ACS chemical biology

Introducing Our Authors

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MAGNUS S. ALPHEY

Image courtesy of Magnus S. Alphey.

Current postion: University of St. Andrews, X-ray Facility Manager

Education: University of Edinburgh, B.Sc. in Biochemistry, 1993−1997; University of Dundee, Ph.D. in X-ray Crystallography with Prof. Bill Hunter, 2001; University of Dundee, postdoctoral researcher with Prof. Bill Hunter, Prof. Daan van Aalten, and Prof. Alan Fairlamb

Nonscientific interests: Playing piano, reading, and being a dad

As X-ray Facility Manager, I enjoy the hands-on maintenance of our state-of-the-art equipment, but the position still allows me some research time where I became involved in the AEROPATH project, an EU-funded research program supporting early stage antimicrobial drug development. The main goal is to identify inhibitors against drug targets in Gram-negative bacteria, focusing primarily on *Pseudomonas aeruginosa*. Collaborating with the Drug Discovery Unit in Dundee, we screened for inhibitors of my particular target enzyme, RmlA. Resulting hits were characterized crystallographically and developed and improved in-house using rational drug design to produce nanomolar inhibitors. Unusually, these inhibitors were found to bind to an allosteric site distinct from the active site yet were competitive with respect to one of the enzyme's two substrates. (Read Alphey's article, DOI: 10.1021/cb300426u)

ZHIZHOU FANG

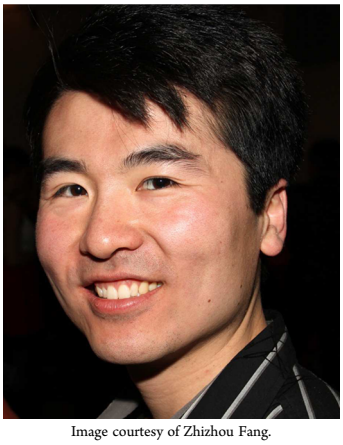

Image courtesy of Zhizhou Fang.

Current postion: Chemical Genomics Centre of the Max Planck Society and Technische Universität Dortmund, Faculty of Chemistry−Chemical Biology, Ph.D. student in the group of Prof. Dr. Daniel Rauh since September 2009

Education: Technische Universität Darmstadt, Dipl.-Ing in Chemistry, thesis advisor Prof. Dr. Herbert Plenio; visiting researcher with Prof. Peter Tasker, University of Edinburgh; visiting researcher with Prof. Dr. Wolfgang Knoll, Max Planck Institute for Polymer Science; visiting researcher with Prof. Tony D. James, University of Bath; undergraduate researcher in the Clemens Schöpf Institute, Prof. Dr. Boris Schmidt

Nonscientific interests: Competitive Latin and ballroom dancing, photography, and badminton

Research in our lab focuses on investigating protein kinases and their role in signaling networks and especially cancer cells. As described in our review, the regulation mechanisms of kinase activity are highly diverse, often involving interdomain or protein−protein interactions, which can be targeted by small molecules. My Ph.D. thesis revolves around developing a biochemical assay system that can easily detect such interactions and thereby identify allosteric modulators that interfere with these interactions. By employing environmentally sensitive fluorophores, we were able to establish such an assay for a clinically relevant target kinase that can determine binding affinities of small molecule inhibitors and distinguish between their different modes of action. From an in-house high-throughput screen, we were then able to find further inhibitors with novel scaffolds. This successful proof-of-concept demonstrates the potential of this assay technology, which can be adapted to other systems with interdomain or protein−protein interactions. (Read Zhang's article, DOI: 10.1021/cb300663j)

YEVGENIY IZRAYELIT

Image courtesy of Theresa O'Malley.

Current postion: Graduate student at Cornell University, pursuing a Ph.D. in Chemistry and Chemical Biology in the lab of Professor Frank C. Schroeder

Published: February 15, 2013

   dx.doi.org/10.1021/cb400054e | *ACS Chem. Biol.* 2013, 8, 269−270

Education: Vassar College, B.A. Biochemistry, 2006

Nonscientific interests: Intramural sports, cycling, traveling, and student governance

For my Ph.D. project, I am using metabolomics and the model organism *C. elegans* to probe signaling pathways associated with aging. I am developing HPLC−MS and 2D NMR-based metabolomic techniques as well as aging bioassays for testing of the identified small molecules. In this publication, we have advanced automated 2D NMR-based metabolomics to probe a *C. elegans* mutant defective in peroxisomal β-oxidation and subsequently production of an important class of molecules termed ascarosides. Identification of novel ascaroside ethanolamide shunt metabolites led us to discover that endocannabinoid production in a series of ascaroside biosynthesis mutants is also depleted. I am excited to investigate this unexpected interaction between endocannabinoid biosynthesis and peroxisomal β-oxidation further. Additionally, I plan to use 2D NMR-based techniques to explore other aging pathways. (Read Izrayelit's article, DOI: 10.1021/cb3004644)

PAUL NEILSEN

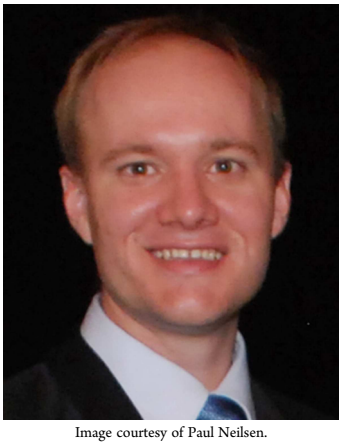

Image courtesy of Paul Neilsen.

Current postion: Sarcoma Research Group, Centre for Personalized Cancer Medicine, University of Adelaide

Education: University of Central Queensland, B.Sc. (Hon), 2004; University of Adelaide, Ph.D., 2008

Nonscientific interests: Walking our dog on the beach

My research interests involve the preclinical investigation into new therapies for childhood cancers. In particular, we are interested in novel agents that activate the p53 tumor suppressor pathway in sarcomas, as we have previously shown that sarcomas are sensitive to such therapeutic approaches. The p53 protein is constantly degraded through the ubiquitin-proteasome system, hence we have explored this as a therapeutic target in sarcoma. Our *ACS Chemical Biology* publication shows that selective inhibition of the CT-L subun it using novel proteasome inhibitors induces robust death of sarcoma cell lines, while not affecting cells from normal tissues. Importantly, these proteasome inhibitors induce cell death through the p53 pathway, highlighting the potential of these agents to restore the p53 tumor suppressor protein to kill sarcoma cells. (Read Nielsen's article, DOI: 10.1021/cb300549d)

ASHOK PEHERE

Image courtesy of Ashok Pehere.

Current postion: ARC Postdoctoral Fellow, at Department of Chemistry, The University of Adelaide at Australia, 2012−Present, Advisors: Professor Andrew D. Abell and Dr. Jonathan George

Education: Pune University, India, B.Sc. in Chemistry, 2000; Pune University, India, M.Sc. in Organic Chemistry, 2002; Research Chemist, Merck KGaA, Mumbai, India, 2002−2008; The University of Adelaide, Australia, Ph.D. in Bio-Organic Chemistry, 2008−2012, Thesis Advisor: Professor Andrew D. Abell

Nonscientific interests: Cricket, cycling, and traveling

My research in Prof. Abell's lab is focused on the design, synthesis, and development of novel peptidomimetic-based protease inhibitors. The inhibitors target therapeutically important proteases, including calpain, cathepsin, and the 26S proteasome. The P1 and P3 residues of these structures are linked by a macrocyclic constraint that contains a key triazole, incorporated via a Huisgen cycloaddition. This then constrains the inhibitor backbone into a β-strand geometry that is known to favor active site binding. The current study is a collaboration between chemistry and biology. We present new peptide-based aldehydes that contain an azide group at P3 and a propargyloxyphenyl group at P1. We show that these inhibitors are highly selective for the chymotrypsin-like activity of the proteasome over its trypsin-like and caspase-like activities. Significantly, these inhibitors display a high degree of specificity for cancer cell lines WE-68, VH-64 STA-ET-1, and TC-252, over normal cell lines fibroblasts and osteoblasts. Hence we further investigated p53-dependent cytotoxic activity. We found that the presence of an intact p53 pathway significantly enhances cytotoxic activity, thus suggesting that this tumor suppressor is a critical downstream mediator of cell death following proteasomal inhibition (Read Pehere's article, DOI: 10.1021/cb300549d).

dx.doi.org/10.1021/cb400054e | *ACS Chem. Biol.* 2013, 8, 269−270