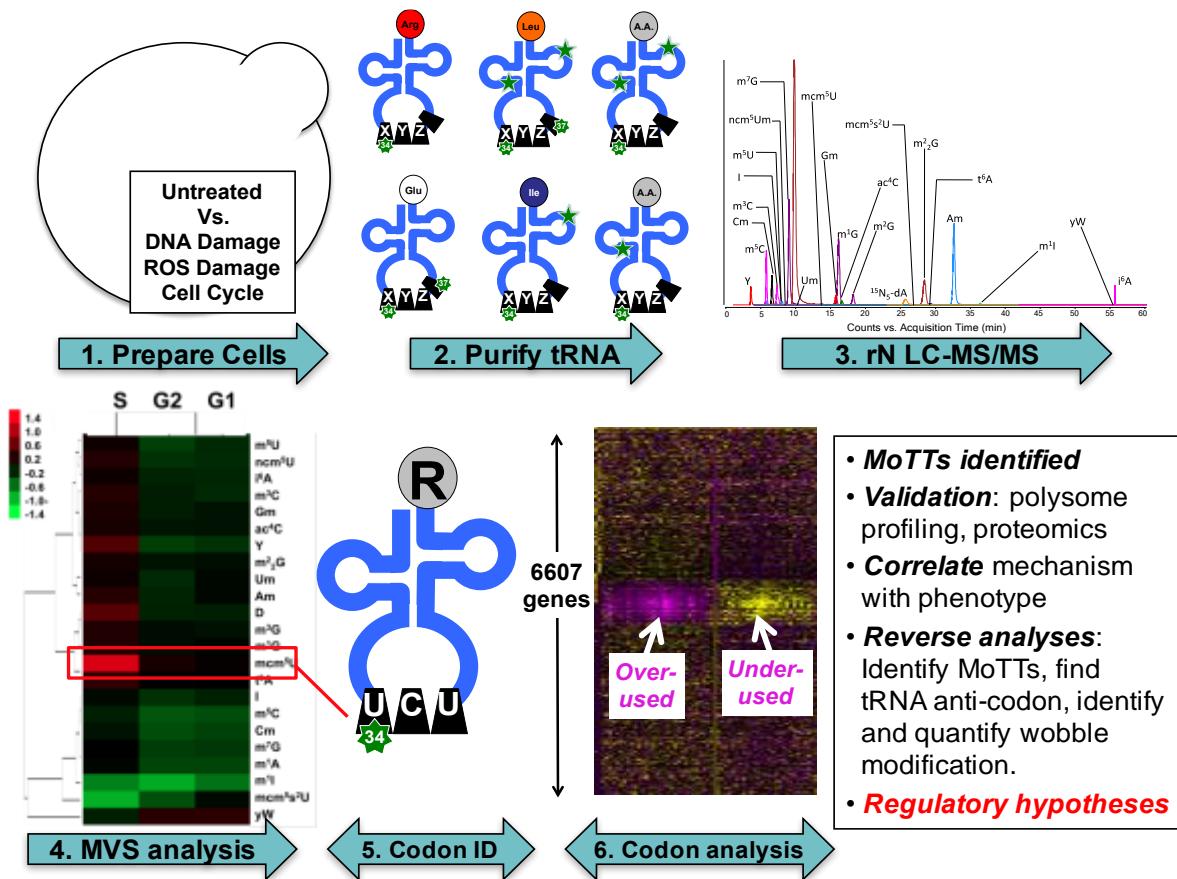
**Scope: Environmental Health, Cancer Biology, DNA & RNA Research and Technology Development**

**Goals: Define (1) new exposure biology paradigms and develop tools for (2) environmental epitranscriptomics and (3) personalized medicine**

### **2016 Accomplishments**

**TOPIC 1: Codon-biased translation can be regulated by wobble-base tRNA modification systems during cellular stress responses.**

Transfer RNA (tRNA) is a key molecule used for protein synthesis, with multiple points of stress-induced regulation that can include transcription, transcript processing, localization and ribonucleoside base modification. Enzyme-catalyzed modification of tRNA occurs at a number of base and sugar positions and has the potential to influence specific anticodon-codon interactions and regulate translation. Notably, altered tRNA modification has been linked to mitochondrial diseases and cancer progression. In this review specific to Eukaryotic systems, we discuss how recent systems-level analyses using a bioanalytical platform have revealed that there is extensive reprogramming of tRNA modifications in response to cellular stress and during cell cycle progression. Combined with genome-wide codon bias analytics and gene expression studies, a model emerges in which stress-induced reprogramming of tRNA drives the translational regulation of critical response proteins whose transcripts display a distinct codon bias. Termed Modification Tunable Transcripts (MoTTs),<sup>1</sup> we define them as (1) transcripts that use specific degenerate codons and codon biases to encode critical stress response proteins, and (2) transcripts whose translation is influenced by changes in wobble base tRNA modification. In this review we note that the MoTTs translational model is also applicable to the process of stop-codon recoding for selenocysteine incorporation, as stop-codon recoding involves a selective codon bias and modified tRNA to decode selenocysteine during the translation of a key subset of oxidative stress response proteins. Further, we discuss how in addition to RNA modification analytics, the comprehensive characterization of translational regulation of specific transcripts requires a variety of tools, including high coverage codon-reporters, ribosome profiling and linked genomic and proteomics approaches. Together these tools will yield important new insights into the role of translational elongation in cell stress response.



**Figure 1: A platform for systems-level quantification of stress-induced changes in tRNA modifications links them to regulation of specific genes based on codon usage.** The pipeline for identifying connections between specific tRNA modifications and codon-biased genes begins with (1) exposing cells to different stresses, (2) isolation and hydrolysis of tRNA, (3) HPLC resolution of individual ribonucleosides, followed by quantification of each ribonucleoside by mass spectrometry, (4) analysis of stress-induced changes by multivariate statistical analysis, (5) assignment of significantly altered ribonucleosides to specific tRNAs, and (6) analysis of the cognate codons in genome-wide, gene-specific methods to identify codon trends in stress-response transcripts.

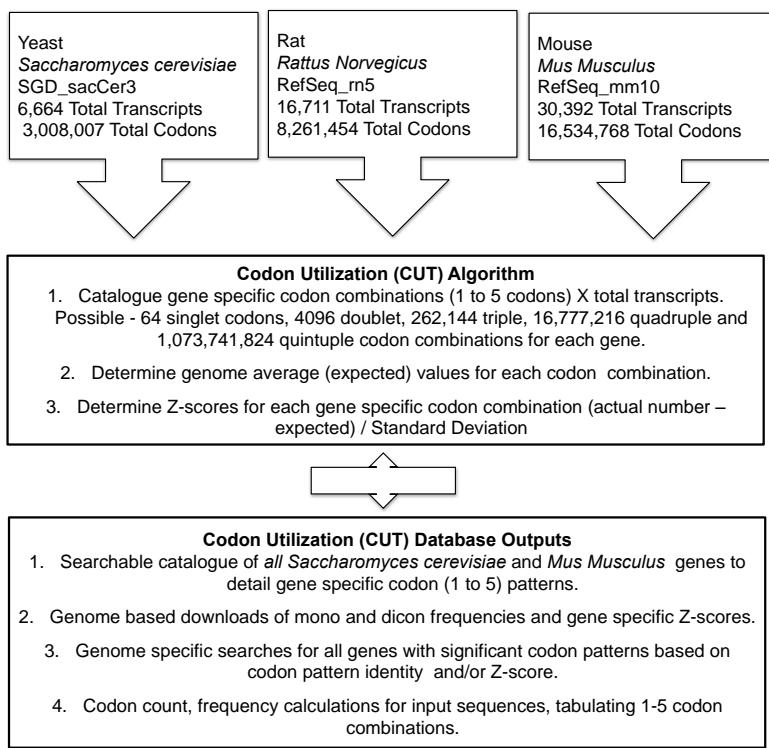
Footnote 1 Lauren Endres<sup>1</sup>, Peter C. Dedon<sup>2,3\*</sup> and Thomas J. Begley<sup>1,4\*</sup>

<sup>1</sup>State University of New York - SUNY Polytechnic Institute - College of Nanoscale Science and Engineering, Albany, NY, 12202; <sup>2</sup>Department of Biological Engineering and Center for Environmental Health Science, Massachusetts Institute of Technology, Cambridge, MA; <sup>3</sup>Singapore-MIT Alliance for Research and Technology, Singapore; <sup>4</sup>RNA Institute, University at Albany, State University of New York.

Endres., L., Dedon., P. C., and Begley, T. J. 2015. *RNA Biol.* 12(6), 603 -14.  
<http://www.ncbi.nlm.nih.gov/pubmed/25892531>

## TOPIC 2: Gene- and Genome-Based Analysis of Significant Codon Patterns in Yeast, Rat and Mice Genomes with the CUT Codon Utilization Tool

The translation of mRNA in all forms of life uses a three-nucleotide codon and aminoacyl-tRNAs to synthesize a protein. There are 64 possible codons in the genetic code, with codons for the ~20 amino acids and 3 stop codons having 1- to 6-fold degeneracy. Recent studies have shown that families of stress response transcripts, termed modification tunable transcripts (MoTTs), use distinct codon biases that match specifically modified tRNAs to regulate their translation during a stress. Similarly, translational reprogramming of the UGA stop codon to generate selenoproteins or to perform programmed translational read-through (PTR) that results in a longer protein, requires distinct codon bias (*i.e.*, more than one stop codon) and, in the case of selenoproteins, a specifically modified tRNA. In an effort to identify transcripts that have codon usage patterns that could be subject to translational control mechanisms, we have used existing genome and transcript data to develop the gene-specific Codon UTILization (CUT) tool and database, which details all 1-, 2-, 3-, 4- and 5- codon combinations for all genes or transcripts in yeast (*Saccharomyces cerevisiae*), mice (*Mus musculus*) and rats (*Rattus norvegicus*). Here, we describe the use of the CUT tool and database to characterize significant codon usage patterns in specific genes and groups of genes. In yeast, we demonstrate how the CUT database can be used to identify genes that have runs of specific codons (*e.g.*, AGA, GAA, AAG) linked to translational regulation by tRNA methyltransferase 9 (Trm9). We further demonstrate how groups of genes can be analyzed to find significant dicodon patterns, with the 80 Gcn4-regulated transcripts significantly ( $P < 0.00001$ ) over-represented with the AGA-GAA dicodon. We have also used the CUT database to identify mouse and rat transcripts with internal UGA codons, with the surprising finding of 45 and 120 such transcripts,



**Figure 2: Algorithm outputs and database design for CUT.**

Species specific inputs for yeast, rat and mouse genes are listed in the upper panel, with these gene (yeast) and transcript (rat and mouse) entries analyzed (middle panel) to catalog and provide searchable fields. Data provided in the CUT database includes species- and gene specific information on codon usage patterns and measures of the significance of said codon patterns in a specific gene (Z-score), relative to species specific genome measures.

respectively, which is much larger than expected. The UGA data suggest that there could be many more translationally reprogrammed transcripts than currently reported. CUT thus represents a multi-species codon-counting database that can be used with mRNA-, translation- and proteomics-based results to better understand and model translational control mechanisms.

<http://pare.sunycnse.com/cut/>

Footnote 2: *Frank Doyle<sup>1\*</sup>, Andrea Leonardi<sup>1\*</sup>, Lauren Endres<sup>2\*</sup>, Scott A. Tenenbaum<sup>1</sup>, Peter C. Dedon<sup>3,4</sup> and Thomas J. Begley<sup>1,5#</sup>*

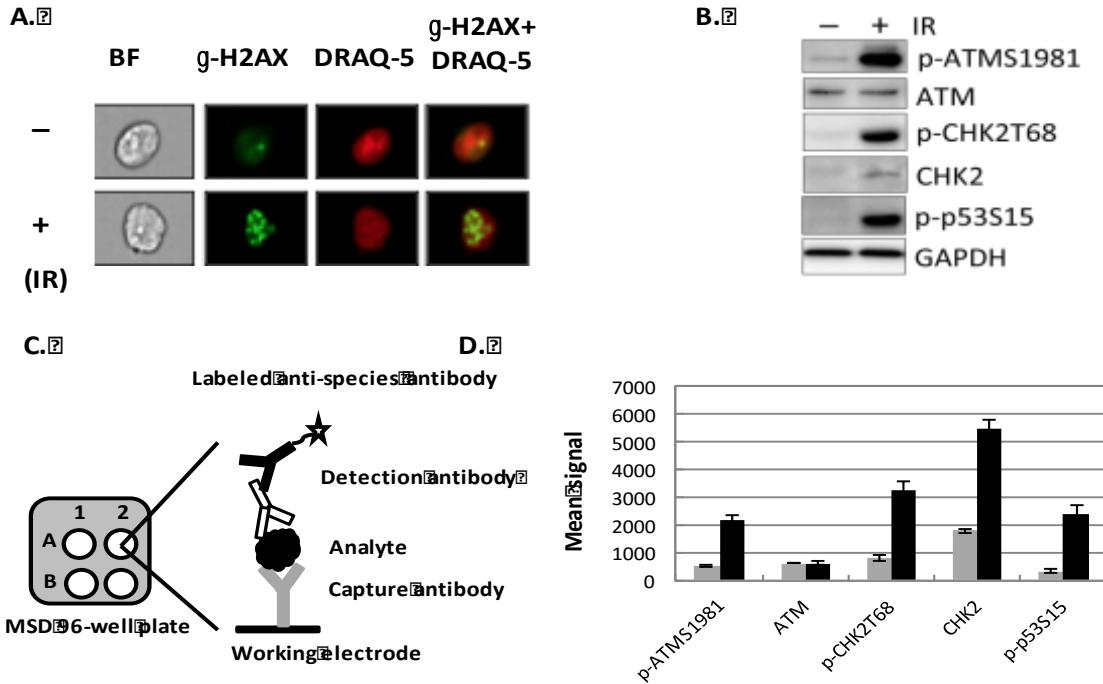
<sup>1</sup>State University of New York – SUNY Polytechnic Institute, College of Nanoscale Science and Engineering, Albany, NY; <sup>2</sup>State University of New York – SUNY Polytechnic Institute, College of Arts and Sciences, Utica, NY; <sup>3</sup>Department of Biological Engineering and Center for Environmental Health Science, Massachusetts Institute of Technology, Cambridge, MA; <sup>3</sup>Singapore-MIT Alliance for Research and Technology, Singapore; <sup>5</sup>RNA Institute, University at Albany, State University of New York.

Doyle, F., Leonardi, A., Endres, L., Tenenbaum, S.A., Dedon, P.C. and Begley, T.J. 2016. Methods. May 28.

<http://www.ncbi.nlm.nih.gov/pubmed/27245397>

**TOPIC 3: Activation of DNA damage signaling components by diagnostic computed tomography (CT) scans detected in patient samples using an electrochemiluminescence-based assay platform**

Technologies that measure activation of components of the DNA damage response (DDR) have applications in exposure assessment and personalized medicine. The DDR and associated DNA repair pathways encompass hundreds of proteins, making detailed measurement of activation technically challenging and laborious. The purpose of our study was to develop protein-specific assays for certain DDR components on a high-throughput electrochemiluminescence (ECL)-based platform. We developed five working assay pairs for ataxia telangiectasia mutated (ATM), checkpoint kinase 2 (CHK2), phosphorylated - ATM S1981, phosphorylated – CHK2 T68 and phosphorylated - tumor protein p53 (p53) S15. We validated the ECL results against traditional immunoblot and  $\gamma$ -H2AX foci measures in cell and cancer models. In an effort to test the ECL-based technology in a clinical setting, we utilized peripheral blood mononuclear cells (PBMCs) from patients undergoing computed tomography (CT) scans. CT scans represent both a valuable medical imaging diagnostic and a controlled environmental exposure to ionizing radiation for research studies, as they deliver ~2 to 31 millisieverts (mSv) and are known to activate DDR components. In this study, we show that ECL-based technology can measure the basal and damage-induced levels of DDR components in patient PBMC samples. Using a blinded study design and patient matched pre- and post CT scan samples, we show that ECL-derived data can consistently (94% of the time, 15/16 patients) identify PBMCs that have been exposed to low dose ionizing radiation associated with CT scans. Ultimately, the results of our pilot clinical study support the idea that ECL-based technology is applicable for use in clinical and population cohorts that study components of the DDR.



**Figure 3. DDR assay development and IR based validation in HEK-293G cells.** HEK293G cells were left unexposed or irradiated with ionizing radiation (4 Gy). Cells were incubated for 1-hour, fixed and (A) stained with  $\gamma$ -H2AX -FITC and DRAQ-5, followed by imaging flow cytometry using the Amnis Imagestream. (B) Immunoblot analysis of specific DDR proteins was performed using anti-phosphorylated ATM S1981, anti-ATM, anti-phosphorylated CHK2 T68, anti-CHK2 and anti-phosphorylated p53 S15. GAPDH was used as a loading control. C. The ECL- based assay design has the target protein captured and detected by antibodies that recognize two different epitopes on a protein. The third labeled anti-species antibody works as a reporter that emits light when electrically stimulated, with the emitted light quantitatively read by the Sector 2400 instrument. (D) HEK293G cells were left unexposed (grey bars) or irradiated (4 Gy, black bars) and harvested 1-hour after exposure. 20  $\mu$ gs of lysates were added to each well of an MSD MULTI-ARRAY 96-well plate that was pre-coated with specific capture antibodies and analyzed by ECL. The mean (N = 3) and standard deviation are reported.

Footnote 3: Yiching Hsieh<sup>a,1</sup>, Ulrike Begley<sup>a</sup>, Lauren Endres<sup>b</sup>, James Keith<sup>a</sup>, Antonietta F. Hansen<sup>b</sup>, Laurence Kaminsky<sup>b</sup>, Brian McCandless<sup>b</sup> and Thomas J. Begley<sup>a,2</sup>

<sup>a</sup>State University of New York Polytechnic Institute, Colleges of Nanoscale Science and Engineering,

<sup>b</sup>State University of New York Polytechnic Institute, College of Arts and Sciences

Albany, NY, <sup>b</sup>Stratton Veterans Administration Medical Center, Albany, NY

<sup>1</sup>Current address: Tainan City 700, Taiwan

Hsieh, Y., Begley, U. Hansen, A. F., Kaminsky, L., McCandless, B., and Begley, T. J. 2017. Activation of DNA damage signaling components by diagnostic computed tomography (CT) scans detected in patient samples using an electrochemiluminescence-based assay platform. (in press at *Advances in Bioscience and Biotechnology, Special Issue on Ionizing Radiation*).

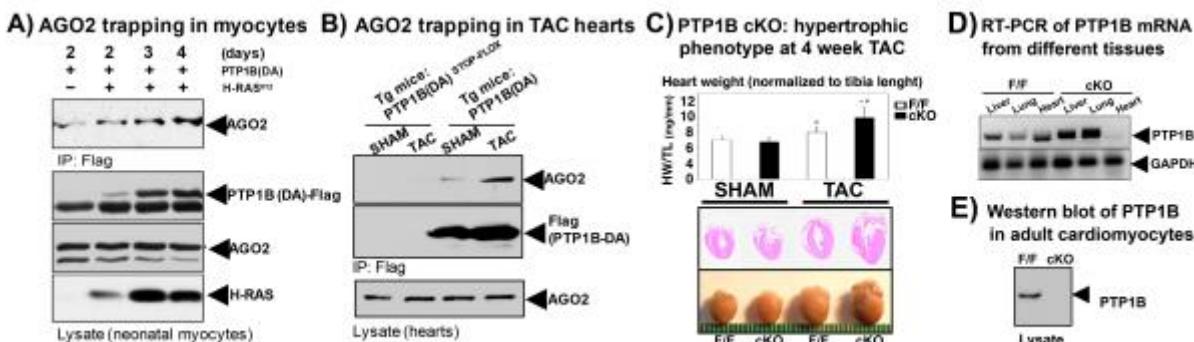
## Redox and Phosphorylation-Dependent Signaling (Boivin Group)

**Scope:** Cells have evolved means to integrate complex cues from their environment. My group explores how these cues are integrated and controlled within cells: we study how cellular oxidants regulate phosphorylation-dependent signaling in cardiovascular biology, cancer biology and environmental health and toxicology with the ultimate goal to develop technology for human health applications.

**Goals:** Identify molecular signaling nodes at the interface of phosphorylation and redox signals and develop strategies and technology to restore physiological response

### 2016 Accomplishments

**TOPIC 1:** Based on our recent publication in which we uncovered a novel function for the Protein Tyrosine Phosphatase 1B (PTP1B) in microRNA-mediated gene silencing in oncogenic senescence (1, 2), the Boivin lab submitted a research proposal to the American Heart Association (AHA). This research proposal from the AHA is titled: Characterization of PTP1B-dependent regulation of Argonaute 2 and gene silencing in pathological cardiac remodeling. This research proposal is based on key experiments that shed light on qualitative aspects of gene reprogramming in cardiac hypertrophy. In these experiments, we confirmed that gene silencing, promoted by Argonaute-2 (Ago2) tyrosine-393 phosphorylation was under the tight control of Protein Tyrosine Phosphatase 1B (PTP1B) in cardiomyocytes and in hearts undergoing hypertrophy. Based on these results, we generated cardiomyocyte-specific PTP1B knockout mice (PTP1B cKO) to further study the role of PTP1B-mediated regulation of Ago2 in cardiac remodeling. We discovered that when they were subjected to chronic pressure overload, PTP1B cKO mice displayed a dramatic left ventricular dilation, systolic and diastolic dysfunction and overall impairment of left ventricular performance compared to wild type mice. We will explore if the regulation of microRNA-mediated post-transcriptional repression by PTP1B fine-tunes gene reprogramming observed in the etiology of cardiac hypertrophy and heart failure



**Figure 1: Ago2 is a substrate of PTP1B in hypertrophied myocytes and hearts.** A) Cultured rat neonatal myocytes (CRNM) were co-transfected with PTP1B trapping mutant (PTP1B DA-Flag) and H-Ras<sup>V12</sup>, for 2, 3 or 4 days. PTP1B DA was (Flag)-immunoprecipitated, resolved and immunoblotted with anti-Ago2 antibody. Ago2 interaction with PTP1B DA increased at 3 and 4 days when PTP1B DA expression was elevated. B) Left ventricular hypertrophy was induced by transverse aortic constriction (TAC). Lysates from Sham-operated or 30-day post-TAC hearts from non-expressing PTP1B trapping mutant transgenic mice (with a STOP-flox-STOP cassette after the transgene) or mice expressing a trapping-mutant of PTP1B [PTP1B(DA), crossed with Meox-Cre mice] were subjected to Flag-immunoprecipitation. PTP1B interacting proteins were resolved, and immunoblotted with anti-Ago-2 antibody. Ago2 levels were also monitored in the heart lysates to monitor changes in expression. C) Quantitative analysis of heart weights and photograph of control PTP1B<sup>FF</sup> and PTP1B cKO mouse hearts 30 days post Sham or TAC surgery. Cardiac gene knockout of PTP1B leads to increased cardiac mass upon increased pressure overload treatment for 30 days when compared to control PTP1B<sup>FF</sup> mice. D) RT-PCR of PTP1B mRNA in different tissues from control PTP1B<sup>FF</sup> and PTP1B cKO mice. PTP1B mRNA is markedly decreased in the cardiac tissue from PTP1B cKO mice. E) Adult cardiac myocytes, freshly isolated from a control PTP1B<sup>FF</sup> or a PTP1B cKO mouse heart, were lysed, proteins were resolved, transferred and immunoblotted using an a PTP1B antibody. PTP1B expression is compromised in PTP1B cKO hearts.

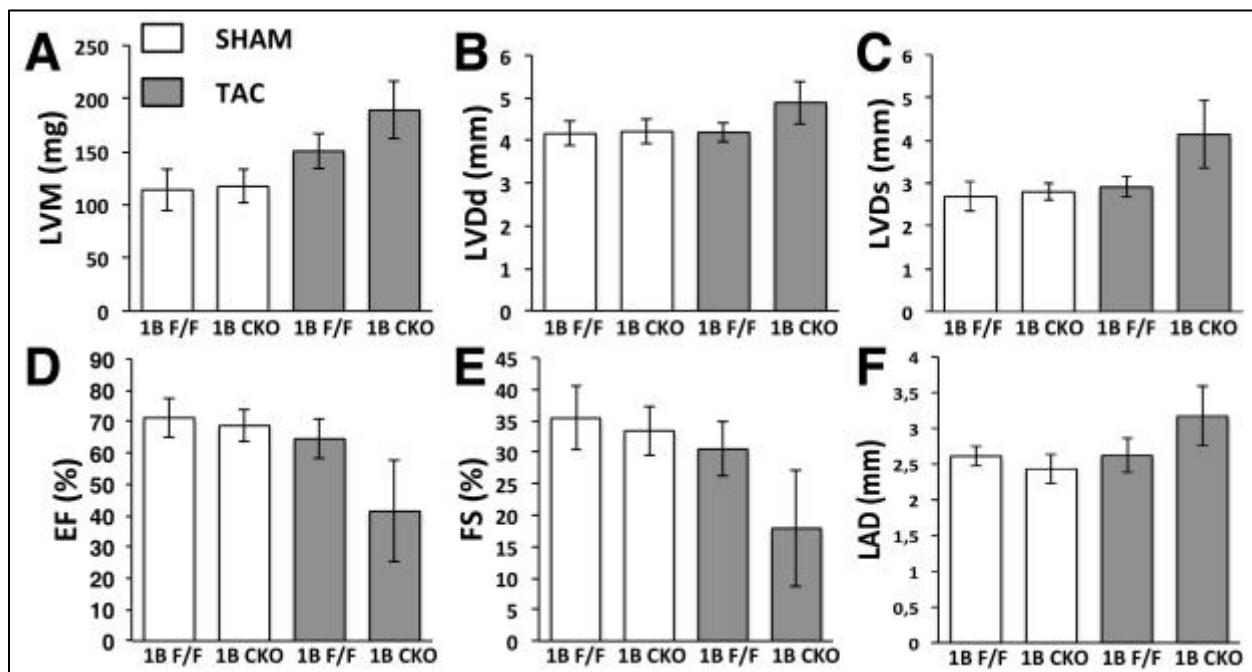
#### Footnotes

(1) Yang, M., Haase, A.D., Huang, F.K., Coulis, G., Rivera, K.D., Dickinson, B.D., Chang, C.J., Pappin, D.J., Neubert, T.A., Hannon, G.J., Boivin, B.\* and Tonks, N.K\*. (2014) Dephosphorylation of Tyrosine 393 in Argonaute 2 by Protein Tyrosine Phosphatase 1B Regulates Gene Silencing in Oncogenic RAS-Induced Senescence. *Mol. Cell.* **55**, 782-790.

(2) \*Boivin, B. and Tonks, N.K. (2015) PTP1B: deciphering ROS signal for gene silencing. *Mol. Cell. Oncol.* **2** (2): e975633-1.

\* Co-senior & co-corresponding authors

**TOPIC 2:** Based on our recent progress studying the function of PTP1B in the heart, the Boivin lab applied for an Academic Research Enhancement Award (AREA) grant (R15) from the National Heart, Lung and Blood Institute, NIH. This research proposal, submitted to the NHLBI is titled: Role of the Phosphotyrosine Phosphatase PTP1B in Cardiac Hypertrophy. This project brings together provocative aspects of cell signaling and gene silencing to further our understanding of cardiac hypertrophy. My laboratory's unique approach to understanding the transition from compensatory cardiac hypertrophy to heart failure by deciphering downstream pathways modulated by redox signaling will shed light on important, evasive molecular events. We are tackling the problem of the deleterious effects of cellular oxidants in cardiac hypertrophy using an assay that I have developed, in which stimulus-induced oxidation is harnessed to specifically "tag" PTPs involved in a given signaling response. Using this assay, we identified PTP1B as a target of redox signaling in pressure-overload hypertrophy. With the exception of indirect global gene inactivation studies, the function of PTP1B has not been studied in cardiomyocytes and in the heart. In this application, we will explore how the perturbation of the delicate balance between the action of PTP1B and an unidentified protein tyrosine kinase phosphorylating argonaute-2 is implicated in the in pathological remodeling.



**Figure 2: PTP1B CKO TAC hearts display characteristics of pathological hypertrophy.** A) TAC caused Left Ventricular (LV) hypertrophy in PTP1B<sup>FloxFloxF</sup> and PTP1B CKO. B-E) Systolic dysfunction, LV dilation, decreased fractional shortening (FS) and ejection fraction (EF) was observed in PTP1B cKO TAC mice. F) Diastolic dysfunction (increased Left Atrial Dilation at the end of systole (LAD)) was observed in PTP1B cKO TAC mice. Data from 6 to 8 mice in each group.

**TOPIC 3:** Building from previous studies in which we described a novel method to “tag” Protein Tyrosine Phosphatases (1) that are turned off by reversible oxidation in cells, regardless of their structure, abundance or substrate specificity, we explored whether haloacid dehalogenase (HAD)-type phosphatases were also redox regulated in cells. In a collaborative study with the Gohla group that specializes on haloacid dehalogenase (HAD)-type phosphatases, we modified the cysteinyl-labeling assay and investigated whether the HAD-type phosphoglycolate phosphatase PGP, also known as AUM or glycerol-3-phosphate phosphatase was redox-sensitive *in vivo* (2). We showed that recombinant, purified murine PGP was inhibited by oxidation and re-activated by reduction. We identified cysteine residues in the catalytic core domain of PGP that mediated the reversible inhibition of PGP activity and the associated, redox-dependent conformational changes. Structural analysis revealed that Cys35 oxidation weakens van-der-Waals interactions with Thr67, a conserved catalytic residue required for substrate coordination. Cys104 and Cys243 form a redox-dependent disulfide bridge between the PGP catalytic core and cap domains, which may impair the open/close-dynamics of the catalytic cycle. In addition, we demonstrated that Cys297 in the PGP cap domain was essential for redox-dependent PGP oligomerization, and that PGP oxidation/oligomerization occurred in response to stimulation of cells with EGF. Finally, employing our modified cysteinyl-labeling assay, we showed that cysteines of cellular PGP are transiently oxidized to sulfenic acids. Taken together, our findings establish that PGP, an aspartate-dependent HAD phosphatase, is transiently inactivated by reversible oxidation in cells.

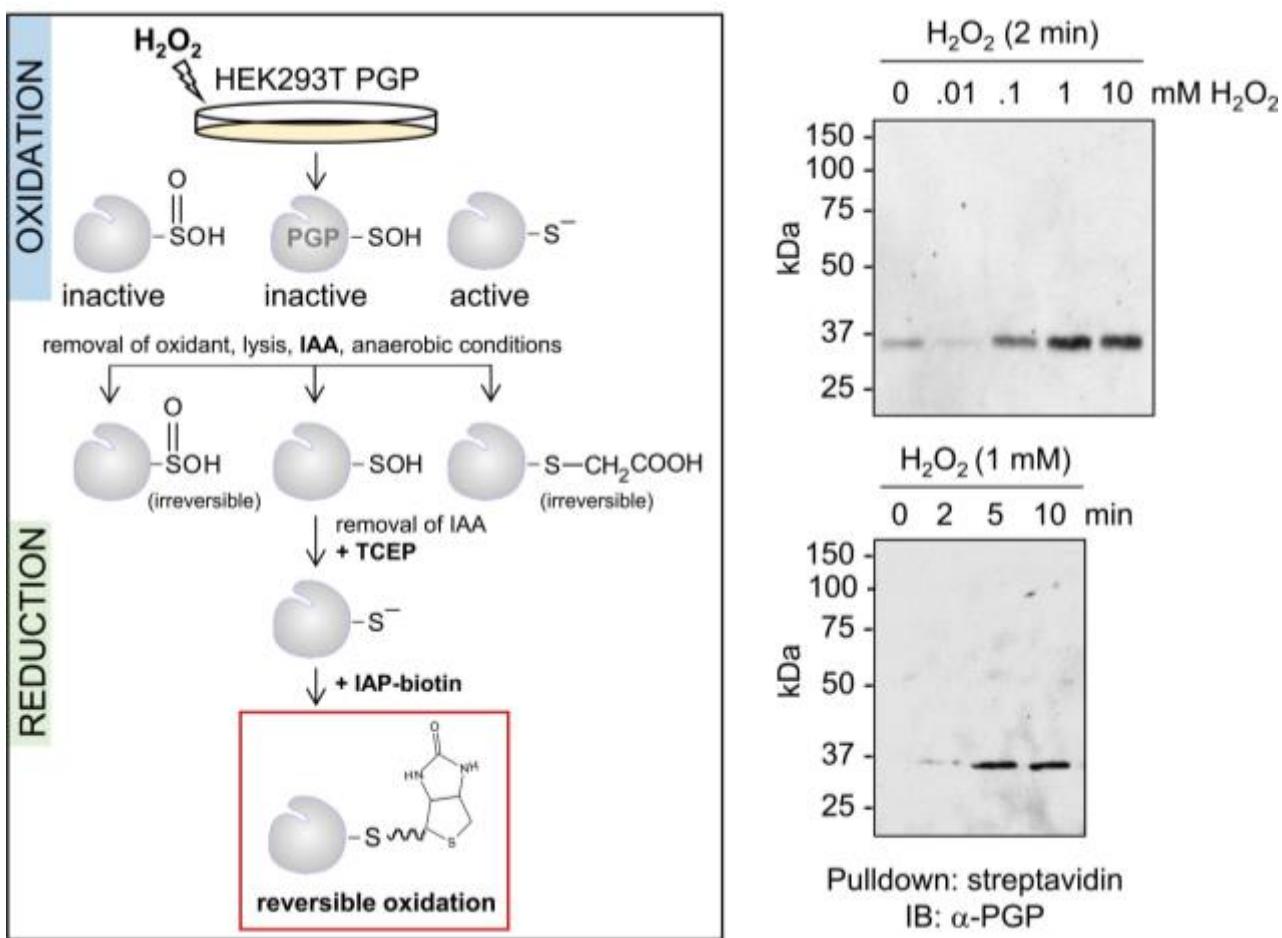


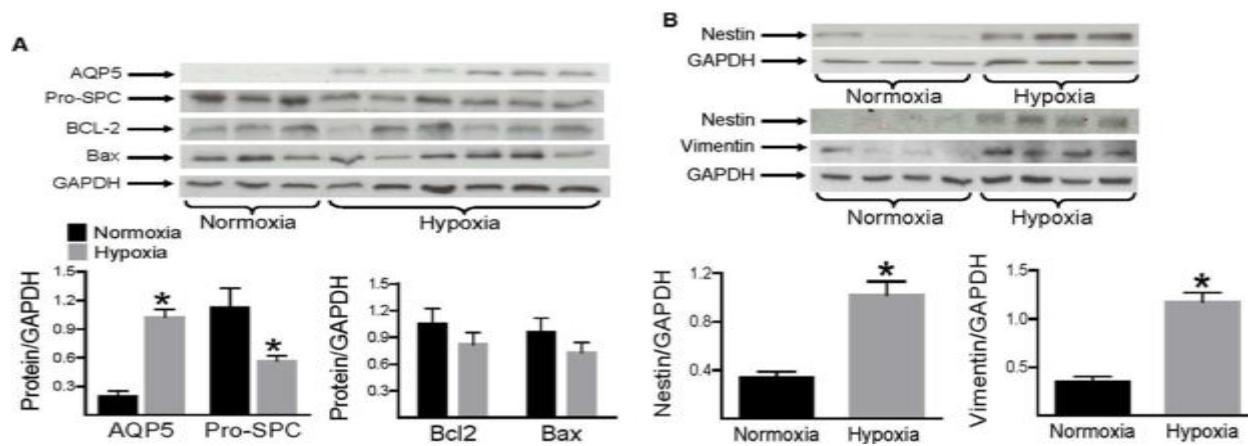
Figure 3: Reversible PGP oxidation depends on cysteine residues 35, 104, 243 and 297, and occurs in cells. (A) Purified proteins (434 nM/sample) were treated with  $\text{H}_2\text{O}_2$  and TCEP as indicated, and labeled with IAP-biotin. Redox-dependent alkylation was analyzed by Western blotting. Note the different exposure times required to reveal alkylation. (B) Principle of the modified cysteinyl-labeling assay. (C) Detection of reversible PGP oxidation in HEK293T cells in response to stimulation with  $\text{H}_2\text{O}_2$ . Cells were treated as depicted in (B), biotinylated proteins were enriched by streptavidin pulldown, and PGP was detected by immunoblotting.

#### Footnotes

(1) Boivin, B., Yang, M., Tonks, N.K. (2010) Targeting the Reversibly Oxidized Protein Tyrosine Phosphatase Superfamily. *Sci. Signal.* **3**, pl2.

(2) Seifried, A., Bergeron, A., Boivin, B., Gohla, A. (2016) Reversible oxidation controls the oligomeric state of the mammalian phosphoglycolate phosphatase AUM. *Free. Radic. Biol. Med.* **97**, 75-84

**TOPIC 4:** We identified endothelial and epithelial cell transition to a mesenchymal phenotype as cellular paradigms implicated in the appearance of reactive fibrosis in lung disease. In this study, we tested the hypothesis that the transition of endothelial and epithelial cells to a mesenchymal phenotype was delineated by nestin expression. Following hypobaric hypoxia, adult rats characterized by alveolar and perivascular lung fibrosis were associated with increased nestin protein levels and collagen type I (+)-fibroblasts. Interestingly, epithelial cells in the lungs of hypobaric hypoxic rats transitioned to a mesenchymal phenotype characterized by the co-expression of E-cadherin and collagen. The results of this publication revealed that the transition of endothelial and epithelial cells to a mesenchymal cell contributes in part to the appearance nestin/collagen type I (+)-fibroblasts and the reactive fibrotic response in the lungs of hypobaric hypoxic rats.



**Figure 4:** Reversible Protein expression in the lungs of hypobaric hypoxic rats. (A) Aquaporin 5 (AQP5) protein levels were significantly increased, pro- surfactant protein C (pro-SPC) levels reduced whereas B-cell lymphoma 2 (Bcl2) and Bcl-2-associated X protein (Bax) expression remained unchanged in the lungs of rats exposed to hypobaric hypoxia. (B) Nestin and vimentin protein levels were significantly increased in the lungs of rats exposed to hypobaric hypoxia.

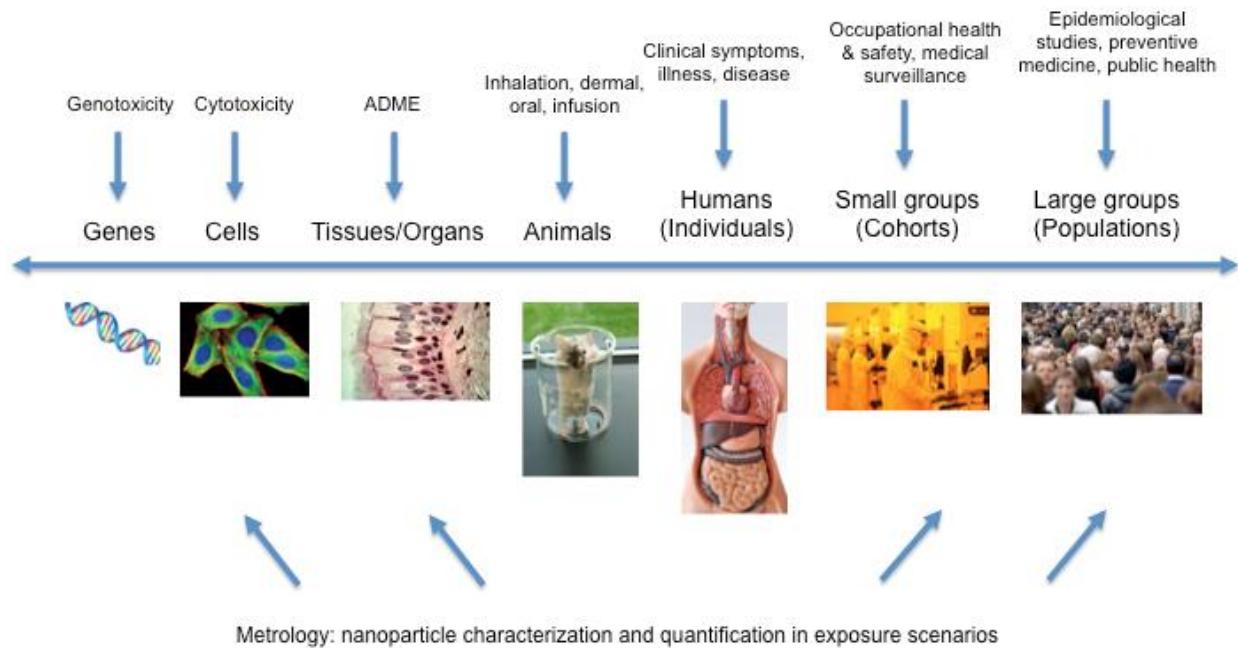
#### Footnote

Chabot, A., Hertig, V., Bosher, E., Nguyen, Q.T., Boivin, B., et al. (2016) Endothelial and Epithelial Cell Transition to a Mesenchymal Phenotype Was Delineated by Nestin Expression. *J. Cell Physiol.* **231**, 1601-10

# Occupational and Environmental Health and Safety of Engineered Nanomaterials

Sara Brenner, MD, MPH

**Scope:** To proactively address the emerging needs of health and safety research related to engineered nanomaterials, seeking to develop in real-time the innovative technologies and methodologies needed to assess, monitor, and safely accelerate nanotechnology.



Stebounova, L, Morgan H, Grassian V, **Brenner S**. Health and Safety Implications of Occupational Exposure to Engineered Nanomaterials. *WIREs Nanomedicine & Nanobiotechnology* 2012, 4, 310-321.

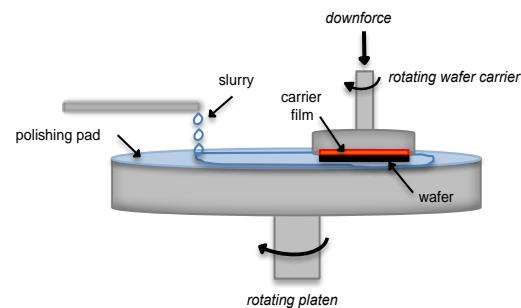
**Goals:** My research focuses on the health and safety of individuals, workers, populations, and the environment as they relate to engineered nanomaterials. Through research projects across a broad portfolio, I serve as a link between basic life science research, clinical translational research, direct patient care, and public health interventions aimed at improving population and individual health outcomes. Over the past seven years, I was involved in the formation and operation of the NanoHealth and Safety Center (NSC) at CNSE, a public-private partnership that addressed gaps in our understanding of the safety and risks associated with the unique characteristics of nanoscale materials used in the semiconductor industry. With a background in basic science, internal medicine, and preventive medicine, I oversee a research team that assesses the health and safety of individuals, workers, and populations through the lens of occupational risks, hazards, and exposures. The disciplines of occupational medicine, environmental health, epidemiology, public policy, health care administration, and social and behavioral health intersect at critical points in the design and implementation of appropriate health and safety research relevant to nanotechnology in the workplace, consumer market place,

and environment. I aim to address these considerations as well as the public policy, social, and ethical implications of nanotechnology in order to guide the vision and direction of occupational and environmental health and safety research and regulation.

## 2016 Accomplishments

### TOPIC 1: Occupational Exposure Assessment of Engineered Nanoparticles During Chemical Mechanical Planarization (CMP) Operation and Maintenance

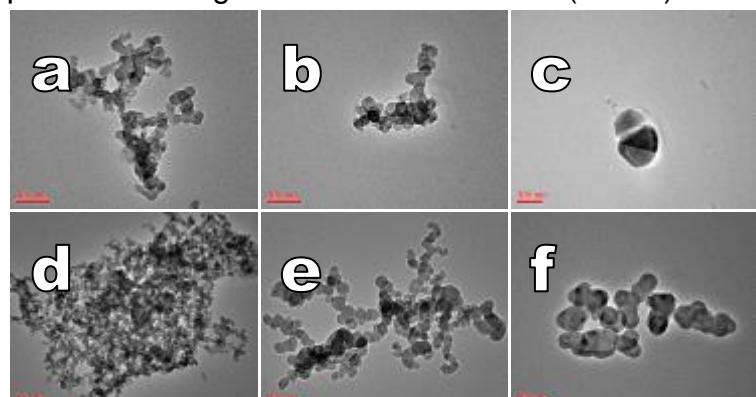
Engineered nanoparticles are used in the semiconductor industry during chemical mechanical planarization (CMP), a process that occurs multiple times at different stages of the integrated circuit (IC) fabrication process for silicon complementary metal-oxide-semiconductor transistors (Fig. 1). Because of their size and novel chemical physical properties, certain nanoparticles (NPs) could be more toxic than their bulk material, with the potential that existing occupational control measures and exposure limits may not be sufficiently protective. Currently, there is little published data available on potential occupational exposures to the engineered nanoparticles used in CMP (nanoscale alumina, silica, ceria). Additional studies are needed to evaluate potential nanoparticle exposures in the workplace.



**Figure 1: CMP polishing mechanism.** (Roth GA, Neu-Baker NM, Brenner SA. SEM analysis of particle size during conventional treatment of CMP process wastewater. *Sci. Tot. Environ.* 2015, 508:1-6. doi:10.1016/j.scitotenv.2014.11.075.)

Our research assesses potential worker exposures to engineered nanomaterials (ENMs) and agglomerates during CMP tool operation, maintenance and related tasks. We obtained air samples from the task area and workers' personal breathing zones to assess the potential for inhalation exposure to ENMs. This was achieved by using multiple complementary instruments and approaches to compare particle number concentrations during tasks with potential exposure to nanoparticles with background levels, and to characterize airborne particulate by size, morphology, and chemical composition. Microvacuum samples of selected surfaces in the workplace were also collected and analyzed for the presence of the materials of interest to assess for potential cutaneous exposure.

Based on findings from 2011-2013, different areas at the sampling location where workers



**Figure 2: TEM images of air samples obtained in the cleanroom, subfab, and WWT.** (a)-(b) Agglomerates of amorphous silica from WWT task area. Scale bars = 100nm. (c) Alumina from worker PBZ in WWT. Scale bar = 100nm. (d) Mixed Al-Si agglomerate from WWT background. Scale bar = 0.2um. (e) Agglomerate of amorphous silica from subfab task area. Scale bar = 100nm. (f) Agglomerate of alumina from the cleanroom task area. Scale bar = 100nm. (Brenner SA, Neu-Baker NM, Eastlake AC, Beaucham CC, Geraci CL. NIOSH Field Studies Team assessment: worker exposure to aerosolized metal oxide nanoparticles in a semiconductor fabrication facility. *J. Occup. Environ. Hyg.* 2016, 13(11): 871-880.)

handle ENMs were identified for further testing based on the likelihood of inhalation or cutaneous exposures. To date, results from air and surface samples collected suggest that ENMs used or generated by CMP become aerosolized during various tasks and may be accessible for inhalation or cutaneous exposures by workers (Fig. 2). A deeper investigation and further exposure assessments have been prioritized based on risk. Additional research is needed to further quantify the level of exposure and determine the potential human health impacts. Furthermore, it is important to interpret this exposure assessment data alongside hazard (toxicological) data in order to assess risk to workers. Risk assessments should also be conducted in conjunction with information available regarding the effectiveness of personal protective equipment and other controls in order to reduce exposures to ENMs.

The most significant hurdle holding back exposure science, risk assessment, and the development of safety guidelines for the nanotechnology workforce is the lack of validated analytical techniques that accurately identify and characterize ENMs captured in occupational settings. The associated costs, time, and lack of standardization of existing methods make it impossible for industries to implement exposure assessment programs or comply with new or forthcoming recommended exposure limits for ENMs. This research team seeks to advance the state of the science by developing and testing a new protocol for analysis of ENMs on filters by: further developing a novel hyperspectral imaging (HSI) method for high-throughput screening; evolving best-known methods for direct visualization of filter-captured ENMs by developing and incorporating advanced techniques into the new protocol; and testing the new protocol on real-world samples obtained during occupational exposure scenarios.



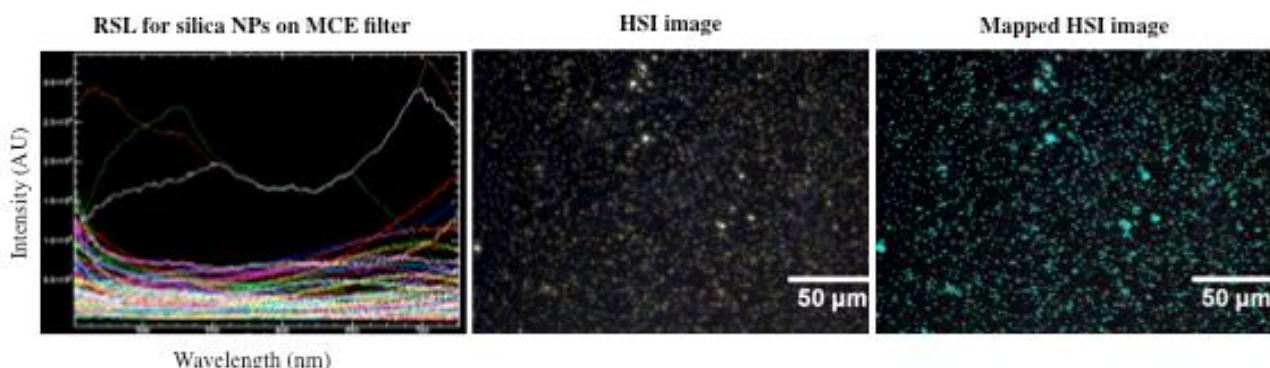
#### Relevant publications:

- 1) Brenner SA, Neu-Baker NM, Eastlake AC, Beaucham CC, Geraci CL. NIOSH Field Studies Team assessment: worker exposure to aerosolized metal oxide nanoparticles in a semiconductor fabrication facility. *Journal of Occupational and Environmental Hygiene* 2016, 13(11): 871-880. doi: 10.1080/15459624.2016.1183015.
- 2) Brenner SA, Neu-Baker NM, Caglayan C, Zurbenko IG. An occupational exposure assessment for airborne metal oxide nanoparticles in a semiconductor fab and subfab. *Journal of Occupational and Environmental Hygiene* 2016, 13(9): D138-D147. doi: 10.1080.15459624.2016.1183012.
- 3) Brenner SA, Neu-Baker NM, Caglayan C, Zurbenko IG. Occupational exposure to airborne nanomaterials: an assessment of worker exposure to aerosolized metal oxide nanoparticles in semiconductor wastewater treatment. *Journal of Occupational and Environmental Hygiene* 2015, 12(7):469-481. doi:10.1080/15459624.2015.1018515.
- 4) Roth GA, Neu-Baker NM, Brenner SA. SEM analysis of particle size during conventional treatment of CMP process wastewater. *Science of the Total Environment* 2015, 508:1-6. doi:10.1016/j.scitotenv.2014.11.075.
- 5) Brenner SA, Neu-Baker NM. Occupational exposure to nanomaterials: assessing the potential for cutaneous exposure to metal oxide nanoparticles in a semiconductor facility. *Journal of Chemical Health and Safety* 2015, 22(4):10-19. doi:10.1016/j.jchas.2014.11.001.
- 6) Shepard M, Brenner S. Cutaneous exposure scenarios for engineered nanoparticles used in semiconductor fabrication: a preliminary investigation of workplace surface contamination. *International Journal of Occupational and Environmental Health* 2014, 20(3):247-257. doi: 10.1179/2049396714Y.0000000074.
- 7) Shepard MN, Brenner S. An occupational exposure assessment for engineered nanoparticles used in semiconductor fabrication. *Annals of Occupational Hygiene* 2014, 58(2):251-265. doi: 10.1093/annhyg/met064.

## TOPIC 2: Development of Advanced Imaging and Analytical Techniques for Occupational Exposure to Nanomaterials

This project assists the U.S. National Institute for Occupational Safety and Health (NIOSH) by advancing risk assessment and reduction strategies for occupational exposures, monitoring of materials that may impact population health and public safety, and the development of industrial practice standards for product safety. Monitoring and surveillance techniques are being developed with NIOSH and other collaborators and partners to assess the occupational impact of exposure to nanomaterials. A framework will be built to employ custom-tailored strategies to mitigate potential risks associated with nanotechnology-based manufacturing and formulation processes that are currently in use to create nano-enabled products already on the market as well as those under development. NIOSH, in dialogue with SUNY Poly CNSE and other research centers, has identified a fundamental hurdle in advancing exposure science for the nanotechnology workforce: the lack of validated analytical techniques that consistently, reliably, and accurately identify and characterize ENMs captured in occupational settings. Exploring new or alternate visualization techniques is critical for addressing exposure assessment needs.

Hyperspectral imaging (HSI) is a versatile technique that has seen use in geological and ecological studies due to its ability to map materials based on their characteristic spectral profile. These profiles on a macroscopic scale are heavily indicative of the material's composition. The Brenner Research Team has employed an Olympus BX-43 microscope equipped with a darkfield camera, a hyperspectral camera, and a CytoViva® light source to enable the same materials analysis on nanoscale materials. Spectral profiles for nine commercial CMP slurries have been assembled into a reference library for comparison to unknown samples. This library has been verified to successfully map pixels in identifiable particles while excluding background pixels. Reference spectral libraries will be developed for each ENM involved in the study (Fig. 3).



**Figure 3: Silica reference spectral library (RSL), hyperspectral image, and mapped hyperspectral image.** Left: RSL for silica NPs (Sigma Aldrich) on MCE filter. Center: 40x hyperspectral image of silica NPs on MCE filter. Right: mapped hyperspectral image of silica NPs on MCE filter. Aqua map indicates pixels with spectra that positively match spectra in the RSL, indicating presence and location of silica NPs. (Neu-Baker NM, Smith D, Segrave A, Beach J, Zurbenko IG, Dunn K, Brenner SA. Protecting the nanotechnology workforce: a new protocol for characterization of filter-captured nanomaterials from occupational exposure assessments. *TechConnect World Innovation Conference & Expo Proceedings*. March 2017.)

**Relevant publications:**

- 1) Neu-Baker NM, Smith D, Segrave A, Beach J, Zurbenko IG, Dunn K, Brenner SA. Protecting the nanotechnology workforce: a new protocol for characterization of filter-captured nanomaterials from occupational exposure assessments. *TechConnect World Innovation Conference & Expo Proceedings*. Accepted March 2017.
- 2) Neu-Baker NM, Eastlake AC, Brenner SA. Developing a rapid screening method for direct visualization of nanoparticles captured on filter media during occupational exposure assessments. *TechConnect World Innovation Conference & Expo Proceedings*. Accepted March 2017.
- 3) Dillon JCK, Bezerra L, Sosa Peña MP, Neu-Baker NM, Brenner SA. Hyperspectral data influenced by sample matrix: the importance of building relevant reference spectral libraries to map materials of interest. *Microscopy Research and Technique*. 2017. doi: 10.1002/jemt.22816
- 4) Idelchik MPS, Neu-Baker NM, Chandrasekaran A, Friedman AJ, Frame MD, Brenner SA. Relative quantitation of metal oxide nanoparticles in a toxicological model using enhanced darkfield microscopy and hyperspectral mapping. *NanoImpact* 2016, 3-4:12-21. doi:10.1016/j.impact.2016.09.006.
- 5) Guttenberg M, Bezerra L, Neu-Baker NM, Sosa Peña MP, Elder A, Oberdörster G, Brenner SA. Biodistribution of inhaled metal oxide nanoparticles mimicking occupational exposure: a preliminary investigation using enhanced darkfield microscopy. *Journal of Biophotonics* 2016, 9(10):987-993. doi:10.1002/jbio.201600125.
- 6) Sosa Peña MP, Gottipati A, Tahiliani S, Neu-Baker NM, Frame MD, Friedman AJ, Brenner SA. Hyperspectral imaging of nanoparticles in biological samples: simultaneous visualization and elemental identification. *Microscopy Research and Technique* 2016, 79(5):349-358. doi:10.1002/jemt.22637.
- 7) Roth GA, Sosa Peña MP, Neu-Baker NM, Tahiliani S, Brenner SA. Identification of metal oxide nanoparticles in histological samples by enhanced darkfield microscopy and hyperspectral mapping. *Journal of Visualized Experiments* 2015, 106:53317. doi:10.3791/53317.
- 8) Roth GA, Tahiliani S, Neu-Baker NM, Brenner SA. Hyperspectral microscopy as an analytical tool for nanomaterials: advanced review. *WIREs Nanomedicine & Nanobiotechnology*. Available online January 2015. doi:10.1002/wnan.1330.

**TOPIC 3: Advancing Nanoscale Imaging Technology for Environmental and Biological Applications: Development and Commercialization of Customized Software Plugins to Expedite Hyperspectral Data Acquisition and Image Analysis**

*Collaborators: James Beach, PhD, CytoViva, Inc.; Brian Northan, True North Intelligent Algorithms, LLC*

Enhanced darkfield microscopy and hyperspectral imaging (EDFM-HSI) is an emerging technique for direct visualization and hyperspectral analysis of ENMs in a variety of matrices. HSI combines spectrophotometry and imaging to capture spectral data in the visible and near-infrared (VNIR) wavelengths for each pixel in a hyperspectral image. Spectral data can be used to identify ENMs of interest using a mapping algorithm, such as the spectral angle mapper (SAM). The CytoViva (CytoViva, Inc., Auburn, AL) EDFM-HSI system has broad-ranging applications across numerous scientific disciplines for the visualization and identification of nanoscale materials. Dr. Brenner and her research team are at the forefront of methods development for EDFM-HSI of engineered NPs in animal tissues from toxicology collaborations, NPs in industrial wastewater, and NPs captured on filter media from occupational exposure assessments. Based on research conducted by the Brenner Research team utilizing this tool since 2012 and other CytoViva users around the world, it is clear that the existing HSI analysis software (ENVI 4.8, Harris Geospatial Solutions) does not allow for high-throughput analysis and is missing essential functions which greatly hinders data acquisition, timely dissemination of research results, and widespread use of EDFM-HSI for biological and environmental applications. This project seeks to break through these existing limitations by developing a new

suite of low-level, open source hyperspectral data analysis and visualization routines, which will be used to build proprietary plugins using ImageJ (NIH) for use with the CytoViva EDFM-HSI system. The overarching goal of this project is to develop a series of low-level libraries that can be shared with other researchers (short-term) and commercialize a full suite of high-level automated analysis plugins that will facilitate applications for HSI research and development for a broad range of scientific and industrial applications (long-term).



**Relevant publications:**

- 1) Neu-Baker NM, Smith D, Segrave A, Beach J, Zurbenko IG, Dunn K, Brenner SA. Protecting the nanotechnology workforce: a new protocol for characterization of filter-captured nanomaterials from occupational exposure assessments. *TechConnect World Innovation Conference & Expo Proceedings*. Accepted March 2017.
- 2) Neu-Baker NM, Eastlake AC, Brenner SA. Developing a rapid screening method for direct visualization of nanoparticles captured on filter media during occupational exposure assessments. *TechConnect World Innovation Conference & Expo Proceedings*. Accepted March 2017.
- 3) Dillon JCK, Bezerra L, Sosa Peña MP, Neu-Baker NM, Brenner SA. Hyperspectral data influenced by sample matrix: the importance of building relevant reference spectral libraries to map materials of interest. *Microscopy Research and Technique*. 2017. doi: 10.1002/jemt.22816
- 4) Idelchik MPS, Neu-Baker NM, Chandrasekaran A, Friedman AJ, Frame MD, Brenner SA. Relative quantitation of metal oxide nanoparticles in a toxicological model using enhanced darkfield microscopy and hyperspectral mapping. *NanoImpact* 2016, 3-4:12-21. doi:10.1016/j.impact.2016.09.006.
- 5) Guttenberg M, Bezerra L, Neu-Baker NM, Sosa Peña MP, Elder A, Oberdörster G, Brenner SA. Biodistribution of inhaled metal oxide nanoparticles mimicking occupational exposure: a preliminary investigation using enhanced darkfield microscopy. *Journal of Biophotonics* 2016, 9(10):987-993. doi:10.1002/jbio.201600125.
- 6) Sosa Peña MP, Gottipati A, Tahiliani S, Neu-Baker NM, Frame MD, Friedman AJ, Brenner SA. Hyperspectral imaging of nanoparticles in biological samples: simultaneous visualization and elemental identification. *Microscopy Research and Technique* 2016, 79(5):349-358. doi:10.1002/jemt.22637.
- 7) Roth GA, Sosa Peña MP, Neu-Baker NM, Tahiliani S, Brenner SA. Identification of metal oxide nanoparticles in histological samples by enhanced darkfield microscopy and hyperspectral mapping. *Journal of Visualized Experiments* 2015, 106:53317. doi:10.3791/53317.
- 8) Roth GA, Tahiliani S, Neu-Baker NM, Brenner SA. Hyperspectral microscopy as an analytical tool for nanomaterials: advanced review. *WIREs Nanomedicine & Nanobiotechnology*. Available online January 2015. doi:10.1002/wnan.1330.

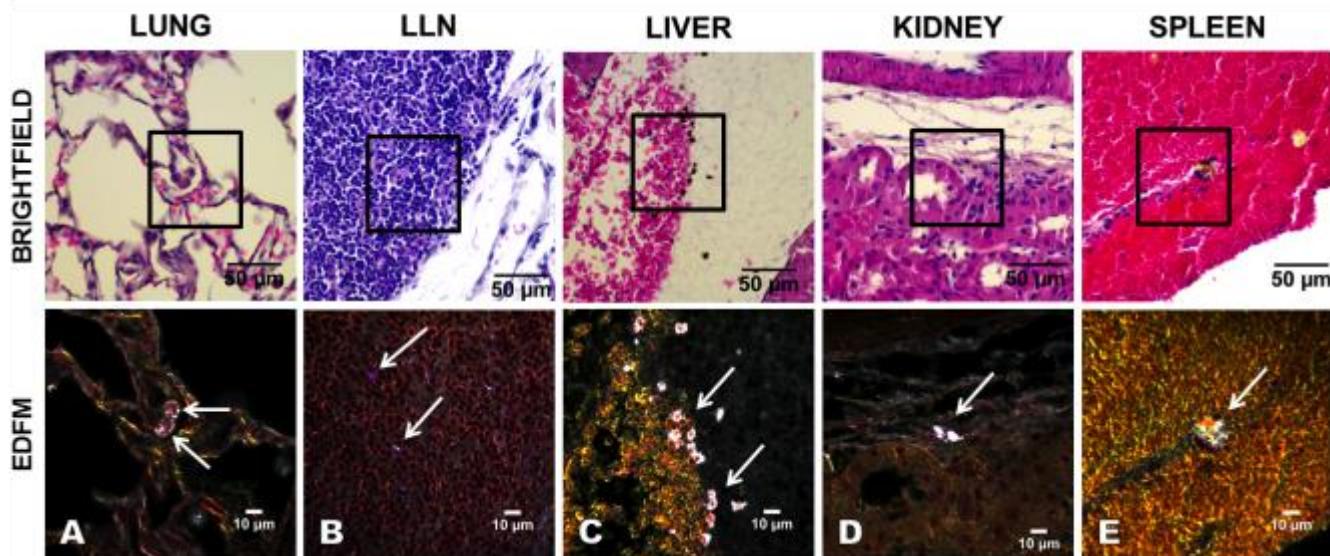
**TOPIC 4: Acute and Subchronic Effects Following Inhalation Exposure to Engineered Metal Oxide Nanoparticles in a Rat Model**

*Collaborators: Günter Oberdörster, DVM, PhD and Alison Elder, PhD, University of Rochester*

Inhalation has been identified as the most prominent potential route of human exposure during manufacturing, distribution and use of engineered nanomaterials. There are, however, major challenges to performing a realistic risk assessment for these materials due to a lack of accurate occupational exposure data and of health effects-related data using realistic exposure conditions. Until now, *in vitro* and *in vivo* studies have identified hazard using bolus type delivery methods and unrealistically high doses in order to induce an inflammatory response. Furthermore, bolus type delivery methods are limited in determining chronic health effects that may result from prolonged exposure to very low concentrations. This study investigates the extent to which dose, dose rate and duration of exposure to slurries containing metal oxide

nanoparticles influences associated health outcomes. Specifically, this study evaluates dose-related outcomes following inhalation exposures in rats to  $\text{SiO}_2$ ,  $\text{Al}_2\text{O}_3$  and  $\text{CeO}_2$  NP-containing slurries, as well as traditional bolus delivery methods for comparison. This study also aims to characterize the retention of inhaled slurry NPs in different regions of the respiratory tract and translocation to secondary organs.

A goal of the study is to identify and characterize nanoparticle retention in the lungs and potential translocation to other organs. Organ sections from the acutely exposed rats were prepared for brightfield and darkfield microscopy. In this way, we are able to elucidate the biodistribution of these metal oxide nanoparticles following inhalation exposure. To date, we have observed materials of interest in each organ type sectioned and prepared from these studies (Fig. 4). We have discovered that nanoparticles reach the circulatory system, likely through the lungs where they have been observed in the blood vessels. Additionally, nanoparticles have been located in other organs as well, though it is as of yet uncertain whether they are the same particles as the exposure. Identifying contaminant at this time remains a major issue, but one that is slowly getting resolved as the ENMs used for exposure become better characterized to allow for easier exclusion of others. This is currently under investigation, as well as determining a method for semi-quantitative analysis of biodistribution using EDFM.



**Figure 4: Biodistribution of NPs in organs of rats exposed via inhalation to ceria NPs.** The top row shows brightfield (BF) images taken at 40x magnification, with their respective EDFM images at 100x magnification shown in the bottom row. From left to right, (A) Multiple NPs (arrows) are seen within two alveolar macrophages in the alveolar space of the lung. This rat was exposed to a medium concentration ( $7.4\text{mg}/\text{m}^3$ ) of ceria NP-containing slurry aerosol for 4 hours, and sacrificed at 7 days post-exposure. (B) Multiple NPs (arrows) are seen among the white blood cells in the lymph node. This rat was exposed to a high concentration ( $9.5\text{mg}/\text{m}^3$ ) of ceria slurry aerosol for 6 hours, and sacrificed at 24 hours post-exposure. (C) A central vein in the liver shows a dilated lumen congested with red blood cells and multiple NPs (arrows). This rat was exposed to a medium concentration ( $7.4\text{mg}/\text{m}^3$ ) of ceria slurry aerosol for 4 hours, and sacrificed at 7 days post-exposure. (D) Two clusters of NPs (arrow) are seen over the connective tissue adjacent to several tubules in the renal cortex. This rat was exposed to a high concentration ( $9.5\text{mg}/\text{m}^3$ ) of ceria slurry aerosol for 6 hours, and sacrificed at 24 hours post-exposure. (E) Multiple agglomerated NPs (arrow) are shown in the red pulp of the spleen surrounded by numerous red blood cells. This rat was exposed to a low concentration ( $3.5\text{mg}/\text{m}^3$ ) of ceria slurry aerosol for 4 hours, and sacrificed at 24 hours post-exposure. (Guttenberg M, Bezerra L, Neu-Baker NM, Sosa Peña MP, Elder A, Oberdörster G, Brenner SA. Biodistribution of inhaled metal oxide nanoparticles mimicking occupational exposure: a preliminary investigation using enhanced darkfield microscopy. *J. Biophoton.* 2016; 9(10):987-993.)



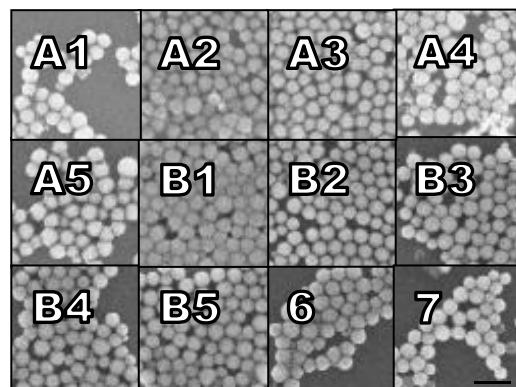
#### Relevant publications:

- 1) Dillon JCK, Bezerra L, Sosa Peña MP, Neu-Baker NM, Brenner SA. Hyperspectral data influenced by sample matrix: the importance of building relevant reference spectral libraries to map materials of interest. *Microscopy Research and Technique*. 2017. doi: 10.1002/jemt.22816
- 2) Idelchik MPS, Neu-Baker NM, Chandrasekaran A, Friedman AJ, Frame MD, Brenner SA. Relative quantitation of metal oxide nanoparticles in a toxicological model using enhanced darkfield microscopy and hyperspectral mapping. *NanoImpact* 2016, 3-4:12-21. doi:10.1016/j.impact.2016.09.006.
- 3) Guttenberg M, Bezerra L, Neu-Baker NM, Sosa Peña MP, Elder A, Oberdörster G, Brenner SA. Biodistribution of inhaled metal oxide nanoparticles mimicking occupational exposure: a preliminary investigation using enhanced darkfield microscopy. *Journal of Biophotonics* 2016, 9(10):987-993. doi:10.1002/jbio.201600125.
- 4) Sosa Peña MP, Gottipati A, Tahiliani S, Neu-Baker NM, Frame MD, Friedman AJ, Brenner SA. Hyperspectral imaging of nanoparticles in biological samples: simultaneous visualization and elemental identification. *Microscopy Research and Technique* 2016, 79(5):349-358. doi:10.1002/jemt.22637.
- 5) Kennell A, Gelein R, Wade-Mercer P, Brenner S, Oberdörster G, Elder A. Acute effects following inhalation exposure to metal oxide nanoparticle containing chemical mechanical planarization slurries. *Toxicologist* 2015. (poster presentation at 2015 Society of Toxicology conference)

#### TOPIC 5: Identification and Determination of Fate of SiO<sub>2</sub> and Metal Oxide Nanoparticles During Conventional Wastewater Treatment

Characterization of ENMs used in or generated by industrial processes, their fate, and their health effects will help to inform employee and environmental health and safety policy. We were able to fully develop a scanning particle mobility particle sizing (SMPS) protocol, which enabled accurate characterization of CMP slurries while minimizing the non-trivial background effects, and should be amenable to other aqueous samples, such as wastewater. We also examined these materials by single-particle inductively-coupled plasma mass spectrometry (SP-ICP-MS) and inductively-coupled plasma optical emission spectroscopy (ICP-OES). Results from ICP-OES and SP-ICP-MS were able to determine the mass and had a high degree of similarity, and indicate that safety data sheets (SDS) provided by slurry manufacturers may be highly inaccurate, which is a safety concern. While SMPS provided some excellent information on particle counts and size, agreeing reasonably with other measurement techniques, SP-ICP-MS yielded unusually low counts and anomalous sizes, and thus it may not be amenable to examining certain materials, such as silica.

We studied the fate of ENMs used in the CMP process throughout the semiconductor fabrication wastewater treatment (WWT) system. The goal of this study was to



**Figure 5: Representative SEM images of nanoparticles in wastewater samples.** Representative SEM images from a single sampling event. Since acid and base WWT systems are independent and parallel, letters "A" and "B" denote samples drawn from each of these systems, respectively. Note the relative uniformity of nanoparticles across each sample point in size and morphology (scale bar equals 100nm; all images are the same scale). (Roth GA, Neu-Baker NM, Brenner SA. SEM analysis of particle size during conventional treatment of CMP process wastewater. *Sci. Tot. Environ.* 2015, 508:1-6.)

assess whether the WWT processes resulted in size-dependent filtration of particles in the nanoscale range by analyzing wastewater samples using scanning electron microscopy (SEM). Statistical analysis demonstrated no significant differences in particle size between sampling points, indicating low or no selectivity of WWT methods for NPs based on size (Fig. 5). This work suggests that NPs could be released to the municipal waste stream from industrial sources.

In addition, we began examining the impact of these materials on primary cell lines. It was clear that silica-based slurries had, by two different metrics, a much more pronounced negative effect on viability, as they did on cancer lines. Curiously, alumina- and ceria-based slurries had positive effects on viability at low concentration.

The Brenner Research Team is also currently investigating the utility of EDFM-HSI (CytoViva) for the identification and characterization of slurry NPs in wastewater.

**Relevant publications:**

- 1) Roth GA, Neu-Baker NM, Brenner SA. Comparative characterization methods for nanoparticle abrasives. *Journal of Chemical Health and Safety* 2015, 22(6):26-32. doi:10.1016/j.jchas.2015.02.001.
- 2) Roth GA, Neu-Baker NM, Brenner SA. SEM analysis of particle size during conventional treatment of CMP process wastewater. *Science of the Total Environment* 2015, 508:1-6. doi:10.1016/j.scitotenv.2014.11.075.

## Nanobiotechnology / Bio-inspired Electronics (Prof. Nathaniel Cady)

**Scope:** The Cady group focuses on the unique interface between nanotechnology and biology. Research in our group falls into the following two general categories:

### Approaching nanotechnology from the biological world -

Nanoscale innovations and technologies from the biological world are harnessed to manipulate and control materials at the nanoscale. Drawing knowledge from biological systems enables unique approaches to nanoscale device design, engineering, processing and manufacturing.

### Approaching biology from the nanoscale -

Nanoscale phenomena, technologies or processes are used to study biology at its fundamental level – the nanoscale. Similarly, nanoscale devices, materials, or phenomena can be harnessed for therapeutics, diagnostics, medicine, pharmaceuticals, and many other biological applications.

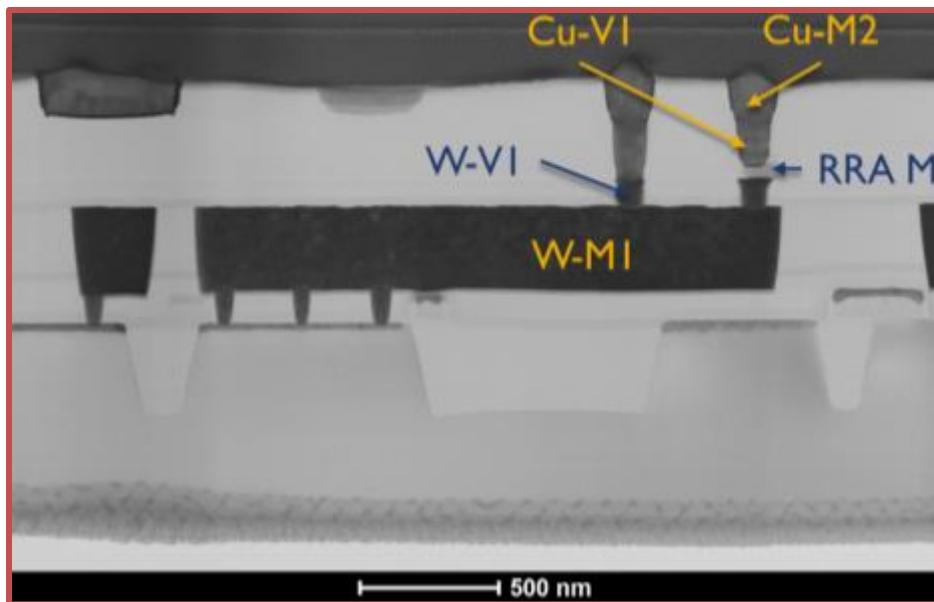
**Goals:** Develop cutting-edge nanotechnologies for biological research and employ biological principles for developing novel nanoscale devices / nanoelectronics.

### 2016 Accomplishments

#### TOPIC 1: Resistive Memory Devices (Memristors)

We have an ongoing research program on resistive memory devices (aka: memristors). These metal-insulator-metal (MIM) devices behave similar to neural synapses, as their “memory state” depends on the current and voltage history of the device. This is a good example of bioinspired/biomimetic research, since the biological process of synapse formation is being mimicked by a physical device. We have previously developed memristors as both non-volatile memory (NVM) elements, as well as devices to control the reconfigurability of CMOS circuits (for encryption applications). Our current work with the Air Force Research Laboratory (AFRL) is focused on integrating memristors with CMOS circuits for neuromorphic computing applications. In this work, memristors serve as on-chip “synapses,” literally encoding the synaptic weight between neural connections in the circuits.

In addition to developing memristors for neuromorphic applications, we are also working on memristors for radiation hardened (rad hard) applications, with a specific focus on tantalum oxide based devices (funded by NASA, and in collaboration with the Jet Propulsion Laboratory). We also have ongoing efforts to characterize the switching mechanism of our devices, to better enable modeling and simulation of memristors in complex circuits.



**Figure 1:** Image of an integrated 1 transistor / 1 RRAM (1T1R) cell fabricated by Prof. Cady's team at SUNY Poly. The hafnium oxide based RRAM device is fully integrated with 65nm CMOS transistors, using the IBM 10 LPe process.

Footnote (recent publications)

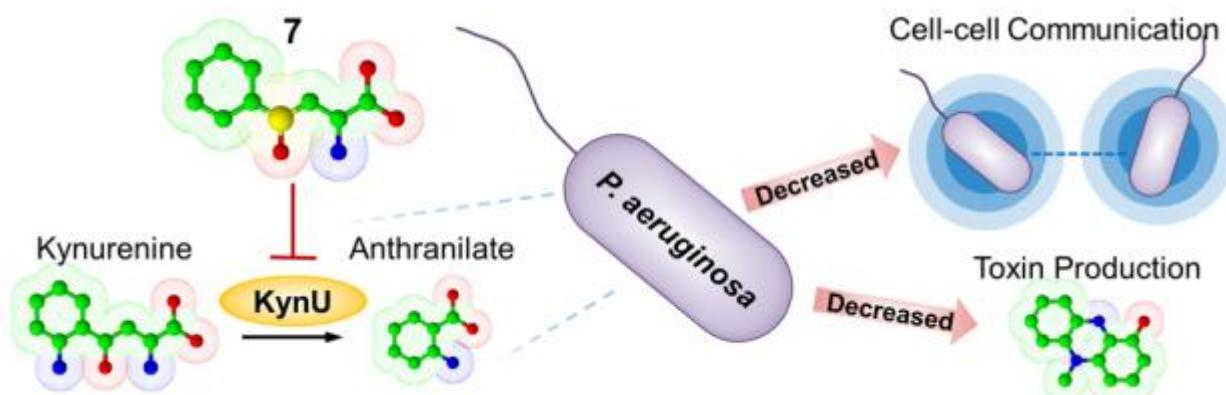
1. J.S. Holt, K. Beckmann, Z. Alamgir, J. Yang-Scharlotta, **N.C. Cady**. Effect of displacement damage on tantalum oxide resistive memory. (2017) *MRS Advances*. 1-7. DOI:10.1557/adv.2017.422
2. K. Beckmann, H. Manem, **N.C. Cady**. Performance enhancement of a time-delay PUF design by utilizing integrated nanoscale ReRAM devices. (2016) *IEEE Transactions on Emerging Topics in Computing – Special issue “Security of Beyond CMOS Devices: Issues and Opportunities*. DOI: 10.1109/TETC.2016.2575448
3. K. Beckmann, J. Holt, W. Olin-Ammentorp, J. Van Nostrand, **N.C. Cady**. Impact of etch process on hafnium dioxide based nanoscale RRAM devices. (2016) *ECS Transactions*. 75(13): 93-99.
4. K. Beckmann, J. Holt, H. Manem, J. Van Nostrand, **N.C. Cady**. Nanoscale hafnium oxide RRAM devices exhibit pulse dependent behavior and multi-level resistance capability. (2016) *MRS Advances*. 1(49): 3355-3360. DOI: <http://dx.doi.org/10.1557/adv.2016.377>

## TOPIC 2: Inhibition of Bacterial Biofilm Formation

We continue to work with collaborators (including Prof. Rabi Musah, UAlbany – Dept. of Chemistry) to develop molecular antagonists of biofilm formation and methods of delivering these antagonists for prophylactic or therapeutic treatment against biofilms. Our initial work in this area has focused on the inhibition of bacterial biofilm formation by a library of natural products inspired compounds. Prof. Musah's group has developed these compounds, which we have shown to have efficacy against *Pseudomonas aeruginosa* biofilm formation. Interestingly, we also showed that these compounds are effective in reducing cell signaling (quorum sensing) behavior of *P. aeruginosa*. Our hypothesis is that disruption of quorum sensing pathways in *P. aeruginosa* affects the

expression of genes involved in biofilm formation. We recently showed that this inhibitor functions by inhibiting the kynureninase (KynU) enzyme in *P. aeruginosa*, which has multiple downstream effects on gene transcription, intracellular iron levels, and various virulence-related proteins. We are also developing methods to deliver this (and other) inhibitory compounds, including encapsulation of compounds in a corn-based protein named “zein”. Our most recent strategy has been to generate micro and nanoparticles of zein that encapsulate various biofilm / bacterial growth inhibitors, and use these particles to create anti-fouling coatings on solid surfaces.

In addition to this work, we continue to work with other collaborators on methods of preventing bacterial biofilm formation, and applications for wound healing.



**Figure 2: Inhibition of the KynU enzyme by S-aryly-L-cysteine sulfoxide, which is an inhibitor of *P. aeruginosa* biofilm formation and quorum sensing. This compound was developed by our collaborator, Prof. Rabi Musah, and utilized by our lab for various bacterial biofilm inhibition and quorum sensing inhibition studies.**

Footnote (recent publications)

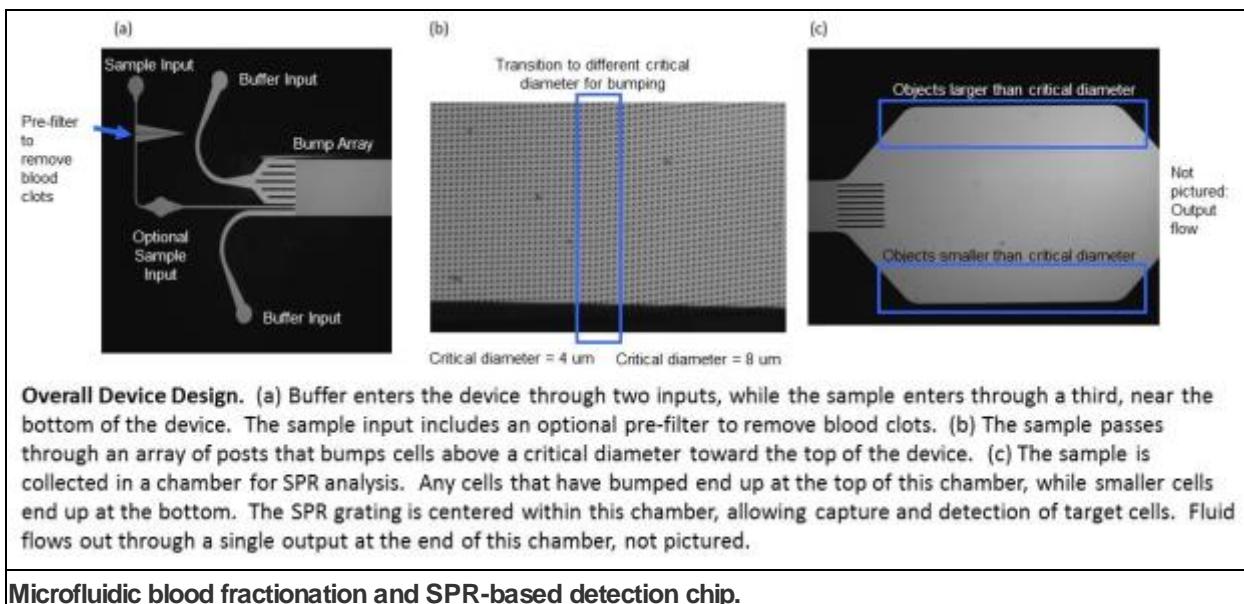
1. S.H. Kasper, R. Hart, M. Bergkvist, R.A. Musah, **N.C. Cady**. Zein nanocapsules as a tool for surface passivation, drug delivery, and biofilm prevention. (2016) *AIMS Microbiology*. 2(4): 422-433.
2. S.H. Kasper, R.P. Bonocora, J.T. Wade, R.A. Musah, **N.C. Cady**. Chemical inhibition of kynureninase reduces *Pseudomonas aeruginosa* quorum sensing and virulence factor expression. (2016) *ACS Chemical Biology*. 11(4): 1106-1117.
3. M. Craven, S. Kasper, M. Canfield, R. Diaz-Morales, J. Hrabie, Joseph; **N. Cady**, A. Strickland. Nitric Oxide-Releasing Polyacrylonitrile Disperses Biofilms Formed by Wound-Relevant Pathogenic Bacteria. (2016) *Journal of Applied Microbiology*. 120(4): 1085-99.

### TOPIC 3: Biosensors

We have developed multiple biosensing strategies for the detection of whole cells, proteins and nucleic acids. Our main focus is on leveraging nanotechnologies / nanoscale devices for biosensing applications. We have also developed unique strategies for linking molecules to relevant surfaces. For example, we created a direct linkage strategy for connecting DNA to semiconductor materials, based on coordination

linkage of phosphate-terminated molecules with metal oxides and Group III-nitride materials.

Our group is also focused on microfluidic devices for sample preparation and target detection, as well as pressure/strain sensors for biomedical applications. Through a collaboration with the Wadsworth Institute (NYS Dept of Health) and Ciencia, Inc., we are developing surface plasmon resonance (SPR) biosensors for targets ranging from circulating tumor cells to biomarkers of disease (eg. Lyme disease). This work has been supported by a National Cancer Institute grant for development of new technologies for evaluating circulating tumor cells. Beyond these efforts, we are working with Dr. Eric Ledet (RPI) to develop wireless pressure/strain sensors that can measure mechanical forces in the body and also serve as infection sensors. This unique infection sensor project is currently being supported by the NIH.



Footnote (recent publications)

1. M.K. Dion, J.F. Drazan, S. Giddings, **N.C. Cady**, R. Dahle, J.T. Roberts, E.H. Ledet. Smart Orthopaedic Implants: Application in Total Knee Arthroplasty. (2016) *American Journal of Engineering and Applied Sciences*. 9(4):1232-38.
2. A. Mendoza, D.M. Torrisi, S. Sell, **N.C. Cady**, D.A. Lawrence. Grating coupled SPR microarray analysis of proteins and cells in blood from mice with breast cancer. (2016) *Analyst*. 141: 704-712.

## Wafer Processing and Nanobioscience Research (Castracane Group)

**Scope: Custom Wafer Processing/Materials Development, Self-balancing Optical Position Sensitive Detector, Ocular Implant Constructs and Multiple Federally funded Nanobioscience Research Projects**

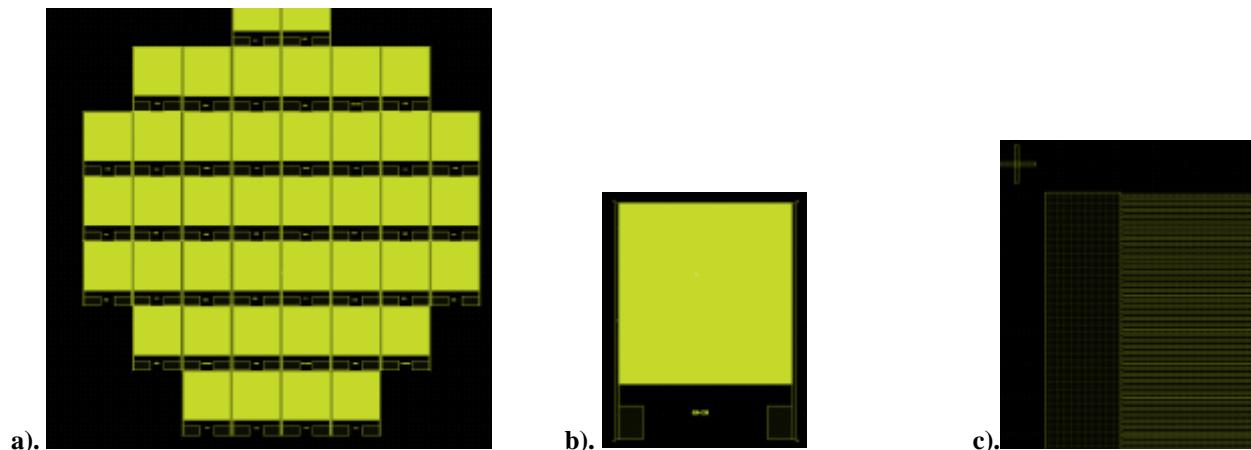
**Goal: Specialized R & D in support of wafer processing/integration activities**

### 2016 Accomplishments

**TOPIC 1: Development of new materials, processes and instrumentation to advance wafer/device research.**

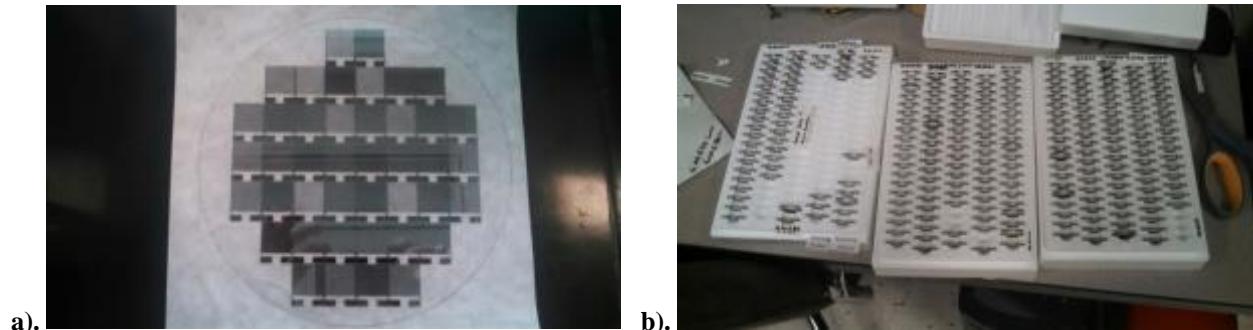
A portfolio of experiments was carried out in support of a variety of corporate sponsors including FreshAir, MMMI, OHR Pharmaceuticals, SpacePharma, among others. Three examples are given below:

FreshAir, Inc. Project: Development of a custom sensor platform for monitoring indoor air quality. This project was focused on the development of prototype sensor platforms which can be used by the company as a component of their products. These sensors can be tailored to sense various targeted components of the air samples.



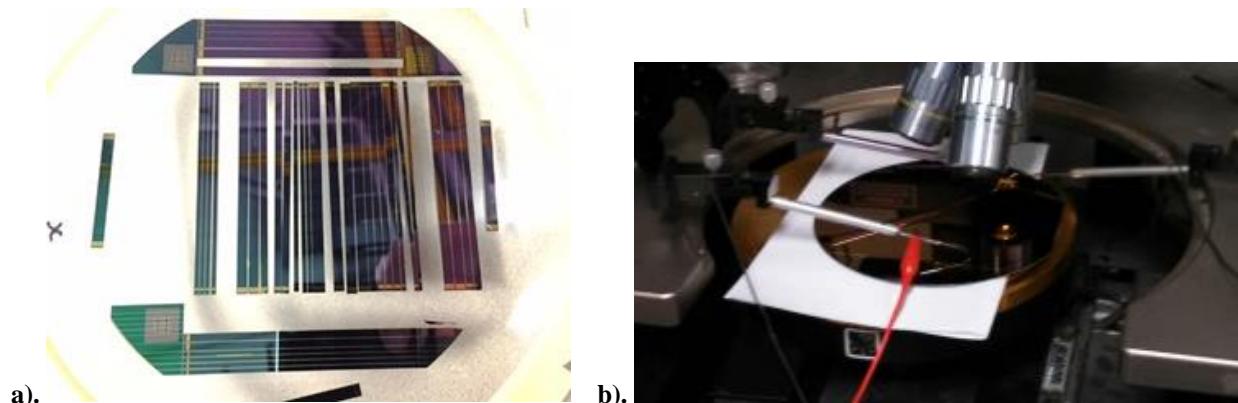
**Figure 1:** Mask Designs for the FreshAir Sensor Platform: a). Full Wafer Mask, b). Individual Sensor Design, c). Close up of Interdigitated Gold Fingers Comprising the Sensor

Multiple wafer runs were carried out to yield prototypes which were fully characterized and delivered to the company for successful integration into their various product lines as seen in Figure 2.

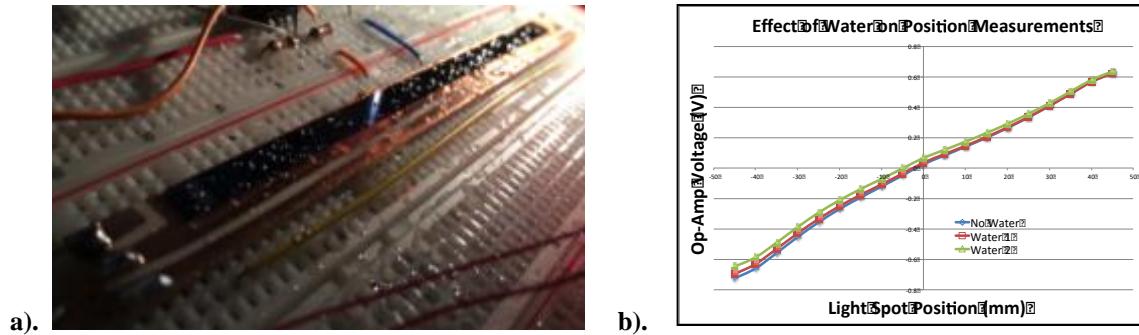


**Figure 2:** Results of the Initial FreshAir Wafer Runs: a). Fully Populated Wafer, b). Individually Diced and Packaged Sensors Delivered to FreshAir, Inc.

**MMMI Inc. Project:** Transitioning a Novel Optical Position Sensitive Detector (OPSD) to Commercial Production. This project is a continuation of a multi-year SUNY Poly collaboration with MMMI, Inc. to develop an optical sensor to replace the company's original mechanical contact-based sensor. As detailed in previous reports, the prototype sensor was successfully developed and tested which set the groundwork for the transition to commercial production. Over this past year, discussions with HVTDC and Noel Technologies have led to initial commercial production. Shown in the following figures are the details of the testing of these initial production runs and the integration into the MMMI Jamboxx product.



**Figure 3:** a). Initial Wafer Level Sensor Production, b). Individual Sensor Testing



**Figure 4:** a). Water Resistance Tests, b). Verification of Performance Consistency post- Immersion



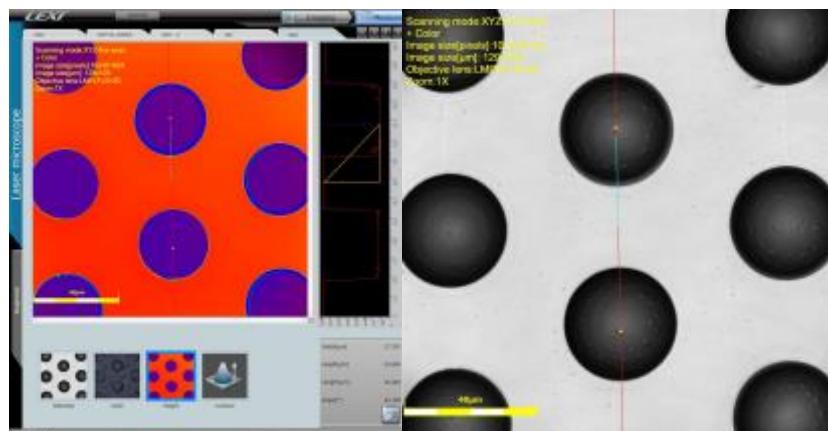
**Figure 5:** Incorporation of the SUNY Poly OPSD Device into MMMI/Jamboxx Product

#### Publications and Degree:

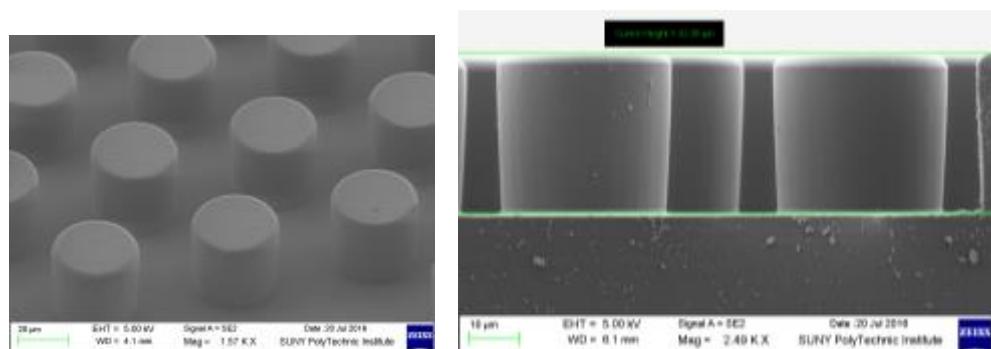
Master's Degree: Leigh Lydecker - "Development of a One-Dimensional Position Sensitive Detector for Tracking Applications".

Ryan Porrazzo, Leigh Lydecker, Suhasini Gattu, Hassaram Bakhru, Natalya Tokranova and James Castracane, "Self-Balancing Position Sensitive Detector (SBPSD)", *Sensors* 2015, 15(7), 17483-17494.

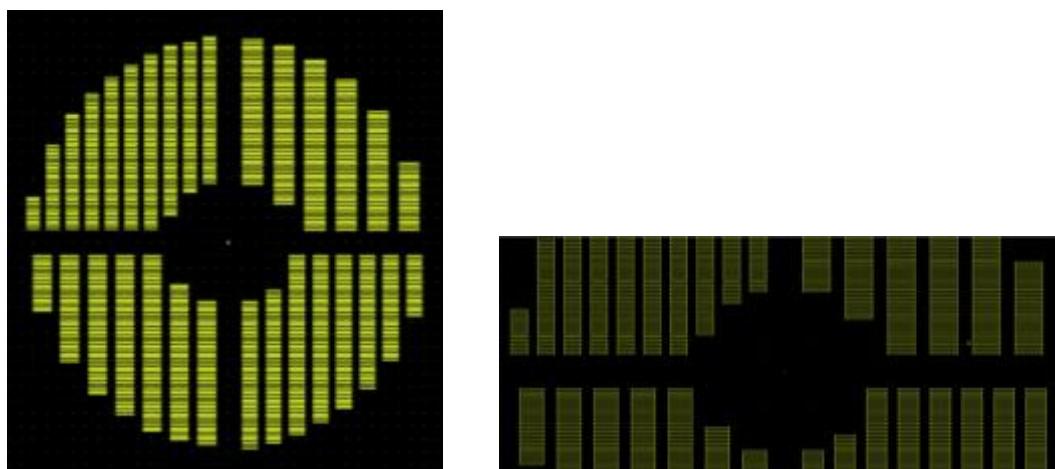
OHR Pharmaceuticals: Development/Production of Micro-molds for Ocular Treatment Implants. This project is focused on the development of microstructures which can be used to produce capsules for treatment of company defined ocular diseases. This collaboration has resulted in the design, fabrication and characterization of several prototype versions of potential products. The following figures show the various stages of production.



**Figure 6:** Metrology of Initial Micromold Wells



**Figure 7:** SEM Images of the Molding Process

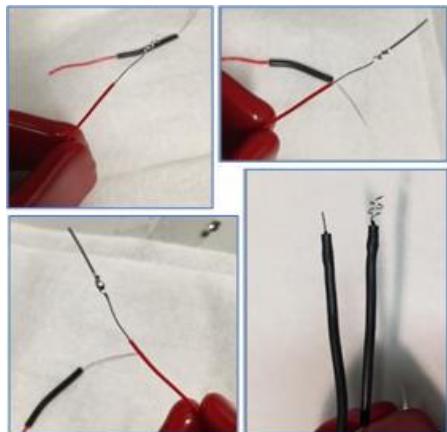


**Figure 8:** Next Step Microtrench Design

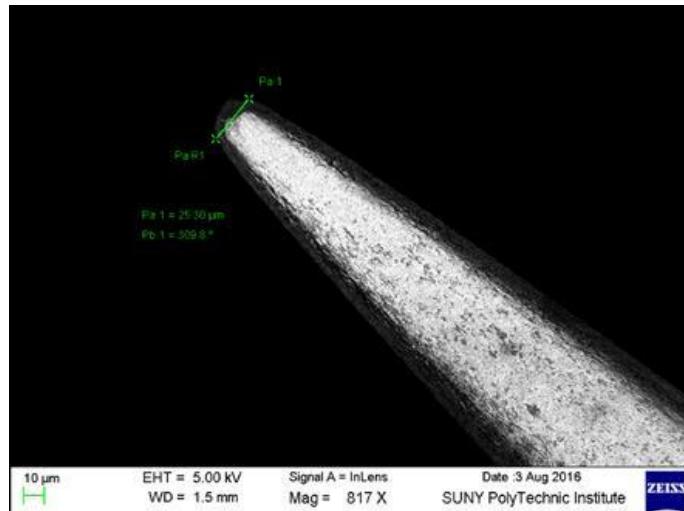
## TOPIC 2: The NANAPHID (NSF-funded): An Innovative Microsensor for Monitoring Living Plant Tissue Carbohydrate Levels

**Goal: Study the relative concentrations of carbohydrates in living plant tissues to establish the effect of climate change on plant vitality.**

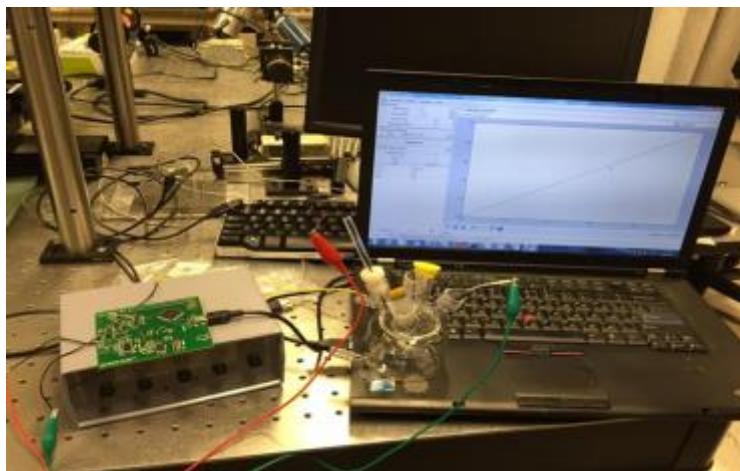
The development path during this year has been focused on the transition of the original NANAPHID design from a flat electrode format to a needle-like format to move more closely to a sensor which will be able to be inserted into the target plant tissue in the field. Secondly, to further enable the field tests which are an integral component of the project, a miniaturized custom potentiostat has been successfully constructed and tested against a much more expensive and bulky commercial potentiostat. Third, to make the sensor system more user friendly, custom data acquisition, analysis and display software has been written in Python to allow for on the spot calibration, sample testing and automatic NSC result output.



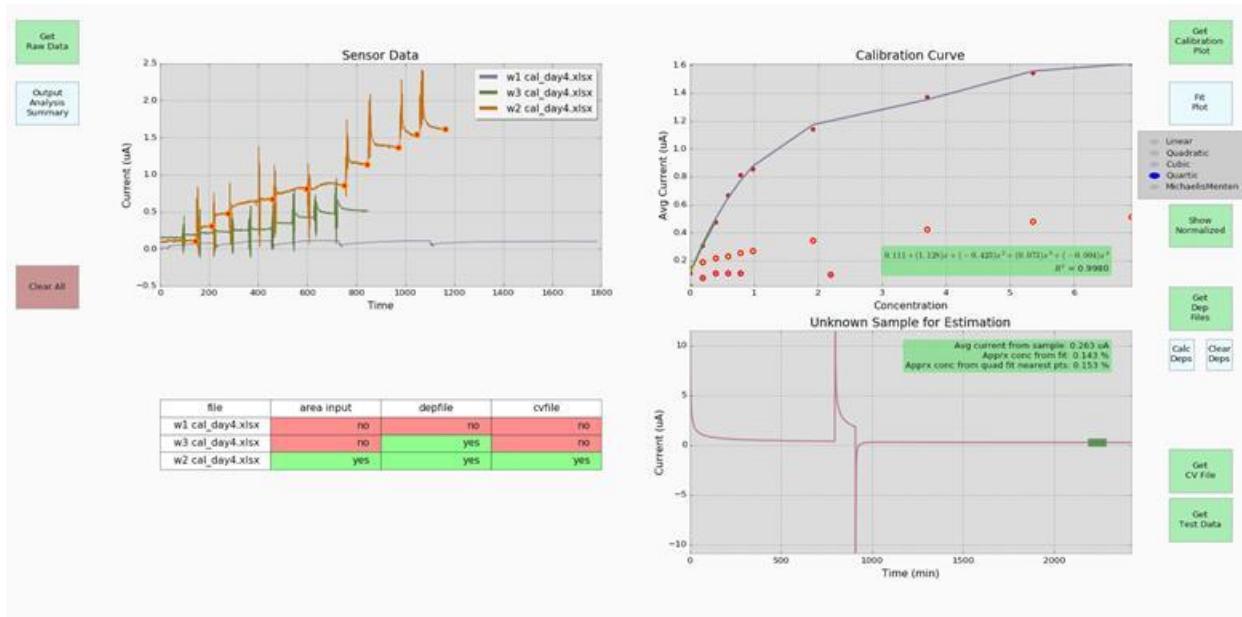
**Figure 1.** Soldering of Pt wire and addition of heat shrink tubing for isolation of Pt.



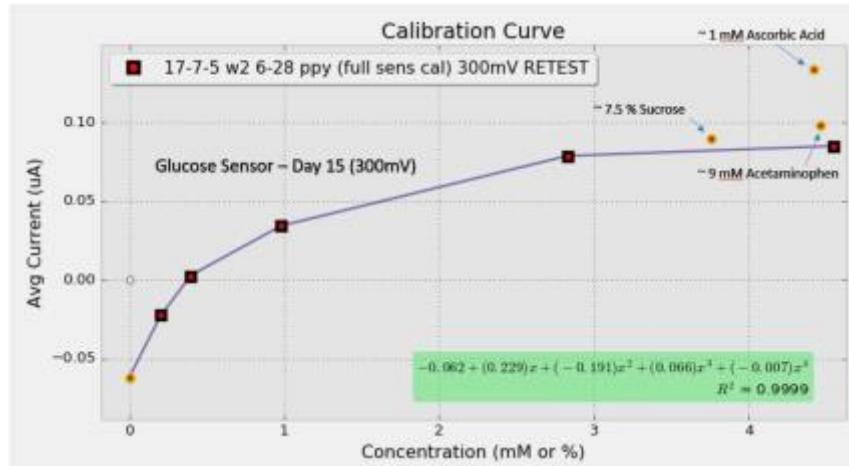
**Figure 9:** Needle-based NANAPHID Sensor Prototype



**Figure 10:** Fully Configured Field Ready NANAPHID System with Integrated Computer-based Data Acquisition, Analysis and Display Software



**Figure 11:** Screenshot of Representative Experiment on Collected Sap Samples

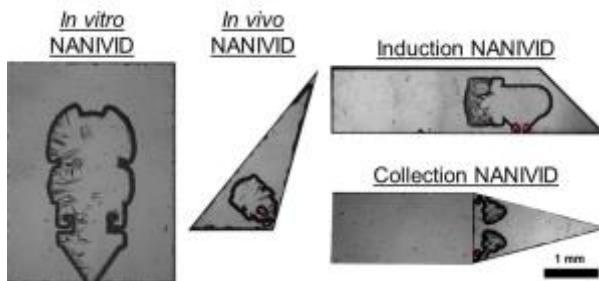


**Figure 12:** Example of Glucose Measurement using Optimized NANAPHID Microsensor Displaying Insensitivity to Interferents

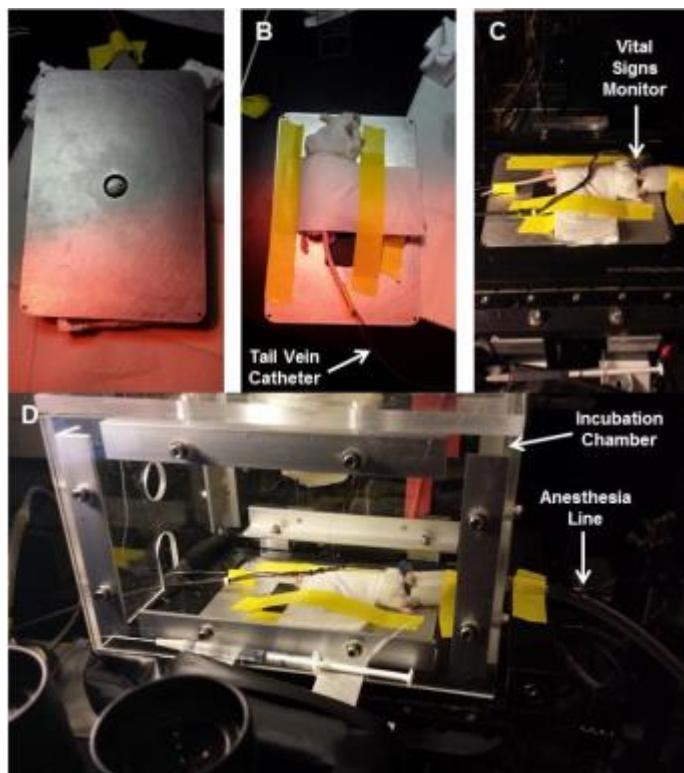
### TOPIC 3: Development of the NANIVID for cancer cell migration studies (NIH-NCI Funded)

**Goal: Create and validate an implantable device to collect migrating cancer cells as they leave primary tumor sites and also to use it as method to induce changes in the tumor microenvironment**

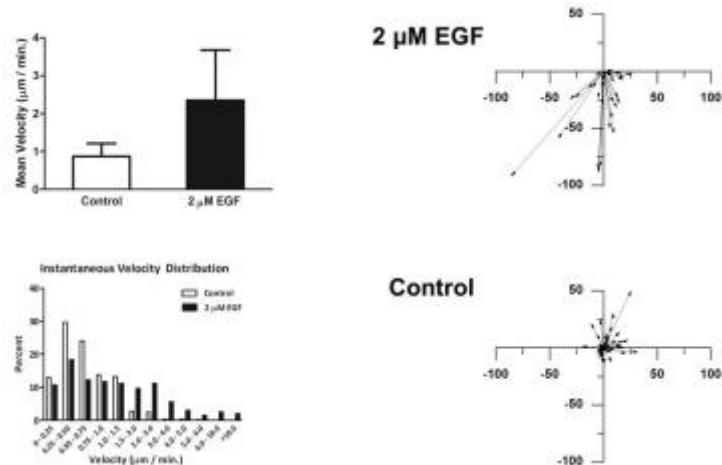
This work focused on the continued development and deployment of the NANo IntraVtal Device (NANIVID) in support of cancer cell metastasis studies. After successfully completing *in vitro* tests, the project moved to *in vivo* studies using a mouse model. In addition, an alternate version of the NANIVID was developed and applied to induce *in vivo* changes in the tumor microenvironment including hypoxia, collagen stiffness, among others. Also, a study of the cancer cell motion on nanofibers was also carried out as a mimic to *in vivo* motility on collagen fibers in the TMEN. The array of NANIVID versions is show below.



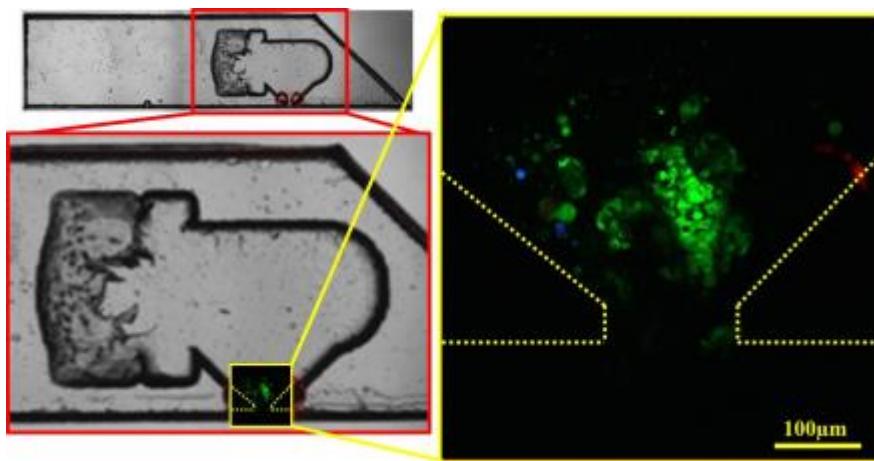
**Figure 13:** Various Configurations of the NANIVID



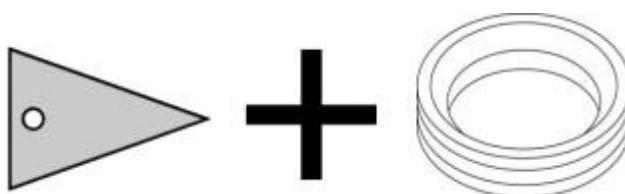
**Figure 14:** Newly Developed *in vivo* Fixturing System to Enable High Resolution Imaging



**Figure 15:** Cell Motility Results from Implanted NANIVID



**Figure 16:** Example of Captured Cells *in vivo* by the NANIVID:  
Green – Cancer Cells, Blue - Macrophages



**Figure 17:** Conceptual Design of the Microfluidic Imaging Window (MFIW) Combining the NANIVID and the Intravital Window



Figure 18: Initial Prototypes of Passive MFIW

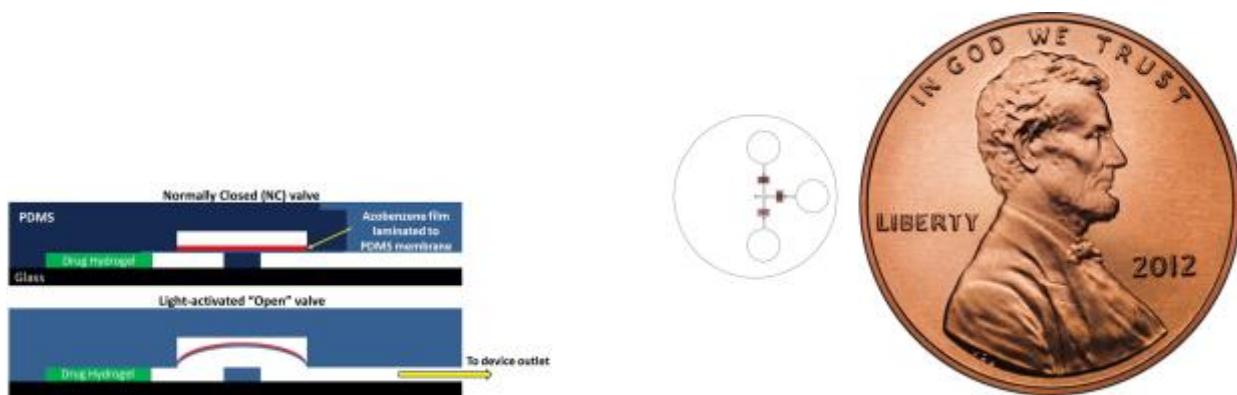


Figure 19: Active MFIW using Photoactuated Azobenzene Microvalves

#### Publications and Degrees:

Georg Fluegen and Alvaro Avivar-Valderas, Yarong Wang, Michael R. Padgen, James K. Williams, Vladimir Verkhusha, David Entenberg, James Castracane, Patricia J. Keely, John Condeelis and Julio A. Aguirre-Ghiso, "Phenotypic heterogeneity of disseminated tumor cells is predetermined by primary tumor hypoxic microenvironments", *Nature Cell Biology*, Vol. 19, No. 2, pp. 120-135, (2017).

Brett Morris, Brian Burkhardt, Suzanne M. Ponik, Jing Fan, Kevin Eliceiri, John Condeelis, Julio Aguirre-Ghiso, James Castracane, John Denu, Patricia J. Keely, "Changes in collagen matrix density alters the metabolic profile of breast cancer cells", *EBioMedicine*, Vol. 13, p146–156 (2016).

Joseph M. Szulczewski, David R. Inman, David Entenberg, Julio Aguirre-Ghiso, James Castracane, John Condeelis, Kevin W. Eliceiri, Patricia J. Keely, "in vivo Visualization of Stromal Macrophages via label-free FLIM-based metabolite imaging", *Scientific Reports*, 6:25086, DOI: 10.1038/srep25086, (2016).

James K. Williams, David Entenberg, Yarong Wang, Alvaro Avivar-Valderas, Michael Padgen, Ashley Clark, Julio A. Aguirre-Ghiso, James Castracane and John Condeelis, "Validation of an implantable chemotaxis device for the study of cell migration in vivo", *Intravital*, vol.5, issue 2, (2016).

Ved P. Sharma, James Williams, Edison Leung, Joe Sanders, Robert Eddy, James Castracane, John S. Condeelis, "Fibrillar 1D tumor microenvironment is the key driver associating high-speed tumor cell motility with nuclear shape in breast cancer", in review, *Nature Cell Biology*, (2016).

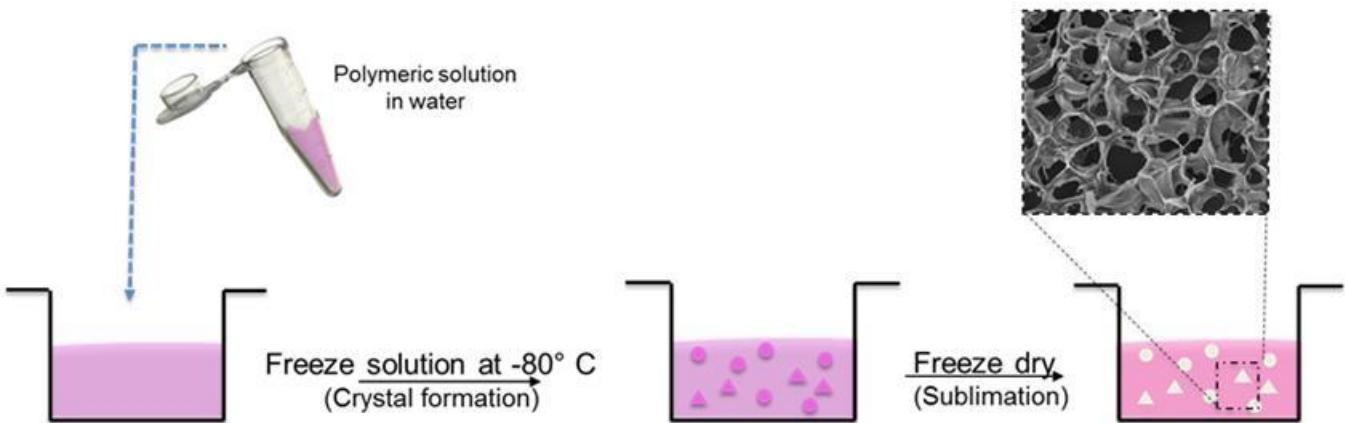


**Figure 20:** Recent Group Journal Covers for NANVID Associated Research

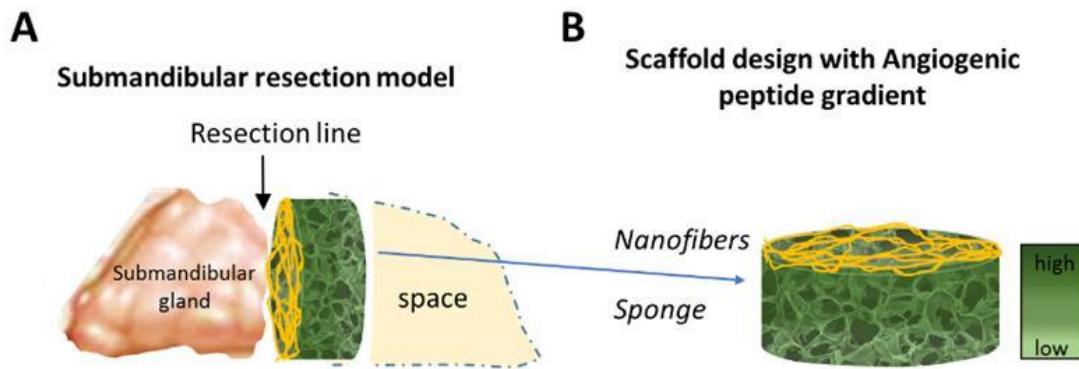
#### TOPIC 4: Bioscaffold Development for Salivary Gland Regeneration (NIH-NIDCR Funded)

**Goal: Create biocompatible scaffolds for effective cell growth and re-generation.**

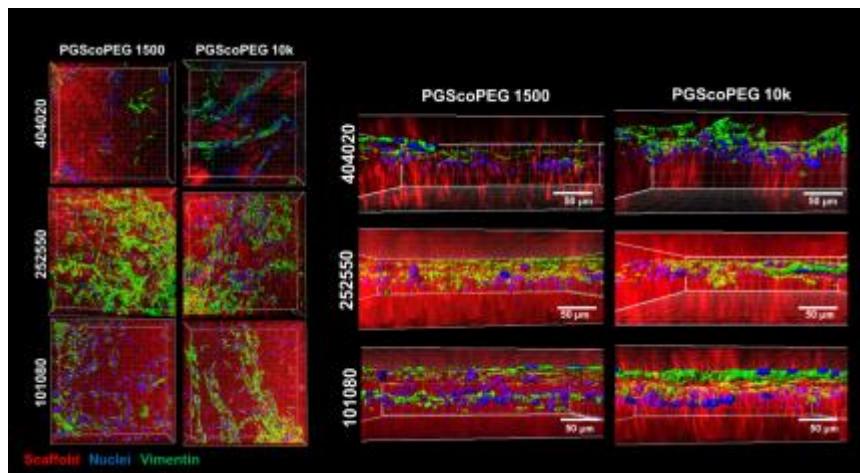
This work focused on the continued development of a custom bioscaffold incorporating functionalized nanofibers and polymer sponges which can assist in salivary gland cell growth and gland formation. During this year, research has focused on developing the fabrication protocols for assembling these constructs setting the stage for implantation during the upcoming year.



**Figure 21:** Production Protocol for Polymeric Sponges



**Figure 22:** Conceptual Model for Creating a Nanofiber/Sponge Construct for Direct Implantation into a Mouse Model



**Figure 23:** Cell Penetration into Prototype Sponges Fabricated from Co-Polymer Material Sets

**Publications and Degrees:**

**Zahraa Foraida, Ph. D.: “Towards a biomimetic elastin-based scaffold for salivary gland tissue regeneration and growth factor delivery”, May, 2017**

**Lauren Sfakis, Ph. D.: “Implantable sponge scaffolds using natural/synthetic polymer blends for salivary gland regeneration”, June 2017**

Melinda Larsen, Zeinab F. Hosseini, Deirdre Nelson, Nicholas Moskwa, Lauren Sfakis, and **James Castracane**, “FGF2-Dependent Submandibular Salivary Gland Mesenchyme Sustains the Epithelial Proacinar Phenotype in Organoids”, in review, Journal of Cell Science, (2017).

Zahraa I. Foraida, Anna Sharikova, Alexander Khmaldze, Lubna N Peerzada, Melinda Larsen, and **James Castracane**, “Double emulsion electrospun nanofibers as a growth factor delivery vehicle for salivary gland regeneration”, to be published, SPIE Proceedings-NanoScience and Engineering, (2017).

Zahraa I Foraida, Tim Kamaldinov, Deirdre A. Nelson, Melinda Larsen and **James Castracane**, “Elastin-PLGA Hybrid Electrospun Nanofiber Scaffolds for Salivary Epithelial Cell Self-Organization and Polarization”, to be published, Acta Biomaterialia, (2017).

Robert A. Schramm, Matthew H. Koslow, Deirdre A. Nelson, Melinda Larsen and **James Castracane**, “A Novel Impedance Biosensor for Measurement of Trans-Epithelial Resistance in Cells Cultured on Nanofiber Scaffolds, under review, Biosensors, (2017).

Lauren Sfakis, Felipe Xavier Costa, David Tuschel, Anna Sharikova, Melinda Larsen, **James Castracane**, Alexander Khmaladze, “Core/Shell Nanofiber Characterization by Raman Scanning Microscopy”, in print, Biomedical Optics Express, (2017).

Lauren Sfakis, Tim Kamaldinoff, Melinda Larsen, **James Castracane** and Alexander T. Khmaladze, “Quantification of Confocal images using LabVIEW for tissue engineering applications”, *Tissue Engineering Part C: Methods*. Nov 2016: 1028-1037.

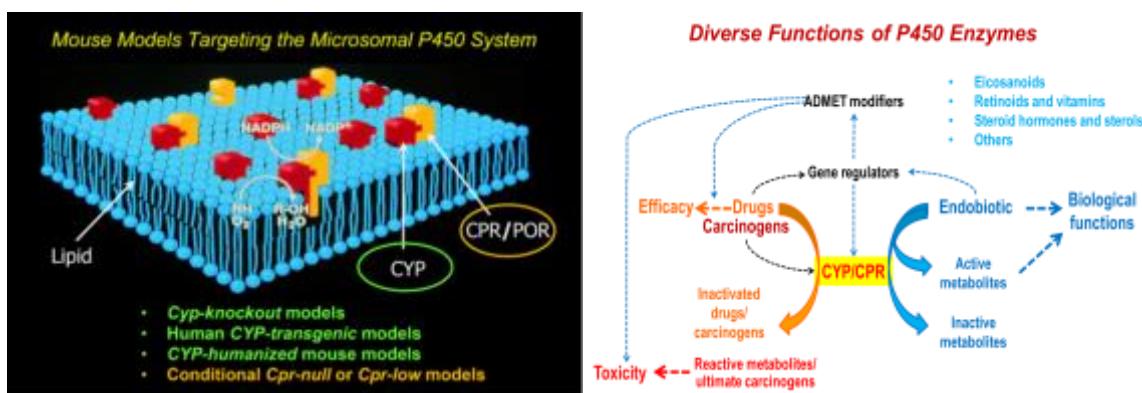
For more information:

<https://sunypoly.edu/faculty-and-staff/james-castracane.html>

## Molecular Toxicology & Nano-Drug Development (Ding Group)

**Scope:** (1) Development and application of genetically engineered mouse models for mechanistic studies on the role of cytochrome P450 (P450 or CYP) enzymes in drug response, chemical toxicity, carcinogenesis, and disease susceptibility; (2) characterization of polymorphisms of human P450 and P450 reductase (CPR or POR) genes, in order to identify the genetic basis for interindividual differences in drug efficacy or susceptibility to environmental diseases; (3) basic and preclinical studies on the pharmacology and toxicology of nano-drugs and other nano devices.

**Goals:** (1) To gain basic knowledge on the function, regulation, and genetics of xenobiotic-metabolizing enzymes, which can be applied to translational research for improvements in drug safety and efficacy; (2) to identify genetic and environmental factors that influence disease risks, such as lung cancer; (3) to develop nanotechnology-based approaches for improving drug efficacy and safety, or for better protection against environmental diseases.



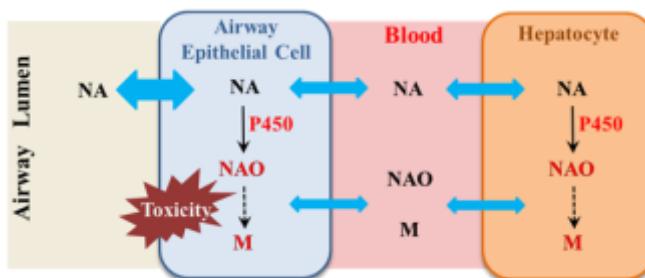
### 2015-2016 Accomplishments

#### TOPIC 1: Metabolic Mechanisms of Naphthalene Toxicity in Lung

Naphthalene (NA) is a ubiquitous pollutant to which humans are widely exposed. NA causes tumors in rats and mice and has been classified as a Possible Human Carcinogen. The mechanism of NA carcinogenicity is believed to involve repeated cycles of NA-induced acute lung injury and repair. A prerequisite for NA cytotoxicity is its bioactivation by P450 enzymes. The major enzymes responsible for NA bioactivation in the mouse include CYP2A5 and CYP2F2. Both human lung and human liver are capable of metabolizing NA, although large interindividual variations exist in the rates of microsomal NA metabolism and bioactivation. However, the roles of human CYP2A13 and CYP2F1 (orthologs of mouse CYP2A5 and CYP2F2, respectively) in NA bioactivation are not well understood, and the potential impact of variations in hepatic P450 function on an individual's risks of developing NA-mediated lung toxicity remains

undefined. The objectives of this project, which is funded by the National Institute of Environmental Health Sciences, NIH, and is a collaboration with the University of California, Davis, and the Wadsworth Center of New York State Department of Health, are to define the role of human CYP2A13 and CYP2F1 in NA bioactivation and toxicity in the lungs of CYP2A13/2F1-humanized mice; identify human lung regions that are enriched in CYP2A13/2F1 expression; and determine whether P450-mediated NA bioactivation and/or detoxification in the liver could contribute to, or otherwise influence, NA lung toxicity.

We have determined whether a decrease in hepatic microsomal P450 activity would impact lung toxicity induced by inhalation exposure to NA (Kovalchuk et al., 2017). We found that hepatic P450 has a significant impact on NA levels in the lung and plasma following inhalation NA exposure. NA induces airway toxicity in liver Cpr-null mice, which have no microsomal P450 activity in liver hepatocytes. Our results, while confirming the ability of extrahepatic organ to bioactivate inhaled NA and mediate NA's lung toxicity, suggest that liver P450-generated NA metabolites also have a significant, although relatively small, contribution to airway toxicity of inhaled NA. This hepatic contribution to the airway toxicity of inhaled NA may be an important risk factor for individuals with diminished bioactivation activity in the lung.



**Figure 1: Schematic representation of the potential impact of hepatic P450-mediated NA metabolism on airway toxicity of NA in an inhalation exposure scenario.** During inhalation NA exposure, the airway epithelial cells are exposed simultaneously to NA aerosols in the airway, and NA, NAO, and other NA metabolites (M) arriving from systemic circulation. Blue double arrow represents diffusion of NA into cells. Both “air-borne” NA and “blood-borne” NA can undergo target tissue bioactivation and cause cytotoxicity, whereas circulating NA metabolites, such as NAO, can also cause airway toxicity. However, the relative contributions of the various sources of reactive NA metabolites to airway toxicity are currently unknown. [from Kovalchuk et al., 2017]

The function of human CYP2A13 and CYP2F1 in NA bioactivation and respiratory tract toxicity was also examined, using CYP2A13/2F1-humanized mice and CYP2A13 (only)-humanized mice (on *Cyp2abfgs*-null background). Definitive data have been obtained to support the conclusion that CYP2F1 is an active enzyme, and that both CYP2A13 and CYP2F1 are active toward NA in the CYP2A13/2F1-humanized mice, where they play significant roles in NA-induced respiratory tract toxicity (Li et al., 2017).

Kovalchuk, N., Kelty, J., Li, L., Hartog, M., Zhang, Q.-Y., Edwards, P., Van Winkle, L. S., and Ding, X.: Impact of hepatic P450-mediated biotransformation on the deposition and respiratory tract toxicity of inhaled naphthalene. *Toxicol. Appl. Pharmacol.* 329:1-8, 2017

Li, L., Carratt, S., Hartog, M., Kovalchuk, N., Jia, K., Wang, Y., Zhang, Q.-Y., Edwards, P., Van Winkle, L. S., and Ding, X.: Human CYP2A13 and CYP2F1 can bioactivate naphthalene and mediate naphthalene toxicity in the lung and nasal mucosa of CYP2A13/2F1-humanized mice. *Env. Health Perspect.* <https://doi.org/10.1289/EHP844>, 2017

## TOPIC 2: Role of P450 Enzymes in Environmental Tobacco Smoke-Induced Lung Toxicity and Identification of Biomarkers for in Vivo Bioactivation

CYP2A13 is an enzyme selectively expressed in human respiratory tract, and is the most efficient human P450 enzyme in the bioactivation of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a major tobacco-derived lung procarcinogen. This National Cancer Institute-funded project tested the hypothesis that CYP2A13 plays an important role in tobacco-related lung carcinogenesis in humans. We had shown for the first time that transgenic expression of human CYP2A13 can increase the incidence of NNK-induced tumorigenesis in the mouse lung, a result suggesting that individuals with elevated CYP2A13 expression in their lungs are at a higher risk of developing tobacco-induced lung tumors. Notably, lung cancer is the leading cause of cancer-related deaths in the U.S. Confirmation of a significant role of CYP2A13 in the risks of lung toxicity in humans may lead to new strategies for chemoprevention via enzyme inhibition.

In a more recent study, we have demonstrated that CYP2A13 expression in the lungs of CYP2A13-humanized mice is suppressed by the presence of lung tumors (Liu et al., 2015). This finding supports the hypothesis that CYP2A13 levels in human lungs can be suppressed by disease-associated inflammation in tissue donors, a scenario causing underestimation of CYP2A13 levels in healthy lungs. Additionally, we have established a novel mouse model for studying biomarkers of human exposure to environmental carcinogens (Sheng et al., 2016). We have also contributed to other studies on genotoxicity of chemical carcinogens (Turesky et al., 2015; Fasullo et al., 2017).

NIH support for this project has been successfully renewed for another five years. In the new funding period, we will determine the in vivo role of human CYP2A13 and other P450 enzymes encoded by the mouse and human CYP2ABFS gene cluster in environmental tobacco smoke (ETS)-induced lung tumorigenesis and lung inflammation; the latter is linked with both tumor initiation and tumor promotion. In Aim 1, we will test the hypothesis that deletion of mouse Cyp2abfs and addition of human CYP2A13 will lead to corresponding changes in the extent of lung tumorigenesis and the levels of O<sup>6</sup>-methylguanine DNA adduct in the lung, in mice exposed chronically to ETS. In Aim 2, we will test the hypothesis that unique subsets of ETS constituents, which depend on CYP2A/B/F/S enzymes for bioactivation, enable ETS to cause lung inflammation in vivo. Our goal is to establish CYP2A13 as a valid genetic marker for lung cancer risk assessment and a logical molecular target for chemoprevention.

Liu, Z., Megaraj, V., Li, L., Sell, S., Hu, J., and Ding, X.: Suppression of pulmonary CYP2A13 expression by carcinogen-induced lung tumorigenesis in a CYP2A13-humanized mouse model. *Drug Metab. Dispos.*, 43:698–702, 2015, PMC4407704

Turesky, R. J., Konorev, D., Fan, X., Tang, Y., Yao, L., Ding, X., Xie, F., Zhu, Y., and Zhang, Q.-Y.: The effect of cytochrome P450 reductase deficiency on 2-amino-9h-pyrido[2,3-b]indole metabolism and DNA

adduct formation in liver and extrahepatic tissues of mice. *Chem. Res. Toxicol.*, 28:2400-10, 2015, PMC4703101

Sheng, J., Wang, Y., Turesky, R. J., Kluztman, K., Zhang, Q.-Y., and Ding, X.: Transgenic mouse development for studying human serum albumin as a biomarker of carcinogenic exposure. *Chem. Res. Toxicol.* 29:797-809, 2016, PMC4868631

Fasullo, M., Freedland, J., St. John, N., Cera, C., Egner, P., Hartog, M., and Ding, X.: An in vitro system for measuring genotoxicity mediated by human CYP3A4 in *Saccharomyces Cerevisiae*. *Env. Mol. Mutagenesis* 58:217-227, 2017

### **TOPIC 3: Role of the P450/P450 Reductase Enzyme System in Drug Metabolism, Drug Efficacy or Disease Susceptibility**

Several studies were conducted to continue to explore the potential role of P450/P450 reductase (POR) in drug metabolism, drug efficacy or disease susceptibility, including susceptibility to adverse drug responses. For example, we have studied the role of brain P450/POR in the therapeutic as well as side effects of morphine, in collaborations with researchers at the Albany Medical College (Hough et al., 2015a; 2015b). We also revealed a role of CYP2B in phenobarbital-induced hepatocyte proliferation in mice (Li et al., in press).

In another study, a collaboration with researchers at the Wadsworth Center, we studied the potential involvement of intestinal microsomal P450 enzymes in defending against colon inflammation and injury in a mouse model of dextran sulfate sodium (DSS)-induced colitis. Our results strongly support the notion that microsomal P450 enzymes in the intestine play an important role in protecting colon epithelium from DSS-induced inflammation and injury, possibly through increased local CC synthesis in response to DSS challenge (Zhu et al., 2015).

Hough, L. B., Nalwalk, J. W., Yang, W., and Ding, X.: Neuronal cytochrome P450 activity and opioid analgesia: relevant sites and mechanisms. *Brain Res.*, 1616:10-18, 2015, PMC4464959

Hough, L. B., Nalwalk, J. W., Ding, X., and Scheer, N.: Opioid analgesia in P450 gene cluster knockout mice: a search for analgesia-relevant isoforms. *Drug Metab. Dispos.*, 43:1326–1330, 2015, PMC4538858

Li, L., Bao, X., Zhang, Q.-Y., Negishi, M., and Ding, X.: Role of CYP2B in phenobarbital-induced hepatocyte proliferation in mice. *Drug Metab. Dispos.*, in Press

Zhu, Y., Xie, F., Ding, L., Fan, X., Ding, X., and Zhang, Q.-Y.: Intestinal epithelium-specific knockout of the cytochrome P450 reductase gene exacerbates dextran sulfate sodium-induced colitis. *J. Pharmacol. Expt. Ther.*, 354:10–17, 2015, PMC4468430

### **TOPIC 4: Regulation of P450 gene expression**

Given the diverse functions of various P450 enzymes in the metabolism of both endogenous and xenobiotic compounds, it is important to understand how the expression of P450 genes is regulated. Interindividual differences in P450 expression may underlie variations in disease susceptibility or drug responses. Our efforts in this

regard include the establishment of a new humanized mouse model for studying CYP2B6 regulation *in vivo* (Liu et al., 2015).

Liu, Z., Li, L., Wu, H., Hu, J., Zhang, Q.-Y., and Ding, X.: Characterization of a CYP2B6-humanized mouse model: inducibility of CYP2B6 in the liver by phenobarbital and dexamethasone and role in nicotine metabolism *in vivo*. *Drug Metab. Dispos.*, 43:208–216, 2015, PMC4293397

## Additional Publications

Spink, B. C., Bloom, M. S., Wu, S., Sell, S., Schneider, E., Ding, X., and Spink, D. C.: Analysis of the AHR gene proximal promoter GGGC-repeat polymorphism in lung, breast, and colon cancer. *Toxicol. Appl. Pharmacol.*, 282:30–41, 2015, PMC4404625.

Shen, B., Jiang, W., Fan, J., Dai, W., Ding, X., and Jiang, Y.: Residues 39-56 of stem cell factor protein sequence are capable of stimulating the expansion of cord blood CD34+ cells. *PLoS ONE* 10:e0141485, 2015, PMC4624785

Guan, X., Qin, M., Zhang, Y., Wang, Y., Shen, B., Ren, Z., Ding, X., Dai, W., Jiang, Y.: Safety and efficacy of megakaryocytes induced from hematopoietic stem cells in murine and nonhuman primate models. *Stem Cells Translational Medicine* 6:897-909, 2017, PMC5442772

Zhang, Y., Wang, C., Wang, L., Shen, B., Guan, X., Tian, J., Ren, Z., Ding, X., Ma, Y., Dai, W., Jiang, Y.: Large-scale *ex vivo* generation of human red blood cells from cord blood CD34+ cells. *Stem Cells Translational Medicine*, 2017, In Press

Ding, X., and Xie, F.: Olfactory Mucosa: Composition, Enzymatic Localization, and Metabolism. In *Handbook of Olfaction and Gustation*, 3<sup>rd</sup> Edition, (Doty, R. L., Ed), Chapter 3, pp 63-92, 2015, Wiley-Blackwell, Hoboken, New Jersey

Xie, F., Ding, X., and Zhang, Q.-Y.: An update on the Role of Intestinal Cytochrome P450 Enzymes in Drug Disposition. *Acta Pharmaceutica Sinica B*, 6:374-383, 2016, PMC5045550

Ding, X., Li, L., Van Winkle, L. S., and Zhang, Q.-Y. *Enzymes Catalyzing the Biotransformation of Xenobiotics in the Respiratory Tract (Chapter 9)*, in Vol 8 (*Respiratory Toxicology*; Reilly, C. A. Ed.), *Comprehensive Toxicology*, 3<sup>rd</sup> Edition (McQueen, C. A. Ed.), in press, Elsevier

Ding, X. and Zhang, Q.-Y. *Enzyme Regulation* (Chapter 2), in Vol 4 (*Biotransformation*; Guengerich, F. P. Ed.), *Comprehensive Toxicology*, 3<sup>rd</sup> Edition (McQueen, C. A. Ed.), in press, Elsevier

## Cytochrome P450 Polymorphisms, Genetic Profiling, Carcinogen Resistance and High Throughput Screening for Carcinogen Resistance (Fasullo Group)

**Scope:** Environmental toxicology, cancer etiology, human genetics, high throughput screening, bioinformatics, budding yeast

**Goals:** To determine human genetic susceptibility to food and environmental carcinogens by (1) characterizing P450 polymorphic enzymes that activate food carcinogens, and (2) performing high throughput screens to determine resistance to environmentally-associated carcinogens in yeast.

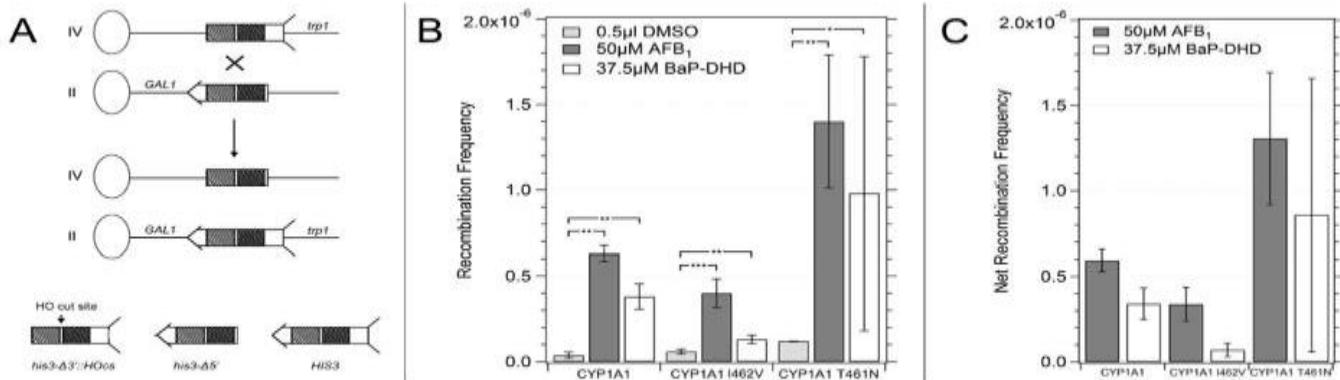
### **2016 Accomplishments**

#### **TOPIC 1: Expression of human P450 genes in budding yeast**

We were awarded a R15 NIH grant, “Genomic profiling of yeast resistance to heterocyclic aromatic amines,” to study how P450 polymorphic enzymes activate a variety of carcinogens to become potent genotoxins. Budding yeasts (*Saccharomyces cerevisiae*) do not express active P450 enzymes that activate the carcinogens we studied; therefore, we can mimic the metabolic state of human tissues by selectively expressing individual human P450 genes in yeast. We had previously characterized four CYP1A2 polymorphisms, as proof of principle. In the last year, we characterized two CYP1A1 polymorphisms, CYP1A1 I462V and CYP1A1 T461N, which are correlated to a higher incidence to lung and breast cancer. The working hypothesis is that the correlation of the expression of these polymorphisms with cancer incidence is linked to a higher enzymatic activity. These CYP polymorphisms were characterized by their ability to activate potent food carcinogens including aflatoxin B1 (AFB1), benzo[a]pyrene, 2-amino-3-methylimidazo [4,5-f] quinolone (IQ), and 2-amino-3,8-dimethylimidazo [4,5-f] quinoxaline (MeIQx). We utilized genotoxic endpoints including growth curves, ribonucleotide reductase induction, recombination, and Rad51 focus formation. The surprising but interesting result we found was that CYP1A1 I462V correlates with lower activation for chemical carcinogens, compared to the CYP1A1 wild type, using multiple genotoxic endpoints. These results indicate that CYP1A1 may have a protective effect, in agreement with results showing that CYP1A1 knockout mice exhibit higher sensitivity to carcinogens. Our results demonstrate that extrahepatic carcinogens can activate food carcinogens in yeast. Julian Freedland, an undergraduate pursuing his capstone research project, won the Society of Toxicology (SOT) travel award based on his contribution to this research. This enabled him to travel, attend, and present a poster at the 2017 SOT Meeting held in Baltimore, MD.

We also demonstrated that the human CYP3A4 can be expressed in yeast to activate chemical carcinogens into potent genotoxins. CYP3A4 expression constitutes over 50% of the hepatic P450 expression and is a major player in activating pharmaceuticals and

carcinogens. We identified DNA adducts resulting from CYP3A4-metabolic activation of aflatoxin, and measured DNA recombination events and ribonucleotide reductase activation resulting from damage exposure. We measured CYP3A4 enzymatic activity in collaboration with Matt Hartog and Xinxin Ding at SUNY Polytechnic Institute. These results demonstrated an *in vitro* assay for monitoring CYP3A4 activity and open an avenue for studying CYP3A4 polymorphisms correlated with drug response and carcinogen activation.



**Figure 1: Frequencies of AFB<sub>1</sub>-associated recombination in diploid cells expressing CYP1A1 (YB428), CYP1A1 I462V (YB429), CYP1A1 T461N (YB430).** Figure in panel A is a model of the recombination assay. The oval represents a centromere and the line represents the chromosome; the left arm of the chromosome is not shown for simplicity. The *his3* fragment is shown with arrow and feathers. The shaded areas represent shared homology. An "X" denotes where a cross-over event would occur. The product of the recombination event is shown below where *CEN2* is linked to the long arm of chromosome IV and *CEN4* is linked to the long arm of chromosome II. Figure in panel B shows the recombination frequencies after cells were exposed to DMSO (solid column), 50 µM of AFB<sub>1</sub> (horizontally striped column) and 37.5 µM of BaP-DHD (diagonally-striped column). Figure in panel C shows the net recombination frequencies, which are obtained by subtracting the spontaneous recombination frequency from the carcinogen-associated frequency. The CYP1A1 allele is indicated on the X axis. Error bars represent standard deviation (SD), N = 3.

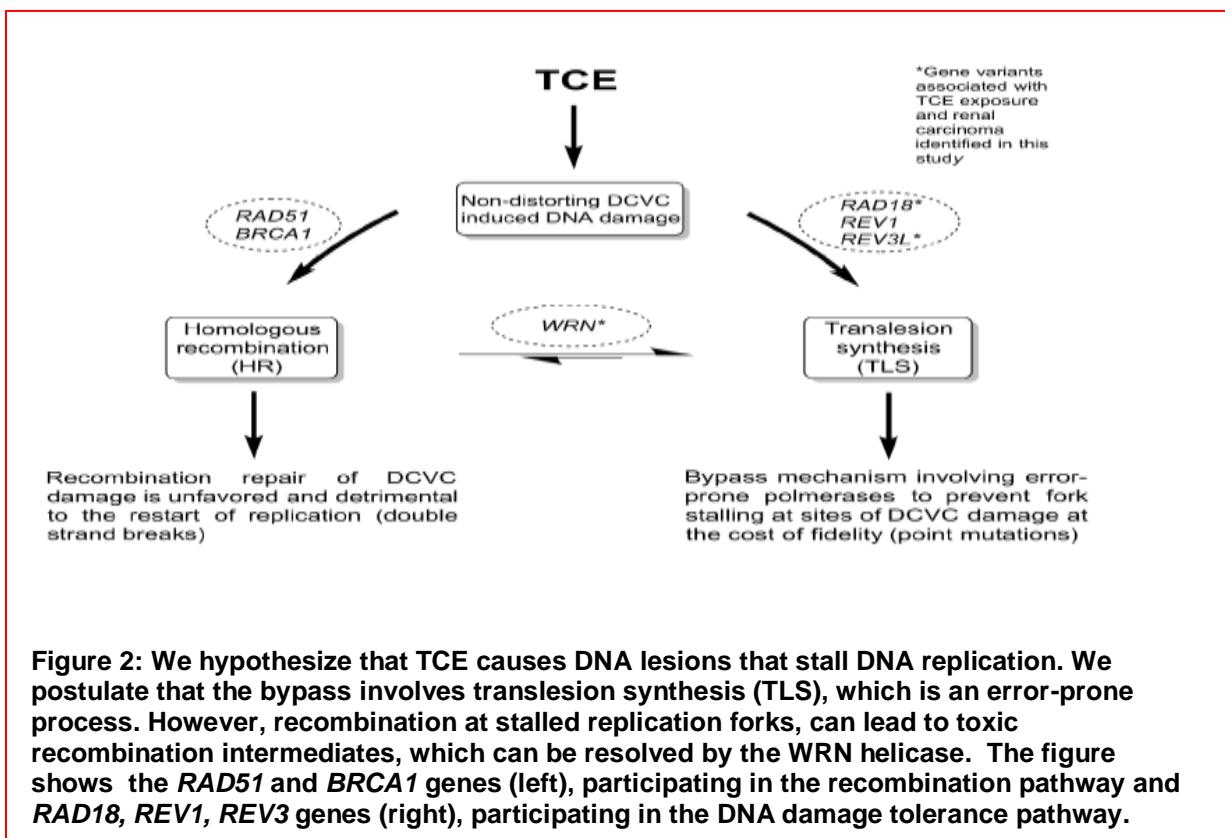
Publications:

1. Freedland, J., Cera, C., **Fasullo, M.** CYP1A1 I462V polymorphism is associated with reduced genotoxicity in yeast despite positive association with increased cancer risk. *Mutation Research* 815:35–43, 2017
2. **Fasullo, M.**, Freedland, J., Cera, C., Egner P., Hartog, M., Ding, X. An *in vitro* system for measuring genotoxicity mediated by human CYP3A4. *Environ. Mol. Mutagen.* 58:217-227, 2017.

## TOPIC 2: High-throughput Screening of Yeast Libraries expressing P450 genes in budding yeast.

An additional aim of the R15 NIH grant was to profile the yeast genome for resistance to potent carcinogens, including P450-activated carcinogens aflatoxin B1 and heterocyclic aromatic amines (HAAs). We have also collaborated on a project to profile the yeast genome for resistance to trichloro ethylene (TCE), an industrial compound associated with renal cancer. Since ~30% of the yeast genes are orthologous to human genes, we reason that identifying yeast genes would also aid in identifying the corresponding human genes. We had earlier shown that several DNA repair pathways were involved in carcinogen resistance, but we wanted to scan the entire genome to identify additional metabolic pathways involved in RNA metabolism, cell cycle checkpoint control, and cell growth control. In order to identify the wide range of gene functions, we scanned the 5,000 non-essential yeast strain collection expressing CYP1A2. This yeast strains contained molecular barcodes, which identify each strain. The yeast strains were pooled and divided into triplicates which either are exposed to carcinogen or exposed to solvent. The DNA barcodes are then counted using the Illumina high-throughput sequencing platform. With the aid of Frank Doyle, we set up a user-friendly bioinformatics platform to identify both sensitive and resistant strains. Using freely available software from the *Saccharomyces* genome data (SGD) base, we have placed the resistant genes into gene ontology groups. These groups include DNA repair, cell cycle checkpoint, RNA metabolism, and mitochondrial genes.

We focused on genes which confer tolerance to DNA damage, since these genes are responsible for both promoting and suppressing DNA mutations. Interestingly, we found that among TCE genes that confer resistance are those involved in recombinational repair while those that confer sensitivity are those involved in DNA damage tolerance or which function to abort recombination intermediates. A model is shown below.



Among the most interesting genes were those that are involved in mutation avoidance which have not been detected in previous studies to identify genes that are transcriptionally induced by aflatoxin B1. These genes included *CSM2*, *PSY3*, and *SHU1*, and *SHU2*. These genes form a complex that serves to assemble Rad51 filaments which catalyze error-free bypass of DNA lesions. We determined that *csm2* mutants exhibit a higher frequency of carcinogen-associated mutation but lower frequencies of DNA damage associated recombination, consistent with this hypothesis. The research was presented at the 2016 Environmental Mutagen and Genomics Society Meeting, Kansas City, MO.

**Publications:**

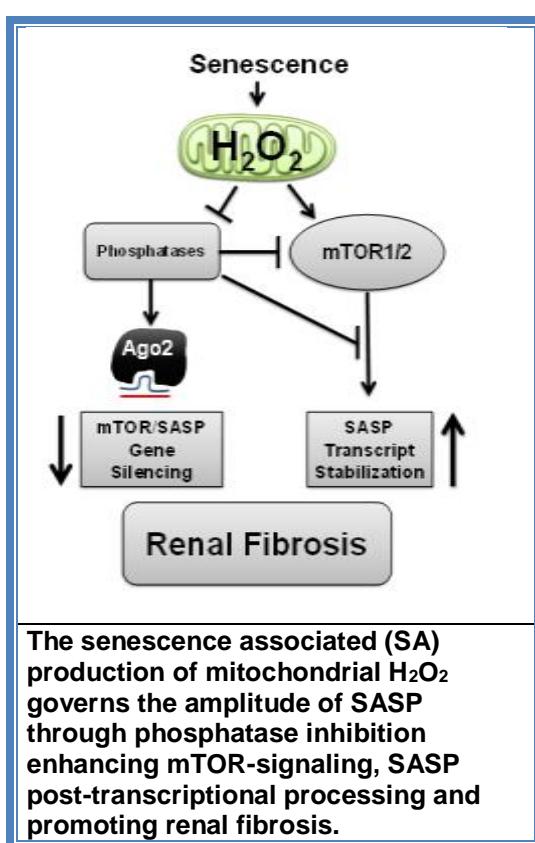
1. **Fasullo, M.** and Sun, M. Both *RAD5*-dependent and independent pathways are involved in DNA damage-associated sister chromatid exchange in budding yeast. AIMS Genetics, 4(2): 84-102, 2017 (special issue on DNA Repair).
2. Dela Rosa, V. Y., Asfaha, J., **Fasullo, M.**, Loguinov A., Li, P., Nakamura J., Swenberg, J.; Smith M. T., Vulpe, C.; Scelo D. G. Functional profiling in yeast reveals genotoxicity mechanisms and candidate susceptibility genes associated with trichloroethylene exposure and renal cell carcinoma. (in revision, Toxicological Sciences).

## Redox-Signaling & Biology (Melendez Group)

**Scope:** Evaluate the role of oxidants in the control of cancer, aging and infectious disease.

**Goals:** Provide R&D for the development of targeted antioxidant based therapies for the treatment of metastatic cancer, aging and infection disease.

### 2016 Accomplishments



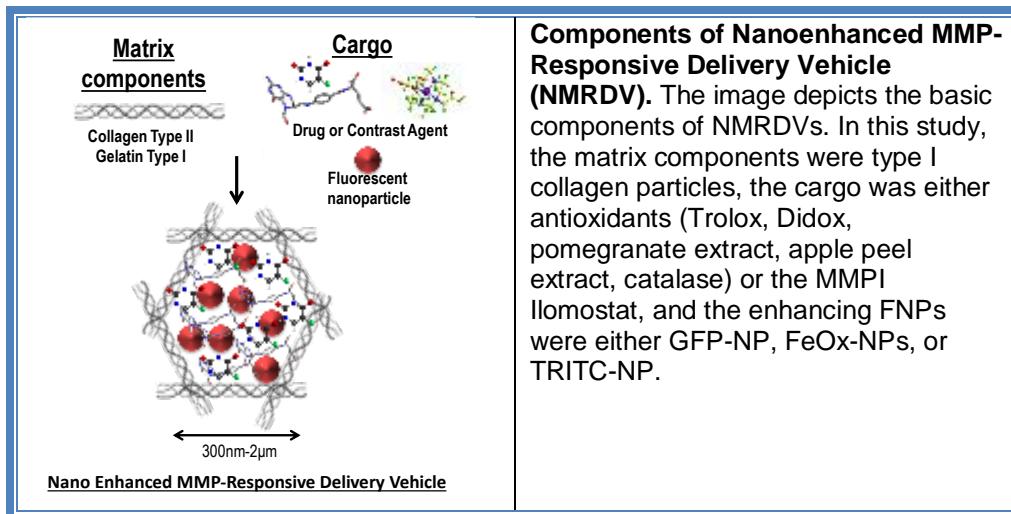
**TOPIC 1:** Fifteen percent of American adults (>30 million) suffer from some degree of chronic kidney disease (CKD). Medicare costs for patients aged 65 years or older with CKD were about \$45 billion in 2012. Globally from 8-16% of the population worldwide is affected by CKD and in 2014 kidney disease was the 9<sup>th</sup> ranked cause of death nationally. Strategies to reduce burden and medical costs related to renal disease are critically needed. Senescence cells have recently emerged as contributors to age-related renal pathology. While cellular senescence has evolved as a protective mechanism to arrest cells exposed to oncogenic insult, chronic senescence activation promotes loss of renal function. The harmful effects of senescence are attributed to high secretory activity, commonly referred to as the Senescence Associated Secretory Phenotype (SASP).

Strategies which limit the amplitude and duration of SASP will serve to delay age related renal decline. SASP activation is reliant on production

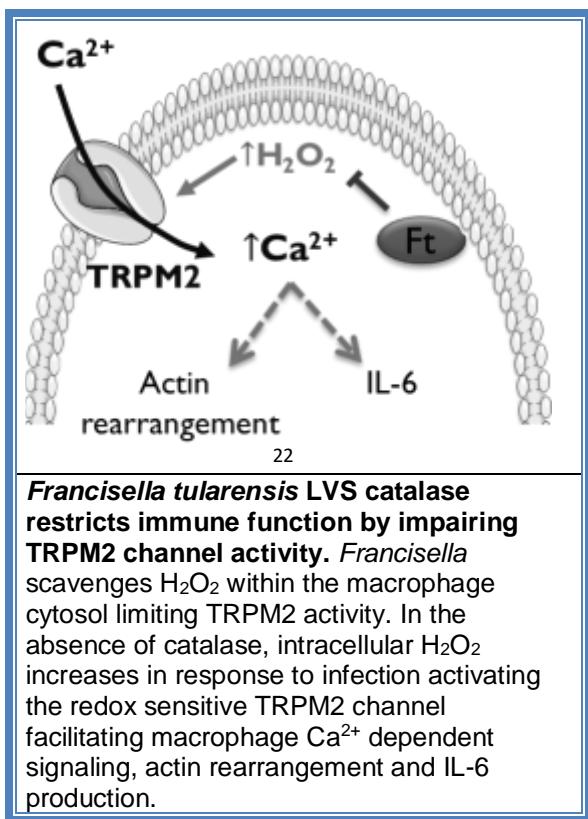
of interleukin-1 alpha (IL-1 $\alpha$ ) and we have shown that H<sub>2</sub>O<sub>2</sub>, likely of mitochondrial origin, regulates IL-1 $\alpha$  transcription and processing in this process. H<sub>2</sub>O<sub>2</sub> signals, in part, through oxidative inactivation of specific protein tyrosine phosphatases (PTPs) that coordinate a broad array of signaling networks. Conversely, IL-1 $\alpha$  mRNA stabilization and translation in SASP is also regulated by mTOR. Hence, we have been defining the interplay between H<sub>2</sub>O<sub>2</sub> and PTPs that govern mTOR signaling and how this contributes to gene silencing and post-transcriptional processing of the SASP. Fibrotic insult is a precursor to loss of renal function and we are developing targeted strategies which restrict mitochondrial H<sub>2</sub>O<sub>2</sub>, mTOR or SASP and can limit renal fibrosis.

Sosa Peña MD, Lopez-Soler R, Melendez JA. Senescence in chronic allograft nephropathy. *Am J Physiol Renal Physiol.* 2016 Jun 15;ajprenal.00195.2016.

**TOPIC 2:** The wide array of proteases, including matrix metalloproteinases (MMPs), produced in response to many pathogenic insults, confers a unique proteolytic signature which is often disease specific and provides a potential therapeutic target for drug delivery. We have been testing the use of Collagen-based Nanoenhanced MMP-Responsive Delivery Vehicles (NMRDVs) that display MMP specific degradation in diverse *in vitro* models of proteolysis. We demonstrate that collagen particles comprised of protease substrates (primarily collagen) can be made of uniform size and loaded efficiently with assorted cargo including fluorescently-labeled mesoporous silica, magnetic nanoparticles, proteins and antioxidants. We also demonstrate that pathologic concentrations of proteases produced *in situ* or *in vitro* display protease specific cargo release. Additionally, we show that the collagen-based particles display bright fluorescence when loaded with a fluorophore, and have the potential to be used as vehicles for targeted delivery of drugs or imaging agents to regions of high proteolytic activity.



McCarthy DA, Nazem AA, McNeilan J, Shakerley NL, Clark RR, Idelchik MD, Yigit M, Melendez JA. Featured Article: Nanoenhanced matrixmetalloproteinase-responsive delivery vehicles for disease resolution and imaging. *Exp Biol Med (Maywood).* 2016 Dec;241(18):2023-2032.

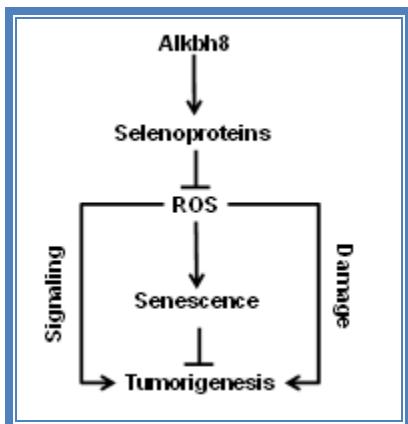


ionomycin. Basal increases in cytosolic Ca<sup>2+</sup> as well as insensitivity to H<sub>2</sub>O<sub>2</sub>-mediated Ca<sup>2+</sup> entry in ΔkatG-infected cells are reversed by the Ca<sup>2+</sup> channel inhibitors, 2-Aminoethyl diphenylborinate (2APB) and SKF-96365. 2APB but not SKF abrogated ΔkatG-dependent increases in macrophage actin remodeling and IL-6 secretion, suggesting a role for H<sub>2</sub>O<sub>2</sub>-mediated Ca<sup>2+</sup> entry through the transient receptor potential melastatin 2 (TRPM2) channel in macrophages. Indeed, increases in basal Ca<sup>2+</sup>, actin polymerization and IL-6 production are reversed in TRPM2-null macrophages infected with ΔkatG. Together our findings provide compelling evidence that *F. tularensis* catalase restricts ROS to temper macrophage TRPM2-mediated Ca<sup>2+</sup> signaling and limit host immune function.

Shakerley NL, Chandrasekaran A, Trebak M, Miller BA, Melendez JA. *Francisella tularensis* Catalase Restricts Immune Function by Impairing TRPM2 Channel Activity. *J Biol Chem*. 2016 Feb 19;291(8):3871-81. doi: 10.1074/jbc.M115.706879. Epub 2015 Dec 17. PubMed PMID: 26679996; PubMed Central PMCID: PMC4759167.

Rabadi SM, Sanchez BC, Varanat M, Ma Z, Catlett SV, Melendez JA, Malik M, Bakshi CS. Antioxidant Defenses of *Francisella tularensis* Modulate Macrophage Function and Production of Proinflammatory Cytokines. *J Biol Chem*. 2016 Mar 4;291(10):5009-21.

**TOPIC 3:** As an innate defense mechanism, macrophages produce reactive oxygen species (ROS) which weaken pathogens and serve as secondary messengers to modify signaling responses involved in immune function. The gram-negative bacterium *F. tularensis* utilizes its antioxidant armature to limit the host immune response but the mechanism behind this suppression has not been defined. We have established that *F. tularensis* limits Ca<sup>2+</sup> entry in macrophages thereby limiting actin reorganization and IL-6 production in a redox-dependent fashion. Wild-type (LVS) or catalase deficient *F. tularensis* (ΔkatG) show distinct profiles in their H<sub>2</sub>O<sub>2</sub> scavenging rates, 1 pM/sec and 0.015 pM/sec, respectively. Murine alveolar macrophages infected with ΔkatG display abnormally high basal intracellular Ca<sup>2+</sup> concentration that did not increase further in response to H<sub>2</sub>O<sub>2</sub>. Additionally, ΔkatG-infected macrophages displayed limited Ca<sup>2+</sup> influx in response to the Ca<sup>2+</sup> ionophore



**TOPIC 4:** Maintenance of the GSH redox cycle is reliant on the activities of selenocysteine-containing GSH metabolizing enzymes. Selenocysteine is the 21<sup>st</sup> amino acid and does not contain a dedicated codon. Selenocysteine incorporation during translation requires UGA-stop-codon recoding, which uses specifically modified tRNA for accurate decoding. Dynamic changes in tRNA modification are an epitranscriptomic signal because they regulate gene expression post-transcriptionally. The Begley lab has shown that the stress-induced translation of many selenocysteine containing ROS detoxifying enzymes is dependent on the Alkbh8 tRNA methyltransferase.

Alkbh8 enzymatically methylates the uridine wobble base on tRNA<sub>Selenocysteine</sub> to promote UGA-stop codon decoding. Surprisingly the *Alkbh8*-deficient (*Alkbh8*<sup>-/-</sup>) mice reproduce, thrive normally and live past 15 months, **suggesting they adapt to the selenoprotein deficiency**, high ROS and increased DNA damage levels. In collaboration with the Begley lab we have been investigating a potential adaption mechanism, we have used molecular, biochemical and genomic approaches to demonstrate that *Alkbh8*<sup>-/-</sup> mouse embryonic fibroblasts (MEFs) and some organs display markers of senescence and a senescence gene signature. Using the *Alkbh8*<sup>-/-</sup> mice we are testing the hypothesis that **senescence occurs *in vivo* as a result of defective epitranscriptomic signals that controls selenocysteine utilization and prevents tumor emergence.**

Idelchik MDPS, Begley U, Begley TJ, Melendez JA. Mitochondrial ROS control of cancer. *Semin Cancer Biol.* 2017 Apr 23. pii: S1044-579X(17)30098-6.

Chandrasekaran A, Idelchik MD, Melendez JA. Redox control of senescence and age-related disease. *Redox Biol.* 2017 Apr;11:91-102. doi: 10.1016/j.redox.2016.11.005.

## Nanomachines, Cancer Therapy and Human Stem Cell Bioengineering

Janet L. Paluh, Ph.D.

**Scope:** The Paluh lab applies nanotechnology and dynamic parameters of biological systems towards improved healthcare and nanofabrication. This includes analysis of cellular nanomachines with applications to drug discovery, nanorobotics and biomimetic improvements to nanofabrication. Human stem cell biology and 3D bioengineering of human tissues and organoids is also underway to elucidate pathways in human development, disease and repair for advances in health care.

**Goals:** Applications of bionanotechnology to 1) human preventative healthcare and personalized medicine (biosensors, development, cell therapy, tissue repair, cancers, neurodegeneration); and 2) biomimicry, biosynthetic interfacing, nanomachines, transformable materials, and bottom up assembly.

### *2017 Most Recent Accomplishments*

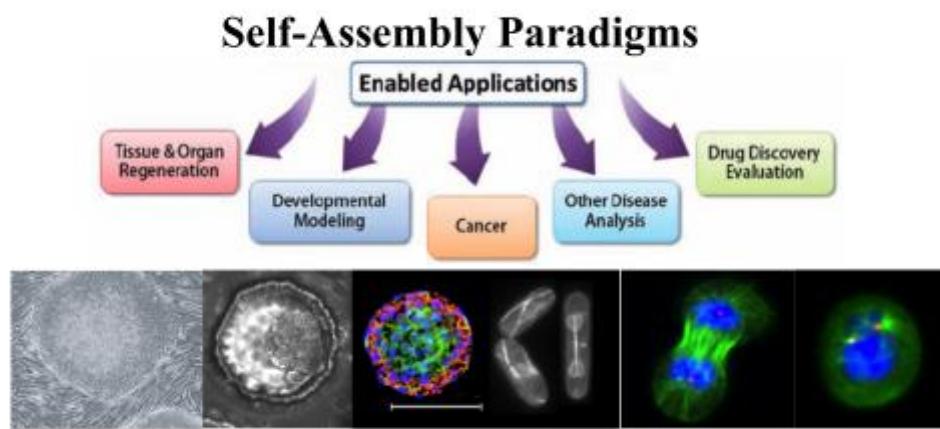
**TOPIC 1: Nanomachines: Microtubule organizing center (MTOC) mechanisms. Novel control of mitotic spindle function and its application to drug discovery for human cancers.**

Self-assembly of biological systems is inherent in sub-cellular nanomachines to higher order assemblies of cells, tissues, organs and organ systems (Figure 1). Biological nanomachines formed by bottom-up assembly and their communication networks incorporate dynamic concepts of error correction, transformability and multi-tasking. These molecular machines offer an incredibly rich and inspiring resource for development of complex materials, architectural designs, and networking to be applied to human made systems. In addition, such parameters are critical considerations in drug discovery/resistance prevention studies.

The Paluh laboratory is harnessing components of the microtubule cytoskeleton and mitotic spindle apparatus. Mitotic mechanisms though studied for over 100 years still have undiscovered underlying complex control networks that operate in spindle functions of chromosome segregation, cell polarity and multi-cellular lineage specification. The microtubule cytoskeleton and its associated proteins (MCPs) also act in broader cellular networks as scaffolds, roadways for motility and trafficking, tethers and signaling hubs and bring versatility into complex and critical tasks of cells and cell-cell networks. These diverse tasks include cell crawling, neuronal signaling, and immune system cytotoxic killer T-cell function. The formation of microtubules, that are dynamic polar polymers typically 25 nm in diameter, is nucleated through a macromolecular Microtubule Organizing Center (MTOC) complex. This complex helps to define microtubule polarity and organization in cells and influences the dynamic growth/shortening cycles of microtubules. Unlike static synthetic counterparts such as

carbon nanotubes (CNTs), biological microtubule networks rapidly transform, adapt and error correct to rapidly self-customize to new architectural designs or meet changing cellular needs.

Prof. Paluh is an international leader in mitotic mechanisms. Recent publications from her lab reveal new mitotic mechanisms and reagents for MTOC control, including proven potential for development as a new target and therapy in breast cancers. This work is expected to have considerable impact to all fields of biology and human disease in which microtubules play a role.<sup>1</sup>



**Figure 1: Drug Discovery:** Self-assembly mechanisms are inherent in biology at subcellular, multi-cellular, organoid and system levels. The Paluh lab discovery of a new mitotic mechanism in spindle assembly and its control elements has led to a pending patent and the potential for a new strategy and target in cancer treatments. Effectiveness has been demonstrated *in vivo* to arrest growth of breast cancer cell lines. Multiple additional applications are expected and being explored and developed.

## TOPIC 2: Nanoscale and Molecular Communication Framework. Development of an IEEE Standard for Advancing Nanotechnology.

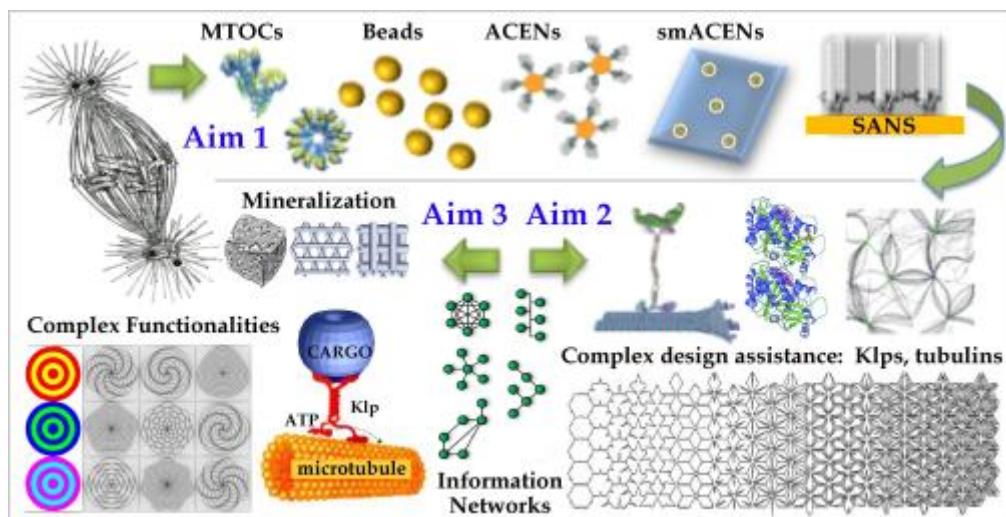
Biological systems form diverse communication networks that scale broadly and with high accuracy from subcellular levels of quantum, nano- and micro- scales to multi-cellular macroscales. This is evident in cellular functions, multi-cellular tissues and organs, or organ systems in organisms. Biomimicry of these complex networks

<sup>1</sup> Footnote: Neural Science Grant proposals pending with NIH (tauopathies) and NYSCIRB (spinal injury) Manuscripts:

Z.T. Olmsted, A. Colliver, T.D. Riehlman, and **J.L. Paluh** (2014) Kinesin-14 and kinesin-5 antagonistically regulate microtubule nucleation  $\gamma$ -TuRC in yeast and human cells. *Nature Communications* 5:5339. doi:10.1038/ncomms6339

Z.T. Olmsted, A. Colliver, and **J.L. Paluh** (2014) The Kinesin-Tubulin Complex: Mechanistic Considerations in Structure and Function. *J. Cell Health and Cytoskeleton*. In press with accompanying video.

increasingly requires the aid of computational and mathematical modeling and virtual simulations. Prof. Paluh participates actively in NIH sponsored Multiscale Modeling and Interagency Modeling and Analysis (MSM IMAG) and Virtual Cell meetings and as an IEEE member since 2012 on the IEEE Standards Association P1906.1 Working Group on Recommended Practice for Nanoscale and Molecular Communication Framework. This multi-disciplinary team of engineers, physicists, biologists and chemists has completed a new IEEE Standard document for academia, industry and clinical advancement of nanoscale communication networks. The work applies Shannon's Rules of Information Theory to biological, synthetic, and biosynthetic systems that include a human made component.<sup>2</sup> Such a framework document establishes common definitions and practice to enable constructive multi-disciplinary collaborations and accelerate nanotechnology discovery and applications. The Paluh laboratory is applying these concepts to self-assembling microtubule networks to be used in biosynthetic systems as in Figure 2 and in modeling neural networks as in Figure 3, Topic 3.



**Figure 2: Molecular Communication Frameworks: Guided Self-Assembly.** This figure outlines the pathway of discovery from isolation of biological components (Aim1), establishment of the bio-synthetic interface (Aim2), and application of information theory mathematical algorithms for controlled patterning of

<sup>2</sup> Footnote: Two publications, includes a new IEEE standard and a manuscript in review.

S.F. Bush, J.L. Paluh, G. Piro, V. Rao, V. Prasad, and A. Eckford (2015) Defining Communication at the Bottom. IEEE Journal series on Selected Areas of Communication: Molecular, Biological and Multi-Scale Communications (JSAC TMBMC). 1:90-96. doi: 10.1109/TMBMC.2015.2465513.

S.F. Bush, J.L. Paluh, G. Piro, V. Rao, V. Prasad, A. Eckford, et al. (2015) P1906.1/D2.1 Approved Draft Recommended Practice for Nanoscale and Molecular Communication Framework. IEEE Standards Association. E-ISBN: 978-1-5044-0032-9.

A. Banerjee, J.L. Paluh, A. Mukherjee, L.G. Kumar, A. Ghosh, M.K. Naskar (2017) Modeling the Neuron as a nanocommunication system to identify key molecular events in neurodegenerative disease. In review. Submitted PLOS One.

simple switchable designs or those with parquet deformation complexity (Aim3). Biological components shown include 25 nm microtubules, kinesin nanomotors and microtubule organizing center (MTOC) molecular machinery, among others.

### **TOPIC 3: Human Stem Cell Bioengineering. Organ specialization, Tissue Bioengineering, Disease and Development Studies.**

Preceding human clinical trials, studies in animal models as well as in vitro tissue bioengineering contribute significantly to advancing discoveries for human health. For the latter, biomimicry of the in vivo environment in architecture, multi-cellular context, physical and chemical parameters, and signaling communication networks are needed to best approximate the natural state. The defined microenvironment also includes dynamic temporal controls for developmental growth, cell differentiation and aging that impact the occurrence/susceptibility, progression and treatment of diseases. The recent merger of nanotechnology with the discovery of human stem cells in 1998, 'stem cell nanotechnology' research, offers unprecedented opportunities in human healthcare.

Stem cell nanotechnology research in Prof. Paluh's lab is directed at understanding the human stem cell niche, developmental pathways and organ function to understand disease mechanisms and optimization preventative treatments or cell therapy. The traditional cell culturing methods of the 1950's have been superseded by eloquent biomimicry of the 3D natural environment with an enormous recognized impact of cellular environment on outcomes of gene regulation, lineage specification and organoid development. The Paluh laboratory applies nanotechnology to create architectural scaffolds for 3D hydrogel microfluidic environments for use with pluripotent, differentiating progenitor or transit amplifying cells, derived mature cells and multi-cellular contexts. This approach increases statistic evaluation of cell-cell communication and complex networks in multi-lineage specification for current applications in neural development and neurodegeneration as well as analysis of cancers of developmental origin (Figure 3)

As part of our ~\$1 million NYSTEM award we have derived and characterized new ethnically diverse and karyotypically normal human stem cell lines of African American, Hispanic-Latino, Asian and Caucasian origin<sup>3</sup>. By including ethnicity in stem cell

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<sup>3</sup> Footnote: Multiple manuscripts published from this effort

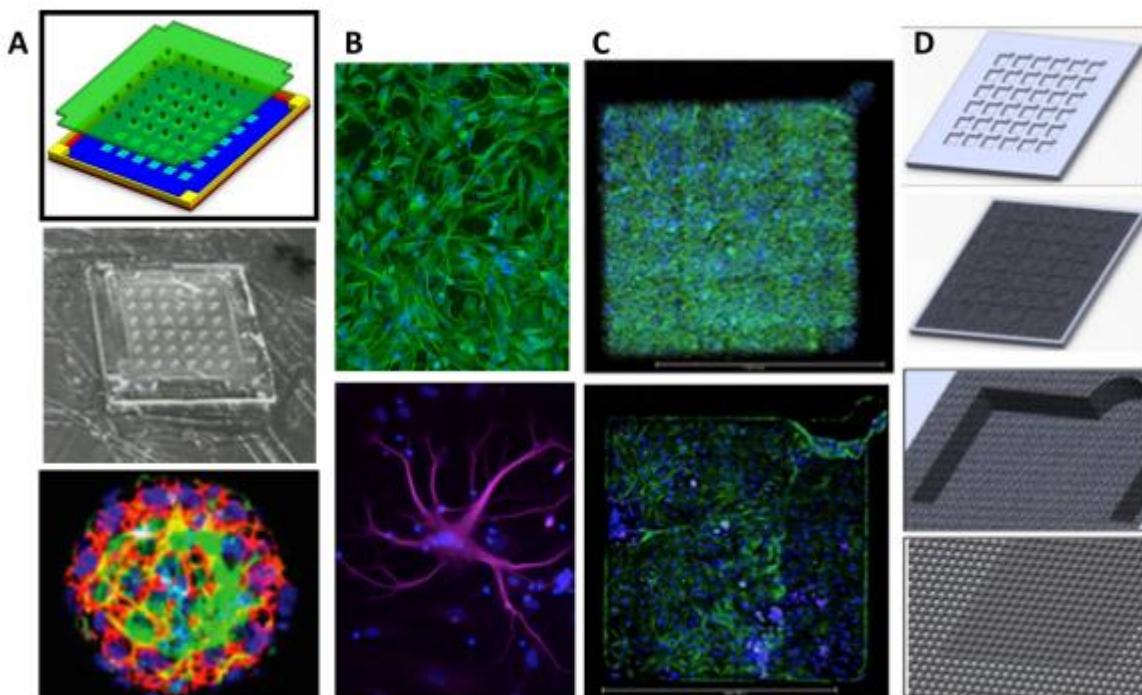
E-A Chang, M. Tomov, S.T. Suhr, J. Luo, Z.T. Olmsted, **J.L. Paluh** and J. Cibelli (2015) Derivation of Ethnically Diverse Human Induced Pluripotent Stem Cell Lines. Nature publishing, Scientific Reports. 5:15234. doi:10.1038/srep15234.

M. Tomov, M. Tsompana, Z.T. Olmsted, M. Buck, and **J.L. Paluh** (2016) Human Embryoid Body Transcriptomes Reveal Maturation Differences Influenced by Size and Formation in Custom Microarrays. Journal of Nanoscience and Nanotechnology, Special Issue on Role of Nanotechnology in Stem Cell Research.

M. Tomov, Z.T. Olmsted, and **J.L. Paluh** (2015). The Human Embryoid Body Cystic Core Exhibits Architectural Complexity Revealed by Use of High Throughput Polymer Microarrays. Macromolecular Biosciences. 15(7): 892-900. Doi 10.1002/mabi.201500051. PMID: 25810201. Note: and Journal Cover.

M Tomov, Z.T. Olmsted, H. Dogan, E. Gungoruler, M. Tsompana, M. Buck, H. Otu, E-A Chang, J. Cibelli, and **J.L. Paluh** (2016) Distinct and Shared Determinants of Cardiomyocyte Contractility in Multi-

research with clinical applications we expect to identify disease biomarkers and protective or debilitating factors in disease treatment and drug studies. Through our work and collaborative efforts we hope to investigate ethnicity in any of a number of human processes including neural networks and neurodegeneration, early retinal development, cardiac drug susceptibility, aging, diabetes, smoke addiction, myopathies and cancers as well as other yet unknown contributing pathways related to human health and longevity.



**Figure 3: Lithography template platforms for stem cell nanotechnology of neural networks.** A. CAD designed multilayer grid for patterning of uniformly sized embryoid bodies that are preformed in custom lithography-generated microwells. B. Derivation of human pyramidal neurons for co-culture studies, including neuronal-glial networks, blood-brain barrier and cancers of neural origin. C. Co-cultures of human gliomas and neuroblastomas. D. CAD designed matrix and porous grid for investigation of blood-brain barrier using human multicellular co-cultures.

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J Wang, B Egnot, JL Paluh (2016) Cell Competition and Cooperation in Tissue Development. J Tissue Science and Engineering

## Mammalian and Microbial Cell Bioprocessing (Sharfstein group)

**Scope:** Production of therapeutic and diagnostic biomolecules from cultured animal and bacterial cells; development of models for *in vitro* testing of small molecule therapeutics; development of sensing technology to support cell culture

**Goal:** Develop fundamental understanding of the role of cell culture conditions and cell physiology on the production of biotherapeutics.

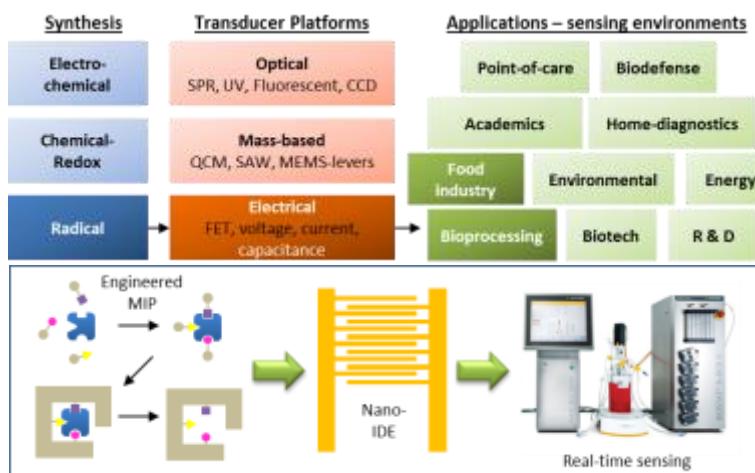
### 2016 Accomplishments

#### TOPIC 1: Analysis of molecularly imprinted polymers for biosensing (with Professor Magnus Bergkvist)

Complex aqueous environments such as those found in food industry and bioreactor processes contain many dissolved metabolites including sugars, salts, vitamins, and amino acids, dissolved gases such as oxygen and carbon dioxide, proteins, and suspended solids at levels that vary from dilute up to greater than 50% by volume. Constant monitoring of this environment is vital to provide precise feedback control to maximize production, reduce costs and improve product safety.

We hypothesized that molecularly imprinted polymer (MIP) matrices could be developed as “artificial receptors” for a wide array of molecules. They represent an approach for analyte recognition that emulates that of antibodies and enzymes, while addressing the stability and robustness concerns of biological recognition systems. MIPs are prepared from monomeric precursors, where the analyte of interest interacts with the monomers and becomes embedded in the final matrix upon polymerization. Upon removal of the analyte “template”, specific recognition sites, complementary in shape, size, and functional groups to the template molecule are created (Figure 1).

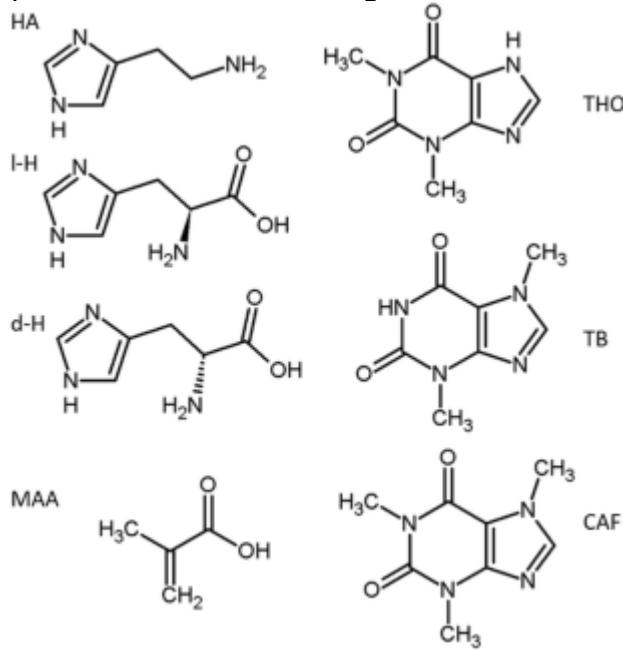
Our initial studies focused on synthesis methods for MIPs, but it rapidly became apparent that a fundamental understanding of how MIPs should be designed for optimal binding to a chemical target. To address that issue, we performed a series of molecular modeling studies combining quantum



**Figure 1:** Synthesis strategies, transducer options, and sensing applications for MIPs. The route for MIP device fabrication, sensor platform, and application areas of interests are highlighted.

mechanical analysis with molecular mechanics simulations and molecular dynamics to simulate monomer-target interactions during the polymerization process and then binding of the target to the polymer after polymerization. Three publications (including one in review) resulted from this project (1-3).

We evaluated the interactions of several targets with similar structures with a polymer matrix of methacrylic acid. The targets were divided into two categories. The first includes imidazole-derived structures: histamine (HA), L-histidine (L-H), and D-histidine (D-H). The second includes xanthine-derived structures: theophylline (THO), caffeine (CAF), and theobromine (TB). These targets were selected for their biological relevance as drugs (THO, CAF, TB), biomarkers (HA), and amino acids (L-H, D-H). Analyzing two groups of compounds allowed for a comparison of the relative binding energies of molecules with varying structural similarity to the imprinted molecule. Methacrylic acid (MAA) was selected as the monomer for these studies based on a strong literature precedent and previous observations of strong interactions with the selected target molecules. The structures of each component can be seen in Figure 2.

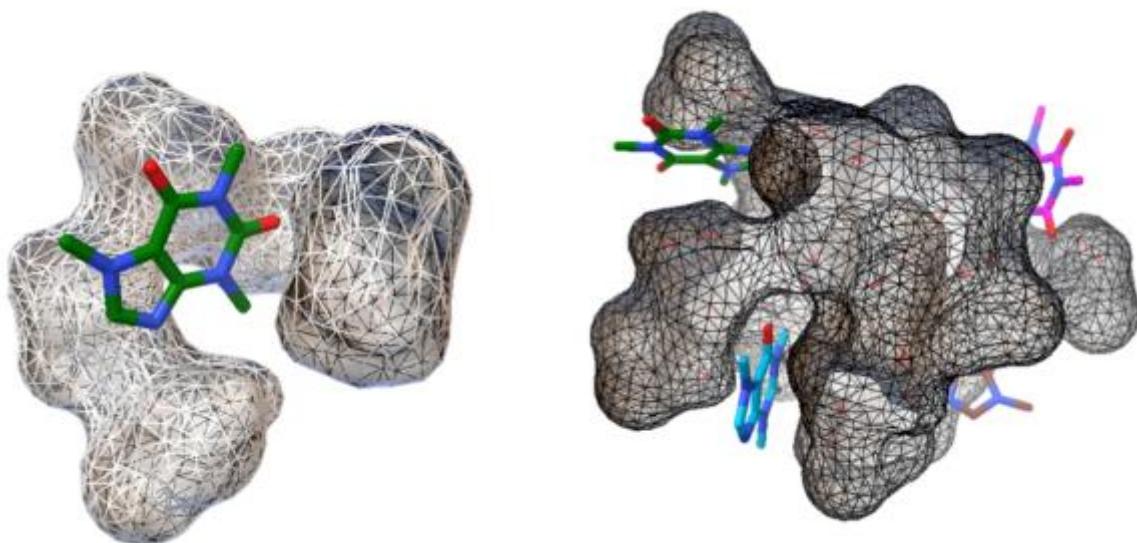


**Figure 2: Molecular structures of the targets and monomer species investigated.**

Ratio optimization was computed at both small (one-target) and larger (five-target) scales. Avogadro, a cross platform molecular editor ([avogadro.cc](http://avogadro.cc)), was used to build the pre-polymerization systems, which include the target(s) and monomers. The porogen was included via implicit solvation, using the Conductor-like Screening Model (COSMO). Chloroform was chosen as the implicit solvent for all QM optimizations. Chloroform is capable of solvating the targets and monomers, does not form strong H-bonds with either, and does not interfere with complexation and the formation of binding sites. Consequently, chloroform has been shown to produce more effective MIPs than many other pre-polymerization solvents. First, the small systems consisting of one target and 2-6 monomers were built in Avogadro. The starting orientations of the molecules were

chosen such that the carboxylic acid functional groups of the monomers were in approximate co-location to the polar groups of the target. The hydrophobic moieties of the monomers, which form the backbone of the MIP, were directed away from the target. The systems were then geometrically optimized using the PM6-DH2 basis set with MOPAC, which has been called the “gold standard” of semi-empirical QM calculations. This method was parameterized to correct for dispersion and H-bonding within the PM6 Hamiltonian, making it suitable for the noncovalent interactions that drive MIP binding.

For the larger systems, five targets and the proportional numbers of monomers (10, 15, 20, 25, or 30) were built into the system. The starting positions of targets and monomers were similar to those described for the one-target systems. Within one geometry file, five separate one-target systems were built containing the relevant number of monomers (2-6). The distances between the one-target systems were then decreased until the monomers of one system were able to interact with those of the adjacent system. Molecular simulation results for small and large-scale systems are shown in Figure 3.



**Figure 3:** Small scale (left) and larger scale (right) modeled systems, displayed with AutoDock Tools. The targets (in this case CAF) are bound to the MAA molecules, represented here by a continuous molecular surface.

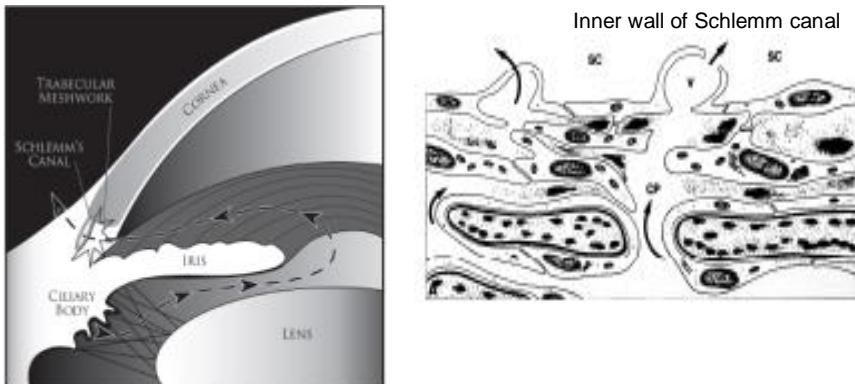
**TOPIC 2: Development of a bioengineered conventional outflow tract for evaluation of glaucoma therapeutics (with Professor Yubing Xie, Magnus Bergkvist and John Danias-Downstate Medical)**

Glaucoma refers to a group of slowly-progressing optic neuropathies characterized by asymptomatic, irreversible loss of retinal ganglion cells (RGC) and optic nerve axons resulting in vision loss. It is a potentially blinding disease. It accounts for approximately 13% of blindness worldwide, being the second leading cause of blindness worldwide and the first leading cause of irreversible blindness. In the US, it is estimated that over 2.7 million people have glaucoma. Of these 50% are undiagnosed and approximately 120,000 are blind.

Elevated intraocular pressure (IOP) is often associated with glaucoma and can cause irreversible blindness if it is undetected or untreated. It is estimated that 10 million people have high IOP that may lead to glaucoma in the US. IOP is one of the most important and the **only** modifiable risk factor for glaucoma. Lowering IOP is currently the only effective target for therapeutic intervention in glaucoma. IOP is controlled by the outflow of the aqueous humor through the HTM, which is determined by the balance between aqueous humor production (flow) and elimination (outflow).

The rate at which aqueous humor leaves the eye at a particular IOP level is defined as outflow facility. In humans,

most of the aqueous humor (~90%) drains through the TM and into the SC (Figure 4). The TM and adjacent endothelium of the SC, known as the conventional (or trabecular) outflow-tract, control the outflow and thus determine IOP.



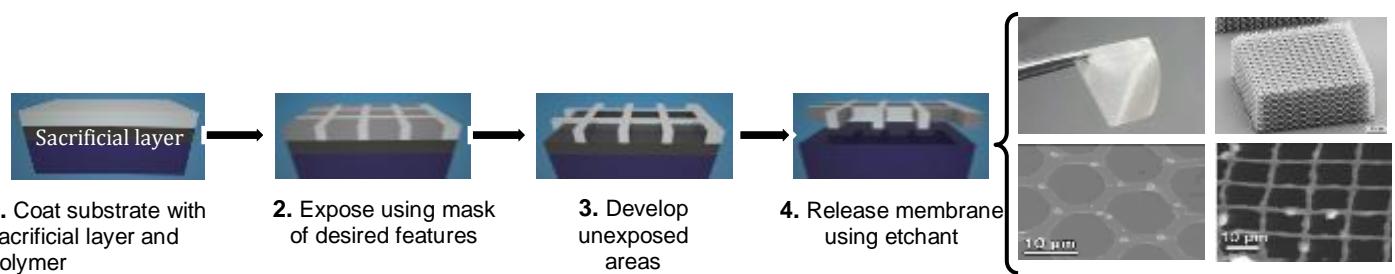
**Figure 4:** (Left) Schematic diagram illustrating the trabecular meshwork conventional outflow pathway. Aqueous humor is produced by the ciliary body and it flows (dashed line shown with arrowheads) from the posterior chamber through the pupil into the anterior chamber. From there it flows out through the trabecular meshwork into the Schlemm's canal and subsequently absorbed into the episcleral veins *via* the collector channels. (Right) Ultrastructure of the cribriform layer of the trabecular meshwork, CP=cribriform pathway, SC=schlemm canal; v=giant vacuole (microchannel) within the endothelial lining of Schlemm canal. Arrows = direction of aqueous humor outflow.

Currently there is no cure for glaucoma, and patient compliance with medication to keep the disease in check is low. This is partly due to the need for frequent doctor's appointments, and use of up to eight different medications. New, more effective drugs could have an impact on both issues and improve medical compliance. Drugs that affect the conventional outflow-tract could increase the outflow facility and lower IOP in the long term; however, there are no such drugs available. While there are ~14 drugs approved for human use to treat glaucoma, none acts directly on the TM or SC to increase the conventional outflow. Current treatments of glaucoma either lower the IOP by decreasing aqueous humor production, or by increasing aqueous humor outflow through non-conventional outflow-tract pathways.

One challenge for development of new potential glaucoma therapeutics, particularly those targeting the conventional outflow-tract, is the lack of proper, *in vitro* models for outflow and IOP (back pressure) studies. While traditional cell cultures of isolated TM and SC cells and organ cultures of isolated anterior chambers are useful for studying the biology of TM cells, they are not suitable for evaluating the effects of medications on outflow facility. Current outflow facility studies mainly rely on anterior segments of animal or human eyes; however, the preparation of these perfusion systems is cumbersome and expensive, and not suitable for high-throughput screening. In addition,

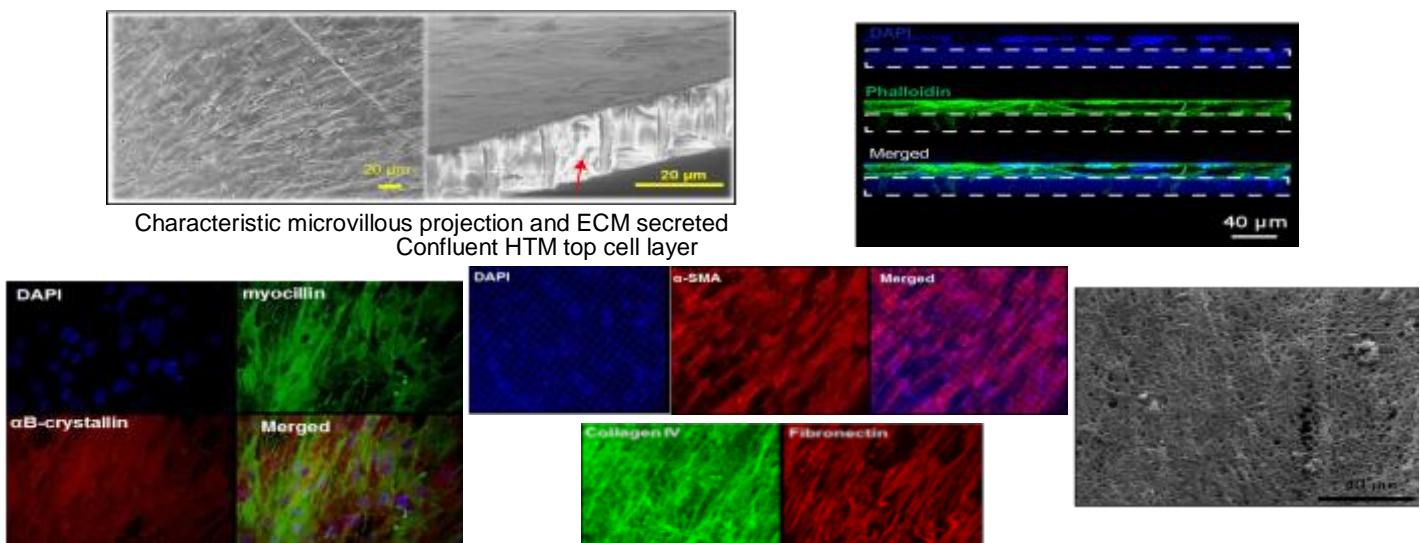
while animal (bovine and swine) anterior segments are readily available, species differences may not allow translation of the results to humans. Conversely primate and human anterior segments are difficult to obtain. A functional *in vitro* test model of the conventional (or trabecular) outflow-tract that would allow effective screening of combinatorial libraries of potential therapeutic agents would be of interest to research laboratories and pharmaceutical companies.

Over the last several years, we have developed an *in vitro* model of the conventional outflow tract based upon a patterned substrate, manufactured using lithographic processes (Figure 5) and demonstrated its utility in evaluating physiological responses to pharmaceutical agents (4-7). In addition, we have demonstrated the ability to transfect the cells grown in this system, something that is very challenging with traditional culture techniques.



**Figure 5: Schematic of substrate manufacture for bioengineered outflow tract**

As shown in Figure 6 below, trabecular meshwork cells grown on the micropatterned substrate exhibit a range of characteristic trabecular meshwork properties including microvilli projection and TM-specific markers.



**Figure 6: Electron and confocal micrographs demonstrating characteristic TM behavior**

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## RNA-Based Nanotechnology (Tenenbaum Group)

**Scope:** All areas of RNA Molecular Biology including gene expression, genomics and  
Cancer biology

**Goals:** To utilize nanoscale technology to study the role of RNA as a gene regulator and to develop RNA based nanotechnologies

### 2016 Accomplishments

(*Patents*)

*Trans-acting RNA switches*  
US 8841438 B2

(*Recent Papers*)

*FASTmiR: an RNA-based sensor for in vitro quantification and live-cell localization of small RNAs.* Huang K, Doyle F, Wurz ZE, Tenenbaum SA, Hammond RK, Caplan JL, Meyers BC. *Nucleic Acids Res.* 2017 Jun 6. doi: 10.1093/nar/gkx504. [Epub ahead of print]

*Engineering Structurally Interacting RNA (sxRNA).* Doyle F, Lapsia S, Spadaro S, Wurz ZE, Bhaduri-McIntosh S, Tenenbaum SA. *Sci Rep.* 2017 Mar 28;7:45393. doi: 10.1038/srep45393.

*Gene- and genome-based analysis of significant codon patterns in yeast, rat and mice genomes with the CUT Codon UTilization tool.* Doyle F, Leonardi A, Endres L, Tenenbaum SA, Dedon PC, Begley TJ. *Methods.* 2016 Sep 1;107:98-109. doi: 10.1016/j.ymeth.2016.05.010. Epub 2016 May 28.

*Integrative genomics positions MKRN1 as a novel ribonucleoprotein within the embryonic stem cell gene regulatory network.* Cassar PA, Carpenedo RL, Samavarchi-Tehrani P, Olsen JB, Park CJ, Chang WY, Chen Z, Choey C, Delaney S, Guo H, Guo H, Tanner RM, Perkins TJ, Tenenbaum SA, Emili A, Wrana JL, Gibbings D, Stanford WL. *EMBO Rep.* 2015 Oct;16(10):1334-57. doi: 10.15252/embr.201540974. Epub 2015 Aug 11.

*Metastatic bladder cancer cells distinctively sense and respond to physical cues of collagen fibril-mimetic nanotopography.* Iuliano JN, Kutscha PD, Biderman NJ, Subbaram S, Groves TR, Tenenbaum SA, Hempel N. *Exp Biol Med (Maywood).* 2015 May;240(5):601-10. doi: 10.1177/1535370214560973. Epub 2014 Dec 2.

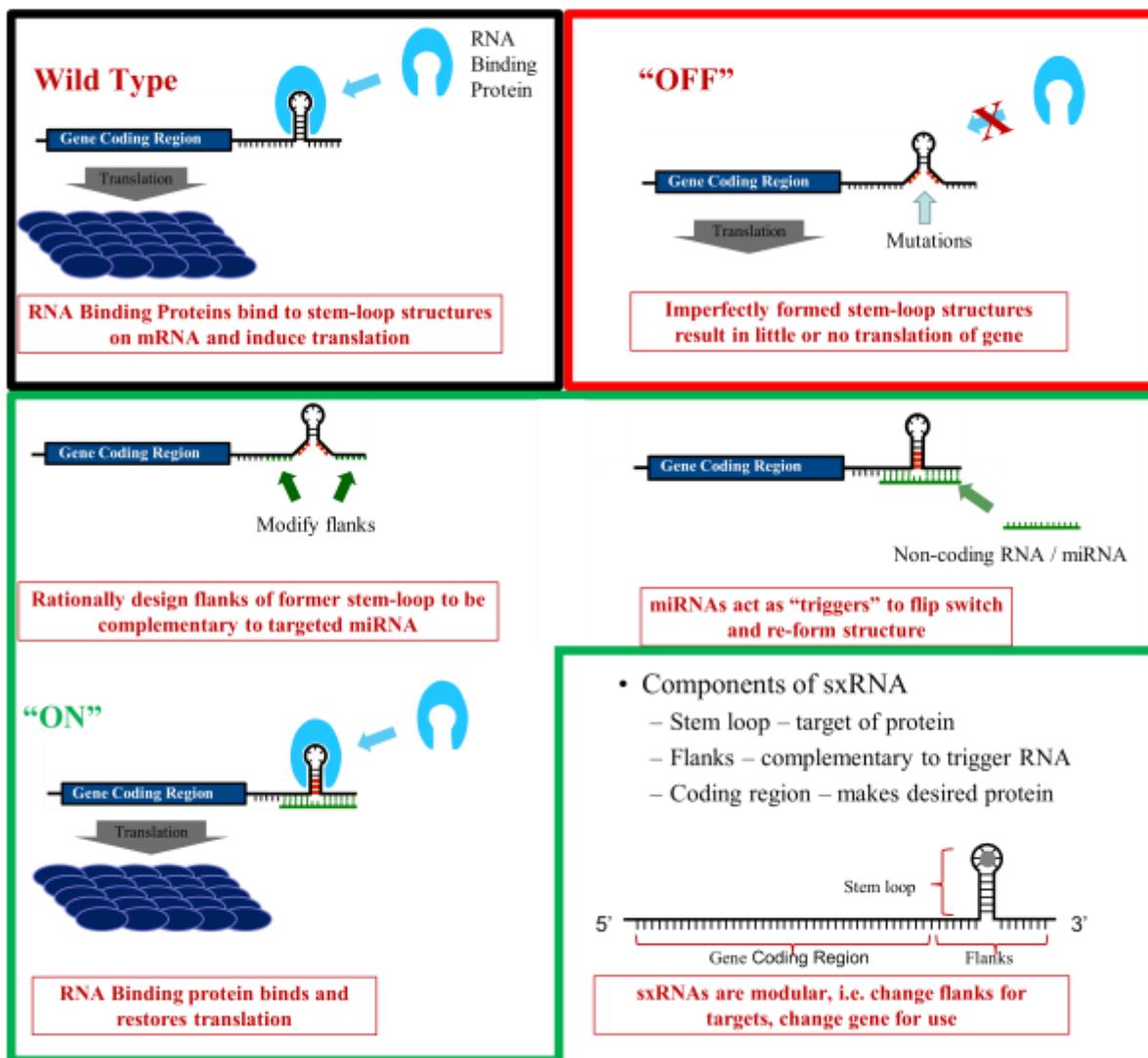
*Identification of SMG6 cleavage sites and a preferred RNA cleavage motif by global analysis of endogenous NMD targets in human cells.* Schmidt SA, Foley PL, Jeong DH, Rymarquis LA, Doyle F, Tenenbaum SA, Belasco JG, Green PJ.

*Nucleic Acids Res.* 2015 Jan;43(1):309-23. doi: 10.1093/nar/gku1258. Epub 2014 Nov 27.

### TOPIC 1: sxRNA: An RNA-based Nanoswitch

Most medicines interact with proteins in the body, but more recently gene therapies have targeted DNA directly to affect bodily functions. That leaves a third class of molecules completely untapped in terms of medical interventions—RNA. We have found a way to target and report the presence of any RNA of interest in a living cell. We developed a nano-based technology called sxRNA that can be injected into cells to seek out a specific RNA molecule. If the target is found, the sxRNA switches on the expression of a reporter gene that glows – literally functioning as an indicator light. Accurate reporting of the presence of an RNA molecule could be used to diagnose certain diseases in which certain genetic pathways are overactive and cause pathology. The invention has been patented as a platform technology. That means that rather than creating a single diagnostic or therapeutic tool, the Tenenbaum group is developing the process to be applicable to any medical intervention that involves RNA molecules. In the future, we envision possibilities where instead of creating a mere signal for the presence of a particular RNA, the sxRNA could switch on a gene that repairs faulty cell function or a gene that causes the self-destruction of a cancer cell. When fully developed, the sxRNA platform technology will not only represent a powerful new molecular tool but will also have tremendous potential for the development of novel therapeutics, anti-virals, and even imaging applications with substantial impact on a multibillion dollar industry. “We have developed a novel, breakthrough technology that acts as a Nano-switch mechanism to turn “on” and “off” expression of a protein using RNA rather than DNA. No other RNA based technology allows a similar control of protein expression, and we believe that this RNA based, Nano-switch platform technology, called structurally interacting RNA (sxRNA), has the potential to replace gene therapy and create an entire new therapeutic class commanding a market value of several billion dollars.” sxRNA has the potential to represent a new category of molecular tool/therapeutic that uses the specificity of unique miRNA (or other non-coding RNA) expression to turn “ON” the expression of a gene to repair or kill the cell. we have biophysically characterized *in vitro* a switch that demonstrated increased binding (by as much as 5X) for the histone stem-loop binding protein (HSLBP). These findings were validated *in vivo* successfully.

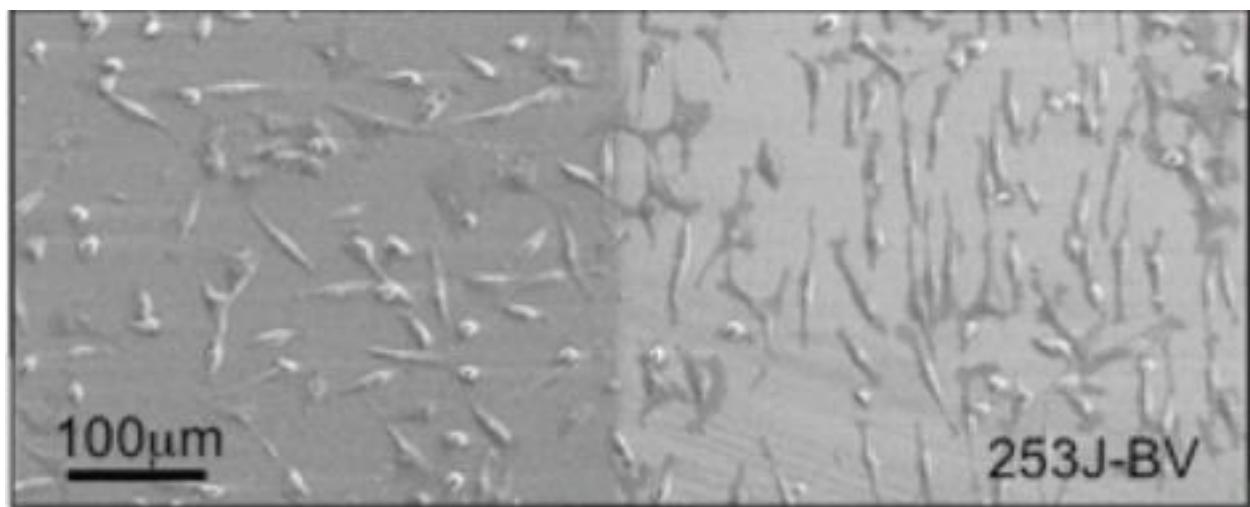
## sxRNA Concept



## TOPIC 2: Effect of Nanoenvironments on Cancer Metastasis

There is a growing need for the development of novel platforms to study the metastatic phenotype of cancer cells and their differences from non-metastatic cells from the same line. Our lab's focus is to utilize recent advances in the field of nanolithography to design surface topographies that mimic physical features of the extracellular matrix (ECM) to better elucidate these effects. These defined features will be utilized to investigate fundamental mechanistic questions on the unique ability of metastatic tumor cells to sense and respond to physical cues at this scale. In addition to these features we would also like to investigate the effects of combining these responses to physical cues with known responses to chemotactic and other chemical gradients to better understand their combinatorial effects on cancer cell lines.

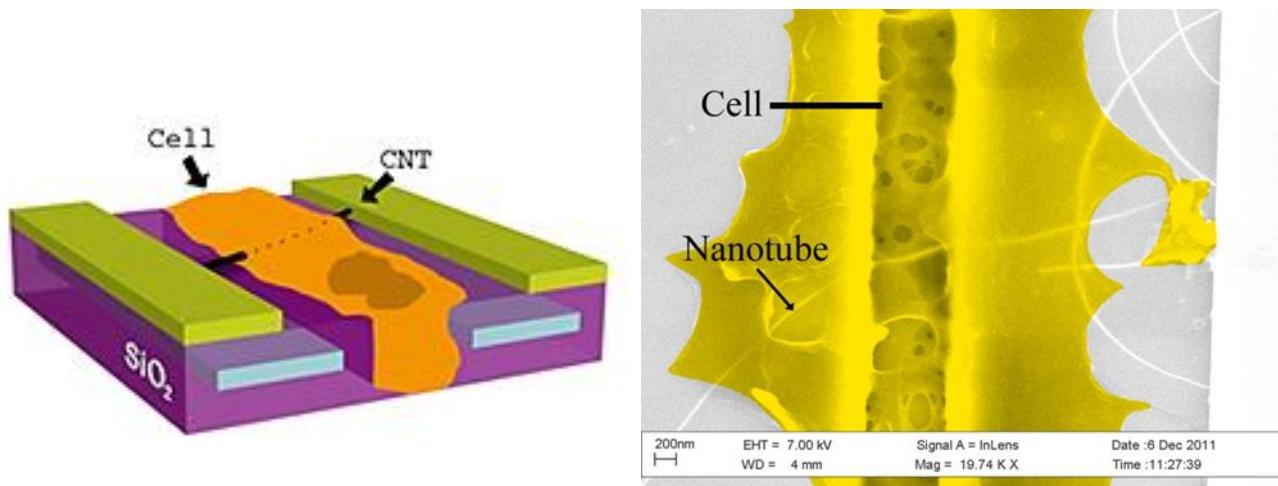
In this regard our preliminary data show that interactions with nanoscale topographies are enhanced in metastatic bladder tumor cells as compared to their non-metastatic counterparts. Our data suggest that these unique cellular interactions with lined nanotopography below 100nm could be utilized to distinguish metastatic from non-metastatic cells. This observation is based on key differences in cell morphology, directional migration, anisotropy to underlying features, length and alignment of filopodia and differential pro-migratory signaling. Our next major focus will be to integrate the effects of photodefined gradients with these features for a better understanding of the total system as well as expanding to encompass several varieties of ovarian cancer. This work shows early indication of the mechanisms underlying cancer cell metastasis. We have established an ongoing and active cancer metastasis-working group at SUNY Poly CNSE, including faculty members Nadine Hempel, Andre Melendez, Scott Tenenbaum, and Timothy Groves.



**Figure 2:** Metastatic Cells on Nanotopography. 253J-BV are metastatic bladder cancer cells derived from the non-metastatic tumor cells 253J. This highly metastatic line was grown both flat and patterned pieces of wafer and grown for 24 hours. Cells were then fixed and dehydrated before being imaged with ESEM.

### TOPIC 3: Carbon Nanotube Filed Effect Transistors as a Multimodal Biosensor

Carbon nanotube field effect transistor (CNTFET) is widely recognized as an excellent platform for chemical and biological sensing. These nanotube/nanowire based field effect transistors are considered to be suitable candidates to potentially replace the current patch-clamp techniques used to study the electrophysiology of cells. Our unique device (CNTFET) design allows us to take advantage of the cell's natural tendency to prefer lower trench regions to grow when allowed to proliferate on a surface with varying topography. These cells in the trench interact with suspended carbon nanotubes which run across the trench, connecting the two metal contact terminals on either ends. The working principle is that when a voltage bias is applied across the terminals, the cell acts as gate material and effectively changes the current flowing through the carbon nanotube. This results in a characteristic current-output. Cells based on its physiological state, type and condition give different characteristic outputs. The device can thus act as a sensor for study cellular activity. We tested our devices for such biosensor applications by growing M4A4 human breast cancer derived cells on them and found that the interaction with the carbon nanotubes did not dramatically reduce the integrity of the cell membrane. The cell proliferation and growth were normal. The results obtained are encouraging for potentially developing our device as a real-time biosensor. Our future goals involve developing methods for electrical passivation of the metal contacts. This project is done in collaboration with Ji Ung Lee.



**Figure 3:** (Left) Schematic of the suspended SWNT device. The M4A4 cell travels into the trench that the suspended SWNT spans, resulting in partial insertion of the nanotube's suspended portion into the cell, with the nanotube remaining functional. (Right) An SEM image of the fixed M4A4 cell and the suspended SWNT showing the location of the carbon nanotube within the cell.

## Yubing Xie, Ph.D. Stem Cell Nanobioengineering and Biomanufacturing

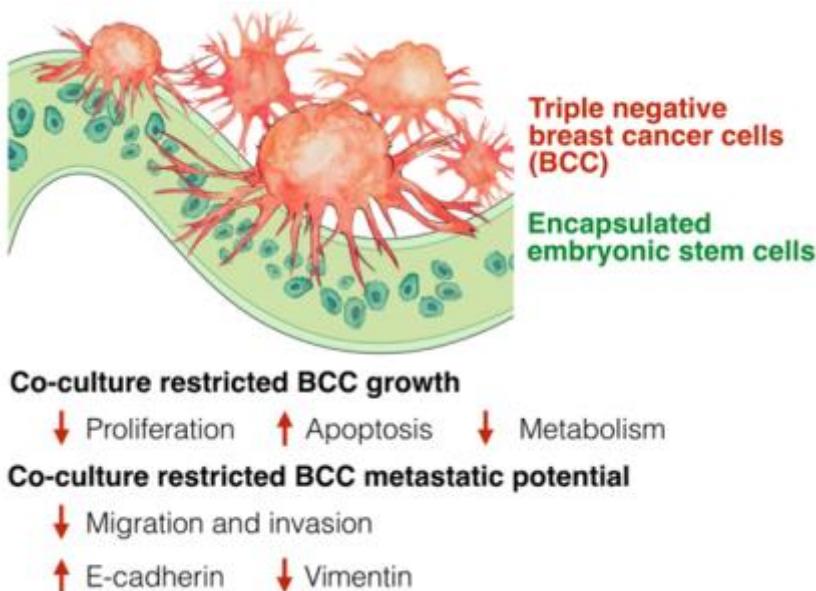
**Scope:** Nanobioengineering pluripotent stem cell microenvironments, cell-cell communications, advanced biomanufacturing, and eye tissue engineering

**Goals:** Create 3D  $\mu$ -tissue complex for understanding stem cell-cancer cell interactions, adipogenesis, trabecular outflow and retina function, leading to better restriction and treatment of cancer metastasis, obesity and eye diseases.

### 2016 Accomplishments

#### TOPIC 1: Synthetic pluripotent signaling for inhibition of cancer metastasis

Cancer cells have been linked to embryonic stem cells (ESCs) since the convergence of embryonic signaling pathways in cancer which drive self-renewal and proliferation. ESCs may release certain pluripotent signaling molecules that can restrict cancer metastasis and reprogram metastatic cancer cells into a less aggressive phenotype. It inspires us to establish a novel system based on 3D co-culture of ESCs and tumor cells (Figure 1) to seek molecules that are released by ESCs to extracellular microenvironment with functions of inhibiting growth and metastatic potential of cancer cells<sup>1</sup> and to understand the underlying mechanisms of these molecules for inhibiting cancer metastasis,<sup>2</sup> leading to restriction of metastatic diseases.



**Figure 1: Bioengineered ESC-microstrands restricted growth and metastatic potential of highly aggressive human breast cancer cells.<sup>1</sup>**

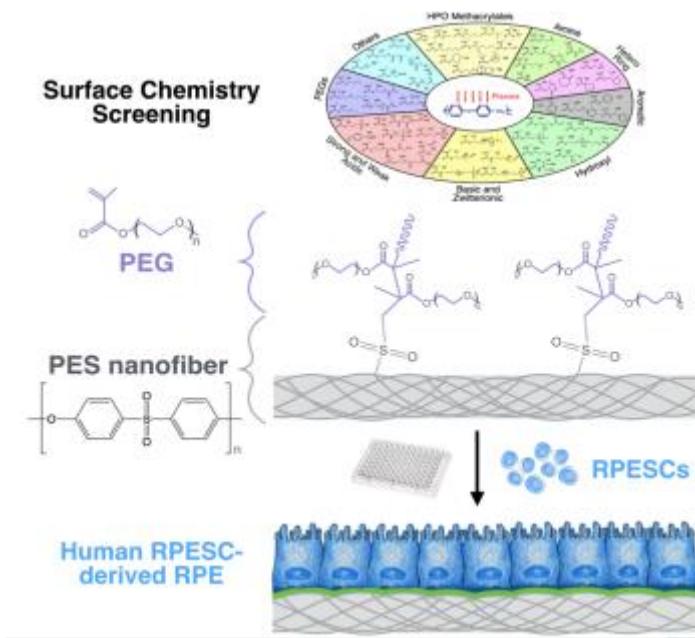
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## TOPIC 2: Identify the optimal substrate chemistry for retinal pigment epithelial stem cells.

A healthy retina is essential for good vision. The pigmented layer of retina—retinal pigment epithelium (RPE) helps nourish and support retina. The structural and functional integrity of the RPE is vital for maintaining the health and function of the retina. Unfortunately, progressive deterioration of RPE occurs in elderly individuals, resulting in visual impairment and ultimately blindness-causing diseases, such as age-related macular degeneration (AMD). There is a significant unmet medical need for treatment of AMD that could replace both RPE cells and the surface of the matrix.

Engineering the surface chemistry at nanoscale has great potential to provide optimal cell adhesion, long-term maintenance of stem cells, and control of stem cell differentiation. Using a rapid high-throughput polymerization and screening platform from a comprehensive library of 66 monomer-grafting membrane surfaces, we have identified surface chemistries that support human retinal pigment epithelial stem cell (RPESC) attachment and functional cobblestone formation. This study offers a unique PEG-modified 3D cell culture system that supports RPESC proliferation, differentiation, and maturation with cobblestone morphology and RPE marker expression.<sup>3</sup> Additionally, in collaboration with Dr. Sally Temple's group, we examined FDA-approved hydrogel materials as injection vehicles for delivery of human RPESC-derived RPE to sub-retinal space.<sup>4</sup> These studies provide a new avenue for RPE cell culture, disease modeling and cell replacement therapy.



**Figure 2: High-throughput screening of surface chemistries for retinal pigment epithelial stem cell (RPESCs).<sup>3</sup>**

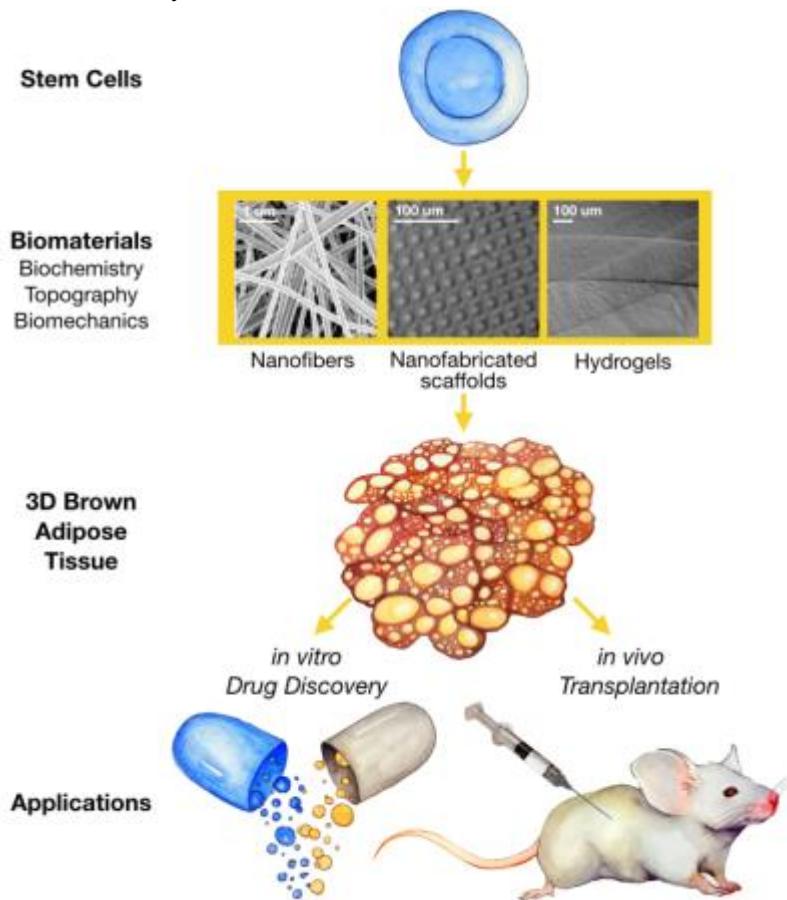
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3. Y. Tian, M.R. Zonca Jr., J. Imbrogno, A.M. Unser, L. Sfakis, S. Temple, G. Belfort, Y. Xie. Polarized, cobblestone, human retinal pigment epithelial cell maturation on a synthetic PEG matrix. *ACS Biomaterials Science and Engineering*, 2017, 3(6):890–902

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### TOPIC 3: Bioengineering stem cell-derived brown fat

Adipocytes play a key role in the development of obesity and metabolic consequence. There are two types of fat cells in the body, white adipocytes for energy storage and brown adipocytes for energy expenditure. While white adipocytes have been well studied, the development, function and therapeutic potential of brown adipocytes have only recently attracted more attention due to the re-discovery of brown fat in adults. It demonstrates that increasing the amount and function of the brown fat may treat obesity and prevent type 2 diabetes and other metabolic disorders. The therapeutic potential of the brown fat creates significant impetus to understand the cellular and molecular aspect of brown adipogenesis.<sup>5</sup> The ability to create an engineered hydrogel microenvironment and manipulate the differentiation of embryonic stem cells to brown fat cells will advance the understanding of early events during brown adipogenesis,<sup>6</sup> leading to new strategies to prevent and treat obesity and other diseases. It provides a unique brown adipocyte culture system and allows unprecedented understanding of brown adipogenesis, leading to new therapeutic strategies for obesity.



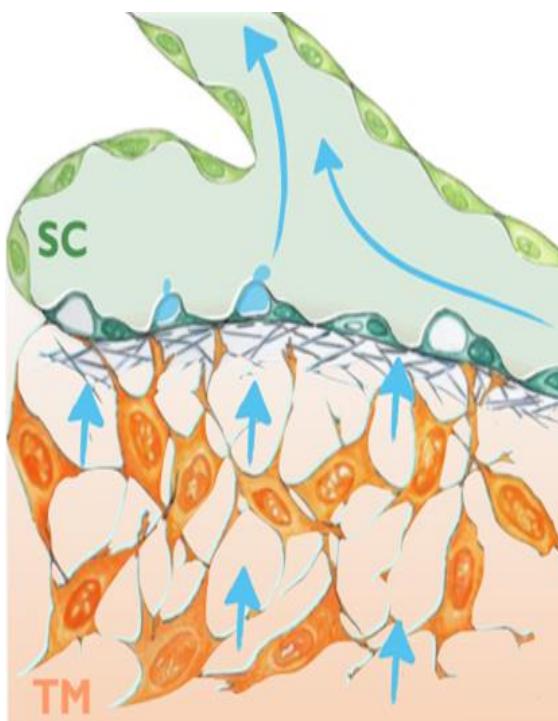
**Figure 3: Bioengineering brown fat as in vitro model for drug development and in vivo transplantation for obesity and diabetes.<sup>5</sup>**

Footnote:

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## TOPIC 4: Bioengineering Trabecular Meshwork for High-Throughput Anti-Glaucoma Drug Screening and Discovery

Glaucoma is an age-related disease and the leading cause of irreversible blindness. The vision loss in glaucoma is caused by the permanent optic nerve damage due to an increased intraocular pressure (IOP). IOP is the most critical and the only modifiable risk factor for development and progression of glaucoma and is controlled by the outflow (elimination) of the aqueous humor. In human, most of the aqueous humor (up to 90%) drains through the trabecular meshwork (TM) into Schlemm's canal (SC), so called conventional outflow pathway (Figure 4).<sup>7</sup> There is an unmet need of a proper *in vitro* model of the trabecular outflow tract for understanding outflow physiology and discovering IOP-lowering anti-glaucoma therapeutics. In collaboration with Drs. Sharfstein, Bergkvist, Torrejon, and Danias, we have bioengineered 3D HTM on micropatterned well-defined scaffolds, which offers an *in vitro* model system for understanding HTM physiology and high-throughput screening of pharmacological or biological agents that affect trabecular outflow facility in human, leading to drug discovery and effective treatment of glaucoma.<sup>8,9</sup> The use of stem cells will offer an alternative HTM and HSC sources for establishing high-throughput 3D HTM complex for drug screening.



**Figure 4: Bioengineering the conventional outflow pathway by co-culture of human trabecular meshwork cells and Schlemm's canal cells.<sup>7</sup>**

Footnote:

7. C.N. Dautriche, Y. Xie, S.T. Sharfstein. Walking through trabecular meshwork biology: Toward engineering design of outflow physiology. *Biotechnology Advances*, 2014, 32(5):971-83,
8. K.Y. Torrejon, E.L. Papke, J.R. Halman, J. Stolwijk, C.N. Dautriche, M. Bergkvist, J. Danias, S.T. Sharfstein, Y. Xie. Bioengineered glaucomatous 3D human trabecular meshwork as an *in vitro* disease model. *Biotechnology Bioengineering*, 2016, 113(6):1357-68
9. K.Y. Torrejon, E.L. Papke, J.R. Halman, M. Bergkvist, J. Danias, S.T. Sharfstein, Y. Xie. TGF $\beta$ 2-induced outflow alterations in a bioengineered trabecular meshwork are offset by a rho-associated kinase inhibitor. *Scientific Reports*, 2016, 6: 38319

## Ion Beam Research Group (H. Bakhru and M. Huang)

**Scope:** Apply ion scattering methods (RBS, Ion channeling, NRA, PIXE, High-Res RBS, microbeam) to understand lattice structures in various crystalline materials and improving the resolution, efficiency and sensitivity of such classical ion scattering methods. Explore the use of ion beams (ion implantation/ irradiation) to modify the optical, electrical and magnetic properties in materials through defect engineering and impurity doping. Develop advanced photonic and optoelectronic devices from Er-doped Si based materials for Silicon Photonics.

**Goals:** Fabrication and characterization of nanoscale and microscale devices and structures for electronic, photonic and spintronic applications

### 2016 Accomplishments

#### TOPIC 1: Exploring embedded magnetic nanostructures in single crystal Si for spintronic applications

Ni nanoparticles with tailorabile magnetic properties are fabricated in a highly crystalline Si (100) wafer using H<sup>+</sup> and Ni<sup>+</sup> ion implantation and annealing. This was achieved using the Extrion 400kV implanter facility. RBS/C analysis was performed on the 4MeV Dynamitron to characterize the implantation damage at both ion ranges.

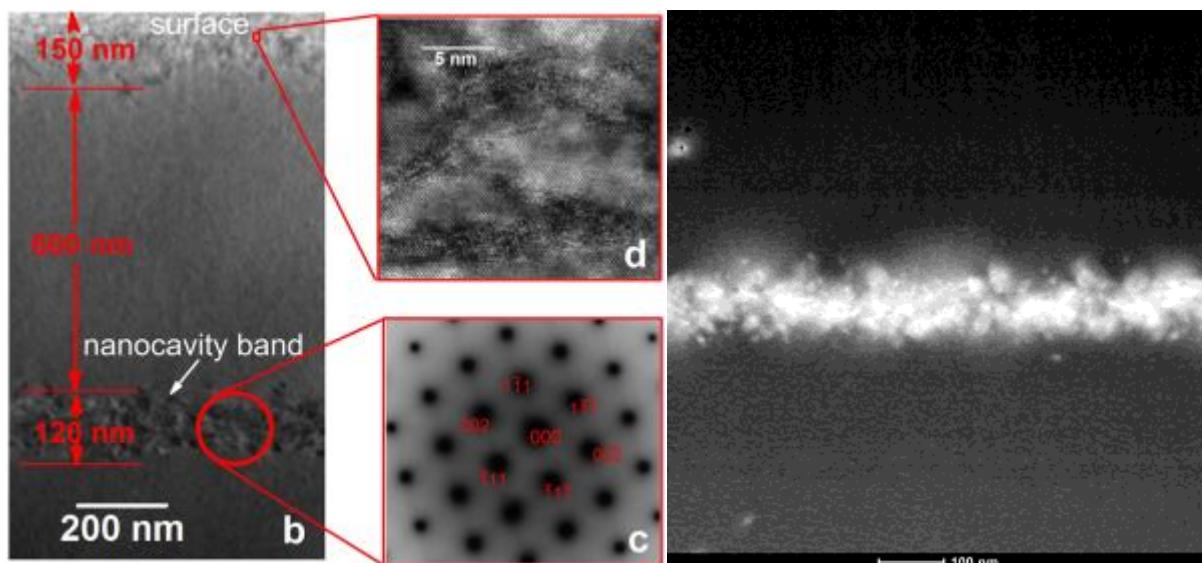
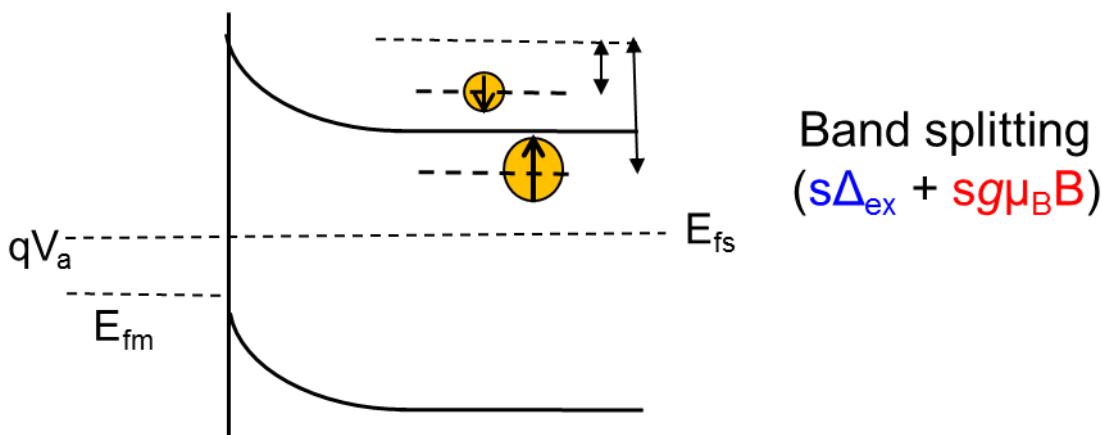


Figure 1: Cross-section TEM image showing the nanoparticle band formed due to co-implantation of H<sup>+</sup> and Ni<sup>+</sup> followed by annealing. The needle-like morphology of Ni silicide near the Ni implanted region and electron diffraction pattern from the nanoparticle vicinity showing high crystal quality of Si surrounding them are shown. HAADF image of the embedded Ni nanoparticles with enhanced Z-contrast against the Si surroundings is also pictured.

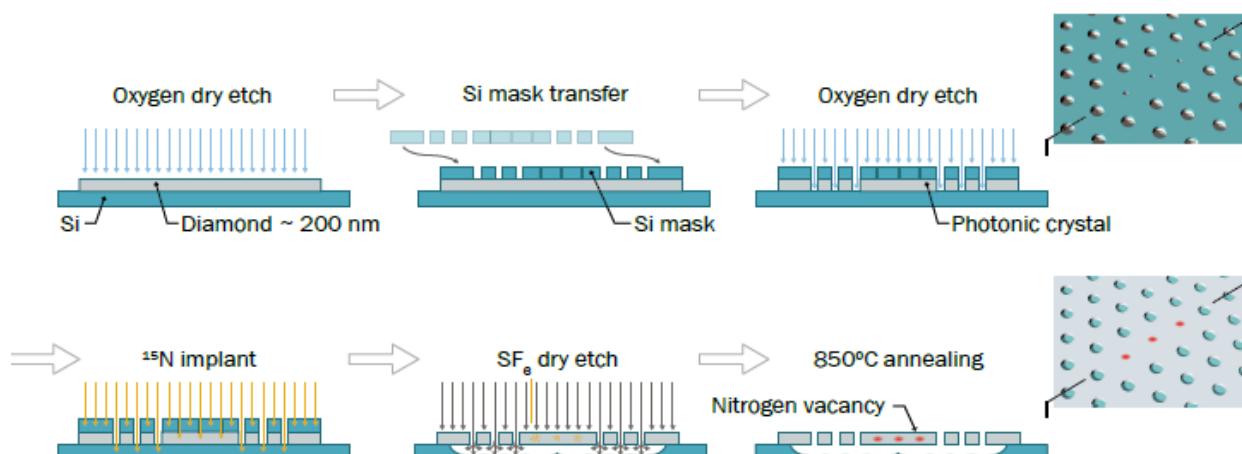


**Figure 2:** Spin split band model schematic showing the spin split sub bands in n-Si. The size of the circles indicates the population of each spin and the double-headed arrows indicate their respective barrier heights.

Electrical characterization on the samples to determine the magnetoresistance (MR) of the magnetic nanoparticle layer are being performed in a 4-terminal vertical geometry. A large positive magnetoresistance (~155 % at 300K and 9T field in p-Si samples) has been observed in both p- and n- type Si samples. The temperature and current dependence of such devices has been explored. A spin-split band model is proposed to explain the origin of magnetoresistance in such samples.

### TOPIC 2: Scalable fabrication of coupled NV center - photonic crystal cavity systems by self-aligned N ion implantation (in collaboration with Quantum Photonics group at MIT)

Creation of NV centers using a self-assigned lithography process to enable simultaneous patterning and precise N-implantation with one mask. Such a technique will make spatially deterministic alignment of the implantation species ( $^{15}\text{N}$ ) into the cavity hot field feasible.



**Figure 3:** Fabrication process illustrating the use of Si mask both for diamond patterning (step 3, oxygen dry etch) as well as implantation mask for  $^{15}\text{N}$  (step 4, implantation).

**Publications and Patents:**

- T. Schröder, M. Walsh, J. Zheng, S. Mouradian, L. Li, G. Malladi, **H. Bakhrus**, M. Lu, A. Stein, M. Heuck, and D. Englund. Scalable fabrication of coupled NV center - photonic crystal cavity systems by self-aligned N ion implantation. *Optical Materials Express* Vol. 7, Issue 5, pp. 1514-1524 (2017)
- Adam Schulz, **Hassaram Bakhrus**, Don DeRosa, Seiichiro Higashiya, Manisha Rane-Fondacaro Pradeep Haldar. Quantifying lithium in the solid electrolyte interphase layer and beyond using Lithium- Nuclear Reaction Analysis technique. *Journal of Power Sources* Vol. 360, 31 129–135 August 2017
- **Mengbing Huang**, Nirag Kadakia, Sebastian Naczas, **Hassaram Bakhrus**. Fabrication of surface textures by ion implantation for antireflection of silicon crystals US 9231061 B2 Jan 5, 2016
- Brian Souhan, Christine P. Chen, Ming Lu, Aaron Stein, **Hassaram Bakhrus**, Richard R. Grote, Keren Bergman, William M. J. Green and Richard M. Osgood Jr. Ar+-Implanted Si-Waveguide Photodiodes for Mid-Infrared Detection. *Photonics* 2016, 3(3), 46
- Schukraft, M., Zheng, J., Schroeder, T., Mouradian, S. L, Walsh, M., Trusheim, M. E., **Bakhrus**, H., Englund, D. R. Invited Article: Precision nanoimplantation of nitrogen vacancy centers into diamond photonic crystal cavities and waveguides. *APL Photonics* 1, (2) 020801 May 2016
- Faisal Yaqoob and **Mengbing Huang**. Effects of high-dose hydrogen implantation on defect formation and dopant diffusion in silver implanted ZnO crystals. *Journal of Applied Physics* 120, 045101 (2016)
- Faisal Yaqoob and **Mengbing Huang**. Lattice site specific diffusion properties for substitutional and interstitial impurity atoms in ZnO crystals. *Journal of Applied Physics* 120, 115102 (2016)
- Subha Chakraborty, Katherine Harris, **Mengbing Huang**. Photoluminescence properties of polystyrene-hosted fluorophore thin films. *AIP Advances* 6, 125113 (2016)
- Natasha Tabassum, Vasileios Nikas, Brian Ford, **Mengbing Huang**, Alain E. Kaloyerous, and Spyros Gallis. Time-resolved analysis of the white photoluminescence from chemically synthesized SiCxOy thin films and nanowires. *Appl. Phys. Lett.* 109, 043104 (2016)
- Vance S. Robinson, Magnus Bergkvist, Daokun Chen, Jun Chen, **Mengbing Huang**. A case for ZnO nanowire field emitter arrays in advanced x-ray source applications. *Proc. SPIE* 9964, *Advances in Laboratory-based X-Ray Sources, Optics, and Applications V*, 996408 (September 16, 2016)

## Materials Science, Characterization, and Metrology of Nanoscale Materials and Structures (Alain C. Diebold / Diebold Research Group)

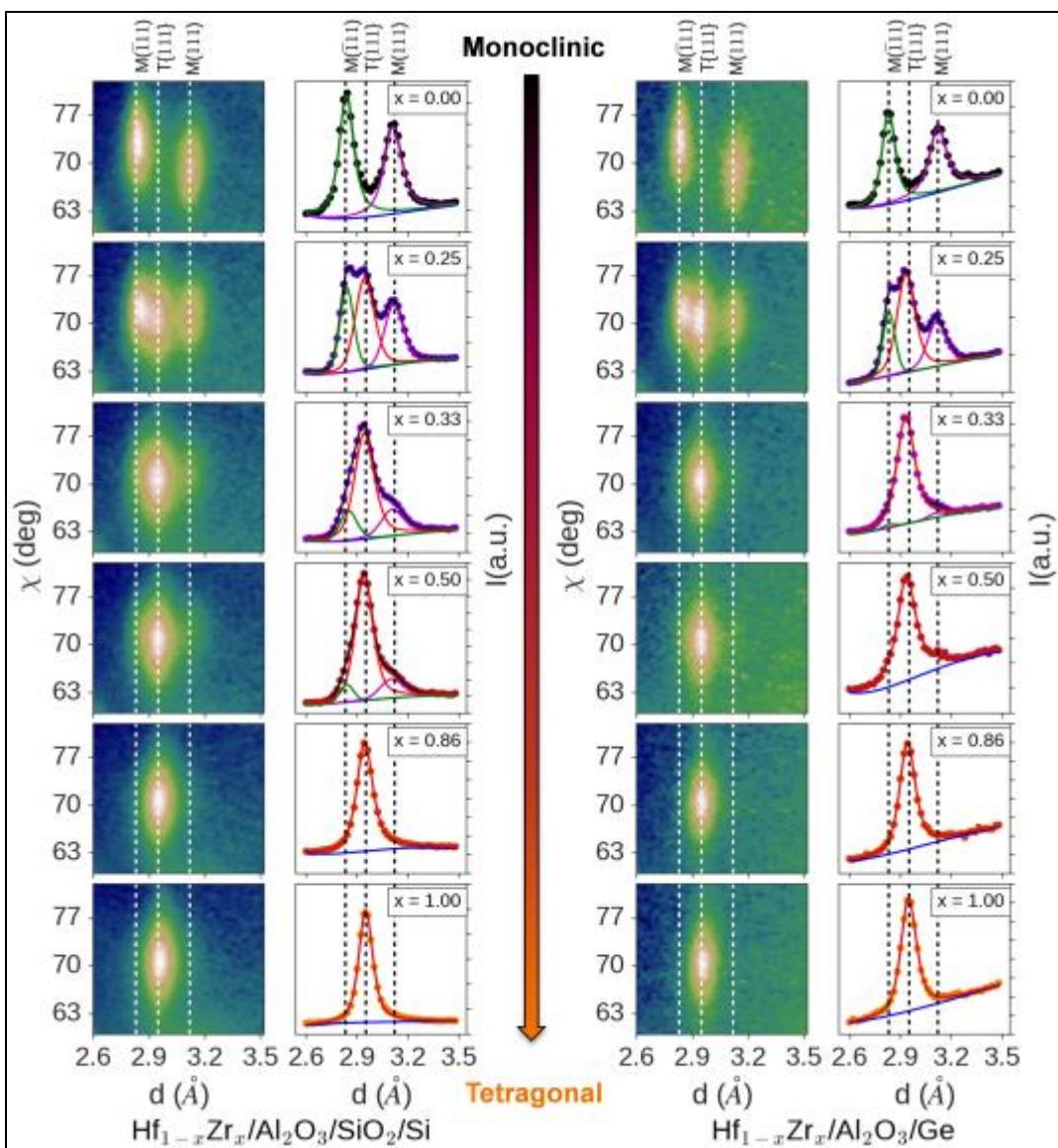
**Scope:** The Diebold group works in all areas of characterization, metrology, and materials science of nanoscale materials and structures. Through collaboration with CNSE partners, measurement is used to advance R&D into new device materials and structures. Example topical areas associated with integrated circuits include lithography, transistor, and interconnect metrology. The group also works on 2D materials such as graphene and transition metal dichalcogenides and materials with topologically protected properties such as Bi<sub>2</sub>Se<sub>3</sub>. Measurement methods frequently used by the group include spectroscopic ellipsometry, scatterometry, photoluminescence, second harmonic generation, high resolution X-Ray diffraction, X-Ray reflectivity, transmission electron microscopy, X-Ray photoelectron spectroscopy, and ion beam analysis.

**Goals:** Measure and understand the properties of materials and structures at the Nanoscale.

### 2016 Accomplishments

#### TOPIC 1: *Multi-Method approach to determining the Phase and Texture of crystalized Hf-oxide based high K*

Collaborative research covering the characterization of high K – metal gate stacks with TEL Technology Center America continued in 2016. We also characterized the temperature dependence of the breakdown of barrier layers for copper interconnect applications. In order to extend Hf oxide based high K to future generations, the semiconductor industry is pursuing new process that result in crystallization of the thin films into higher dielectric constant phases. In 2016, the research extended to studies of the effect of germanium substrates and Al<sub>2</sub>O<sub>3</sub> interfacial layers on the crystal phase of the high K as shown in Figure 1. The crystal phase of ultra-thin films is difficult to measure. Synchrotron based grazing incidence in-plane X-ray diffraction (GIIXRD) and X-Ray texture studies provided key results in 2016. The higher dielectric constant tetragonal phase can be achieved by changes in the percentage of zirconium in the Hf<sub>1-x</sub>Zr<sub>x</sub>O<sub>2</sub> alloy. Synchrotron X-Ray measurements were done at the CHESS facility at Cornell University. (Use of Cornell High Energy Synchrotron Source (CHESS) was supported by the National Science Foundation and the National Institutes of Health/National Institute of General Medical Sciences under NSF award DMR-1332208.)



**Figure 1:** The monoclinic to tetragonal transition for the  $\text{Hf}_{1-x}\text{Zr}_x\text{O}_2$  films deposited on  $\text{Al}_2\text{O}_3$  passivated Si and Ge substrates with increasing  $\text{ZrO}_2$  content. The  $m\{111\}$  peaks gradually evolve into  $t\{111\}$  peak with increasing Zr concentration  $x$ .

Footnote:

S. Dey, K. Tapily, S. Consiglio, R. D. Clark, C. S. Wajda, G. J. Leusink, A.R. Woll, and A.C. Diebold, Role of Ge and Si substrates in higher- $k$  tetragonal phase formation and interfacial properties in cyclical ALD-anneal  $\text{Hf}_{1-x}\text{Zr}_x\text{O}_2/\text{Al}_2\text{O}_3$  thin film stacks, *J. Appl. Phys.* 120, (2016), 125304.

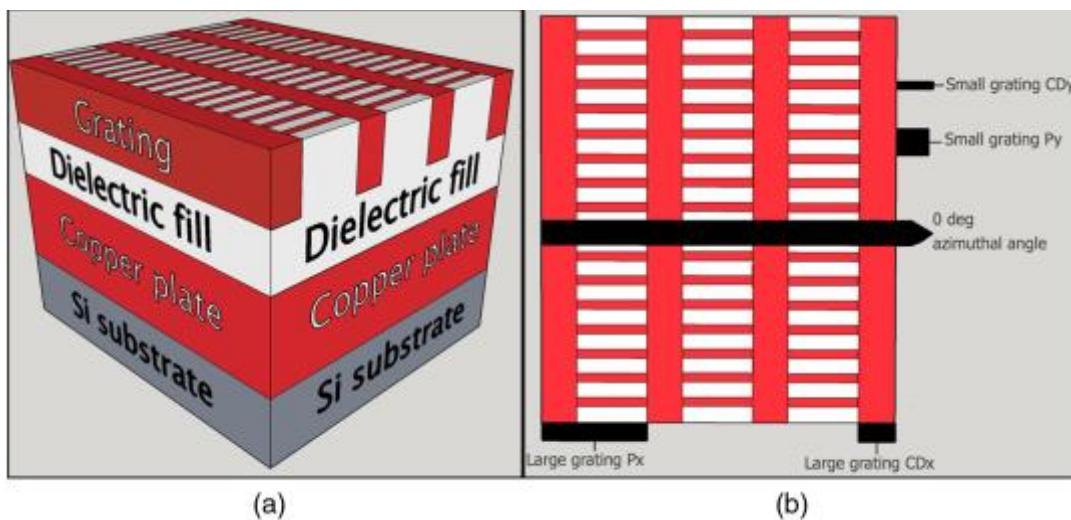
S. Consiglio, K. Yu, S. Dey, K. Tapily, R. D. Clark, T. Hasegawa, C. S. Wajda, G. J. Leusink, and A. C. Diebold, In-situ Ramp Anneal X-ray Diffraction Study of Atomic Layer Deposited Ultrathin TaN and  $\text{Ta}_{1-x}\text{Al}_x\text{Ny}$  Films for Cu Diffusion Barrier Applications, *ECS Journal of Solid State Science and Technology*, 5, (2016), P509-P513.

**TOPIC 2: Designed new structure showing greatly enhanced sensitivity of scatterometry to changes in CD for copper metal lines using plasmonics**

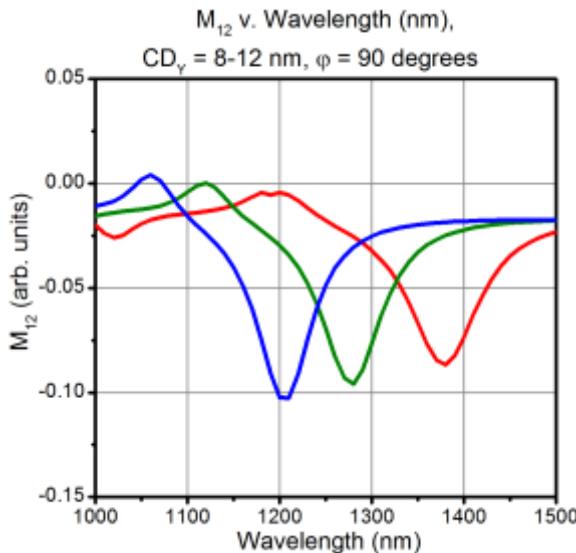
Scatterometry is used for the characterization and control of critical dimensions (CD) during patterning. In this method, spectroscopic ellipsometry is used to measure grating structures that have a repeated array of the feature of interest. A rigorous coupled wave approximation (RCWA) is used to solve Maxwell's equations for an optical model of the grating. Scatterometry software determines the feature dimensions for the optical model that best fit the experimental data. The RC2 spectroscopic ellipsometer used in this project measures the full 16 element Mueller Matrix scattering and the NanoDiffract™ software is uniquely able to simulate the full Mueller Matrix data. RCWA simulations were verified by the finite element method (FEM). This project was funded by and done in collaboration with Nanometrics Inc. who provided NanoDiffract™ software.

As CD continues to shrink, sensitivity to changes in CD are becoming more difficult to measure. Simulations of the Mueller Matrix elements show that a cross-grating structure greatly increased sensitivity to changes in the linewidth of thin metal lines that are intersected with a much larger cross-grating that has dimension necessary for a plasmonic response. The cross grating structure is shown in Figure 2, and a demonstration of the sensitivity to changes in CD for 8 to 12 nm wide copper lines in Figure 3.

This research demonstrates how engineering the grating structure used for scatterometry can greatly increase CD sensitivity.



**Figure 1:** Schematics of cross-grating test structure. (a) 3-D view of cross-grating with labeled stack: Si substrate—Cu plate—dielectric fill—top copper grating layer. (b) Top-down view with labeled azimuthal angle convention and relevant simulation parameters P, CD.



**Figure 2:** M12 Mueller Matrix Element vs wavelength for copper metal lines with a CD if 8 to 12 nm.

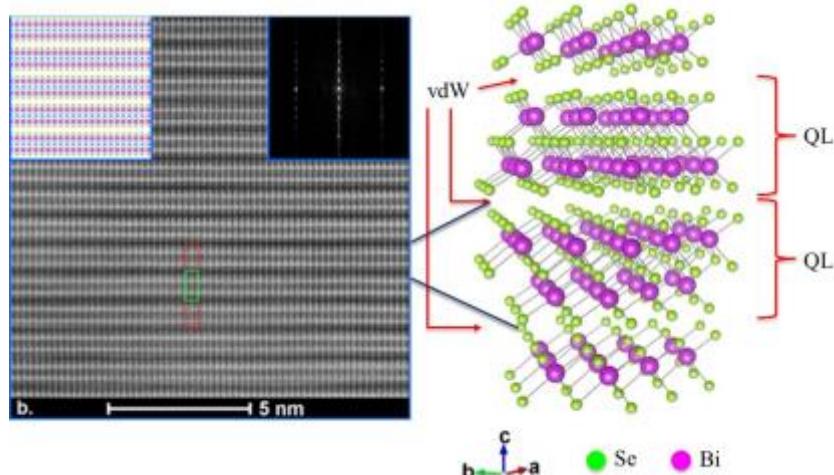
Footnote:

Samuel O'Mullane, Nick Keller, Alain C. Diebold, "Modeling ellipsometric measurement of three dimensional structures with rigorous coupled wave analysis and finite element method simulations," J. Micro/Nanolith. MEMS MOEMS 15(4), 044003 (2016), doi: 10.11117/1.JMM.15.4.044003.

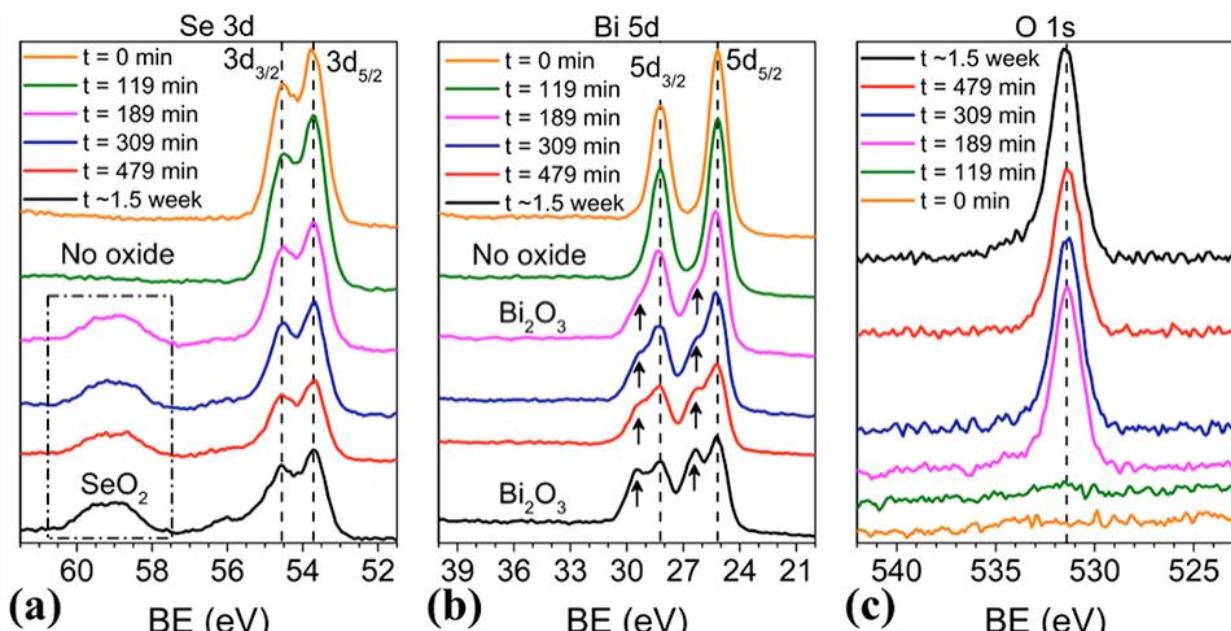
### TOPIC 3: Time Dependent Study of the Oxidation of the Surface of a Topological Insulator Bi<sub>2</sub>Se<sub>3</sub>

A new class of materials known as topological insulators is being considered for application in spintronic devices. Spin transport at the surface of Topological Insulators can occur with loss due to scattering from defects due to the unusual nature of the electronic structure at the surface. Materials such as Bi<sub>2</sub>Se<sub>3</sub> have shown to have topologically protected surface electronic states, but the effect of oxidation is not well characterized. An important step in characterizing a new material is to verify that the crystal has as few defects as possible. High resolution, Scanning Transmission Electron Microscopy (STEM) [Figure 4] and X-Ray diffraction were used to characterize the crystal structure. The time dependent oxidation was measured using X-Ray Photoelectron spectroscopy (XPS), atomic force microscopy, spectroscopic ellipsometry, and optical second harmonic generation. This data allowed us to arrive at a unified understanding of the changes that occur at the (0001) surface of high quality Bi<sub>2</sub>Se<sub>3</sub> when exposed to air based on surface characterization and electron microscopy. AFM measurements provided the first evidence for the growth of small Bi bilayer patches. This explains the inconsistency of their presence in various previous microscopic measurements. The time-dependent topography also provided information about oxide growth and corresponding roughness. The incubation time for oxidation of the top QL with an oxide thickness of 1.9 nm after 1.5 weeks from exfoliation were determined using the Bi 5d, Se 3d, and O 1s ARXPS spectra as shown in Figure 5. The findings that Bi<sub>2</sub>Se<sub>3</sub> does not immediately oxidize in air contrasted some previous XPS

findings. Non-linear optical Pump – Probe measurements allow us to probe inversions of the spin population at the surface of the  $\text{Bi}_2\text{Se}_3$ .



**Figure 4:** Aberration corrected Scanning Transmission Electron Microscopy cross-sectional image of the quintuple layer structure of  $\text{Bi}_2\text{Se}_3$ . The spacing due to the van der Walls bonding between the quintuple layers is easily observed in these high quality images.



**Figure 5:** XPS spectra of (a) Se 3d, (b) Bi 5d, (c) O 1s region for various times after exfoliation. The oxide peaks corresponding to  $\text{SeO}_2$  (marked by a dotted box in (a)) and  $\text{Bi}_2\text{O}_3$  (marked by vertical arrows in (b)) are observed after  $\sim 119$  minutes from exfoliation along with the observation of a strong O 1s peak. The results also indicate that oxygen adhesion and subsurface oxidation proceed simultaneously.

#### Footnote:

Y. An, A.J. Green, and A.C. Diebold, Tracking quintuple layer oxidation on cleaved  $\text{Bi}_2\text{Se}_3$  by optical second-harmonic anisotropy, Phys. Rev. B. **93**, (2016), 241308(R).

A.J. Green, S. Dey, Y.Q. An, B. O'Brien, S. J. O'Mullane, B. Thiel, and A.C. Diebold, Surface Oxidation of the Topological Insulator  $\text{Bi}_2\text{Se}_3$ , J. Vac. Sci. Technol. A34, (2016), 061403.

## Dunn Research Group

**Scope:** Using charged particle beams to uncover relationships between crystalline defects and chemical inhomogeneities in advanced materials.

**Goals:** Manipulate defect microstructure to improve performance and tailor functionality.

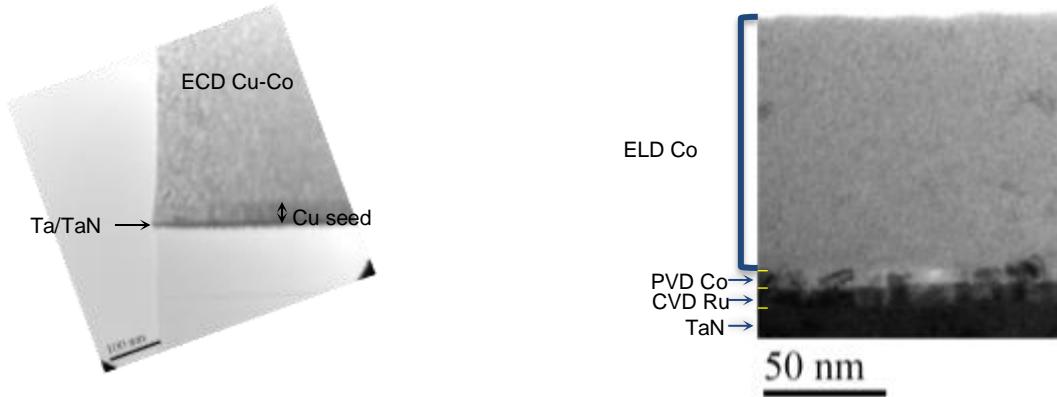
### 2016 Accomplishments

#### TOPIC 1: Back End of the Line, Beyond Copper: Alloys and Alternatives

As interconnect dimensions continue downscaling, the proportion of atoms which sit at interfaces or grain boundaries (GBs) increases. Even trace amounts of dissimilar metals at those interfaces or GBs can therefore have a disproportionately large impact on interconnect properties. On the other hand, this disproportionate relationship can be exploited to tailor properties with excellent granularity. For example, alloying Cu with Mn or Co will increase electrical resistance through impurity scattering, but this disadvantage is offset by improved electromigration and/or enhanced diffusion barrier performance. The mechanisms responsible for these improvements, however, remain in dispute.

The Dunn group is studying both pure and alloyed interconnect materials, pursuing electrolytic and electroless deposition methodologies, and analyzing the resulting microstructure, with a focus on diffusion, segregation and recrystallization. This work builds on over a decade of publications elucidating the mechanisms and driving forces for recrystallization in pure copper. Figure 1 shows examples of alternative metals under investigation including a copper-cobalt alloy deposited electrolytically, and a pure cobalt film deposited via electroless plating. The liner and seed layers in both cases were obtained through from the 300 mm wafer fabrication line at CNSE.

**Figure 1: Bright field TEM images of alternative interconnect materials under investigation.**



Related Products

- K. Musick and K.A. Dunn, "Controlling the microstructure of electroless cobalt for semiconductor interconnect applications," oral at *Spring meeting of the Materials Research Society* (2017).
- T. Tsurumaru, L. Prestowitz, B. O'Brien and K.A. Dunn, "The impact of solute segregation on grain boundaries in dilute Cu alloys," oral at *Spring meeting of the Materials Research Society* (2017).
- B. DeProspo, "Capstone Research Paper: Fundamental Interdiffusion Analysis of Ruthenium and Cobalt Films," 2016.
- B. B. O'Brien, M. Rizzolo, L. C. Prestowitz, and K.A. Dunn, "Rapid trench initiated recrystallization and stagnation in narrow Cu interconnect lines," *Appl. Phys. Lett.* 107, 171906 (2015).

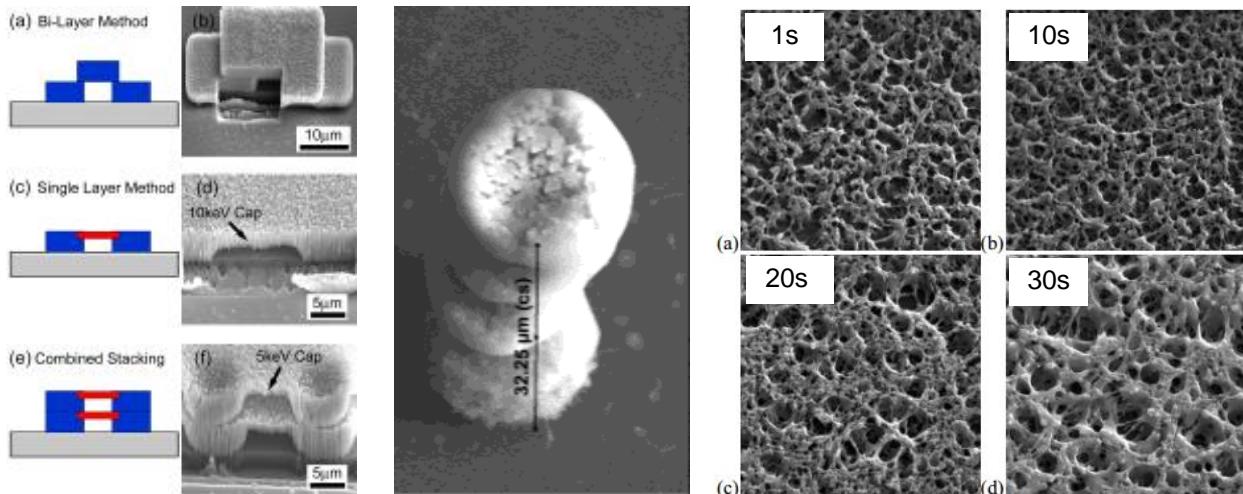
## TOPIC 2: Cryogenic electron beam induced deposition of metallic structures for additive manufacturing

Electron beam induced deposition (EBID) has been used to develop nanoscale structures for plasmonics, nanoscale templating, field emitters and contacts to nanoscale objects. However, the primary disadvantages of EBID are poor growth rates, low target purity and little ability to tailor deposit structure. Using a custom-built cryogenic stage for EBID, we demonstrated the growth is reaction-rate limited, yielding growth rates 4-5 orders of magnitude higher than conventional EBID. The exposure process was modeled by Monte Carlo simulations of electron-condensate interactions, which were used to develop fabrication schemes for three-dimensional self-supporting structures with incorporated gaps (Fig. 2, left).

These growth rates cleared the first hurdle for additive manufacturing feasibility. The next stage involves mechanical testing of cryo-EBID structures. Mechanical properties are being evaluated by nanoindentation of pads and nanocompression testing of high aspect ratio pillars (see Figure 2, middle), in collaboration with Ralph Spolenak and Alain Reiser at ETH Zürich.

Finally, we have also demonstrated the ability to tailor the morphology to control porosity of the resultant deposit (Fig 2, right). This property is the basis of one pending grant proposal for plasmonic gas sensors with Prof. Carpenter of the Nanoengineering and a second planned proposal for catalytic applications.

**Figure 2: Cryo-EBID images.** Left: 3D structures with incorporated gaps showing schematic illustrations of the exposure schemes and SEM images ( $52^\circ$  tilt) of a corresponding deposit that had been cross-sectioned with a focused  $\text{Ga}^+$  beam to show the anchor and cap deposits. Middle (unpublished): High aspect-ratio pillar for nanocompression testing, made in four cryo-EBID cycles. Right: Demonstration of porosity control in electron-limited regime.



#### Related Products

1. M. Bresin, M. Toth, and K.A. Dunn, "Direct-write 3D Nanolithography at Cryogenic Temperatures," *Nanotechnology* 24, 035301-1 – 035301-7 (2013).
2. M. Bresin, B.L. Thiel, K.A. Dunn, and M. Toth, "Focused Electron Beam-Induced Deposition at Cryogenic Temperatures," *J. Mater. Res.* 26(3), 357-364 (2011).
3. J. Li, M. Toth, K.A. Dunn, and B.L. Thiel, "Interfacial mixing and internal structure of Pt-containing nanocomposites grown by room temperature electron beam induced deposition," *J. Appl. Phys.* **107** (10), 103540-103545 (2010).
4. J. Li, M.D. Bresin, K.A. Dunn, and B.L. Thiel, "Determination of Impurity Carbon  $\text{sp}^2/\text{sp}^3$  Bond Ratio in Electron Beam Deposited Tungsten Nanostructures using Electron Energy Loss Spectroscopy," *Microscopy & Microanalysis* **13**(Suppl. 2), 1472-1473 (2007).

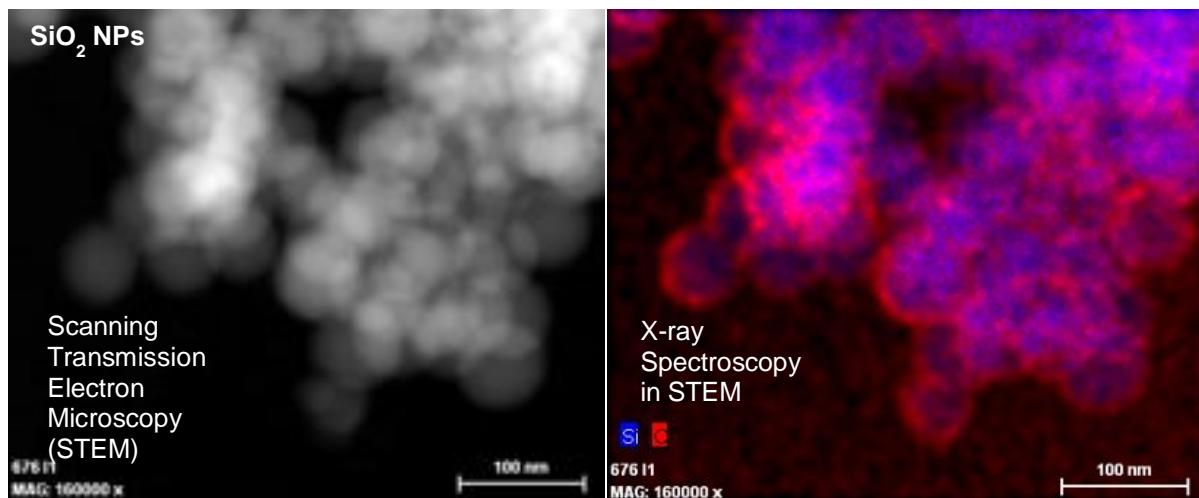
### TOPIC 3: Morphological and chemical changes in CMP slurries with toxicological implications

The assessment of the potential toxicity of engineered nanomaterials (ENMs) to the growing nanotechnology workforce is still in its infancy; because of their size and novel chemical and physical properties, nanoscale materials may be more toxic than their bulk counterparts. Thus, existing occupational exposure limits may not be sufficient to protect against exposure to these materials. The National Institute for Occupational Safety and Health (NIOSH) thus recommends treating ENMs "as if" they are hazardous. This approach, while understandably cautious, treats all ENMs as equally dangerous, regardless of chemistry, morphology, or reactivity. Furthermore, it neglects evidence that suggests that ENMs, during their lifecycle, may change in ways that affect these properties and their toxicity from that of the virgin material. Thus, greater understanding of these changes and the hazards they present could be used to refine and concentrate mitigation efforts where they are most needed.

Prof. Dunn's group examines structural and chemical changes in slurry nanoparticles of interest to the semiconductor industry, particularly silica (most commonly used) and

ceria (established bio-reactivity). Figure 3 shows a HAADF STEM image and corresponding elemental map of silica nanoparticles with a thin carbonaceous “rind” which will impact their bioactivity *in vivo*. The abrasive action of CMP may also change this coating; thus work with silica (funded by SUMCO Corporation, to begin 2018) will focus on morphology and chemistry changes induced during use. Work with ceria focuses on the valence state of the cerium (3+ or 4+), which influences whether the particles are bioprotective or biohazardous when mixed with cells *in vitro*. This topic is of high interest to the Occupational Health and Safety community, and is the subject of a NIOSH proposal submitted by Prof. Dunn and Dr. Sara Brenner in the Nanobioscience Constellation at CNSE.

**Figure 3:** (unpublished data). Scanning transmission electron microscope image (left) of silica slurry particles, with corresponding elemental map (right), showing a thin carbon “rind” surrounding each silica particle.



## Eric Eisenbraun Group: Nanomaterials Fabrication for Electronics, Renewable Energy, and Emerging Applications

**Scope:** Develop strategies for the growth of nanoscale materials to address specific technological challenges in technology-heavy fields including electronics, renewable energy, flexible electronics, and biotechnology, with a focus on manufacturability and sustainability.

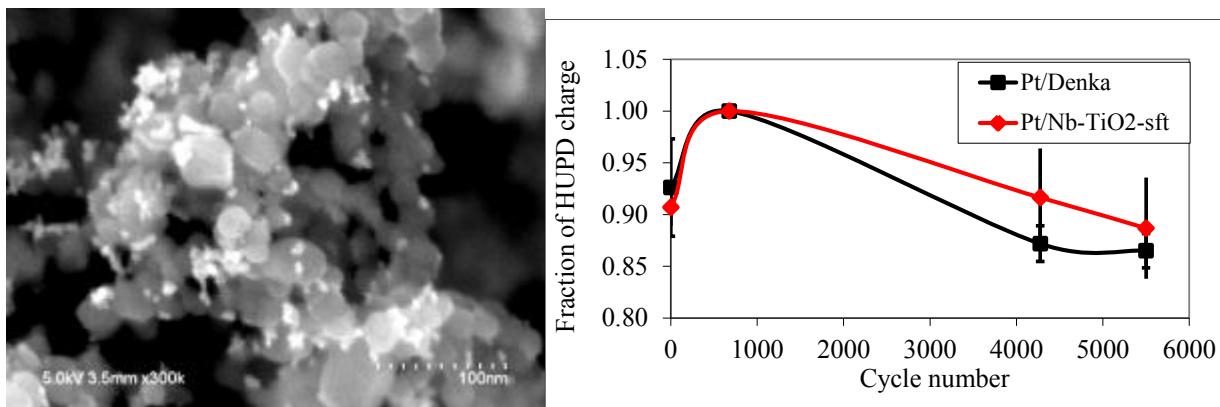
**Goals:** Collaborate with corporate and institutional partners to solve challenges by developing ways of fabricating functional layers and structures at the nano- and micro-scales.

### 2016 Accomplishments

#### TOPIC 1: “Design and fabrication of nanostructured fuel cell electrodes with ultralow loadings of precious metal or alloy catalysts”

Collaborators: The New York State Energy Research and Development Authority (NYSERDA), Ballard Power Systems, Inc., Proton On-Site, Inc., Professor Alex Xue (SUNY Poly).

A major shortcoming of conventional low temperature proton-exchange membrane (PEM) fuel cells is the high cost associated with the use of platinum (Pt) as a catalyst for the oxidation-reduction reaction. This serves to effectively prevent fuel cells from being considered as an electricity-producing option for many applications. This NYSERDA-funded program has a primary goal of demonstrating the potential of fuel cell electrodes which either use very little platinum or use other catalyst materials that are less expensive while not sacrificing performance or stability. During 2016 initial testing with our commercial partners revealed potentially enabling electrochemical performance from a low-cost Nb-TiO<sub>2</sub> electrode structure.

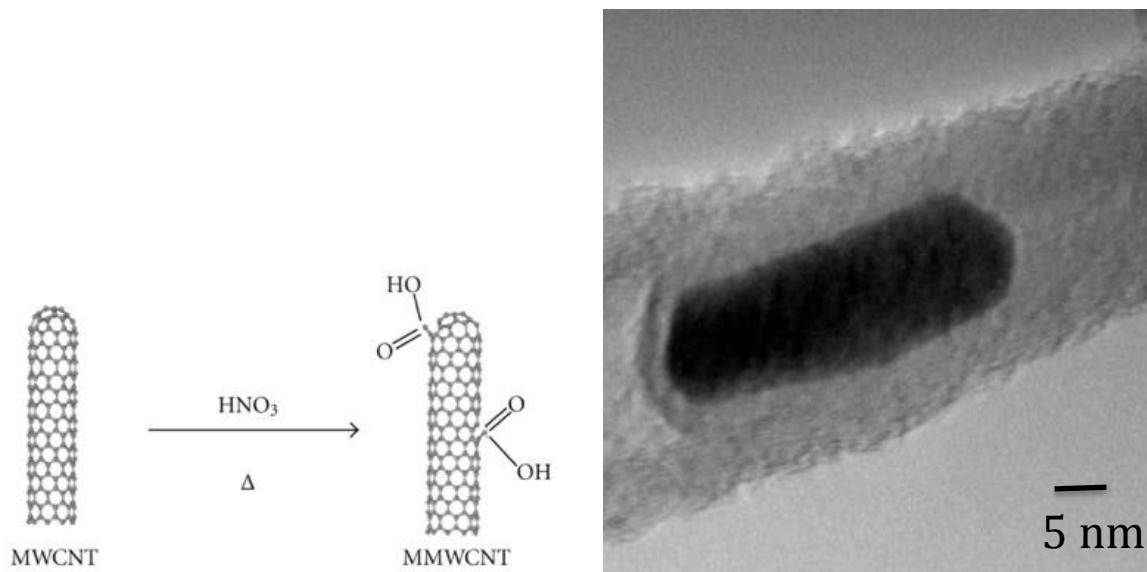


**Figure 1:** Scanning electron micrograph (SEM, left) and cyclic voltammogram (right) of Pt-free Nb/TiO<sub>2</sub> structure for future fuel cell electrode applications. The large surface area and high charge transport performance make this an interesting substitution for expensive Pt-based fuel cell electrodes.

## TOPIC 2: “Metal Filled Carbon Nanotubes for Targeted Cancer Therapy”

Collaborators: Albany Medical Center, Integrated Medical Technologies, Inc., Dr. Michael Fasullo (SUNY Poly).

Many disease-fighting therapies, in particular those for cancer, suffer from a non-specificity which leads to unintentional damage to otherwise healthy tissues or even the entire body. Targeted therapies hold promise to specifically attack the disease (i.e. cancer) cells without affecting nearby tissue. This project employs nanotechnology to fabricate metal (copper) filled carbon nanotubes (CNTs) which are specially functionalized to seek out and bind to cancer cells, where the metal can act as a focusing point for radiation treatments, thus reducing the exposure of the rest of the body to dangerous radiation. Preliminary studies have demonstrated a repeatable method for filling CNTs with metal nanoparticles, a critical step in the use of such materials for cancer therapy. Upcoming tests will determine the ability of the copper-filled structures to enhance the local radiation effects of a MeV-range gamma ray source.



**Figure 2:** Simplified schematic (left) for functionalizing of CNTs to allow targeting of specific cells within the body, transmission electron micrograph (TEM, right) showing copper metal nanoparticle (dark feature) assembled inside CNT.

# Visualizing the Nanoscale Electrostatics of Material Interfaces

## Vincent P. LaBella (LaBella Group)

**Scope:** Controlling and understanding the electrostatics of material interfaces is paramount to the development of current and future electronic and optoelectronic devices. The continued scaling of devices into the sub-20-nm length scale is straining our ability to measure and control their interfaces. Futuristic devices such as quantum computers rely on controlling the electrostatics to nanoscale dimensions via placement of individual impurity atoms. Two-dimensional layered materials offer great promise to enable devices with novel features, but challenges remain in achieving robust electrical contacts to them. These technological drivers create a fundamental need for nanoscale visualization of the electrostatic fluctuations at material interfaces. The PI's group has recently made a transformational breakthrough in the ability to map the electrostatic potential of a material interface to nanoscale dimensions.

**Goals:** The LaBella Group utilizes the unique capability to visualize the electrostatics of a buried material interface to nanoscale dimensions in several studies. The current focus is to measure and model the effects that stoichiometry changes such as silicide formation have on the nanoscale uniformity of the interface electrostatic barrier.

### 2016 Accomplishments

#### TOPIC 1: Silicide formation detection at a buried metal semiconductor interface

Metal/semiconductor interfaces form a rectifying contact known as a Schottky diode characterized by a barrier height that is governed by the charge transfer and localized bonding at the interface. Conventional current voltage spectroscopy measures a spatially averaged barrier height. Ballistic electron emission microscopy (BEEM) is a scanning tunneling microscopy (STM) technique that can measure barrier heights with nanoscale resolution due to the nano-positioning of the STM tip as displayed in Fig. 1 [1-3].

The ability to detect localized silicide formation at a buried metal semiconductor Schottky interface is demonstrated via nanoscale measurements of the electrostatic barrier [3]. This is accomplished by mapping the Schottky barrier height of the

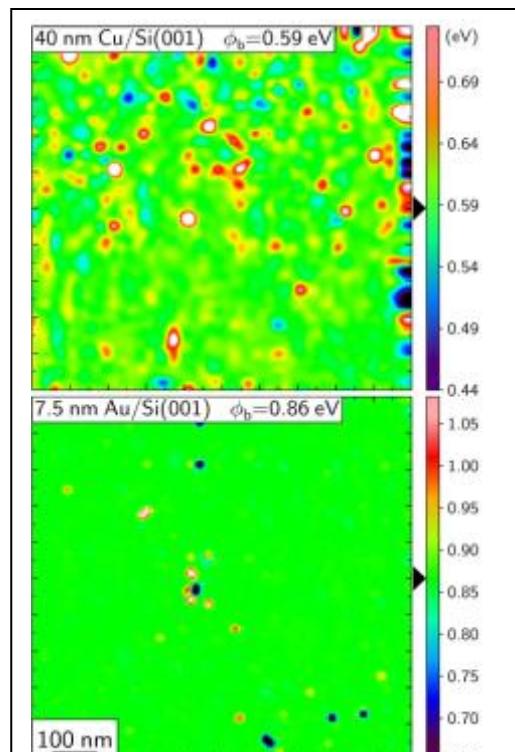
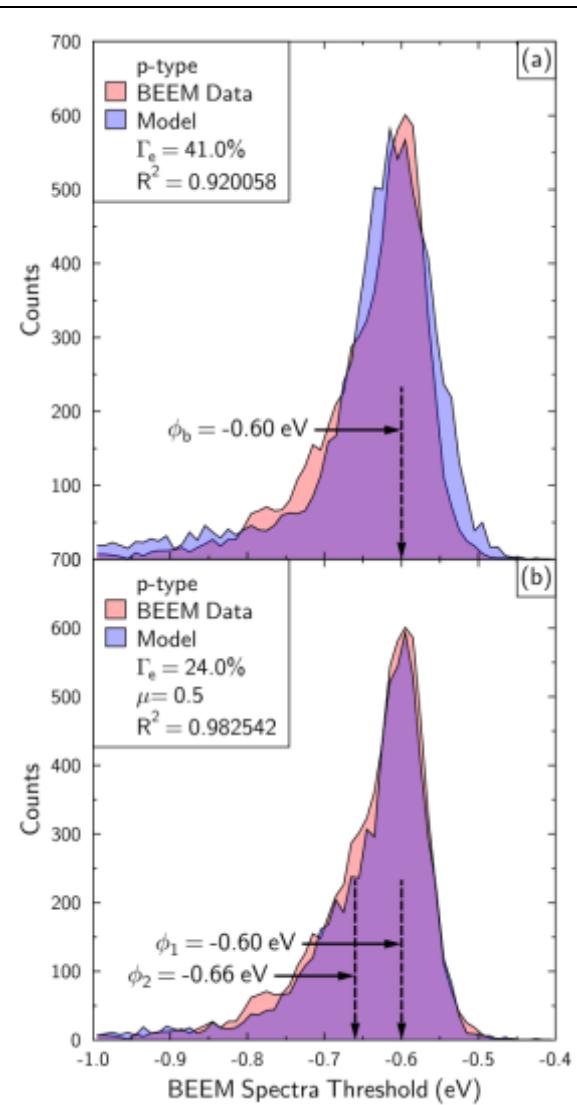


Figure 1: Schottky barrier height maps of a one micron region of the (top) Cu/Si(001) and (bottom) Au/Si(001) interface acquired at 77~K.



**Figure 2:** (a) Cr/p-Si(001) modelled histogram and data showing skewing to higher energies and degree of agreement between the two. (b) Improved agreement when a second threshold is added to the simulation with a mixture factor of 0.5 and a reduced elastic scattering

Cr/Si(001) interface utilizing ballistic electron emission microscopy (BEEM). Monte-Carlo modeling is employed to simulate the distributions of barrier heights that includes scattering of the electrons that traverse the metal layer and a distribution of electrostatic barriers at the interface. The best agreement between the model and the data is achieved when specifying two barrier heights less than 60~meV from one other instead of a singular barrier as displayed in Fig. 2. Typically, changes in barrier heights due to silicide formation are on the order of tens of meV as has been observed when comparing annealed and non annealed W/Si measurements [3]. These findings provide strong evidence that localized silicide formation is occurring that would be difficult to observe in an averaged BEEM spectra or conventional current voltage measurements. The partial chromium-silicide formation at the interface, is also supported by TEM images (not shown) [3].

Detection of localized silicide formation at a buried metal semiconductor interface via measurement of the electrostatic barrier to nanoscale dimensions and modeling with Monte-Carlo simulation is demonstrated. This unique capability of the LaBella Group is now focused on understanding the complex electrostatics of other technologically important interfaces such as W/Si and HfO/Si. This work is supported by the National Science

Foundation under grant DMR-1308102.

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- [1] Chris A. Durcan, Robert Balsano, Vincent P. LaBella, Journal of Applied Physics, 116 023705 (2014).
- [2] Westly Nolting, Chris Durcan, Avyaya J. Narasimham, Vincent P. LaBella, Journal of Vacuum Science and Technology B 34 04J110 (2016).
- [3] Westly Nolting, Chris Durcan, Vincent P. LaBella, Applied Physics Letters, 110 141606 (2017).

## Scanning Electron Microscopy and X-ray Microanalysis (Lifshin Group)

**Scope:** The Lifshin Group performs research in the development and application of scanning electron microscopy (SEM) and x-ray microanalysis. Electron beams from both thermionic and field emission electron guns are focused to probes as small as 1.0 nanometers causing the generation of a variety of measurable signals used to provide information about, or alteration to, highly localized regions of a sample. A key component of this research is to understand the theory of image formation and related experimental conditions in order to optimize the information obtained. This work involves both experiments and modeling techniques. As an example, a major thrust is underway to determine the spatial distribution of electrons in a focused electron beam. This information is then used in conjunction with deconvolution and regularization algorithms to restore images with less noise and improved spatial resolution.

**Goals: Provide New and Improved Methods in Materials Characterization Based on Focused Electron and X-ray beams.**

### *2016 Accomplishments*

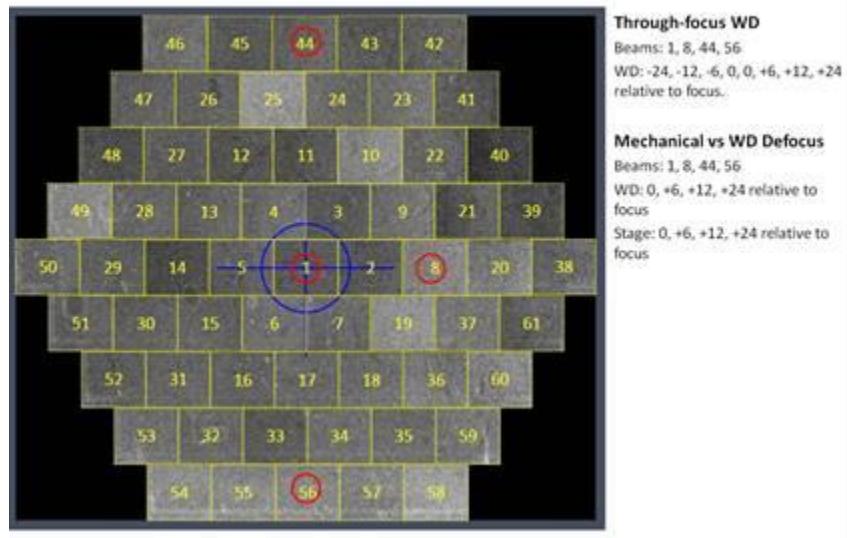
1. U.S. Patent Application No. 14/978,845 granted, Title: Determination of Spatial Distribution of Charged Particle Beams
2. Winner of a Microscopy Today Innovation Award in 2016. Awarded by Microscopy Today at the National Meeting of the Microscopy Society of America in Columbus Ohio, August 2016

### **TOPIC 1: Analysis of the point spread function of a multibeam instrument.**

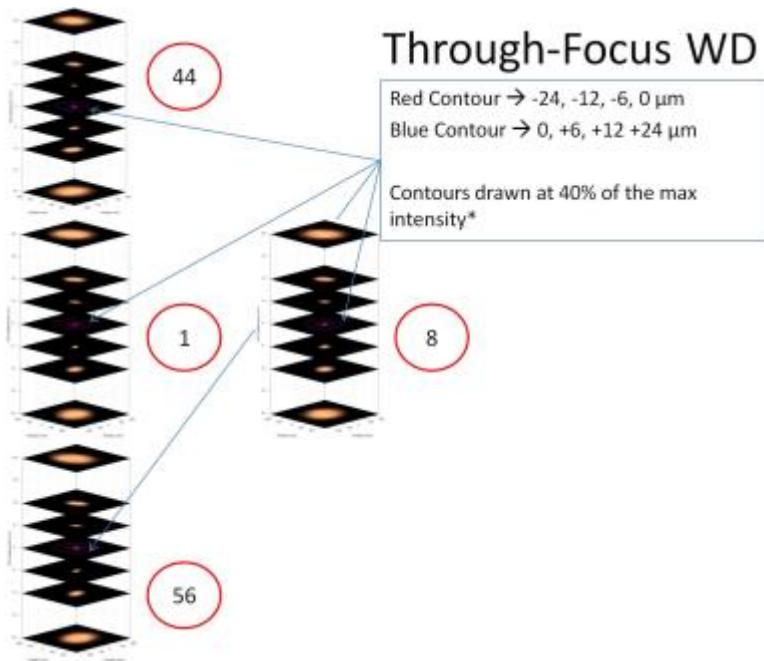
An example of the determination of the spatial distribution of electrons, the point spread function (PSF), is given in figures 1 and 2. This data was collected using a Zeiss MultiSEM at Harvard University's Center for Brain Science and was done with the cooperation of Dr. Richard Schalek of that institution. Images were collected at several different working distances to simulate the effect of either slight height variations in the sample or difference in focus between each of the beams. The Harvard research requires the collection of an enormous number of images in order to map out interconnections between neurons and this is facilitated by an SEM that produces 61 images simultaneously using 61 electron beams. The samples used are serial sections collected by an automated microtome and placed on a Kapton film that goes into the SEM. Figure 1 shows a single set of images collected from just one region of a sample. Figure 2 shows how our approach was used to map out the PSF's between the different beams in space. Preliminary results indicate that the potential exists for both reducing noise in the images and also corrected for any differences due to out of focus distortion.

**Figure 1:**

## Multisem Beam Map



**Figure 2:**



### References:

- [1] Kandel, Y.P. *et al*, Microscopy and Microanalysis (2015) 21(S3) p. 699–700
- [2] Lifshin *et al*, Microscopy and Microanalysis, **20(1)** (2014), p. 78–89
- [3] Lifshin, E. *et al*, Microscopy and Microanalysis (2014) 20(S3) p. 12–13
- [4] Lifshin, E. *et al*, Microscopy and Microanalysis (2014) 20(S3) p. 386–387
- [5] Zotta, M.D. *et al*, Microscopy and Microanalysis (2015) 21(S3) p. 33–34
- [6] Lifshin, *et al*, Microscopy Today, (2017) May, p. 18-24

## Jim Lloyd

**Scope: Fundamental Studies into the Reliability of Nanoscale Electronic Devices**

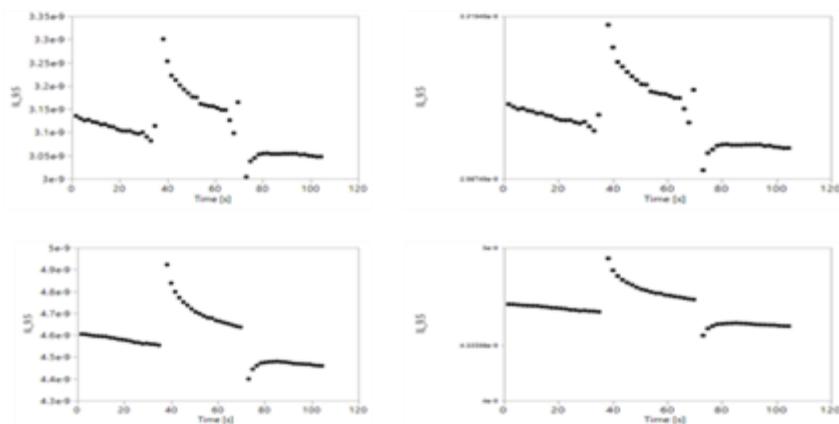
**Goals: Investigate the basic physics of failure and develop testing procedures to be able to predict the lifetime of electronic devices under use conditions from accelerated testing conditions.**

### **2016 Accomplishments**

**TOPIC 1: Discovery of Magnetoresistance in a low-k interlevel dielectric. (Brian McGowan Ph.D. awarded 2016)**

Discovered and characterized the magnetoresistance of the low-k dielectric SiCOH as a function of magnetic field, voltage applied to the sample and temperature. Identified a zero field splitting of the conductivity of SiCOH as a function of magnetic field. The zero field splitting may be used as a possible tool to measure trap generation in SiCOH as a function of accelerated testing. Also the behavior of Magnetoresistance as a function of time under stress was investigated. This work is continuing with a new student (Philip Williams).

**Figure 1:**



**TOPIC 2: Evaluation of possible recovery in TDDB damage (Austin Thomas Undergraduate Research Program graduated BS 2017)**

For low-k SiCOH dielectric there was no recovery detected even at ultra low frequency ( $\mu$ Hz regime) intermittent (pulsed) powering. This suggests that DC accelerated stressing is adequate for predicting reliability. Paper written and now in review.

Wafer #1	100%	66%	33%	Wafer #2	100%	66%	33%
Scale Parameter	153	156	160	Scale Parameter	82	92	64

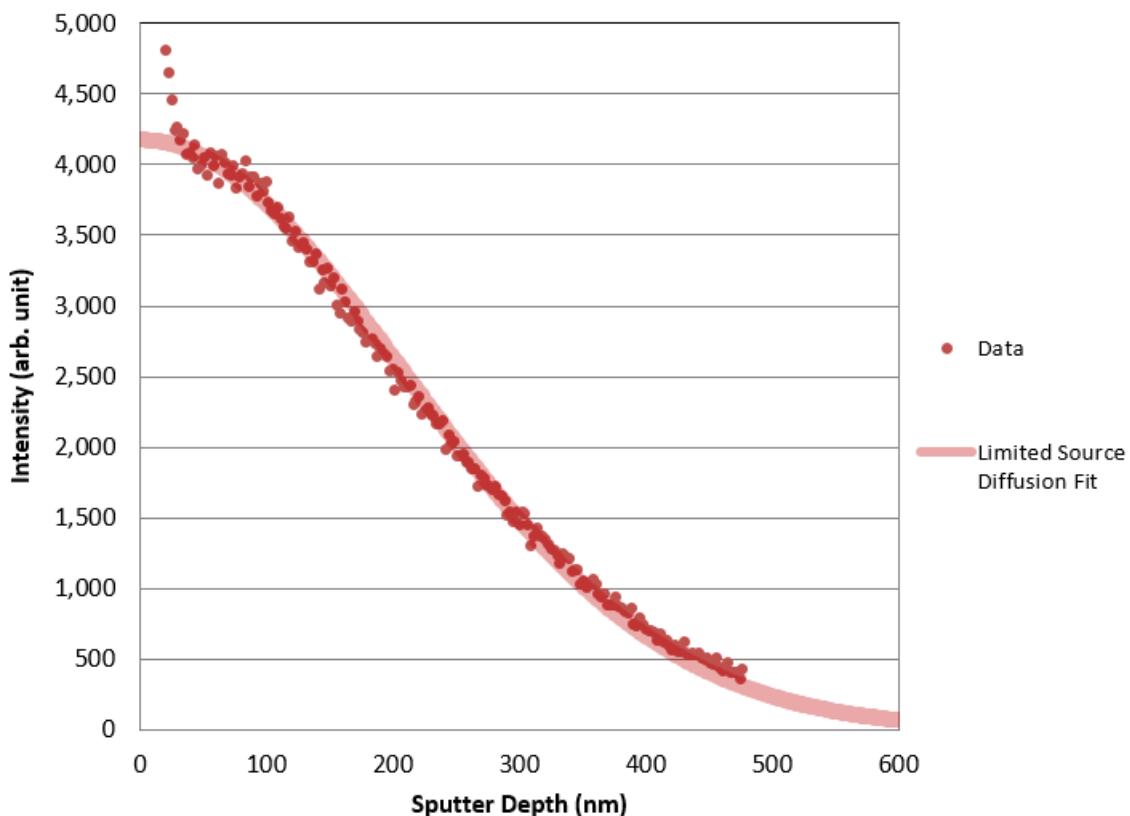
(t <sub>63</sub> in hours)				(t <sub>63</sub> in hours)			
Shape Parameter	2.3	3.3	3.4	Shape Parameter	3.6	3.0	2.1

Table I: Results of the Weibull fit to the data for both wafers and all duty cycles

**TOPIC 3: Determination of the Diffusion Mechanism of Cadmium in Copper Indium Gallium Selenide (CIGS) thin film solar cell material. (Norb Biderman Ph.D. awarded 2016)**

A complex two component diffusion mechanism incorporating both lattice and grain boundary diffusion of cadmium in copper indium gallium diselenide (Cu(In,Ga)Se<sub>2</sub> or CIGS) thin films was investigated in 700-nm thick CIGS at temperatures between 250 and 300 °C. Diffusion profiles of cadmium were analyzed by dual-beam time-of-flight secondary ion mass spectroscopy (TOF-SIMS). In addition to fast cadmium grain boundary diffusion, experiments revealed cadmium diffusion profiles with two distinct lattice diffusion stages, which could be indicative of simultaneous vacancy and dissociative diffusion mechanisms.

## Cadmium Diffusion in CuInGaSe<sub>2</sub> 5 Minutes at 300° C



### TOPIC 4: Investigation of Contact Properties and Degradation of Metal Graphene Junctions (Zhenjun Zhang Ph.D. awarded 2016)

A three component series resistance model was used to analyze the metal graphene junction. Post-fabrication degradation at a nickel/graphene junction due to interfacial oxidation was observed and characterized. A metal/channel length dependent transfer curve abnormality near the graphene charge neutral point was observed and an analytical model developed to describe the dual-Dirac point feature of the contact. We studied the effect of ambient doping and bias induced stress on the contact resistance and concluded that the impact of both are minimal when the resistance is dominated by the metal graphene tunneling resistance. d-band theory was adapted to predict the intrinsic limitations of metal graphene junctions and used x-ray photoemission spectroscopy to study the interface, suggesting a strong correlation between d band in transition metals and tunneling resistance at metal graphene junctions.

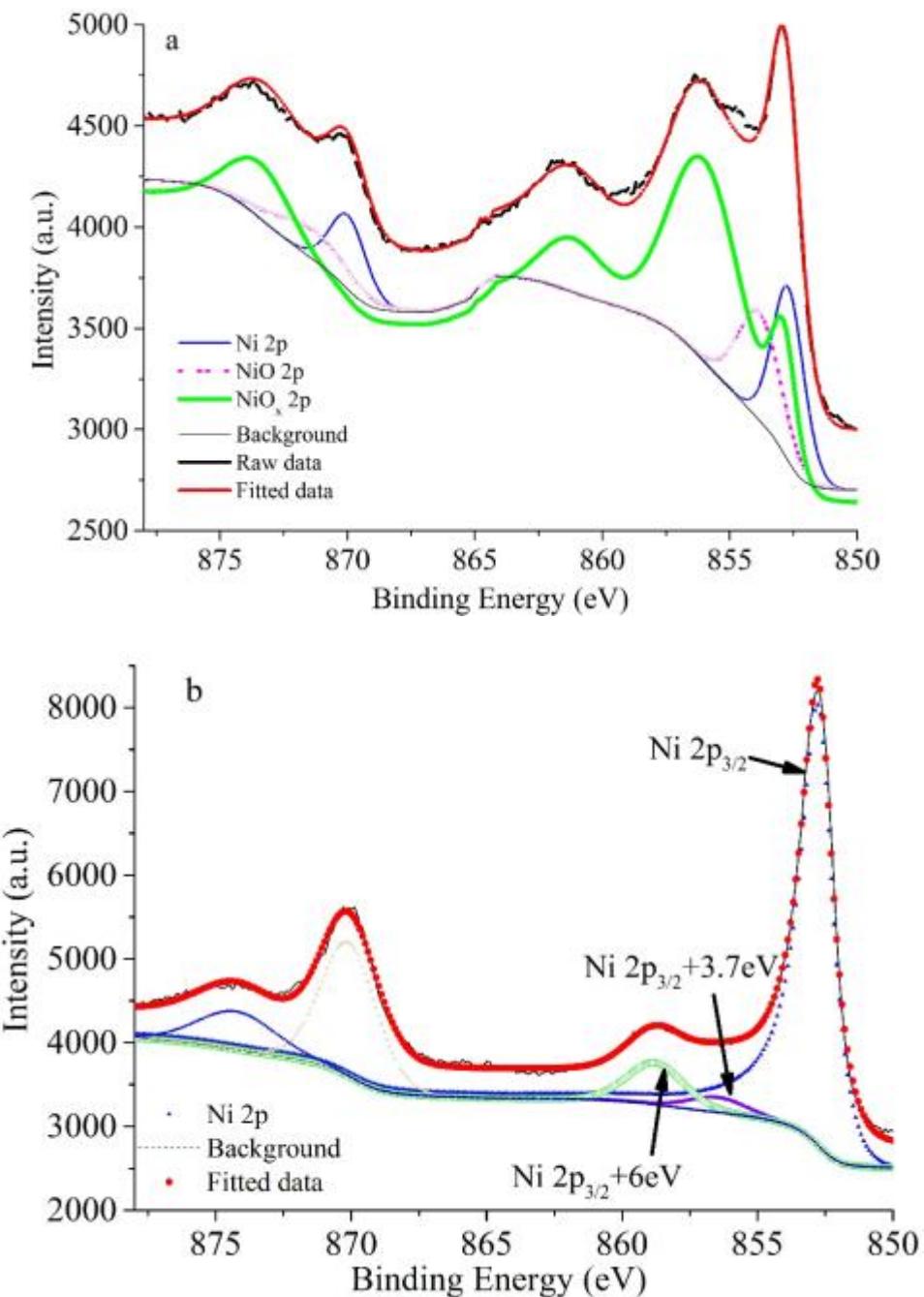
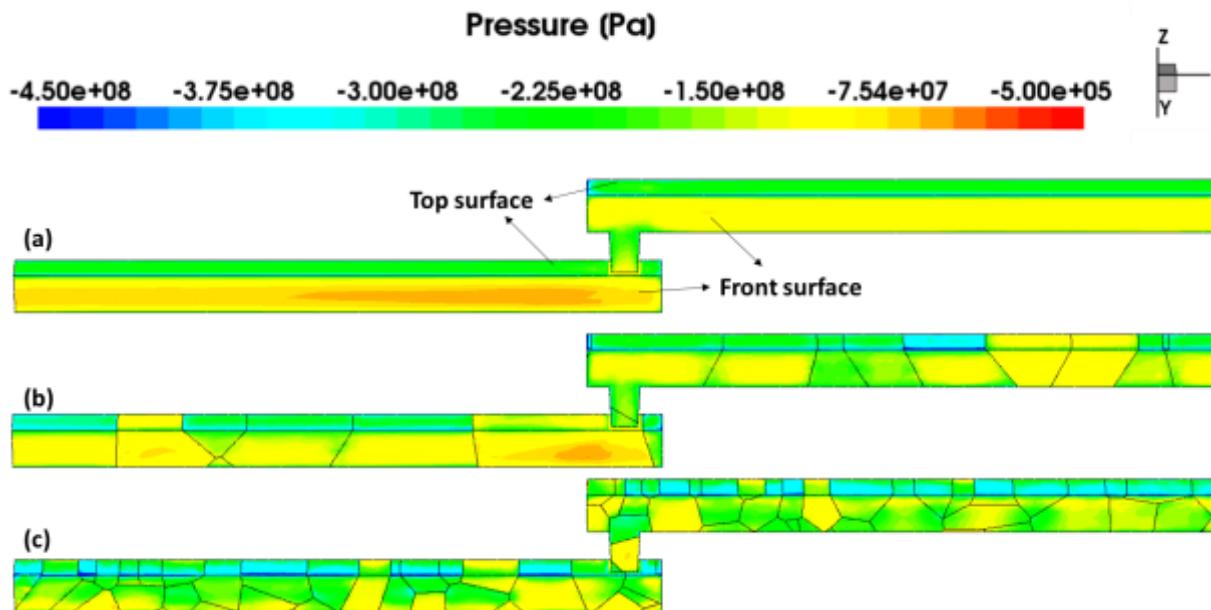


Figure 5.1: Ni 2p X-ray photoelectron peaks: a) as-grown, b) 300 °C annealed.

**TOPIC 5: Theoretical Investigation of Electromigration and Thermally induced stresses in Cu thin film conductors considering the anisotropy of mechanical properties. (Adarsh Bavasalingappa, awarded Ph.D 2017)**

The localized mechanical response of Cu thin narrow metal conductors was investigated as a function of electromigration and stress voiding conditions. The strong anisotropy of the mechanical properties of Copper were considered as well as a “real” grain size distribution. The results compared well to experimental observations including a bi-modal lognormal failure distribution with an approximately 25% early fail population. The effects of grain size and orientation were investigated.



#### **TOPIC 6: 1/f Noise and reliability of low-k dielectrics (Niaz Mahmud, current Graduate Student)**

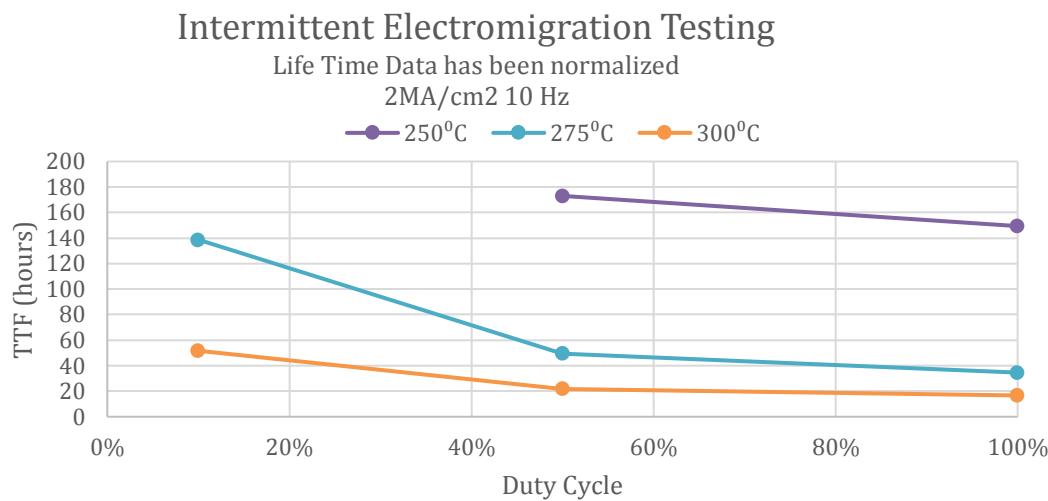
1/f noise, basically fluctuations in the resistance of a material has been related to the presence of defects and has been shown to be related to many forms of degradation of semiconductor devices. We investigated 1/f noise and failure in a ReRAM structure as well. There are interesting relationships of the magnitude and the slope ( $1/f^n$ ) of the low frequency noise, but nothing yet definitive.

#### **TOPIC 7: Relaxation of electromigration induced damage and/or stress profiles with intermittent (pulsed) powering. (Ingrid Ringler, M.S. awarded in 2016 and Jennifer Passage current graduate student)**

The present understanding of stress caused by electromigration mass flow and the role of this stress in electromigration induced failure leads one to expect that if the current flow is interrupted, the stress gradients induced by electromigration would tend to relax when the current is not flowing. The stress gradient that forms in opposition to the electromigration driving force would then be the sole driving force and the stress gradient would then be reduced. This should increase failure time for electromigration

where the lifetime is seen to be longer than the sum of the times when the power is applied. This was observed. In one case it was not observed, but there may be a simple explanation that we are considering.

In addition, the electromigration lifetime as a function of previous exposure to stress voiding conditions is being investigated.



## Compound Semiconductor Research (Oktyabrsky Group)

**Scope:** The Oktyabrsky Group research focuses on physics, materials and technologies of quantum confined structures, photonic/optoelectronic devices, group III-arsenide/antimonide MOSFETs.

### Goals:

1. Improve physical understanding and technology of high-efficiency quantum dot solar cells.
2. Develop integrated laser-modulator module for microwave photonics with the same gain/electro-absorption medium for both laser section of the device and modulator section.
3. Demonstrate a novel approach to ultrafast and efficient scintillation detector based on quantum dots imbedded into semiconductor waveguide.
4. Demonstrate viability of group III-Sb material for high mobility p-MOSFETs on Si substrate.

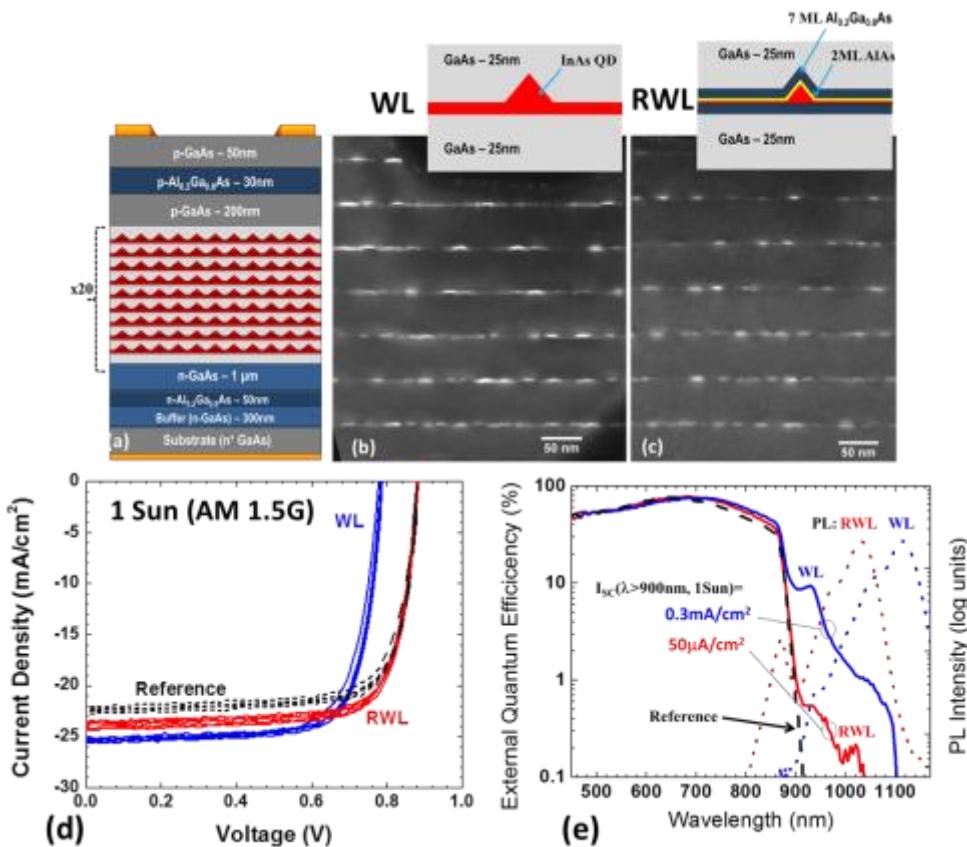
### 2016 Accomplishments

#### TOPIC 1: Physics and technology of quantum dot solar cells.

Intriguing possibilities for nanoscale engineering of energy transfer between photons, electrons, and phonons have inspired numerous investigations of quantum dot (QD) structures for photovoltaic conversion of solar radiation. Extensive investigations of recent years show that an addition of quantum dots (QDs) to a single-junction solar cell decreases the open circuit voltage,  $V_{oc}$ , with respect to the reference cell without QDs. Despite numerous efforts, the complete voltage recovery in QD cells has been demonstrated only at low temperatures. To minimize the  $V_{oc}$  reduction, a new approach is proposed that combines nanoscale engineering of band structure and potential profile. Our studies of GaAs solar cells with various InAs QD media demonstrate that the main cause of the  $V_{oc}$  reduction is the fast capture of photoelectrons from the GaAs conduction band (CB) to localized states in QDs. As the photoelectron capture into QDs is mainly realized via the wetting layers (WLs), we substantially reduced the WLs using two monolayer AlAs capping of QDs. In the structures with reduced WLs, the direct CB-to-QD capture is further suppressed due to charging of QDs via doping of the interdot space. The QD devices with suppressed photoelectron capture show the same  $V_{oc}$  as the GaAs reference cell together with some improvements in the short circuit current.

#### Highlights (Figure 1):

- Complete voltage recovery in QD solar cells with reduced wetting layer was demonstrated. The recovery has been reached due to suppression of electron capture processes from CB to QDs.
- Reduction of the WL and n-charging of QDs strongly reduces capture of photoelectrons and, therefore, maintain the light-induced shift between chemical potentials of electrons in QDs and the CB.



**Figure 1:** (a) Schematic of a QD solar cell structure grown on n-GaAs (001) substrate with 20 layers (1.1 μm thick) of InAs QDs. (b-c) Dark field g = (002) TEM micrographs of the QD structures (b) with wetting layer (WL) and (c) with a reduced wetting layer (RWL). Insets: detailed structures of the WL and RWL QD samples. (d) Current – voltage characteristics of a reference GaAs and two QDSC samples under 1 Sun (AM 1.5G) illumination. Data from five devices from each wafer are shown. (e) EQE spectra of reference GaAs and two QDSCs showing bulk GaAs and sub-bandgap absorption regions. The integrated sub-band gap short circuit current is measured under 1 Sun simulator with an IR longpass ( $\lambda > 900$  nm) filter. Dotted lines show PL spectra of QD samples. [1]

## TOPIC 2: Integrated Semiconductor Quantum Dot Scintillation Detector

A picosecond-range timing of charged particles and photons is a long-standing challenge for many high-energy physics, biophysics, medical and security applications. We present a design, technological pathway and challenges, and some properties important for realization of an ultrafast high-efficient room-temperature semiconductor scintillator based on self-assembled InAs quantum dots (QD) embedded in a GaAs matrix. Compared to traditional inorganic scintillators, the semiconductor-QD based scintillators could have about 5x higher light yield and 20x faster decay time, opening a way to gamma detectors with the energy resolution better than 1% and sustaining counting rates  $> 100$  MHz. Picosecond-scale timing requires segmented low-capacitance photodiodes integrated with the scintillator. For photons, the proposed detector inherently provides the depth-of-interaction information.

### Highlights (Figure 2,3):

- We proposed a design and technological pathway for an integrated semiconductor scintillation detector based on InAs QDs embedded in a GaAs matrix with a promise of unsurpassed speed and light yield.
- Design rules, target parameters and commercial viability are analyzed; critical properties of the medium, such as self-absorption, radiation hardness, waveguiding are tested for feasibility.

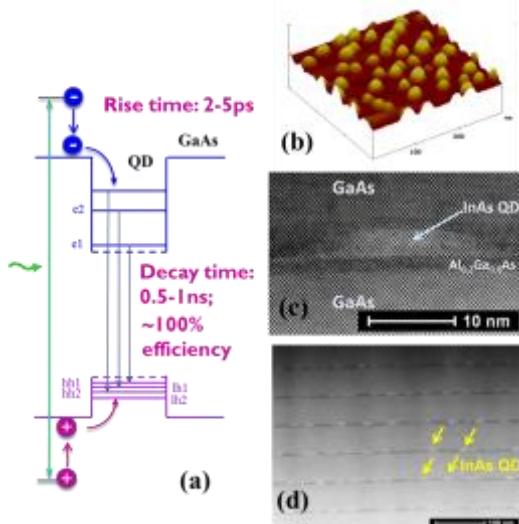


Figure 2: (a) Schematic band-structure of InAs QDs in GaAs matrix with typical transition time scales; (b) Atomic force microscopy image of self-assembled InAs QDs on GaAs surface; (c-d) Scanning transmission electron microscopy images of a multilayer QD structure with reduced wetting layer [2].

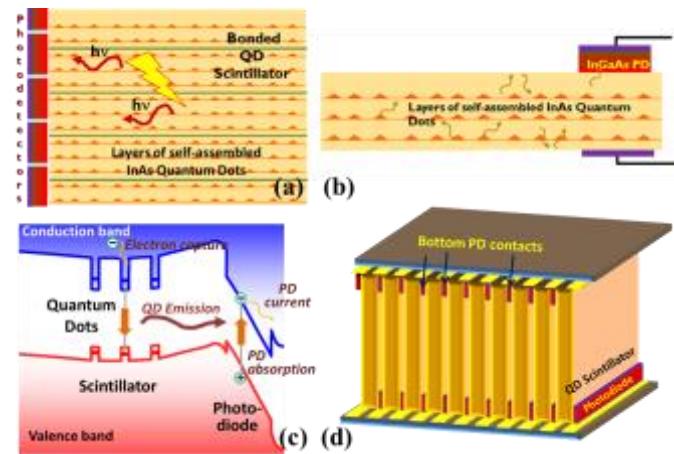


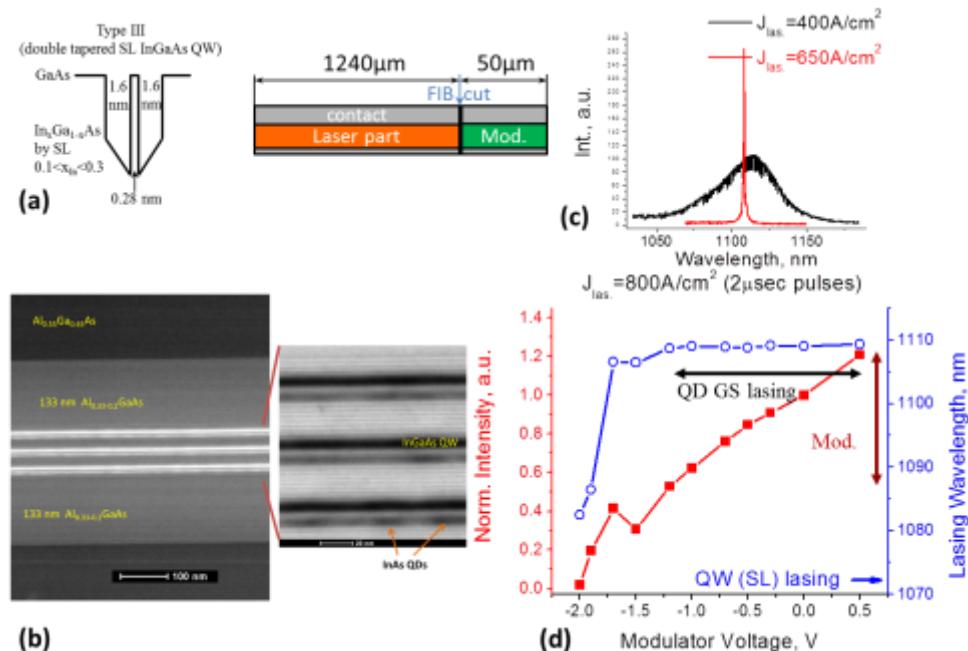
Figure 3: (a) Multiple stacked waveguides with light extraction from the edge. (b-d) Waveguide scintillation detector with an integrated photodiode (PD). (b) Single-layer detector layout; (c) band structure; (d) Integration of QD sheets into bulk scintillator with segmented photodetector array [2].

### TOPIC 3: Integrated microwave optical source

The scope of this SBIR subcontract was design, fabrication and bench-testing of the first-generation prototype of a diode waveguide laser with integrated modulator with a quantum well on dots (QW-on-QDs) medium providing both gain at forward bias and electro-absorption modulation at reverse bias. The device with adequately designed inter-section reflector and travelling mode modulator will be capable of 100+ GHz operation. The main original idea of the current project is to utilize the same medium for both gain laser section of the device and integrated modulator section.

### Highlights (Figures 4):

- For the first time achieved monolithic integration of quantum dot (QD) medium with an electro-absorption modulator, where the quantum well (QW) performs as a tunnel injector into QDs in the laser diode section and quantum Stark effect absorber in the modulator section.
- Ground state energy matching in the QW-on-QDs active medium was demonstrated for lasing with tunnel QW-to-QD injection and modulation by the same active medium in directly and inversely biased sections, respectively.
- For the first time, a wave-function engineered double tapered QW-on-QDs structure was used for in-plane integrated laser-modulator with improved linearity.



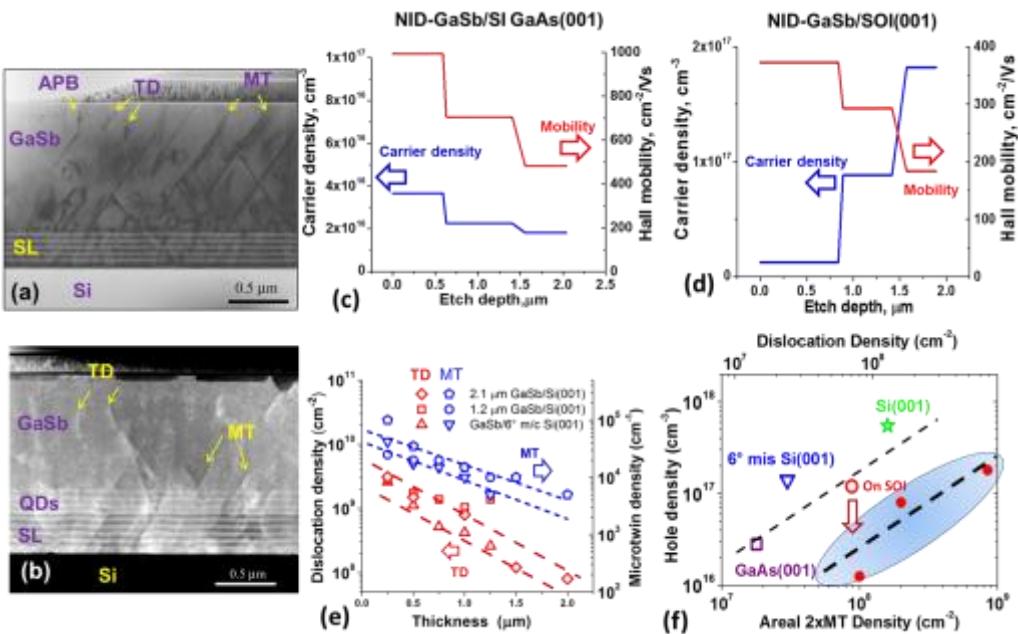
**Figure 4:** (a) Geometry of a laser-modulator test structure. (b) High angle annular dark field scanning TEM cross-sectional image of the active QW-on-QDs medium. Brighter contrast corresponds to higher Z material; (b-inset) Magnified bright field STEM image with higher QD contrast. Dark contrast corresponds to higher-Z material. (c) Spontaneous and lasing spectra of the structure with 50  $\mu\text{m}$  long intracavity absorber section. (d) Intensity modulation overlapped with spectral shift of the laser line. Intensity modulation of 60% at +0.5...-1.2V bias swing is indicated.

## TOPIC 4: Epitaxial growth of III-Sb's on metamorphic buffers

GaSb and its compounds have attracted attention as materials for IR optoelectronic devices and for high speed and low power electronics due to their narrow band gaps (0.72eV in GaSb), superior electron and hole mobility and capability for flexible band engineering in heterostructures. To improve the quality of GaSb films grown on lattice-mismatched Si and GaAs substrates we investigated the growth defects and electrical properties of various GaSb epitaxial films by employing metamorphic superlattice buffers and alternative substrates that can potentially mitigate growth defects.

### Highlights (Figure 5):

- The relationship between electrical properties (hole density and mobility) and growth defects in GaSb epitaxial films was quantified in structures grown on different Si substrates (Si(001), miscut Si and SOI) using metamorphic buffers and compared to similar structures on GaAs.
- The TD density of just below  $10^8 \text{ cm}^{-2}$  and MT density below  $10^4 \text{ cm}^{-1}$  were obtained in 2.1  $\mu\text{m}$  thick structures that are 4x higher than in similar structures grown on GaAs substrates.
- Hole density and mobility profiles were measured using differential Hall method and correlated to the profiles of growth-related extended defects. Correlating areal dislocation density with hole density indicates that dislocations (both TDs or MT partials) generate about 25 acceptors/nm. Minimum midgap interface trap density  $D_{it}$  values are similar in the MOS structures prepared on GaAs and Si,  $\sim 2 \times 10^{12} \text{ cm}^2 \text{ eV}^{-1}$ .



**Figure 5:** (a) Cross-sectional TEM BF micrograph of a  $0.8 \mu\text{m}$  GaSb on Si(001), and (b) STEM DF image of a  $0.8 \mu\text{m}$  GaSb on  $6^\circ$  miscut Si (001), both grown on Si substrates with superlattice (SL) buffer. The imaging conditions in (b) make the InSb QD layers readily visible. Growth related defects are indicated: threading dislocations (TD), microtwins (MT) and antiphase domain boundary (APB). (c-d) Hole concentration and Hall mobility vs. depth in (c) NID GaSb on SI GaAs(001) and (d) NID GaSb on SOI(001) extracted with differential Hall technique. (e) Comparison of depth profiles of TD and MT densities in GaSb grown on Si(001) and on  $6^\circ$  miscut Si. (f) Correlation between the hole density and defect density in NID GaSb films grown on Si and GaAs. The solid circles and the shaded area are the differential Hall vs. TEM defect density results for the GaSb-on-SOI sample.[7]

#### Selected recent publications:

1. A. Varghese, M. Yakimov, V. Tokranov, V. Mitin, K. Sablon, A. Sergeev and S. Oktyabrsky. "Complete Voltage Recovery in Quantum Dot Solar Cells due to Suppression of Electron Capture." *Nanoscale*, **8**, 7248 (2016) DOI: 10.1039/C5NR07774E.
2. S. Oktyabrsky, M. Yakimov, V. Tokranov, and P. Murat, "Integrated Semiconductor Quantum Dot Scintillation Detector: Ultimate Limit for Speed and Light Yield," *IEEE Trans. Nuclear Science*, **63**, 656-663 (2016). doi:10.1109/TNS.2015.2502426
3. K. Sardashti, K.-T. Hu, K. Tang, S. Madisetti, P. McIntyre, S. Oktyabrsky, S. Siddiqui, B. Sahu, N. Yoshida, and J. Kachian, "Nitride passivation of the interface between high-k dielectrics and SiGe," *Appl. Phys. Lett.*, **108**, 011604 (2016). doi:/10.1063/1.4939460
4. T. Chidambaram, D. Veksler, S. Madisetti, M. Yakimov, V. Tokranov, and S. Oktyabrsky, "InGaAs Inversion Layer Mobility and Interface Trap Density From Gated Hall Measurements," *IEEE Electron Device Letters*, **37**, 1547-1550 (2016). doi:10.1109/LED.2016.2617119
5. J. Kapaldo, S. Rouvimov, J. Merz, S. Oktyabrsky, S. Blundell, N. Bert, P. Brunkov, N. Kalyuzhnny, S. Mintairov, and S. Nekrasov, "Ga-In intermixing, intrinsic doping, and Wigner localization in the emission spectra of self-organized InP/GaInP quantum dots," *J. Phys. D*, **49**, 475301 (2016).
6. T. Orzali, A. Vert, B. O'Brian, J. L. Herman, S. Vivekanand, S. S. Papa Rao, and S. R. Oktyabrsky, "Epitaxial growth of GaSb and InAs fins on 300 mm Si (001) by aspect ratio trapping," *J. Appl. Phys.*, **120**, 085308 (2016).
7. S. Sasaki, K. Dropiewski, S. Madisetti, V. Tokranov, M. Yakimov, S. Oktyabrsky, S. Bentley, R. Galatage, and A. P. Jacob, "Electrical properties related to growth defects in metamorphic GaSb films on Si," *J. Vac. Sci. Tech. B*, **35**, 011203 (2017).

## Publications and Presentations

### Nanobioscience Constellation

#### Thomas Begley

(#) Denotes graduate students or post-doctoral associates who were under the direct supervision of Dr. Begley.

#### Peer reviewed articles

#Onanuga, K. A., **Begley, T. J.**, Chen, A., and Ranganathan, S. V. 2017. tRNA Modification detection using graphene nanopores: a simulation study. (in press at Biomolecules).

#Hsieh, Y., Begley, U., Hansen, A. F., Kaminsky, L., McCandless, B., and **Begley, T. J.** 2017. Activation of DNA damage signaling components by diagnostic computed tomography (CT) scans detected in patient samples using an electrochemiluminescence-based assay platform. (in press at Advances in Bioscience and Biotechnology, Special Issue on Ionizing Radiation).

Sosa Pena, P., Begley, U., **Begley, T. J.**, and J. A. Melendez. 2017. Mitochondrial Redox Control of Cancer. Semin Cancer Biol. [Epub ahead of print]  
<https://www.ncbi.nlm.nih.gov/pubmed/28445781>

Nagel, Z., Engelward, B. P., Brenner, D. J., **Begley, T.J.**, Sobol, R.W, Bielas, J., Stambrook, P., Wei, Q., Hu, J., Terry, M. B., Dilworth, C., McAllister, K.A., Reinlib, L., Worth, L., and Shaughnessy, D.T. 2017. Towards Precision Prevention, Identifying Healthy Individuals with High Risk of Disease. Mutat Res. 800-802, 14-28.  
<https://www.ncbi.nlm.nih.gov/pubmed/28458064>

Chionh, Y.H., McBee, Ramesh Babu, I., Hia, F., Lin, W., Zhao, W., Cao, J., Dziergowska, A., Małkiewicz, A., **Begley, T.J.**, Alonso, S., and Dedon P.C. 2016. tRNA-mediated Codon-biased Translation in Mycobacterial Hypoxic Persistence. Nature Communications. 7, 13302  
<https://www.ncbi.nlm.nih.gov/pubmed/27834374>

Doyle, F., #\*Leonardi, A., #Endres, L., Tenenbaum, S.A., Dedon, P.C. and **Begley, T.J.** 2016. Gene- and Genome-Based Analysis of Significant Codon Patterns in Yeast, Rat and Mice Genomes with the CUT Codon Utilization Tool. Methods. 107, 98-109.  
<http://www.ncbi.nlm.nih.gov/pubmed/27245397>

Klionsky, D. J.,... **Begley T. J.**, ... Zuckerbraun B. 2016. Guidelines for the use and interpretation of assays for monitoring autophagy. Autophagy. 12(1), 1-222. (note, over 200 authors)  
<http://www.ncbi.nlm.nih.gov/pubmed/26799652>

## **Presentations**

#Leonardi, A., #Endres, L., and Begley, T.J. "Alkbh8 dependent detoxification of reactive oxygen species.", 4<sup>th</sup> Annual Symposium on RNA Science, Albany, NY, Poster, March 2017

Onanuga, K.A., Begley, T.J., Chen, A, and Ranganathan, S. " tRNA Modification Detection Using Graphene Nanopores: A Simulation Study", 4<sup>th</sup> Annual Symposium on RNA Science, Albany, NY, Poster, March 2017

#Onanuga, K.A., Begley, U., and Begley, T.J. "Understanding the role of Selenium in Reactive Oxygen Species Management in Colorectal Cancers", Society for Free Radical Biology and Medicine National Meeting, San Francisco, CA, Poster, November 2016

## **Sara Brenner**

### **Publications**

J.C.K. Dillon, L. Bezerra, M.P. Sosa Peña, N.M. Neu-Baker, and S.A. Brenner. Hyperspectral data influenced by sample matrix: the importance of building relevant reference spectral libraries to map materials of interest, *Microsc. Res. Tech.* 80(5), (2017), 462.

B. Alam, A. Philippe, R.R. Rosenfeldt, F. Seitz, S. Dey, M. Bundschuh, G.E. Schaumann, and S. Brenner. Synthesis, characterization, and ecotoxicity of CeO<sub>2</sub> nanoparticles with differing properties, *J. Nanopart. Res.* 18, (2016), 303.

M.P.S. Idelchik, N.M. Neu-Baker, A. Chandrasekaran, A.J. Friedman, M.D. Frame, and S.A. Brenner. Relative quantitation of metal oxide nanoparticles in a cutaneous exposure model using enhanced darkfield microscopy and hyperspectral mapping, *NanoImpact* 3-4, (2016), 12.

M. Guttenberg, L. Bezerra, N.M. Neu-Baker, M.P.S. Idelchik, A. Elder, G. Oberdörster, and S.A. Brenner. Biodistribution of inhaled metal oxide nanoparticles mimicking occupational exposure: a preliminary investigation using enhanced darkfield microscopy, *J. Biophotonics* 9(10), (2016), 987.

S.A. Brenner, N.M. Neu-Baker, C. Caglayan, and I.G. Zurbenko. Occupational exposure to airborne nanomaterials: an assessment of worker exposure to aerosolized metal oxide nanoparticles in a semiconductor fab and subfab, *J. Occup. Environ. Hyg.* 13(9), (2016), D138.

S.A. Brenner, N.M. Neu-Baker, A.C. Eastlake, C.C. Beaucham, C.L. Geraci. NIOSH Field Studies Team assessment: worker exposure to aerosolized metal oxide nanoparticles in a semiconductor fabrication facility, *J. Occup. Environ. Hyg.* 13(11), (2016), 871.

## **Presentations**

“Nanotechnology: Human and Environmental Implications,” Evening Branch of the Women’s Alliance (EBWA), Schenectady, NY, May 25, 2017.

Special Panelist, Student Leaders Conference: Nano & Emerging Technologies, TechConnect World Innovation Conference & Expo, Washington, DC, May 16, 2017.

“Safety and Innovation as Partners for Success in Advanced Manufacturing”, TechConnect World Innovation Conference & Expo, Washington, DC, May 16, 2017.

“Occupational and Environmental Health & Safety: Enabling Nanotechnology Commercialization and Advanced Manufacturing”, Eastern New York American Society of Safety Engineers (ASSE) Meeting, Albany, NY, October 17, 2017.

“Implications of Nanotechnology on Human and Environmental Health”, SESHA Mini-Conference, Albany, NY, October 10, 2017.

## **Nate Cady**

### **Publications**

M. Uddin, M.B. Majumder, K. Beckmann\*, H. Manem\*, Z. Alamgir\*, **N.C. Cady**, G.S. Rose. Exploring Best Region of Operation of a Memristive Crossbar Physical Unclonable Function. *Journal on Emerging Technologies in Computing Systems*. Accepted – *in press*.

Z. Alamgir\*, K. Beckmann\*, J. Holt\*, **N.C. Cady**. Pulse width and height modulation for multi-level resistance in bi-layer TaOx based RRAM. *Applied Physics Letters*. Accepted - *in press*.

V. Desai\*, M. Mellish, S. Bennett, **N.C. Cady**. Process development for high resolution Hydrogen Silsesquioxane (HSQ) patterning using commercial scanner for Extreme Ultraviolet Lithography (EUVL). (2017) *Journal of Vacuum Science & Technology, B*. 35: 021603. DOI: <http://dx.doi.org/10.1116/1.4975797>

J.S. Holt\*, K. Beckmann\*, Z. Alamgir\*, J. Yang-Scharlotta, **N.C. Cady**. Effect of displacement damage on tantalum oxide resistive memory. (2017) *MRS Advances*. 1-7. DOI:10.1557/adv.2017.422

C.M. Hanes, A.E. D’Amico, T. Ueyama, X. Zhang, W.F. Hynes\*, M.M. Barroso, **N.C. Cady**, M. Trebak, N. Saito, M.R. Lennartz. Golgi-associated PKC-e is delivered to phagocytic cups: Role of PI4P. (2017) *Journal of Immunology*. 35(2): 021603.

M.K. Dion, J.F. Drazan, S. Giddings, **N.C. Cady**, R. Dahle, J.T. Roberts, E.H. Ledet. Smart Orthopaedic Implants: Application in Total Knee Arthroplasty. (2016) *American Journal of Engineering and Applied Sciences*. 9(4):1232-38.

K. Beckmann\*, H. Manem\*, **N.C. Cady**. Performance enhancement of a time-delay PUF design by utilizing integrated nanoscale ReRAM devices. (2016) *IEEE*

*Transactions on Emerging Topics in Computing – Special issue “Security of Beyond CMOS Devices: Issues and Opportunities. DOI: 10.1109/TETC.2016.2575448*

K. Beckmann\*, J. Holt\*, W. Olin-Ammentorp\*, J. Van Nostrand, **N.C. Cady**. Impact of etch process on hafnium dioxide based nanoscale RRAM devices. (2016) *ECS Transactions*. 75(13): 93-99.

S.H. Kasper\*, R. Hart\*, M. Bergkvist, R.A. Musah, **N.C. Cady**. Zein nanocapsules as a tool for surface passivation, drug delivery, and biofilm prevention. (2016) *AIMS Microbiology*. 2(4): 422-433.

V. Desai\*, J.G. Hartley, **N.C. Cady**. Electron beam lithography patterned hydrogen silsesquioxane resist as a mandrel for self-aligned double patterning application. (2016) *Journal of Vacuum Science and Technology, B*. 34(6): 061601.

K. Beckmann\*, J. Holt\*, H. Manem\*, J. Van Nostrand, **N.C. Cady**. Nanoscale hafnium oxide RRAM devices exhibit pulse dependent behavior and multi-level resistance capability. (2016) *MRS Advances*. 1(49): 3355-3360. DOI: <http://dx.doi.org/10.1557/adv.2016.377>

S.H. Kasper\*, R.P. Bonocora, J.T. Wade, R.A. Musah, **N.C. Cady**. Chemical inhibition of kynureninase reduces *Pseudomonas aeruginosa* quorum sensing and virulence factor expression. (2016) *ACS Chemical Biology*. 11(4): 1106-1117.

M. Craven, S. Kasper\*, M. Canfield, R. Diaz-Morales, J. Hrabie, Joseph; **N. Cady**, A. Strickland. Nitric Oxide-Releasing Polyacrylonitrile Disperses Biofilms Formed by Wound-Relevant Pathogenic Bacteria. (2016) *Journal of Applied Microbiology*. 120(4): 1085-99.

A. Mendoza, D.M. Torrisi, S. Sell, **N.C. Cady**, D.A. Lawrence. Grating coupled SPR microarray analysis of proteins and cells in blood from mice with breast cancer. (2016) *Analyst*. 141: 704-712.

### **Peer-reviewed Conference Proceedings Papers**

J.S. Plank, G.S. Rose, M. E. Dean, C.D. Schuman, **N.C. Cady**. A Unified Hardware/Software Co-Design Framework for Neuromorphic Computing Devices and Applications. ICRC: IEEE International Conference on Rebooting Computing. November 2017, Washington, DC.

S. Amer, S. Sayyaparaju, K. Beckmann\*, **N.C. Cady**, G.S. Rose. A Practical Hafnium-Oxide Memristor Model Suitable for Circuit Design and Simulation. ISCAS: International Symposium on Circuits and Systems. May 2017, Baltimore, MD.

S. Amer, G.S. Rose, K. Beckmann\*, **N.C. Cady**. Design Techniques for in-Field Memristor Forming Circuits. 60th IEEE International Midwest Symposium on Circuits and Systems. August 2017, Boston, MA.

M. Uddin, M.B. Majumder, G.S. Rose, K. Beckmann\*, H. Manem\*, Z. Alamgir\*, **N.C. Cady**. Techniques for Improved Reliability in Memristive Crossbar PUF Circuits. 2016 IEEE Computer Society Annual Symposium on VLSI (ISVLSI), Pittsburgh, PA, pp. 212-217. doi: 10.1109/ISVLSI.2016.33

W. Olin-Ammentorp\*, K. Beckmann\*, J.E. Van Nostrand, G.S. Rose, M.E. Dean, J.S. Plank, G. Chakma, **N.C. Cady**. Applying Memristors Towards Low-Power, Dynamic Learning for Neuromorphic Applications. *GOMACTECH Conference, Reno, NV March 2017.*

G. Chakma, M.E. Dean, G.S. Rose, K. Beckman\*, H. Manem\*, **N. Cady**, A Hafnium-Oxide Memristive Dynamic Adaptive Neural Network Array. International Workshop on Post-Moore's Era Supercomputing (PMES), *Salt Lake City, UT, November 2016.*

J.F. Drazan, O.T. Abdoun, M.T. Wassick, G. Marcus, R. Dahle, L.A. Beardslee\*, **N.C. Cady**, E.H. Ledet. Reducing the Effect of Parasitic Capacitance on Implantable Passive Resonant Sensors. *2016 Annual Meeting of IEEE/EMBC. Orlando, FL, August, 2016.*

J.F. Drazan, M.T. Wassick, R. Dahle, L.A. Beardslee\*, **N.C. Cady**, E.H. Ledet. A Simple Sensing Mechanism for Wireless, Passive Pressure Sensors. *2016 Annual Meeting of IEEE/EMBC. Orlando, FL, August, 2016.*

### **Presentations**

Wadsworth Institute, NY State Dept. of Health, Albany, NY, July 14, 2017

National Youth Science Camp, Bartow, WV, June 24, 2017

Materials Research Society, Phoenix, AZ, April 20, 2017

GOMAC Tech Conference, Reno, NV, March 20, 2017

### **James Castracane**

#### **Publications**

Melinda Larsen, Zeinab F. Hosseini, Deirdre Nelson, Nicholas Moskwa, Lauren Sfakis, and **James Castracane**, “FGF2-Dependent Submandibular Salivary Gland Mesenchyme Sustains the Epithelial Proacinar Phenotype in Organoids”, in review, Journal of Cell Science, (2017).

Zahraa I. Foraida, Anna Sharikova, Alexander Khmaldze, Lubna N Peerzada, Melinda Larsen, and **James Castracane**, “Double emulsion electrospun nanofibers as a growth factor delivery vehicle for salivary gland regeneration”, to be published, SPIE Proceedings-NanoScience and Engineering, (2017).

Zahraa I Foraida, Tim Kamaldinov, Deirdre A. Nelson, Melinda Larsen and **James Castracane**, "Elastin-PLGA Hybrid Electrospun Nanofiber Scaffolds for Salivary Epithelial Cell Self-Organization and Polarization", to be published, *Acta Biomaterialia*, (2017).

Robert A. Schramm, Matthew H. Koslow, Deirdre A. Nelson, Melinda Larsen and **James Castracane**, "A Novel Impedance Biosensor for Measurement of Trans-Epithelial Resistance in Cells Cultured on Nanofiber Scaffolds, accepted, *Biosensors*, (2017).

Georg Fluegen and Alvaro Avivar-Valderas, Yarong Wang, Michael R. Padgen, James K. Williams, Vladimir Verkhusha, David Entenberg, **James Castracane**, Patricia J. Keely, John Condeelis and Julio A. Aguirre-Ghiso, "Phenotypic heterogeneity of disseminated tumor cells is predetermined by primary tumor hypoxic microenvironments", *Nature Cell Biology*, Vol. 19, No. 2, pp. 120-135, (2017).

Lauren Sfakis, Felipe Xavier Costa, David Tuschel, Anna Sharikova, Melinda Larsen, **James Castracane**, Alexander Khmaladze, "Core/Shell Nanofiber Characterization by Raman Scanning Microscopy", *Biomedical Optics Express* 8(2) 1025-1035 , (2017).

Lauren Sfakis, Tim Kamaldinoff, Melinda Larsen, **James Castracane** and Alexander T. Khmaladze, "Quantification of Confocal images using LabVIEW for tissue engineering applications", *Tissue Engineering Part C: Methods*. Nov 2016: 1028-1037.

Brett Morris, Brian Burkell, Suzanne M. Ponik, Jing Fan, Kevin Eliceiri, John Condeelis, Julio Aguirre-Ghiso, **James Castracane**, John Denu, Patricia J. Keely, "Changes in collagen matrix density alters the metabolic profile of breast cancer cells", *EBioMedicine*, Vol. 13, p146–156 (2016).

Joseph M. Szulczewski, David R. Inman, David Entenberg, Julio Aguirre-Ghiso, **James Castracane**, John Condeelis, Kevin W. Eliceiri, Patricia J. Keely, "in vivo Visualization of Stromal Macrophages via label-free FLIM-based metabolite imaging", *Scientific Reports*, 6:25086, DOI: 10.1038/srep25086, (2016).

James K. Williams, David Entenberg, Yarong Wang, Alvaro Avivar-Valderas, Michael Padgen, Ashley Clark, Julio A. Aguirre-Ghiso, **James Castracane** and John Condeelis, "Validation of an implantable chemotaxis device for the study of cell migration in vivo", *Intravital*, vol.5, issue 2, (2016).

Logan Butt, Dave Entenberg, L.P.Madhubhani Hemachandra, Matthew Strohmayer, Patricia Keely, Julio Aguirre-Ghiso, John S. Condeelis, and **James Castracane**, "Development of microfluidic-based cell collection devices for *in vitro* and *in vivo* use", *Proc. SPIE* 9705, Microfluidics, BioMEMS, and Medical Microsystems XIV, 97051A (2016); doi:10.1117/12.2213316.

Potter, G., Tokranova, N., Rastegar, A. and **Castracane, J.**, "Design, Fabrication and Testing of Surface Acoustic Wave Devices for Semiconductor Cleaning Applications", *Microelectronic Engineering*, Volume 162, 16 August 2016, Pages 100-104.

## Xinxin Ding

### Publications

- Sheng, J., Wang, Y., Turesky, R. J., Kluztman, K., Zhang, Q.-Y., and Ding, X.: Transgenic mouse development for studying human serum albumin as a biomarker of carcinogenic exposure. *Chem. Res. Toxicol.* 29:797-809, 2016, PMC4868631
- Guan, X., Qin, M., Zhang, Y., Wang, Y., Shen, B., Ren, Z., Ding, X., Dai, W., Jiang, Y.: Safety and efficacy of megakaryocytes induced from hematopoietic stem cells in murine and nonhuman primate models. *Stem Cells Translational Medicine* 6:897-909, 2017, PMC5442772
- Li, L., Carratt, S., Hartog, M., Kovalchuk, N., Jia, K., Wang, Y., Zhang, Q.-Y., Edwards, P., Van Winkle, L. S., and Ding, X.: Human CYP2A13 and CYP2F1 can bioactivate naphthalene and mediate naphthalene toxicity in the lung and nasal mucosa of CYP2A13/2F1-humanized mice. *Env. Health Perspect.* <https://doi.org/10.1289/EHP844>, 2017
- Kovalchuk, N., Kelty, J., Li, L., Hartog, M., Zhang, Q.-Y., Edwards, P., Van Winkle, L. S., and Ding, X.: Impact of hepatic P450-mediated biotransformation on the deposition and respiratory tract toxicity of inhaled naphthalene. *Toxicol. Appl. Pharmacol.* 329:1-8, 2017
- Fasullo, M., Freedland, J., St. John, N., Cera, C., Egner, P., Hartog, M., and Ding, X.: An in vitro system for measuring genotoxicity mediated by human CYP3A4 in *Saccharomyces Cerevisiae*. *Env. Mol. Mutagenesis* 58:217-227, 2017
- Zhang, Y., Wang, C., Wang, L., Shen, B., Guan, X., Tian, J., Ren, Z., Ding, X., Ma, Y., Dai, W., Jiang, Y.: Large-scale ex vivo generation of human red blood cells from cord blood CD34<sup>+</sup> cells. *Stem Cells Translational Medicine* In Press
- Li, L., Bao, X., Zhang, Q.-Y., Negishi, M., and Ding, X.: Role of CYP2B in phenobarbital-induced hepatocyte proliferation in mice. *Drug Metab. Dispos.* In Press.
- Jie, Z., Zhang, Y., Wang, C., Shen, B., Guan, X., Ren, Z., Ding, X., Dai, W., Jiang, Y.: Large-scale ex vivo generation of human neutrophils from cord blood CD34+ cells. *PLoS ONE*, 12(7): e0180832. <https://doi.org/10.1371/journal.pone.0180832>, 2017
- Wang, L., Guan, X., Wang, H., Shen, B., Zhang, Y., Ren, Z., Ma, Y., Ding, X., and Jiang, Y.: A small-molecule/cytokine combination enhances hematopoietic stem cell proliferation via inhibition of cell differentiation. *Stem Cell Res. Ther.*, 8:169, <https://doi.org/10.1186/s13287-017-0625-z>, 2017

Xie, F., Ding, X., and Zhang, Q.-Y.: An update on the Role of Intestinal Cytochrome P450 Enzymes in Drug Disposition. *Acta Pharmaceutica Sinica B*, 6:374-383, 2016, PMC5045550

### **Presentations**

Assessing Carcinogenesis and Biomarkers in Transgenic Mice, 21<sup>st</sup> International Symposium on Microsomes and Drug Oxidations, Davis, CA, USA, Oct 7, 2016

Role of P450 Enzymes in Environmental Toxicity, Carcinogenesis, and Disease Susceptibility, Baylor College of Medicine, Houston, Jan 15, 2017

Metabolic Mechanisms of Chemical Toxicity in Lung and Other Organs, University of Colorado, Denver, May 15, 2017

### **Andre Melendez**

#### **Publications**

Sosa Peña MD, Lopez-Soler R, Melendez JA. Senescence in chronic allograft nephropathy. *Am J Physiol Renal Physiol.* 2016 Jun 15:ajprenal.00195.2016.

McCarthy DA, Nazem AA, McNeilan J, Shakerley NL, Clark RR, Idelchik MD, Yigit M, Melendez JA. Featured Article: Nanoenhanced matrixmetalloproteinase-responsive delivery vehicles for disease resolution and imaging. *Exp Biol Med (Maywood).* 2016 Dec;241(18):2023-2032.

Shakerley NL, Chandrasekaran A, Trebak M, Miller BA, Melendez JA. Francisella tularensis Catalase Restricts Immune Function by Impairing TRPM2 Channel Activity. *J Biol Chem.* 2016 Feb 19;291(8):3871-81. doi: 10.1074/jbc.M115.706879. Epub 2015 Dec 17. PubMed PMID: 26679996; PubMed Central PMCID: PMC4759167.

Rabadi SM, Sanchez BC, Varanat M, Ma Z, Catlett SV, Melendez JA, Malik M, Bakshi CS. Antioxidant Defenses of Francisella tularensis Modulate Macrophage Function and Production of Proinflammatory Cytokines. *J Biol Chem.* 2016 Mar 4;291(10):5009-21.

Idelchik MDPS, Begley U, Begley TJ, Melendez JA. Mitochondrial ROS control of cancer. *Semin Cancer Biol.* 2017 Apr 23. pii: S1044-579X(17)30098-6.

Chandrasekaran A, Idelchik MD, Melendez JA. Redox control of senescence and age-related disease. *Redox Biol.* 2017 Apr;11:91-102. doi: 10.1016/j.redox.2016.11.005.

### **Presentations**

Interplay of Redox and Calcium Signaling in Senescence, Karolinska Institute, February 2016

Nano delivery vehicles for targeting the proteolytic degradome, Union College, February 2016

Control of Senescence and Metastasis through redox-signaling, Umea University, Sweden, February 2016.

Epitranscriptomic control of selenoprotein synthesis, senescence, mitochondrial bioenergetics and clear cell renal cell carcinoma. Society for Free Radical Biology & Medicine, San Francisco, November 2016.

Identifying redox-responsive senescence control networks, Hudson Valley RNA Club, UAlbany, January 2017.

Navigating a Biology Ph. D. Career. Biology Honors Club, UAlbany, February 2017  
Identifying redox-responsive senescence control networks, Lebanese American University, Beirut, March 2017.

Redox-control of inflammaging through  $\text{Ca}^{2+}$  and thiol signaling, Penn State University, September 2017

## **Janet L. Paluh**

### **Publications**

J.L. Paluh. Epigenetics, ethnicity, bioinformatics and nanotechnology opening new frontiers in cardiac medicine. *Int. J. Stem Cell Res. Ther.* (2016) 3:027. ISSN: 2469-570X

M.L. Tomov, M. Tsompana, Z.T. Olmsted, M. Buck, and J.L. Paluh Human embryoid body transcriptomes reveal maturation differences influenced by size and formation in custom microarrays. *J. Nanosci Nanotech* (2016) 16: 8978-8988.

M.L. Tomov, Z.T. Olmsted, H. Dogan, E. Gongorurler, M. Tsompana, M. Buck E-A Chang, J. Cibelli, and J.L. Paluh. Distinct and shared determinants in cardiomyocyte contractility in multilineage competent ethnically diverse hiPSCs. (2016) *Sci Rep.* (2016)

J. Wang, B. Egnot, and J.L. Paluh. Cell competition and cooperation in tissue development. *J. Tissue Sci. Eng.* (2016) 7(2): 1000131. DOI: 10.4172/2157-7552.1000131

### **Presentations**

“Developing cardiomyocyte contractility bioinformatics insights from ethnically and epigenetically diverse hiPSC lines” in NYSTEM Annual Conference, NYC, May 2016

“Manipulating Kinesin-Tubulin-MTOC Interactions for Engineering Polarized Networks” in Biophysica Society Engineering Approaches to Biomolecular Motors Conference, Vancouver Canada, June 2016

"Distinct and Shared Determinants Impacting Cardiomyocyte Contractility in Multilineage Competent Ethnically Diverse hiPSCs" in Society of Biological Engineers Translational Medicine and Bioengineering Conference. San Francisco, November 2016

## Susan Sharfstein

### Publications

\*J.J. Terracina, S.T. Sharfstein, M. Bergkvist, In Silico characterization of Enantioselective Molecularly Imprinted Binding Sites, Journal of Molecular Recognition, e2612 (2017) doi: 10.1002/jmr.2612

S. Zhang, ^D.E. Speed, ^S.R. Trammell, and S.T. Sharfstein, Reactivity of Deposited Byproducts Generated from ZrO<sub>2</sub> Atomic Layer Deposition, Journal of Loss Prevention in the Process Industries, 45: 78-87 (2017) doi: 10.1016/j.jlp.2016.11.008

\*K.Y. Torrejon, #E.L. Papke, #J.R. Halman, M. Bergkvist, J. Danias, S.T. Sharfstein, and Y. Xie, TGF $\beta$ 2-induced outflow alterations in a bioengineered trabecular meshwork are offset by a Rho-associated kinase inhibitor, Scientific Reports, 6: 38319 (2016) doi:10.1038/srep38319

Hussain Dahodwala and Susan T. Sharfstein, "The 'Omics revolution in CHO biology: Roadmap to improved CHO productivity", in Heterologous Protein Production in CHO Cells, P. Meleady, ed. Methods in Molecular Biology, Humana Press v1603, p153-168 (2017).

H. Dahodwala and S.T. Sharfstein, Biosimilars: Imitation games, ACS Medicinal Chemistry Letters, 8:690–693 (2017) DOI: 10.1021/acsmedchemlett.7b00199

## Scott Tenenbaum

### Publications

FASTmiR: an RNA-based sensor for in vitro quantification and live-cell localization of small RNAs.

Huang K, Doyle F, Wurz ZE, Tenenbaum SA, Hammond RK, Caplan JL, Meyers BC. Nucleic Acids Res. 2017 Aug 21;45(14):e130. doi: 10.1093/nar/gkx504. PMID: 28586459

Engineering Structurally Interacting RNA (sxRNA).

Doyle F, Lapsia S, Spadaro S, Wurz ZE, Bhaduri-McIntosh S, Tenenbaum SA. Sci Rep. 2017 Mar 28;7:45393. doi: 10.1038/srep45393. PMID: 28350000

Gene- and genome-based analysis of significant codon patterns in yeast, rat and mice genomes with the CUT Codon UTilization tool.

Doyle F, Leonardi A, Endres L, Tenenbaum SA, Dedon PC, Begley TJ.

Methods. 2016 Sep 1;107:98-109. doi: 10.1016/j.ymeth.2016.05.010. Epub 2016 May 28.

## Dan White

### Presentations

Invited talk: June, 26, 28, 29 2017 National Museum of Costa Rica, San Jose, Costa Rica

Museo Nacional de Costa Rica “El cerebro humano desde el principio: evolución, función, y comportamiento”

Museo del Banco Central “La historia evolutiva de nuestro cerebro”

Museo del Jade “La historia de nuestra evolución cerebral: desde el molde endocraneano hasta el comportamiento humano”

## Yubing Xie

### Publications

Y. Tian, M.R. Zonca Jr., J. Imbrogno, A.M. Unser, L. Sfakis, S. Temple, G. Belfort, and Y. Xie, Polarized, cobblestone, human retinal pigment epithelial cell maturation on a synthetic PEG matrix, ACS Biomat. Sci. Eng. 3, (2017), 890–902

B. Mooney, N. Abdul-Raof, Y.I. Tian, and Y. Xie, Restriction of cancer metastatic potential using embryonic stem cells encapsulated in alginate hydrogel microstrands, ACS Biomat. Sci. Eng. 3 (2017), 1769–1779

K.Y. Torrejon, E.L. Papke, J.R. Halman, M. Bergkvist, J. Danias, S.T. Sharfstein, and Y. Xie, TGF $\beta$ -2-induced outflow alterations in a bioengineered trabecular meshwork are offset by a rho-associated kinase inhibitor, Sci. Rep. 6 (2016), 38319

## **Publications and Presentations**

### **Nanoscience Constellation**

#### **Alain Diebold**

##### **Journal Publications**

Atomic layer deposited ultra-thin metal nitride barrier layers for ruthenium interconnect applications, S. Dey, K-H Yu, S. Consiglio, K. Tapily, T. Hakamata, C.S. Wajda, and G.J. Leusink, J. Jordan-Sweet, C. Lavoie, D. Muir and B. Moreno, and A.C. Diebold, J. Vac. Sci. Technol. A35, (2017), 03E109.

Role of Ge and Si substrates in higher-k tetragonal phase formation and interfacial properties in cyclical ALD-anneal  $Hf_{1-x}Zr_xO_2/Al_2O_3$  thin film stacks, S. Dey, K. Tapily, S. Consiglio, R. D. Clark, C. S. Wajda, G. J. Leusink, A.R. Woll, and A.C. Diebold, J. Appl. Phys. 120, (2016), 125304.

Surface Oxidation of the Topological Insulator  $Bi_2Se_3$ , A.J. Green, S. Dey, Y.Q. An, B. O'Brien, S. J. O'Mullane, B. Thiel, and A.C. Diebold, J. Vac. Sci. Technol. A34, (2016), 061403.

Utilizing Tunable Absorption Properties of Light for Enhanced Ellipsometry of Metal Gratings, S. O'Mullane, Nick Keller, J. Race, A.C. Diebold, Journal of Micro/Nano Lithography, MEMS & MOEMS 15, (2016), 044003.

Tracking quintuple layer oxidation on cleaved  $Bi_2Se_3$  by optical second-harmonic anisotropy, Y. An, A.J. Green, and A.C. Diebold, Phys. Rev. B. 93, (2016), 241308(R).

##### **Conference Proceedings**

Characterization And Control Of The Surface Of MBE-Grown  $Bi_2Se_3$  Topological Insulator Films, A.J. Green, L. Walsh, W. Nolting, C. Ventrice, C. Hinkle, and A.C. Diebold, Frontiers of Characterization and Metrology for Nanoelectronics 2017, Monterey, March 21 -23, 2017.

Ferroelectricity in Atomic Layer Deposited  $Hf_{1-x}Zr_xO_2$  Nanoscale Films: Characterization by Synchrotron Grazing Incidence X-ray Diffraction and Polarization Measurements, S. Dey, K. Tapily, S. Consiglio, R.D. Clark, C.S. Wajda, G.J. Leusink, A.R. Woll, P. Sharma, S. Datta, and A.C. Diebold, Frontiers of Characterization and Metrology for Nanoelectronics 2017, Monterey, March 21 -23, 2017.

Study of Ru Silicidation with and without Sub-nm ALD TiN and TaN Barrier/nucleation Layers for Ru Interconnect Applications, S. Dey, K-H Yu, S. Consiglio, K. Tapily, C.S. Wajda, G.J. Leusink, J. Jordan-Sweet, C. Lavoie, A.C. Diebold, 63<sup>rd</sup> AVS National Symposium, Nashville, Nov. 6-11, 2016.

Electrically Scaled Hf Oxide based Ge Devices, K. Tapily, S. Consiglio, R.D. Clark, C.S. Wajda, G.J. Leusink, S. Dey, A.C Diebold, 230th ECS Meeting, Electronic Materials and Processing, Honolulu, October 2-7, 2016 and ECS Transactions 75, (2016), 135-140

### **Invited Presentations**

Muller matrix-based scatterometry, 2017 International Conference on Frontiers of Characterization and Metrology for Nanoelectronics, Monterey, CA, Mar. 21-23, 2017.

Semiconductor Industry Needs for Electron Microscopy, in “Electron Microscopy Frontiers: Metrology Opportunities and Challenges”, NIST, Gaithersburg, March 8 & 9, 2017.

Characterization and Metrology from FinFETS & Interconnect to Beyond CMOS materials, Semicon Korea 2016, Seoul, Korea, February Feb. 9, 2017.

Materials Characterization at the Nanoscale, Materials Characterization Workshop, University of Delaware, August 17, 2016

### **Hassa Bakhru**

Schröder, M. Walsh, J. Zheng, S. Mouradian, L. Li, G. Malladi, H. Bakhru, M. Lu, A. Stein, M. Heuck, and D. Englund, “Scalable fabrication of coupled NV center - photonic crystal cavity systems by self-aligned N ion implantation”, Optical Materials Express Vol. 7, Issue 5, pp. 1514-1524 (2017)

Adam Schulz, Hassaram Bakhru, Don DeRosa, Seiichiro Higashiya, Manisha Rane-Fondacaro, Pradeep Haldar, “Quantifying lithium in the solid electrolyte interphase layer and beyond using Lithium- Nuclear Reaction Analysis technique”, Journal of Power Sources Vol. 360, 31 129–135 August 2017

Brian Souhan, Christine P. Chen, Ming Lu, Aaron Stein, Hassaram Bakhru, Richard R. Grote, Keren Bergman, William M. J. Green and Richard M. Osgood Jr., “Ar+-Implanted Si-Waveguide Photodiodes for Mid-Infrared Detection”, Photonics 2016, 3(3), 46

Schukraft, M., Zheng, J., Schroeder, T., Mouradian, S. L, Walsh, M., Trusheim, M. E., Bakhru, H., Englund, D. R., “Invited Article: Precision nanoimplantation of nitrogen vacancy centers into diamond photonic crystal cavities and waveguides”, APL Photonics 1, (2) 020801 May 2016

Mengbing Huang, Nirag Kadakia, Sebastian Naczas, Hassaram Bakhru. Fabrication of surface textures by ion implantation for antireflection of silicon crystals US (Patent) 9231061 B2 Jan 5, 2016

## Robert L. Brainard and Students

### Journal Publications and Patents

A. Narasimhan, L. Wisehart, S. Grzeskowiak, L. E. Ocola, G. Denbeaux, **R. L. Brainard**, "What We Don't Know About EUV Exposure Mechanisms", *J. Photopolym. Sci. Technol.* 30(1), 113-120 (2017).

M. Murphy, A. Narasimhan, S. Grzeskowiak, J. Sitterly, P. Schuler, J. Richards, G. Denbeaux, **R. L. Brainard**, "EUV Mechanistic Studies of Antimony Resists", *J. Photopolym. Sci. Technol.* 30(1), 121-131 (2017).

S. Rangan, R. A Bartynski, A. Narasimhan, **R. L. Brainard**, "Electronic structure, excitation properties, and chemical transformations of extreme ultra-violet resist materials", *J. Applied Phys.* 122(2), 025305 (2017).

D. Soucie, W. Earley, K. Hosoi, A. Takahashi, T. Aoki, B. Cardineau, K. Miyauchi, R. **Brainard**, "Higher-Order Lithography: Double-Deprotected Chemically Amplified Photoresists (DD-CAMP)", *J. Photopolym. Sci. Technol.* 30(3), 351-360 (2017).

W. Earley, D. Soucie, K. Hosoi, A. Takahashi, T. Aoki, B. Cardineau, K. Miyauchi, J. Chun, M. O'Sullivan, **R. L. Brainard**; "Double-deprotected chemically amplified photoresists (DD-CAMP): higher-order lithography"; *Proc. SPIE*, 9779, *Adv. Pat. Mat. Proc.*, 101460H (2017).

**R. L. Brainard**, W. G Earley, B. Cardineau, T. Aoki, "Double-deprotected chemically amplified photoresists", *PCT Int. Appl.* (2016), WO 2016161067 A1 20161006

S. Grzeskowiak, A. Narasimhan, E. Rebeyev, S. Joshi, **R. L. Brainard**, G. Denbeaux; "Acid generation efficiency of EUV PAGs via low energy electron exposure", *J. Photopolym. Sci. Technol.* 29(3), 453-458 (2017).

S. Grzeskowiak, A. Narasimhan, M. Murphy, L. Napolitano, D. A. Freedman, **R. L. Brainard**, G. Denbeaux; "Reactivity of metal-oxalate EUV resists as a function of the central metal"; *Proc. SPIE*, 10146, *Adv. Pat. Mat. Proc.*, 1014605 (2017).

A. Narasimhan, S. Grzeskowiak, C. Ackerman, T. Flynn, G. Denbeaux, **R. L. Brainard**; "Mechanisms of EUV exposure: electrons and holes"; *Proc. SPIE*, 10143, EUVL, 101430W (2017).

J. Hotalen, M. Murphy, W. Earley, M. Vockenhuber, Y. Ekinci, D. A. Freedman, **R. L. Brainard**; "Advanced development techniques for metal-based EUV resists"; *Proc. SPIE*, 10143, EUVL, 1014309 (2017).

M. Murphy, A. Narasimhan, S. Grzeskowiak, J. Sitterly, P. Schuler, J. Richards, G. Denbeaux, **R. L. Brainard**; "Antimony photoresists for EUV lithography: mechanistic studies"; *Proc. SPIE*, 10143, EUVL, 1014307 (2017).

S. Grzeskowiak, A. Narasimhan, E. Rebeyev, S. Joshi,; **R. L. Brainard**, G. Denbeaux, "Acid generation efficiency of EUV PAGs via low energy electron exposure", J. Photopolym. Sci. Tech. 29(3), 453-458 (2016).

#### **Invited Presentations\***

**R. L. Brainard**, "Chemically Amplified Photoresists (CAMP)"; Heidenhain; Traunreut, Germany, November 2016.

**R. L. Brainard**, "Acid Amplifiers"; Heidenhain; Traunreut, Germany, November 2016.  
A.Narasimhan, S. Grzeskowiak, C. Ackerman, L.E. Ocola, G. Denbeaux, **R. L. Brainard**, "EUV Exposure Mechanisms: Photons, Electrons and Holes"; LEESIS Conference; Amsterdam NL, November 2016.

A. Narasimhan, S. Grzeskowiak, C. Ackerman, L.E. Ocola, G. Denbeaux, **R. L. Brainard**, "What Don't We Know about EUV Reaction Mechanisms?"; Technical Working Group on Photoresists; San Jose, CA, February 2017.

**R. L. Brainard**, "Introduction to Photoresists: Basic principles, photochemistry, polymer chemistry and pattern transfer"; NYS Master Teacher Program; Albany NY, April 13, 2017.

**R. L. Brainard**, "Extreme Ultraviolet Lithography: State of the art photoresists for best resolution"; NYS Master Teacher Program; Albany NY, April 27, 2017.

**R. L. Brainard**, "Bio Roll-Up: Self-assembled hydrogels for tissue engineering"; NYS Master Teacher Program; Albany NY, May 4, 2017.

A. Narasimhan, L. Wisehart, S. Grzeskowiak, L. E. Ocola, G. Denbeaux, **R. L. Brainard**, "What We Don't Know About EUV Exposure Mechanisms", Photopolymer Conference, Chiba Japan, June 2017.

M. Murphy, A. Narasimhan, S. Grzeskowiak, J. Sitterly, P. Schuler, J. Richards, G. Denbeaux, **R. L. Brainard**, "EUV Mechanistic Studies of Antimony Resists", Photopolymer Conference, Chiba Japan, June 2017.

D. Soucie, W. Earley, K. Hosoi, A. Takahashi, T. Aoki, B. Cardineau, K. Miyauchi, **R. L. Brainard**, "Higher-Order Lithography: Double-Deprotected Chemically Amplified Photoresists (DD-CAMP)", Photopolymer Conference, Chiba Japan, June 2017.

#### **Other Public Presentations and Posters\***

J. Hotalen, M. Murphy, D. Freedman, **R. L. Brainard**, "Reactive Development of Positive and Negative Tone Molecular Organometallic Resists for EUV (MORE)", LEESIS Conference; Amsterdam NL, November 2016.

R. Del Re, M. Sortland, J. Passarelli, M. Murphy, J. Hotalen, A. Narasimhan, B. Cardineau, M. Vockenhuber, Y. Ekinci, D.A. Freedman, **R. L. Brainard**, "Super-Low

LER or Super-Fast Metal Based Resists: Molecular Organometallic Resists for EUV (MORE)" LEESIS Conference; Amsterdam NL, November 2016.

W. Earley, D. Soucie, K. Hosoi, A. Takahashi, T. Aoki, B. Cardineau, K. Miyauchi, J. Chun, M. O'Sullivan, **R. L. Brainard**; "Double-deprotected chemically amplified photoresists (DD-CAMP): higher-order lithography"; Proc. SPIE, 9779, Adv. Pat. Mat. Proc., 101460H (2017).

S. Grzeskowiak, A. Narasimhan, M. Murphy, L. Napolitano, D. A. Freedman, **R. L. Brainard**, G. Denbeaux; "Reactivity of metal-oxalate EUV resists as a function of the central metal"; Proc. SPIE, 10146, Adv. Pat. Mat. Proc., 1014605 (2017).

A. Narasimhan, S. Grzeskowiak, C. Ackerman, T. Flynn, G. Denbeaux, **R. L. Brainard**; "Mechanisms of EUV exposure: electrons and holes"; Proc. SPIE, 10143, EUVL, 101430W (2017).

J. Hotalen, M. Murphy, W. Earley, M. Vockenhuber, Y. Ekinci, D. A. Freedman, **R. L. Brainard**; "Advanced development techniques for metal-based EUV resists"; Proc. SPIE, 10143, EUVL, 1014309 (2017).

M. Murphy, A. Narasimhan, S. Grzeskowiak, J. Sitterly, P. Schuler, J. Richards, G. Denbeaux, **R. L. Brainard**; "Antimony photoresists for EUV lithography: mechanistic studies"; Proc. SPIE, 10143, EUVL, 1014307 (2017).

A. Panneerselvam, K. Carufe, L. Sfakis, C. Brisbois, J. Castracane, **R. L. Brainard**, "Bio Roll-Up: Self-Assembled Hydrogel Constructs for 3D Cell Growth", Combined Symposium, University at Albany, March 2017

S. Hasan, V. Brunner, M. Murphy, **R.L. Brainard**, "Bio Roll-Up: Disulfide Release Layer for Initiation of Self Assembly", SUNY Poly Internship Poster Presentation, Albany NY, August 2017.

V. Brunner, S. Hasan, M. Murphy, K. Carufe, **R.L.Brainard**, "Bio Roll-Up: Process Optimization for Release Layer and Bilayer", SUNY Poly Internship Poster Presentation, Albany NY, August 2017.

J. Sitterly, M. Murphy, T. Flynn, S. Grzeskowiak, **R. L. Brainard**, "Synthesis of Novel Organoantimony Carboxylates: Molecular Organometallic Resist for EUV (MORE)", SUNY Poly Internship Poster Presentation, Albany NY, August 2017.

T. Flynn, J. Sitterly, M. Murphy, A. Narasimham, S. Grzeskowiak, **R. L. Brainard**, "Development of EUV Mass Spec Techniques: Mechanistic Studies of Novel Antimony Photoresists", SUNY Poly Internship Poster Presentation, Albany NY, August 2017.

\*Some presentations given by Professor Brainard's students. In all cases, the name of the speaker is underlined.

## Mengbing Huang

### Publications

Subha Chakraborty and Mengbing Huang, "Ionoluminescence properties of polystyrene-hosted fluorophore films induced by helium ions of energy 50--350 keV", accepted for publication in *Physical Review Materials*.

Vance S. Robinson, Magnus Bergkvist, Daokun Chen, Jun Chen and Mengbing Huang, "A Case for ZnO Nanowire Field Emitter Arrays in Advanced X-ray Source Applications", *Proceedings of SPIE (Society of Photo-Optical Instrumentation Engineers)*, 996408-996408-10 (2016).

Subha Chakraborty, Katherine Harris and Mengbing Huang, "Photoluminescence properties of polystyrene-hosted fluorophore thin films", *AIP Advances* 6, 125113 (2016).

Faisal Yaqoob and Mengbing Huang, "Lattice-site-specific diffusion for substitutional and interstitial impurity atoms in ZnO crystals", *Journal of Applied Physics* 120, 115102 (2016).

Faisal Yaqoob and Mengbing Huang, "Effects of high-dose hydrogen implantation on defect formation and dopant diffusion in silver implanted ZnO crystals", *Journal of Applied Physics* 120, 045101 (2016).

Natasha Tabassum, Vasileios Nikas, Brian Ford, Mengbing Huang, Alain E. Kaloyerous and Spyros Gallis, "Time-resolved analysis of the white photoluminescence from chemically synthesized SiCxOy thin films and nanowires", *Applied Physics Letters* 109, 043104 (2016).

## Vince LaBella

### Publications

Avyaya J. Narasimham, Farheen N Sayed, Praneet Adusumilli, Steve Novak, Vincent P. LaBella, Weak dependence of phase fraction and dopant concentration in  $\beta$ ,  $\alpha$  phase mixture of W, [arXiv:1708.06033v1 \[cond-mat.mtrl-sci\]](https://arxiv.org/abs/1708.06033v1) (2017)

Westly Nolting, Chris Durcan, Vincent P. LaBella, *Detection of Silicide Formation in Nanoscale Visualization of Interface Electrostatics*, **Applied Physics Letters**, **110**, 141606, (2017).

Avyaya J. Narasimham, Daniel Pennock, Graham J. Potter, Brian Taylor, Vincent P. LaBella, *Economical rotatable holder for magneto-transport measurements*, **Journal of Vacuum Science and Technology B**, **35**, 023201, (2017).

## **Presentations**

BEEMfit: Ballistic Electron Emission Microscopy Spectra Fitting for Schottky Barrier Visualization, Vincent LaBella and Westly Nolting, American Physical Society March Meeting, New Orleans, LA, March, 2017.

Signatures of Silicide Formation in Measurements of Nanoscale Interface Electrostatics with BEEM, Westly Nolting, Chris Durcan and Vincent LaBella, American Physical Society March Meeting, New Orleans, LA, March, 2017.

Switching symmetry of in-plane current induced spin orbit effects in beta-W/Ta/CoFeB/MgO/Ta multilayers, Avyayajayanthi Narasimham, Meng Zhu, and Vincent LaBella, American Physical Society March Meeting, New Orleans, LA, March, 2017.

## **Carl A. Ventrice, Jr.**

### **Journal Publications**

Growth and Characterization of Al<sub>2</sub>O<sub>3</sub> Films on Fluorine Functionalized Epitaxial Graphene, Z. R. Robinson, G. G. Jernigan, V. D. Wheeler, S. C. Hernández, C. R. Eddy, Jr., T. R. Mowll, E. W. Ong, C. A. Ventrice, Jr., H. Geisler, I. Pletikosic, H. Yang, and T. Valla, Journal of Applied Physics, Vol. 120, MS #075302 (2016).

### Conference Presentations:

Role of Oxygen on the Nucleation and Growth Kinetics of Graphene on Cu Substrates, Z. R. Robinson, E. W. Ong, T. R. Mowll, and C. A. Ventrice, Jr., 2017 Conference on Emerging Technologies: Communications, Microsystems, Optoelectronics, and Sensors, Warsaw, Poland, May 30, 2017.

Cu Single Crystal Substrates for Growth of CVD Graphene, T. R. Mowll, Z. R. Robinson, and C. A. Ventrice, Jr., 2017 March Meeting of the American Physical Society, New Orleans, Louisiana, March 15, 2017.

Growth of Graphene on Cu Single Crystal Substrates, T. R. Mowll, Z. R. Robinson, and C. A. Ventrice, Jr., 63rd International Symposium of the American Vacuum Society, Nashville, Tennessee, November 9, 2016.

Role of the Strong Metal Support Interaction on the Catalytic Activity of Platinum Deposited on TiO<sub>2</sub> Supports, R. P. Hansen, R. S. Phillips, E. T. Eisenbraun, and C.A. Ventrice, Jr., 63rd International Symposium of the American Vacuum Society, Nashville, Tennessee, November 8, 2016.

Growth of Graphene on Cu Single Crystal Substrates, T. R. Mowll, Z. R. Robinson, and C. A. Ventrice, Jr., 2016 Fall Meeting of the Hudson Mohawk Chapter of the American Vacuum Society, Troy, New York, October 24, 2016.

### **Invited Talks**

Synthesis of Device-Quality Graphene Films, Department of Physics, Union College, Schenectady, New York, March 9, 2017.

Synthesis of Device-Quality Graphene Films, Department of Chemistry, University of North Texas, Denton, Texas, February 25, 2017.

Role of the Strong Metal Support Interaction on the Activity of Pt Fuel Cell Catalysts Supported on TiO<sub>2</sub>, Department of Physics, The College at Brockport-SUNY, Brockport, New York, October 7, 2016.