ACS chemical biology

Introducing Our Authors

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Image courtesy of Myles Dillon.

MYLES DILLON

Current position: Ph.D. Candidate in the Chemical Physiology Department at The Scripps Research Institute in La Jolla, CA; Advisor: Kerri Mowen

Education: B.S. Animal Physiology and Neuroscience from University of California, San Diego

Nonscientific interests: Cycling, bread baking, playing with my dogs, and rooting for my wife playing roller derby!

My graduate research focuses on the molecular mechanisms of regulation for protein arginine methyltransferases (PRMTs) and their cellular functions. Many biological processes are regulated by PRMTs, including transcription, DNA repair, RNA processing, and signal transduction. PRMT1 is the predominant arginine methyltransferase, accounting for >85% of cellular PRMT activity. Aberrant PRMT1 activity has been associated with cardiovascular, malignant, infectious, and autoimmune disease, making it a viable therapeutic target for several indications. Thus, modulating the activity of PRMT1 may provide therapeutic treatments for many diseases. (Read Dillon's article, DOI: 10.1021/cb300024c)

Image courtesy of David Ferrero.

DAVID FERRERO

Current position: Harvard Medical School, Dr. Stephen Liberles, Neuroscience Ph.D. Candidate

Education: Ecole Polytechnique Federale de Lausanne (EPFL) and Eidgenössische Technische Hochschule Zürich (ETHZ), Dr. Richard Hahnloser, Physics MS

Nonscientific interests: Music, arts, traveling, tennis, winter sports

Mammals release and detect a great variety of natural products such as pheromones that influence physiology and behavior through activation of the olfactory system. However little is known about the ligands, receptors and circuits underlying innate odor-driven behaviors. In my Ph.D. work, I address this problem by concentrating on a particular family of olfactory receptors termed Trace Amine-Associated Receptors (TAARs). TAARs are found in diverse vertebrates, including human and mouse, and the properties of some suggest a role in detecting social cues and influencing instinctive behaviors such as aversion or attraction. Here we report new ligands for several TAARs and provide insight into the structural basis of odorant recognition. Characterizing the chemoreceptive properties of TAARs constitutes an essential step toward understanding their physiological functions. (Read Ferrero's article, DOI: 10.1021/cb300111e)

Image courtesy of Susanne Stark.

STEFANIE FRITSCHE

Current position: Ph.D. student in group of Professor Gottfried Alber at the Institute of Immunology, College of Veterinary Medicine, University of Leipzig, Germany; presently completing Ph.D. thesis in immunology

Education: Studies of Biology (2003−2008) at University of Leipzig, Germany; Diploma in Biology, 2008; advisor: Prof. Dr. Sunna Hauschildt (Department of Immunobiology, Leipzig).

Nonscientific interests: Traveling, astronomy, concerts, swimming and English literature

My Ph.D. research focuses on antimicrobial and immunomodulatory effects displayed by optimized short proline-rich antimicrobial peptides. The peptides exhibit strong antibacterial and antifungal activities *in vitro*. Moreover, even at high concentrations, the peptides have no toxic effects *in vivo* and *in vitro*, while already low doses of the optimized peptides are sufficient to efficiently protect mice in a septicaemia model using pathogenic *Escherichia coli*. Moreover, the peptides do not exhibit stimulatory or modulatory activities on key innate immune cells such as dendritic cells or macrophages. This will simplify further pharmaceutical investigation and development of insect peptides as therapeutic compounds against bacterial infections. I will complete my Ph.D. thesis by the end of 2012 and plan to continue my career in industry. (Read Fritsche's article, DOI: 10.1021/cb300063v)

JEANE GOVAN

Current position: Ph. D. candidate in Chemistry at North Carolina State University under the direction of Prof. Alexander Deiters.

Published: July 20, 2012

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Image courtesy of Jie Zhang.

Education: B.A. in Chemistry and Biology at Kalamazoo College, Kalamazoo, Michigan; Advisor: Prof. Laura Lowe Furge.

Nonscientific interests: Scuba diving, beach activities, baking, reading, and gardening.

My research encompasses the development of tools for the photochemical regulation of gene expression. Cellular processes, particularly gene function, are naturally organized with high spatial and temporal resolution. In order to investigate and to re-engineer these processes, external control with the same level of spatiotemporal regulation found in nature needs to be achieved. Toward this goal, we use light to regulate gene expression, as light irradiation is easily controlled in timing, location, and amplitude, thus enabling the precise activation and inactivation of biological function. In this study, we have applied this concept to the light regulation of triplex-forming oligonucleotides in order to light-activate and -deactivate transcription in mammalian cells. (Read Govan's article, DOI: 10.1021/cb300161r)

Image courtesy of Sung-Wook Jang.

SUNG-WOOK JANG

Current position: Postdoctoral fellow with Dr. James Inglese at the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH)

Education: Yonsei University, Republic of Korea, B.S. in Biochemistry; University of Wisconsin-Madison, Ph.D. in Cellular and Molecular Biology

Nonscientific interests: Traveling, swimming, and hiking

My research interest revolves around the strategic use of technology in assay development as part of the translational science focused on rare genetic diseases. These disorders are often neglected due to mechanistic complexity and a limited market hindering pharmaceutical company investments. Over the past years, I have been involved in a drug development program for inherited peripheral neuropathy called Charcot-Marie-Tooth (CMT) diseases at NIH in close partnership with a patient advocate group known as CMT association (CMTA). The paper presents an assay development and drug repurposing strategy for CMT as well as our approach to address fundamental issues in the use of sensitive reporters frequently blighted by their artifactual outcomes. In my future research, I hope to continue to utilize tools of chemical biology to explore therapeutic avenues for a broad spectrum of disorders. (Read Jang's article, DOI: 10.1021/cb300048d)

Image courtesy of Katie O'Connor-Jenkins.

RONALD JENKINS

Current position: Graduate student in the laboratory of Prof. Garry D. Dotson at the University of Michigan, Department of Medicinal Chemistry.

Education: B.S. in Biochemistry at Temple University, 2008; Research Advisor: Dr. Jonathan G. Shackman.

Nonscientific interests: Baseball, soccer, and spending time with family and friends.

My graduate research has focused on the development of chemical and biological tools for the identification of antimicrobial probes targeting lipid A biosynthesis. Lipid A forms the hydrophobic anchor of the outer cell membrane and is exclusive to Gram-negative bacteria. In this study we have identified antimicrobial peptides which inhibit the LpxD acyltransferase and have provided proof of principle that dual targeting inhibitors can be identified against the two essential acyltransferases within the pathway. Furthermore, the peptides were used as surrogate ligands to develop a binding assay which will be instrumental in the screening of chemical libraries for the identification of small molecule inhibitors of these acyltransferases. Read Jenkins' article, DOI: 10.1021/cb300094a)

Image courtesy of Kam Lau.

KAM LU

Current position: Griffith University Gold Coast, Institute of Glycomics, Postdoctoral Researcher with Prof. Mark von Itzstein

Education: Brigham Young University, B.S. in Biochemistry, 2006; University of California, Davis, Ph.D. in Chemistry with Prof. Xi Chen, 2012.

Nonscientific interests: Music, reading, hiking, and fishing.

My Ph.D. research focused on developing one-pot multienzyme chemoenzymatic synthesis of complex naturally occurring and non-natural carbohydrates such as galactosides, fucosides, sialyl T antigens, sialyl Lewis^x antigens, Lyso-GM3, and their derivatives. Chemical synthesis of carbohydrates requires multiple protection, deprotection, and purification steps

which are complicated and time-consuming and often lead to low yields. Glycosyltransferases (GTs), on the other hand, are powerful tools for synthesizing natural and unnatural oligosaccharides and glycoconjugates. They catalyze the formation of glycosidic linkages by transfer protected monosaccharides from sugar nucleotides onto acceptors without tedious protection and deprotection processes. One-pot multienzyme processes are highly efficient in obtaining diverse carbohydrate-containing structures. As a postdoctoral researcher in Prof. Mark von Itzstein's group, I continue to explore my interest in one-pot multienzyme chemoenzymatic synthetic approaches and apply it in designing and developing carbohydrate-based drugs against malaria. (Read Lau's article, DOI: 10.1021/cb300125k)

Image courtesy of Graziano Lolli.

GRAZIANO LOLLI

Current position: Postdoctoral Fellow at Dept. of Chemical Sciences − University of Padua and Venetian Institute of Molecular Medicine, Padua, Italy.

Education: Degree in Chemistry, University of Naples "Federico II", Italy, 2000; Research Fellow, Pharmacia Corp., Nerviano, Italy, 2000−2002; Ph.D. in Biochemistry, Laboratory of Molecular Biophysics, University of Oxford, UK, supervisor Prof. Dame Louise Johnson, 2005; Postdoctoral Fellow, Laboratory of Molecular Biophysics, University of Oxford, UK, 2006; FEBS (Federation of the European Biochemical Societies) Long-Term Fellowship, IRBM − Merck, Pomezia, Italy 2006−2008 and Venetian Institute of Molecular Medicine, Padua, Italy 2008−2009.

Nonscientific interests: Photography, traveling, and gardening.

Since 2000, I have been working mainly on protein kinases, first with proteomics approaches and then as a crystallographer, with brief excursions from the "kinase world" to other classes of proteins. Having moved a couple of times from company to academia, my work oscillated between basic and applied research. My work is currently focused on CK2. We solved the structure of the tetrameric holoenzyme updating some features that were previously poor defined. We showed that the holoenzyme can self-assemble in trimers of tetramers and subsequently in filaments postulating an autoinhibitory model for CK2 regulation, which is in accordance with a plethora of biochemical and biophysical data available in literature. (Read Lolli's article, DOI: 10.1021/cb300054n)

MATEO I. SÁNCHEZ LÓPEZ

Current position: Ph.D. student at the University of Santiago de Compostela (Spain) under the supervision of Dr. José Luis Mascareñas and Eugenio Vázquez Sentís.

Education: Universidad de Santiago de Compostela, B.S. in Chemistry, 2008

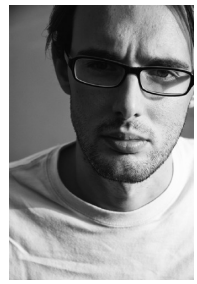

Image courtesy of Mateo I. Sánchez López.

Nonscientific interests: Spending time with my friends and family, fishing, playing football, athletics, music, walking on the beach, going out, drinking mojitos, and cooking tiramisu.

My research is focused on the design and synthesis of new fluorescent molecules that are able to recognize specific sequences of DNA. This strategy, therefore, provides a simple means for triggering site selective, DNA-promoted biochemical and physicochemical processes. These days I am working on caged small molecules that bind DNA in a spatiotemporal regulated process and its *in vitro* and *in vivo* applications. On the other hand I am developing synthetic strategies to attach different metals to these DNA binding molecules and I am also interested in organometallic chemistry in living systems. (Read Sánchez's article, DOI: 10.1021/cb300100r)

Image courtesy of Mark F. Mabanglo.

MARK F. MABANGLO

Current position: Duke University, Department of Biochemistry, Postdoctoral fellow in the laboratory of Prof. Lorena S. Beese

Education: Ateneo de Manila University (Philippines), B.S. in Chemistry, 2002 and undergraduate research with Prof. Nina Rosario L. Rojas; University of Utah, Ph.D. in Chemistry, 2012 with Prof. C. Dale Poulter

Nonscientific interests: Paleontology (especially the K-T mass extinction event), news and current events, creative writing

My graduate work at the University of Utah focused on the enzyme isopentenyl phosphate kinase (IP kinase). This enzyme is important in the Archaeal mevalonate pathway for the biosynthesis of isopentenyl diphosphate from which all of their isoprenoid molecules are obtained. I solved the crystal structure of IP kinase from *Thermoplasma acidophilum* and *Methanothermobacter thermautrophicus*, which are characterized by a fold similar to other enzymes in the amino acid kinase superfamily. The structures then allowed us to identify active site residues that could be mutated to allow the binding and phosphorylation of longer chain isoprenoid monophosphates. In this article, we present mutants of IP kinase that can phosphorylate geranyl phosphate (GP), and to a lesser extent, farnesyl phosphate (FP). These mutants can be exploited for the chemoenzymatic synthesis of GPP, FPP and other isoprenoid diphosphates labeled with ^{32}P at the β-position.

After my graduate work at the University of Utah, I transferred to Duke University as a postdoctoral fellow in Prof. Lorena Beese's structural biology laboratory to study fungal prenyltransferases. Our goal is to take advantage of structural differences between human and fungal prenyltransferases for the development of antifungal drugs. I am also involved in discovering regulatory roles of prenyltransferases in the cell, especially in complex with other proteins. I enjoy solving crystal structures because of the wealth of information that they contain, including the ability to present targets for drug inhibition to treat human diseases. (Read Mabanglo's article, DOI: 10.1021/cb300106e)

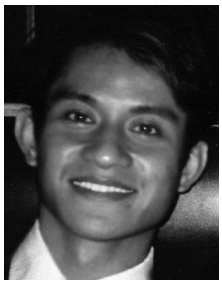

Image courtesy of Edward Motea.

EDWARD A. MOTEA

Current position: University of Texas Southwestern Medical Center at Dallas, Simmons Comprehensive Cancer Center, Postdoctoral Scholar with Prof. David Boothman.

Education: Gannon University, B.S. in Chemistry, magna cum laude, 2006. Case Western Reserve University, Ph.D. in Chemistry (Cancer Pharmacology Training Program) under the mentorship of Dr. Anthony Berdis and Dr. Irene Lee, 2012.

Nonscientific interests: Painting, music, movies, traveling, dancing, trekking and meditation.

During the course of my graduate work, I have become very interested in the mechanism of drug resistance and/or carcinogesis induced by endogenous and exogenous DNA-damaging agents. In fact, my doctoral work was focused on understanding the chemistry and enzymology of translesion DNA synthesis (TLS), or the replication of damaged DNA (particularly noninstructional or nontemplated DNA lesions), using rationally designed non-natural nucleotides as biochemical probes. In this work, we describe the development of a novel chemical agent with combined therapeutic and diagnostic (theranostic) potentials – an innovative strategy for improving the treatment of cancer patients. This theranostic agent selectively targets acute lymphoblastic leukemia (ALL) cells that overexpress terminal deoxynucleotidyl transferase (TdT), a unique DNA polymerase which serves as a biomarker and is found in the majority of patients with ALL. (Read Motea's article, DOI: 10.1021/cb300038f)

ANGELA PARRISH

Current position: Research Fellow in Kathryn Anderson's lab at Memorial Sloan-Kettering Cancer Center.

Education: Cornell University, B.S. in Biology, 2003; University of California, San Diego, Ph.D. in Biology, 2011; advisor: Lei Wang at the Salk Institute

Nonscientific interests: Cooking, cocktails, yoga

My graduate work at the Salk Institute focused on the development of a new research tool in the model organism *C. elegans*. The introduction of modified tRNA and aminoacyl-tRNA

Image courtesy of Adam Paré.

synthetases derived from *E. coli* supports the incorporation of structurally divergent, or unnatural, amino acids into proteins during translation. Applying this technology to multicellular organisms could enable its use to study the role of specific residues in proteins during cell–cell interactions. While incorporating two different unnatural amino acids into the coding region of three different proteins, I uncovered factors affecting the efficiency of incorporation, including the structure of the delivered unnatural amino acid and the number of generations that the animals were exposed to the amino acid, among other factors. (Read Parrish's article, DOI: 10.1021/cb200542j)

Image courtesy of Julie Pollock.

JULIE POLLOCK

Current position: University of Illinois at Urbana–Champaign, Department of Chemistry, Postdoctoral Researcher with Prof. John Katzenellenbogen

Education: Hope College, B.S. in Chemistry, 2006; Duke University, Ph.D. in Chemistry with Prof. Dewey McCafferty, 2011.

Nonscientific interests: Cooking, reading, golf, and watching college basketball

My graduate work at Duke University focused on understanding the role of the histone demethylase, LSD1, in breast cancer. By the use of synthetic irreversible inhibitors and small interfering RNA, we were able to determine that the enzymatic activity of LSD1 is necessary for proliferation of both estrogen receptor positive and negative breast cancer cells. Additionally, LSD1 was found to be recruited to gene promoters alongside estrogen receptor in order to assist in transcription. In 2012, I moved to UIUC and have continued to focus on using small molecule probes to evaluate the function of nuclear receptors in disease states. (Read Pollock's article, DOI: 10.1021/cb300108c)

STÉPHANIE RAVAUD

Current position: Assistant Professor, University of Grenoble, department of Chemistry and Biology, Institute for Structural Biology, since 2009. Research advisor: Prof. Eva Pebay-Peyroula

Education: B. S. in Physics and Chemistry, University of Lyon, France, 2000; Master in Structural Biology, University of Grenoble, France, 2002; PhD in Biochemistry and Structural


Image courtesy of Stéphanie Ravaud.

Biology with Dr. R. Haser, University of Lyon, France, 2005; Postdoctoral fellow with Prof. I. Sinning, University of Heidelberg, Germany, 2006–2008; Postdoctoral fellow with Prof. E. Pebay-Peyroula, CEA Grenoble, France, 2008–2009.

Nonscientific interests: Music, reading, movies, cooking and traveling

My research is focused on functional and structural studies of membrane proteins. My interest arose from my Ph.D. project on the multidrug membrane transporter BmrA from *Bacillus subtilis*. During my postdoctoral work at the University of Heidelberg I then studied the YidC family, which is an essential component of the membrane proteins translocation machinery. Since 2009, I have been working at the Institute for Structural Biology in Grenoble. A major part of my research is dedicated to structure–function studies of mitochondrial carriers and in particular of the ADP/ATP carrier (AAC), a prominent actor in the energetic regulation of the cell. We aimed at deciphering the transport mechanism and properties of this protein combining structural studies by X-ray crystallography and functional characterizations. In this paper we have carried out a synergistic experiment-theory study in collaboration with the group of Dr. C. Chipot (University of Nancy) to decipher the molecular mechanisms underlying genetic diseases ascribed to mutations of AAC. Combining functional assays and molecular-dynamics simulations, we studied the impact of all identified pathological mutations and more importantly to bridge the pathologies and their molecular origins. (Read Ravaud's article, DOI: 10.1021/cb300012j)


Image courtesy of Malgorzata Sierant.

MALGORZATA SIERANT

Current position: Ph.D. fellow at Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Bioorganic Chemistry, Lodz, Poland.

Education: M.Sc. in Chemistry, Technical University of Lodz, the Faculty of Biotechnology and Food Science, Lodz, Poland, 1989; Ph.D. in Chemistry with Prof. A. Okruszek, Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Lodz, Poland, 2004; Postdoctoral fellowship with Prof. K. Taira, Gene Function Research Center, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Japan, 2004–2006.

Nonscientific interests: Classic literature and music, movies, traveling, cooking and gardening.

My current research is focused on the identification of the substrate specificity of proteins involved in the RNA interference (RNAi) pathway by elucidation their interactions with natural and chemically modified nucleic acids. Additionally, I am interested in the exploration of RNAi for specific modulation of expression of genes involved in Alzheimer's disease, like β-Secretase, mutated forms of Presenilins or Cyclin Dependent Kinases 4/6, which are responsible for the earliest causes of neurodegeneration. In our article we present a new class of modified siRNAs containing phosphorodithioate substitutions. PS2-siRNAs exhibit an A-form helical structure and biological activity dependent on the site of modification. Incorporation of PS2 substitutions into siRNA duplexes increases their lipophilicity and stability in serum. Our results offer preliminary evidence of the potential value of PS2-modified siRNAs. (Read Sierant's article, DOI: 10.1021/cb300078e)


Image courtesy of Go Sugiarto.

GO SUGIARTO

Current position: University of California – Berkeley, Department of Bioengineering, Postdoctoral Fellow with Prof. J. Christopher Anderson.

Education: Universitas Airlangga, Surabaya, Indonesia, B.S. in Chemistry, 1996; University of California–Davis, Ph.D. in Chemistry with Prof. Xi Chen, 2011.

Nonscientific interests: Reading, music, piano, guitar, badminton.

My graduate work focused on obtaining sialyltransferases that can efficiently sialylate Lewis^x to produce sialyl Lewis^x antigen and analogues containing different sialic acid forms and derivatives. These enzymes are essential for developing highly effective chemoenzymatic approaches to synthesize sialyl Lewis^x containing diverse forms of sialic acid for elucidating their biological roles. Sialyl Lewis^x is involved in inflammation and known as a tumor-associated carbohydrate antigen. I was able to clone, express, and characterize a viral sialyltransferase (vST3Gal I), which showed activity toward Lewis^x although with a low expression level in *E. coli*. Based on the protein crystal structure, I successfully engineered a multifunctional bacterial sialyltransferase PmST1 from *Pasteurella multocida* to increase its sialylation efficiency toward Lewis^x. In addition, PmST1 mutants with decreased sialidase activity were also generated via the same approach. As a Postdoctoral Fellow, my research goal is to develop a high-throughput enzyme screening platform to identify active enzymes and their substrate specificity. (Read Sugiarto's article, DOI: 10.1021/cb300125k)

BENJAMIN WEGER

Current position: Ph.D. candidate at the Heidelberg University under the supervision of Dr. Thomas Dickmeis, Institute of

Image courtesy of Meltem Weger.

Technology and Genetics, Karlsruhe Institute of Technology, Germany.

Education: Heidelberg University, Diploma (equivalent to M.S.) in Biology, 2009.

Nonscientific interests: sports, hiking, traveling

During my Ph.D. project I developed an interest in one of the smallest vertebrate model systems: zebrafish larvae and their applications in high-throughput drug screening. In the paper published in this issue, we describe a glucocorticoid responsive zebrafish line which allows us to monitor glucocorticoid signaling *in vivo* and in real time. Glucocorticoid hormones are among the most prescribed anti-inflammation drugs, but they can cause severe side effects such as diabetes. Current screening methods for novel drugs frequently rely on cell culture assays. In an organism, however, such drugs might show additional undesired effects. Thus, *in vivo* screening systems may permit the discovery of alternative glucocorticoid drugs that are better tolerable. Exploiting the advantages of the zebrafish for high throughput screens, such as its high fecundity and its small size, we developed a zebrafish based screening assay for glucocorticoids. In a pilot screen with 640 FDA approved compounds that included known glucocorticoids, we could show that this "GRIZLY" assay is a cost-efficient, reliable and highly specific *in vivo* screening method for glucocorticoids. It combines the complexity of a complete organism with the simplicity of a cell culture assay. (Read Weger's article, DOI: 10.1021/cb3000474)

Image courtesy of Benjamin Weger.

■ MELTEM WEGER (NEE SAHINBAS)

Current position: Graduate student pursuing Ph.D. at the Heidelberg University under the supervision of Dr. Thomas Dickmeis, Institute of Technology and Genetics, Karlsruhe Institute of Technology, Germany.

Education: Heidelberg University, Germany, Diploma (equivalent to M.S.) in Biology, 2009.

Nonscientific interests: Music, dancing, movies and reading

My research interest is focused on the analysis how glucocorticoid hormones regulate rhythmic cell proliferation via metabolism. This includes the development of several biological tools, such as the transgenic zebrafish line for monitoring glucocorticoid signaling *in vivo* used in our **G**lucocorticoid **R**esponsive ***I**n vivo* **Z**ebrafish **L**uciferase activity (GRIZLY) assay. One of the main outcomes of the work described in our article is that in contrast to *in vitro* or to cell culture methods the GRIZLY assay is able to detect systemic effects of compounds on glucocorticoid signaling that can only be observed in an intact living organism. For example, we could show that certain compounds have to be first metabolized in the organism before they can act on the glucocorticoid signaling pathway. This fact might be not only important in regard to understand glucocorticoid signaling in general, including stress research, but also to identify environmental endocrine disruptors or even to obtain new drugs for future treatments of glucocorticoid hormones based disorders. (Read Weger's article, DOI: 10.1021/cb3000474)