ACS chemical biology

Introducing Our Authors

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Image courtesy of Steve Bremmer.

KRISTOFFER R. BRANDVOLD

Education: Minnesota State University Moorhead, B.A. Chemistry and B.A. Biology, 2008; University of Michigan, Ph.D. Candidate in Medicinal Chemistry, Research Advisor: Matthew B. Soellner

Nonscientific interests: Major League Baseball, music, fishing

My graduate research is focused on developing small-molecule inhibitors with unique selectivity profiles for the investigation of protein kinase activity in whole cells. As described in our manuscript, we have recently created a highly selective inhibitor of c-Src kinase, which we propose interacts with a nonconserved structural feature. Using this probe, we have shown that selective inhibition is more effective than multikinase inhibition in the treatment of several cancer cell lines. Furthermore, we specifically demonstrate that inhibition of a common off target of c-Src inhibitors, c-Abl, significantly decreases the efficacy of c-Src inhibitors in the treatment of breast cancer cells. I am excited that our probe provides a means to study c-Src biology in manner that was not previously possible. Hopefully use of this probe will increase our understanding of basic cell biology and also aid in the design of therapeutically useful small-molecules. (Read Brandvold's article, DOI: 10.1021/cb300172e)

Image courtesy of Josie Giles.

JULIE CHAMPION

Current position: Assistant Professor, Chemical & Biomolecular Engineering, Georgia Institute of Technology

Education: University of Michigan, BSE in Chemical Engineering, 2001; University of California, Santa Barbara, Ph.D. in Chemical Engineering, 2007, Advisor: Samir Mitragotri; California Institute of Technology, NIH Postdoctoral Fellow 2007–2009, Advisor: David Tirrell

Nonscientific interests: Cooking, wine, traveling

My lab is interested in building therapeutic materials – materials made directly from biologically active proteins. Proteins are unique, compared to polymers or small molecules, in that they have the potential for not just biological activity but to form a variety of different materials. We engineer potentially therapeutic proteins to endow them with additional polypeptide domains that provide the physical and chemical properties needed to form self-assembled or covalently assembled structures such as particles, fibers, films, or gels. We work with complex proteins such as proteases and growth factors from humans, bacteria, and viruses. The goal is that these materials elicit desired effects in diseased or damaged tissue based on direct contact with cells or native proteins. We are investigating proteins and subsequent therapeutic materials for applications in cancer, wound healing, autoimmunity, and vaccination. (Read Champions' article, DOI: 10.1021/cb300238w)

Image courtesy of Liane Ware.

ALLISON DOAK

Current position: University of California, San Francisco, Dept. of Pharmaceutical Chemistry, Staff Research Associate III in Dr. Brian Shoichet's Lab since November 2008

Education: University of Wisconsin-Madison, B.S. in Biochemistry and French, Undergraduate Researcher in Dept. of Biochemistry, Advisor: Dr. Sebastian Bednarek

Nonscientific interests: Soccer, yoga, archery, enjoying San Francisco!

After studying small molecule aggregation for the past few years, I have come to appreciate how important this phenomenon is to drug discovery and development. After embarking on this journey into the unknown, my predecessors on the "Aggregation Project" made significant headway in alerting the world to the high percentage of false positive hits in HTS attributable to promiscuous inhibition caused by colloidal aggregation. I have now taken over the exploration and am heading into the realm of colloidal aggregation by drugs in biological systems (simulated gastric fluids, cell culture, serum). We will continue this quest *in vivo*, identifying drug colloids in the body, manipulating or exploiting their colloidal properties to develop more efficacious drugs. It will certainly be an adventure. (Read Doak's article, DOI: 10.1021/cb300189b)

Published: August 17, 2012


Image courtesy of Bernadette M. Henares.

BERNADETTE M. HENARES

Education: University of the Philippines Los Baños, Philippines, B.S in Agricultural Chemistry, 1998 with Dr. Ernesto del Rosario; Ateneo de Manila University, Philippines, M.S. in Chemistry, 2007, with Dr. Nina Rojas; Stony Brook University, Ph.D. candidate, Advisor: Prof. Elizabeth Boon

Nonscientific interests: Cooking, movies, reading, traveling

My Ph.D. research is focused on nitric oxide (NO) signaling in bacteria. NO, a well- known signaling molecule in mammals, binds to a soluble guanylate cyclase (sGC) homologue in bacteria known as heme-nitric oxide/oxygen binding protein (H-NOX). NO bound H-NOX regulates the activity of its binding partner histidine kinase (HqsK, H-NOX associated quorum sensing kinase) which leads to a signaling cascade that contributes to increased bioluminescence in *Vibrio harveyi*. We were excited to discover that NO functions like the characterized quorum sensing signal molecules, also known as autoinducers, and participates in community-wide cellular processes. This new pathway, which we speculate is needed by bacteria to assess the environment, also opens the possibility of an interkingdom signaling. (Read Henares' article, DOI: 10.1021/cb300215t)


Image courtesy of Yohkheved Ihejirika.

ARMANDO R. HERNÁNDEZ

Current position: Ph.D. student at Stanford University in the Department of Chemistry; Advisor: Prof. Eric. T. Kool.

Education: University of California, Santa Cruz, B.S. Chemistry/Biochemistry, 2005; Ventura College, A.A. General Liberal Arts, 2002.

Nonscientific interests: Running, cycling, hiking, baseball, weightlifting, bojutsu, traveling, cooking, and spending time with family.

My Ph.D. thesis project revolves around the synthesis and use of size-expanded ribonucleic acid (xRNA) analogues for biophysical and biological applications. xRNAs are expanded linearly by 2.4 Å, retain the canonical Watson−Crick base pairing groups found in native RNAs, and possess interesting fluorescent properties. Recently, we utilized xRNAs as a novel component in siRNAs to investigate the steric restrictions that exist in the RNA-induced silencing complex (RISC), the protein complex at the center of the RNA interference mechanism. From this work, we were able to identify key sites within RISC that are able to tolerate size-expanded RNAs, which we hope will promote further investigations into these sites. Furthermore, we described other biophysical and biological properties of xRNA-substituted siRNAs that should be of great interest to the siRNA research community. Aside from xRNAs, my other scientific interests line in ribozymes and noncoding RNAs. (Read Hernández' article, DOI: 10.1021/cb300174c)


Image courtesy of Kate Higgins.

KATE HIGGINS

Current position: Stony Brook University, Department of Chemistry and Institute for Chemical Biology and Drug Discovery, Graduate Student with Prof. Elizabeth M. Boon

Education: Rochester Institute of Technology, B.S. Chemistry, 2008; Rochester Institute of Technology, M.S. Chemistry, 2010

Nonscientific interests: Cooking, music, reading

My current research focuses on the role of H-NOX (heme nitric oxide/oxygen binding domain) proteins in quorum sensing (QS), a bacterial signal transduction system used to regulate gene expression changes in response to the local cell population. In the bioluminescent, marine bacterium *Vibrio harveyi*, QS takes the form of three parallel phosphorelay cascades that converge on a common protein, LuxU. In the present article we describe how nitric oxide (NO) and H-NOX integrate into the established QS circuit of *V. harveyi* by regulating the activity of a histidine kinase, HqsK, which we show transfers phosphate to LuxU. (Read Higgins' article, DOI: 10.1021/cb300215t)


Image courtesy of Petra Parizek.

PETRA PARIZEK

Current position: Ph.D. student in the laboratory of Prof. Andreas Plückthun at the University of Zurich, Department of Biochemistry, Switzerland.

Education: University of Zurich, Diploma in Molecular Biology, 1999; University of Zurich, Diploma for Gymnasium-level Science Teaching, 2001.

Nonscientific interests: Mountain sports, diving, traveling ,and different cultures.

My current research interests include both engineered binding proteins, in particular Designed Ankyrin Repeat Proteins (DARPins), as well as various selection technologies to generate specific binders with desired functions. I was involved in projects that focused on the development of DARPins as phosphorylation-specific kinase binders, as adapters for adenoviral gene targeting and as potential therapeutics for Alzheimer's disease. In my Ph.D. research I focused on intracellular applications of DARPins by generating inhibitors that can interfere with prokaryotic and eukaryotic kinase function, respectively, within cells. In this work, we report the selection of specific DARPins that can discriminate between two very similar isoforms of the c-Jun N-terminal kinase and, furthermore, selectively inhibit the activation of this kinase *in vitro* and in human cells. (Rea Parizek's article, DOI: 10.1021/cb3001167)

Image courtesy of Pierre Wickramarachi.

WILLIAM POMERANTZ

Current position: Assistant Professor at the University of Minnesota, Department of Chemistry, Minneapolis, Minnesota.

Education: Ithaca College, B.S. Chemistry; ETH, Zürich, Switzerland, Fulbright Fellow with François Diederich; University of Wisconsin-Madison, Ph.D. in Chemistry with Prof. Sam Gellman and Prof. Nicholas Abbott; University of Michigan, NIH Postdoctoral Research Fellow, Chemical Biology, with Prof. Anna Mapp

Nonscientific interests: Coffee roasting, letterboxing, and running

While in graduate school, I enjoyed reading the physical organic perspective by Dunitz, *Organic Fluorine: Odd Man Out*, that highlighted peculiarities of organofluorine regarding noncovalent interactions including its inability to form strong hydrogen bonds. Conversely, my research interests in chemical biology and a growing community of scientists treat fluorine as the *odd man in* due to mounting interest in the physicochemical and spectroscopic properties of fluorine for probing biological interactions. In this manuscript, we use ^{19}F NMR to dissect binding interfaces and allosteric effects of transcription complexes via monitoring resonance perturbations of fluorine nuclei at protein−protein interaction hotspots and exploit fluorine's environmental sensitivity to discover small molecules ligands for the coactivator CBP. As the *new man in* at the University of Minnesota, I will use fluorine as a structural probe for ligand discovery and protein engineering. (Read Pomerantz' article, DOI: 10.1021/cb3002733)

REBECCA SCHECK

Education: Yale University, Department of Chemistry, Postdoctoral Fellow with Prof. Alanna Schepartz; University of California, Berkeley , Ph.D. in Organic Chemistry, 2008 with Prof. Matt Francis; Columbia University, B.A. Chemistry, 2004, with Prof. Colin Nuckolls

Image courtesy of Rebecca Scheck.

Nonscientific interests: Spending time with friends and family, cooking, swimming.

My research interests include the development and implementation of chemical methods to study dynamic changes in protein function that occur upon structural rearrangement. One of the challenges in this area is to develop encodable protein labeling chemistries that do not rely solely on primary sequence and can therefore be used to monitor such inducible changes directly. In this work, we use a novel chemical tool called bipartite tetracysteine display, which enables us to discover that discrete, intracellular, interhelical interactions are formed depending on the identity of extracellular ligand that is used to activate the epidermal growth factor receptor. This research highlights what I believe are two exciting and interesting topics in chemical biology: the first is the ability to detect seemingly subtle structural changes with high spatial resolution in the dynamic environment of the cell; the second is the implication that such small structural changes may lead to large differences in the resulting signaling. (Read Scheck's article, DOI: 10.1021/cb300216f)

Image courtesy of Matthew A. Smith.

MATTHEW A. SMITH

Current position: I am attending the George Mason University School of Law to become a scientific patent attorney.

Education: Virginia Tech, B.S. in Biochemistry and Chemistry, 2007; Medical University of South Carolina, Ph.D. in Pharmaceutical and Biomedical Sciences with Dr. Rick Schnellmann, 2012.

Nonscientific interests: Reading, music, cooking and watching college football

For my Ph.D. research I studied calpain 10, which is a ubiquitously expressed Ca^{2+}-activated cysteine protease. My research elucidated the degradation pathway of both cytosolic and mitochondrial calpain 10, determined that loss of calpain 10 *in vivo* causes mitochondrial dysfunction, optimized a calpain 10 specific inhibitor to be efficacious in cells and revealed that

treatment of this inhibitor on renal proximal tubular cells induces mitochondrial dysfunction, autophagy, and apoptosis. Our paper in *ACS Chemical Biology* is important because it details the optimization and characterization of a calpain 10 specific inhibitor that is efficacious in cells. Hopefully, future use of this inhibitor will help unravel more information about how calpain 10 affects type 2 diabetes, renal aging, and acute kidney injury. (Read Smith's article, DOI: 10.1021/cb300219h)

Image courtesy of Xi Chen.

MENGMENG ZHANG

Current position: University of Texas at Austin, Department of Chemistry and Biochemistry, Ph.D. candidate with Prof. Yan Jessie Zhang

Education: Shanghai Jiao Tong University, B.E. in Bioengineering, 2006; Clemson University, M.S. in Biological Sciences, 2008.

Nonscientific interests: Traveling, movies, music, swimming

My research focused on the function of CTD phosphatases in the regulation of the CTD. Using Scp1 as a model, I have studied the enzymatic mechanism of Scp1, identified a small molecule inhibitor for Scp1, and have been investigating the underlying mechanism of how it reads and changes the "CTD code". In this study, we provided structural snapshots and kinetic evidence that support the concept of cross-talk between prolyl isomerization and phosphorylation of the CTD by using a model system of Scp1, Ssu72, and Pin1. We also presented here the complex structures of Pin1 bound with cis and trans peptidomimetic inhibitors, demonstrating the utility of both cis- and trans-locked alkene isosteres as close geometric mimics of peptides bound to a protein target. (Read Zhang's article, DOI: 10.1021/cb3000887)