BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Lee, David John

eRA COMMONS USER NAME (credential, e.g., agency login): DJL002

POSITION TITLE: Postdoctoral Researcher

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of California, Santa Cruz	B.S.	09/2005	06/2009	Biology
University of California, Santa Cruz	B.S.	09/2005	06/2009	Chemistry
University of California, San Diego	M.S.	09/2010	06/2012	Chemistry
University of California, San Diego	Ph.D.	06/2012	12/2016	Chemistry
University of California, San Diego	Postdoctoral	12/2016	10/2017	Structural Biology
University of California, San Francisco	Postdoctoral	11/2017	Current	Structural Biology

A. Personal Statement

My philosophical approach to science aligns with my greater philosophical approach to life—I like to know how things work. I like to take things apart, and learn how they function. I have found great satisfaction in my graduate work exploring how modular synthases produce a multitude of natural products. Using small molecules to study protein structure and protein function is analogous to using a wrench to work on a small engine, and philosophically draws me to chemical and structural biology.

During my undergraduate years, I was introduced to organic chemistry. I performed a substrate study, and enjoyed pushing a simple reaction to its limits to learn what guiding principles dictated its applicability. Similarly I was tasked with producing a family of glucosamine analogs, ultimately for incorporation into biological systems. I was especially interested in this project, and it was my first true introduction to chemical biology.

During graduate school and a brief postdoctoral position, I expanded on this interest in Professor Michael Burkart's laboratory at UC San Diego. The Burkart laboratory studies carrier protein dependent modular synthases and synthetases using structural and biophysical approaches. Collaborating with Professor Stan Opella, I learned solution state protein NMR techniques, solving multiple NMR structures of several different carrier proteins. I truly enjoy mentoring, and trained three undergraduate researchers and multiple graduate students in protein NMR. Together, we used NMR approaches to reveal specific information about proteins—specific pulse sequences to study dynamics, others to measure distance constraints for structural calculations, etc. We found that the carrier protein's cargo had significant ramifications on the carrier protein's structure, likely a structural handle to direct molecules through the pathway by tuning reaction partner protein affinity; small molecules with significant effects on protein structure. We focused on the mechanisms of substrate delivery from the carrier protein to the appropriate reaction partner, with minor conformations proving to be crucially important but difficult to study.

Ultimately, interest in minor conformational states and allostery guided my search for post-doctoral laboratories. I am engaged in my continuing training in Prof. James Fraser's laboratory, with additional technical training in Prof. Yifan Cheng's laboratory and collaboration with Prof. Ian Seiple's synthetic chemistry laboratory. This synergistic set of labs provides the ideal complement of skills to learn and study conformational heterogeneity, structural motions, and how function arises from structure in human-health

relevant systems. CryoEM studies on inhibitor-bound ribosomes, with the specific intent to understand and counteract antimicrobial resistance, perfectly tailor my continued training in chemical and structural biology. I have continued to learn and teach within the positive and collaborative environment at UCSF, rapidly advancing through CryoEM training and now guiding my labmates through CryoEM data collection and processing techniques. Additionally, UC San Francisco provides many career development opportunities, both academic and industrial interactions, and leadership and mentorship opportunities.

B. Positions and Honors

Positions and Employment

2007–2007 Intern, Medicinal Chemistry, University of Utah
2010–2010 Intern, Synthetic Chemistry, Intel Labs, Santa Clara
2010–2014 Teaching Assistant, UC San Diego
2016–2017 Professional Consultant, Biochemistry, Jones Day
2016–2017 Postdoctoral Researcher, UC San Diego
2017– Postdoctoral Researcher, UC San Francisco

Other Experience and Professional Memberships

2014–2017 Co-organizer, Natural Products Affinity Group, UC San Diego
2014– Member, Royal Society of Chemistry
2015– Member, American Chemical Society

Honors

2007 American Heart Association Summer Research Fellowship
2009 Dean's Award in Physical and Biological Sciences, UC Santa Cruz
2010 Harold Urey Award, UC San Diego
2014 Bruno Zimm Award, UC San Diego
2015 President's Dissertation Year Fellowship, UC San Diego

C. Contributions to Science

1. *Organic synthesis efforts towards chiral glucosamine analogs and asymmetric reduction of α,β-unsaturated ketones:* My early introduction to laboratory science and research, as an undergraduate, was predominantly through synthetic organic chemistry. As an American Heart Association Undergraduate fellow, I interned with Prof. Kuberan Balagurunathan at the University of Utah, synthesizing glucosamine analogs for future incorporation into heparan sulfate glycosaminoglycan chains. Heparan sulfate chains are crucial for intercellular communication and developmental processes, and we were attempting to modulate sulfation patterns of the chains through perturbation of the glucosamine monomers. After the end of the internship, I volunteered with Prof. Bakthan Singaram at the University of California, Santa Cruz, executing a substrate study to quantify and validate the efficacy of a chiral director, "Tar-B-NO_2". Tar-B-NO_2 facilitates asymmetric reduction of α,β-unsaturated ketones via directed hydride delivery. Prof. Singaram instilled in me the importance of applying science to benefit human health, ultimately culminating in my undergraduate thesis, "*Efforts towards an enantioselective synthesis of the HIV inhibitor abacavir".*
    a. Kim J, Bruning J, Park KE, **Lee DJ**, Singaram B. Highly enantioselective and regioselective carbonyl reduction of cyclic α,β-unsaturated ketones using TarB-NO2 and sodium borohydride. *Organic Letters.* 2009; 11(19):4358–61.

2. *Graduate work on Fatty Acid Synthases: Carrier protein structure* – During graduate school, I refocused my studies towards chemical biology and structural biology. Joining Prof. Michael Burkart's laboratory at the University of California, I began studying protein structure by NMR. I performed many studies of carrier proteins from carrier protein dependent modular synthases, including fatty acid synthases (FAS). Several studies of the bacterial FAS were carried out, with two primary focuses. Carrier proteins sequester and protect intermediates as they transport them from partner to partner, but the nature of sequestration is poorly understood. We characterized cargo-induced structural changes to the carrier protein. First, we turned to solution-state NMR methods, observing significant chemical shift

perturbations upon binding cargo corresponding to a global tightening of the carrier protein around the cargo. Additionally, we found that unnatural probes could be appropriately sequestered, encouraging us to explore covalent crosslinking by attaching modified cargo to carrier proteins.

a. Ishikawa F, Haushalter RW, **Lee DJ**, Finzel K, Burkart MD. Sulfonyl 3-alkynyl pantetheinamides as mechanism-based cross-linkers of acyl carrier protein dehydratase. *Journal of the American Chemical Society*. 2013; 135(24):8846–9. PMCID: PMC3713789
b. **Lee DJ***, Finzel K*, Burkart MD. Using modern tools to probe the structure-function relationship of fatty acid synthases. *ChemBioChem*. 2015; 16(4): 528–547. PMCID: PMC4545599

3. *Graduate work on Fatty Acid Synthases: Protein-protein interactions* – The protein-protein interactions required for fatty acid biosynthesis were observed by exploiting mechanism-based crosslinking probes. These probes allowed us to covalently trap the transient carrier protein-partner protein interaction for crystallographic and solution-state NMR evaluation. This approach was applied specifically to the *E. coli* acyl carrier protein and a partner dehydratase, yielding the first structural observations of an interaction between two partners within a fatty acid biosynthetic pathway. Additionally, NMR was used to observe the non-crosslinked *in vitro* interaction by titration, with regions of the protein perturbed in these titration experiments matching well with the interacting residues identified crystallographically. Molecular Dynamics simulations, supported by Residual Dipolar Coupling measurements, was used to quantify the flexibility of the carrier protein before and during interaction with the partner dehydratase. Together, these efforts allowed conclusive mapping of the acyl carrier protein and dehydratase interaction, with significant implications in future engineering and inhibition efforts.
    a. **Lee DJ***, Nguyen C*, Haushalter RW*, Markwick PRL, Bruegger J, Caldara-Festin G, Finzel K, Jackson DR, Ishikawa F, O'Dowd B, McCammon JA, Opella SJ, Tsai S-C, Burkart MD. Trapping the dynamic acyl carrier protein in fatty acid biosynthesis. *Nature.* 2014; 505(7483): 427–31. PMCID: PMC4437705
    b. Beld J, **Lee DJ**, Burkart MD. Fatty acid biosynthesis revisited: structure eluctidation and metabolic engineering. *Molecular Biosystems.* 2015; 11(1): 38-59. PMCID: PMC4276719

4. *Graduate work on Hybrid polyketide synthase/non-ribosomal peptide synthetases* – Several pyrrole containing hybrid PKS/NRPS systems were studied and structurally characterized to engineer cross-pathway activity, between carrier proteins of closely related synthetases and non-cognate adenylation enzymes. Specifically, the pyoluteorin and prodigiosin carrier proteins were structurally characterized using traditional NOE solution-state NMR methods. The pyoluteorin carrier protein was also characterized bearing cargo, demonstrating structurally, for the first time, sequestration of cargo in a hybrid PKS/NRPS system. Computational and mutagenesis efforts were employed to produce a mutant prodigiosin carrier protein that could be acted upon by pyoluteorin biosynthetic partner proteins. Together, these efforts advance and highlight engineering opportunities in these modular synthases and synthetases, ideally to eventually allow development of custom synthases.
    a. Jaremko MJ, **Lee DJ**, Opella SJ, Burkart MD. Structure and substrate sequestration in the pyoluteorin type II peptidyl carrier protein PltL. *Journal of the American Chemical Society*. 2015; 137(36): 11546–9. PMCID: PMC4847951
    b. Jaremko MJ, **Lee DJ**, Patel A, Winslow V, Opella SJ, McCammon JA, Burkart MD. Manipulating protein–protein interactions in nonribosomal peptide synthetase type II peptidyl carrier proteins. *Biochemistry*. 2017; 56(40): 5269–73. PMCID: PMC5873958

5. *Graduate work on Polyketide Synthases* – Polyketide synthases, the secondary-metabolic relatives of fatty acid synthases, use similar proteins and pathways as fatty acid synthases but produce secondary metabolites by various alterations to tailoring and iterative chain extensions. Understanding the substrate recognition and sequestration of cargo is critical to the success of engineering efforts. Unfortunately, many polyketides are formed by repetitive elongation steps yielding an elongated, highly reactive polyketide that can spontaneously cyclize. Studying carrier protein sequestration in the biosynthesis of the antimicrobial polyketide actinorhodin required the preparation of atom-replaced geometrically and electronically similar substrate mimics. Both linear and cyclized atom-replaced mimics were prepared. Subjecting these mimics to sequestration studies by solution-state protein NMR revealed that only the full-length and cyclized mimics were well sequestered, suggesting that the elongating polyketide remains within the partner ketosynthase until full elongation.

a. Shakya G, Rivera H, **Lee DJ**, Jaremko MJ, La Clair JJ, Fox DT, Haushalter RW, Schaub AJ, Bruegger J, Barajas JF, White AR, Kaur P, Gwozdziowski ER, Wong F, Tsai S-C, Burkart MD. Modeling linear and cyclic PKS intermediates through atom replacement. *Journal of the American Chemical Society*. 2014; 136(48): 16792–9. PMCID: PMC4277753

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/david.lee.7/bibliography/57262207/public/?sort=date

D. Additional Information: Research Support and/or Scholastic Performance

YEAR	COURSE TITLE	GRADE
	University of California, San Diego	
2010	Enzyme Catalyzed Reactions	A
2010	Synthetic Methods/Organic Chemistry	A-
2010	Mechanisms/Organic Reactions	B-
2011	Synthesis of Complex Molecules	B+
2011	Structure and Properties of Organic Molecules	A
2011	Natural Products Chemistry	A
2011	Applied Spectroscopy	B+
2012	Protein NMR	A

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Pellegrino, Jenna

eRA COMMONS USER NAME (credential, e.g., agency login): jenna_pellegrino

POSITION TITLE: Doctoral Trainee

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Ursinus College, Collegeville, PA	B.S.	05/2017	Biochemistry and Molecular Biology
Ursinus College, Collegeville, PA	B.A.	05/2017	French
University of California, San Francisco, CA	Ph.D.	Present	Biophysics

A. Personal Statement

Since my first research experience with Dr. Amanda Reig as a rising first year in Ursinus College, I have gained a growing admiration for the complexities of nature. As proteins have evolved to excel at their functions, there remains a clear element of a logical and predictable nature from their primary sequence to their tertiary structure and function. Although this nature remains meagerly understood by modern science, I enjoyed prying for the answers to our questions regarding the structure-function relationships of diiron carboxylate enzymes. In my work, I created a library of model variants via site-directed mutagenesis, characterized their metal-binding properties through divalent metal titration assays, probed their ability to perform two-electron oxidation using a ferroxidase assay, and also began work exploring the peroxidase capabilities of my protein variants. Looking back in my final year of college, I felt fortunate to have been able to watch my project develop so broadly over the years as well as get to know and understand the protein model variants with which I worked in what felt like a personal way.

This way of observing nature through the lens of structure-function relationships has guided me in my current work in Dr. James Fraser's lab at UCSF: the rational design of stronger ribosome-inhibiting antibiotics. Through the use of cryoelectron microscopy (cryoEM), I am able to observe antibiotic analogs, developed by our collaborators in the synthetic chemistry lab of Dr. Ian Seiple, bound to the ribosome – a fascinating new and visual way for me to become acquainted with the small molecules with which I work. As I grow in my understanding of cryoEM and rational drug design, I am surrounded by a multitude of excellent resources at UCSF, coming from the aforementioned labs as well as from Dr. Yifan Cheng's lab. I am confident that, with the support and expertise of my mentors, I will be able to successfully carry out the proposed research project.

B. Positions and Honors

Positions and Employment

2013 - 2017 Undergraduate Research Assistant, Ursinus College
2016 NSF Research Experience for Undergraduates (REU) Student Researcher, National Science Foundation, University of Pennsylvania
2018 - Present Doctoral Trainee, UC San Francisco

Other Experience and Professional Memberships

2013 - 2017 Member, American Chemical Society
2014 - 2017 Member, American Society for Biochemistry and Molecular Biology
2017 - Present Member, Phi Kappa Beta Honor Society

Honors

2017 - 2023 Fellow of the NSF Graduate Research Fellowship Program, National Science Foundation

C. Contribution to Science

1. **Undergraduate Work:** As an undergraduate, I worked in the lab of Dr. Amanda Reig, where I studied the structure-function relationship of the diiron carboxylate proteins rubrerythrin (Rbr) and symerythrin (Sym). These proteins exhibit ferroxidase and uniquely preferential peroxidase activity, compared to other diiron carboxylate proteins. The preference for reactivity with peroxide is thought to result from the addition of one and two carboxylate active site residues, respectively, compared to the protein archetype of this family. The goal of my research was to elucidate the role of these additional residues in rendering this preferential peroxidase activity, with the long-term aim being to assist in the rational design of proteins with specific function. From analysis on eight total protein variants, my data showed that the addition of two carboxylates rendered weaker metal-binding capacity. Interestingly, only one model variant, a Rbr-like protein, exhibited greater oxidation compared to the parent protein. It is possible that these data suggest a switch in reaction preference away from oxidation and towards peroxidase activity. Preliminary data on the oxidation and reduction at the iron center showed reversibility in the analyzed Rbr proteins. This research culminated into my distinguished honors research composition, “Biophysical Characterization and Catalytic Reactivity of Rubrerythrin and Symerythrin Model Proteins”. I also presented my findings at multiple conferences and on campus.

2. **REU Work:** Hydrogels are a type of biomaterial characterized by a porous, 3D network of hydrophilic polymers that absorb high water content without dissolving. Specifically, peptide hydrogels are of particular interest due to their ability to self-assemble. Harnessing control over the dissolution of such hydrogels, particularly those that encapsulate a small molecule, is a rewarding technique with medical applications, such as in drug-delivery systems. To investigate the feasibility of this technique, in the lab of Dr. Feng Gai, I studied the incorporation and release of various small dyes upon irradiation in self-assembling hydrogels made from short peptide repeats. I observed from my fluorescence studies that, while some dyes incorporated well, others either incorporated incompletely or not at all. Since I observed this trend in hydrogel systems built by fibrils of different lengths, I concluded that the dyes’ sizes or electronic states were disrupting aggregate assembly. In conclusion of the REU program, I composed a summary of my work and presented this before my peers.

3. **Graduate Work:** The growing rise of antibiotic resistance, coupled with a lack of new antibiotics, is a dire dilemma in modern medicine and public health. The problem of synthesizing new streptogramin analogs with unprecedented diversity has been solved by Dr. Ian Seiple and his lab. In collaboration with the Seiple Group and under the guidance of Dr. James Fraser, I am currently working on developing a platform to produce stronger streptogramin A (SA) antibiotics that overcome the most problematic SA-resistance mechanisms, such as resistance via VatA, an acetyltransferase that causes resistance-conferring drug modification. This goal is only feasible thanks to breakthroughs in cryoelectron microscopy (cryoEM), which has already allowed us to quickly and efficiently obtain high-resolution (2.4-2.7 Å) data for our analogs bound to *E. coli* ribosomes. Given greater accessibility to cryoEM microscopes, we hope to further establish our platform for the rational design of better SA ribosomal inhibitors so that we can turn our attention towards tackling VatA and other resistance mechanisms.

D. Additional Information: Research Support and/or Scholastic Performance

Where grades are listed as “S”: These classes utilized a satisfactory/unsatisfactory (S/U) scale.

YEAR	COURSE TITLE	GRADE
	Ursinus College, Collegeville, PA	
2013	Intro Research in Biochemistry	S
	Ecology and Evolution	B
	General Chemistry I	A
	General Chemistry I Lab	A-
	Common Intellectual Experience (CIE) I	A-
	French Conversation and Composition	A
	Science and Math in Society	S
	Wind Ensemble	S

2014	Intro Research in Biochemistry	S
	Cellular Biology	A
	Organic Chemistry I	A
	Organic Chemistry I Lab	A-
	CIE II	A
	French Film and Literature	A
	Wind Ensemble	S
	Research in Biochemistry	S
	Genetics	A
	Organic Chemistry II	A-
	Organic Chemistry II Lab	A
	Intro French Literature	A
	Wind Ensemble	S
	Ethics 240	A-
	General Physics I	A
2015	Foundations in Biochemistry	A-
	Intro Research in Biochemistry	S
	General Chemistry II	A-
	General Chemistry II Lab	A-
	Inorganic Chemistry	A-
	Le Mode Francophone	A
	Wind Ensemble	S
	General Physics II	A-
	Science and the Common Good	A
	Biochemistry I	A
	Chemistry Focus Inquiry	A
	Spoken French	A
	Wind Ensemble	S
	Biomedical Ethics	A
	Intro Psychology	A
2016	Biochemistry II	A-
	Structural Biology	A
	Chemistry Focus Inquiry	A
	French Independent Study	A
	Decoding Science	A
	Wind Ensemble	S
	Physical Chemistry	A
	Research	A
	Dir Research	A
	Instrumental Analysis	C
	Instrumental Analysis Lab	A
	Advanced French Grammar and Translation	A-
	Intro Research in Physics	S
	Zionism	A-
2017	Intro Computer Science	A
	Intro Computer Science Lab	A
	French Seminar	A
	Honors Research in Biochemistry	A
	Bucks County Community College, Holland, PA	
2014	Calculus II	A
	University of California, San Francisco, CA	
2017	Critical Topics in Biomedical Informatics	S
	Graduate Research Opportunities Seminar	S
	Macromolecular Structure and Interactions A	A
	Physiological Underpinnings of Biological Systems	A
2018	Critical Topics in Biomedical Informatics	S

Graduate Research Opportunities Seminar	S
Macromolecular Structure and Interactions B	A
Molecular Thermodynamics	S
Critical Topics in Biomedical Informatics	S
Special Topics in Biophysics	S

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Fraser, James Solomon

eRA COMMONS USER NAME (credential, e.g., agency login): FRASERJA

POSITION TITLE: Associate Professor of Bioengineering and Therapeutic Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
McGill University, Montreal, QC, Canada	B.Sc.	05/2005	Biology
University of California, Berkeley, CA	Ph.D.	12/2010	Molecular and Cell Biology

A. Personal Statement

The long-term goals of our research are to understand how protein conformational ensembles are reshaped by perturbations and to quantify how these perturbations impact protein function and organismal fitness. To accomplish these goals, we create new computational and biophysical approaches to study how proteins move between different conformational states. A primary guiding principle of our research is that physical perturbations (such as temperature or pressure) can often reveal the same “hidden” conformations exploited by biochemical perturbations (such as ligand binding or mutation).

In 2011, I started my independent research career as a QB3 at UCSF Fellow and in 2013 was appointed as an Assistant Professor of Bioengineering and Therapeutic Sciences, with promotion to Associate Professor with tenure in 2016. Although my group has pioneered methods to model and evaluate the data emerging from the “resolution revolution” in cryo-electron microscopy, I took advantage of a Sackler Sabbatical Fellowship at UC Berkeley (hosted by Eva Nogales) to increase my own immersion in the practical aspects of electron microscopy. I have brought this new perspective back to UCSF, as my group integrates high resolution EM, X-ray, NMR, and computation to improve protein engineering and small molecule discovery.

I care deeply about mentorship and guiding trainees into their next positions. My first two postdoctoral fellows are on their desired career trajectories (Daniel Keedy is now an Assistant Professor at CCNY and Brandi Hudson is now a Scientist at Relay Therapeutics); my first three graduate students have moved onto postdoctoral training (Rahel Woldeyes with Wah Chiu at Stanford, David Mavor with Dan Bolon at UMass) or launched successful careers (Andrew van Benschoten is a data scientist at Oracle). In addition, throughout my time at UCSF, I have incorporated new technologies in teaching, establishing the BBC PUBS (a deep sequencing-based project course) and core grad Biophysics class (with data collection at UCSF/LBNL).

Key Citations

1. Keedy DA*, Hill ZB*, Biel JT, Kang E, Rettenmaier TJ, Brandao-Neto J, Pearce NM, von Delft F, Wells JA, **Fraser JS**. An expanded allosteric network in PTP1B by multitemperature crystallography, fragment screening, and covalent tethering. *eLife.* 2018. PMCID: PMC6039181.
2. Otten R*, Liu L*, Kenner LR, Clarkson MW, Mavor D, Tawfik DS, Kern D, **Fraser JS.** Rescue of conformational dynamics in enzyme catalysis by directed evolution. *Nature Communications.* 2018. PMCID: PMC5883053.
3. Barad BA, Echols N, Wang RY, Cheng Y, DiMaio F, Adams PD, **Fraser JS**. EMRinger: Side-chain-directed model and map validation for 3D Electron Cryomicroscopy. *Nature Methods*. 2015. PMCID: PMC4589481.
4. Fischer M, Coleman RG, **Fraser JS#**, Shoichet BK. Incorporation of protein flexibility and conformational energy penalties in docking screens to improve ligand discovery. *Nature Chemistry*. 2014. PMCID: PMC4144196.

B. Positions and Honors

Positions and Employment

2011-2012 QB3 at UCSF Faculty Fellow (Principal Investigator)
Department of Cellular and Molecular Pharmacology, UCSF
California Institute of Quantitative Biosciences (QB3)

2013-2016 Assistant Professor
Department of Bioengineering and Therapeutic Sciences, UCSF
California Institute of Quantitative Biosciences (QB3)

2016 - Consulting Professor
Department of Photon Science
SLAC National Accelerator Laboratory

2016 - Associate Professor
Department of Bioengineering and Therapeutic Sciences, UCSF
California Institute of Quantitative Biosciences (QB3)

2018 - Faculty Scientist
Molecular Biophysics and Integrated Bioimaging Division
Lawrence Berkeley National Lab

Other Experience

2007 - Author of problems/solutions manual for physical biochemistry textbook "The Molecules of Life" (Garland Science, Authors: John Kuriyan, Boyana Konforti, David Wemmer)
2008-2009 Assistant to Professor Howard Schachman for NIH Ethics Training (MCB 293C)
2013-2015 Advanced Light Source Proposal Review (Structural Biology), Panel Member
2015-2018 Linac Coherent Light Source (XFEL) Proposal Review Panel (BIO-C), Chair
2016- Beamline 8.3.1. at the Advanced Light Source, Head of Participating Research Team
2016- ASAPbio (Accelerating Science and Publication in biology) Board of Directors, Treasurer
2016- Relay Therapeutics, Consultant
2017- Quantitative Biosciences Institute of UCSF, Associate Director
2017- ALS-ENABLE P30 Resource, Deputy Director
2017- Collaboration for Structural Simulations and Scattering, Project Director
2018 Protein Society Annual Symposium, Co-Chair
2018- PHENIX (Python-based Hierarchical ENvironment for Integrated Xtallography), Advisory Board

Honors

2001-2005 Canadian Millennium Excellence Undergraduate Scholarship
2004 NSERC Undergraduate Summer Research Award (Mentor: Alan Davidson)
2006-2007 Natural Sciences and Engineering Research Council (Canada) Postgraduate Fellowship
2007-2010 Natural Sciences and Engineering Research Council (Canada) Doctoral Fellowship
2007-2010 National Science Foundation Graduate Research Fellowship
2010 EMBO Short Term Fellowship (Host: Dan Tawfik, Weizmann Institute, Israel)
2010 Warren DeLano Award for Structural Bioinformatics and Computational Biophysics
2011 Nicholas Cozzarelli Prize for Best Dissertation in Molecular and Cell Biology (UCB)
2011 Forbes 30 under 30 Science
2014 Searle Scholar, Kinship Foundation
2014 Pew Scholar, Pew Charitable Trusts
2014 Packard Fellow, The David and Lucile Packard Foundation
2017-2018 Raymond and Beverly Sackler UCSF/Berkeley Sabbatical Exchange (Host: Eva Nogales)

C. Contributions to Science ($^{\#}$ - corresponding author)

1. **Identifying hidden alternative conformations of proteins in biophysical data**. We study proteins as conformational ensembles. Although X-ray crystallography is an ensemble experiment, the results are typically summarized with a single static structure. As a graduate student, and now in my own lab, we have developed software to discover the structural ensembles present in the crystal. The ensemble nature of proteins highlighted by this work feeds into all of our mechanistic studies that interpret the functional effects of mutations, that characterize designed and artificially-evolved proteins, or that seek to modulate protein function with small molecules. We are expanding this direction to include modeling and validating protein structural data generated by cryoelectron microscopy, through EMRinger and collaborations with Gabe Lander's lab on ensemble modeling, and through integrative approaches to discover cryptic sites.

a. Keedy DA, **Fraser JS**, van den Bedem H. Exposing Hidden Alternative Backbone Conformations in X-ray Crystallography Using qFit. *PLOS Computational Biology*. 2015. PMCID: PMC4624436.
b. van den Bedem H, Bhabha G, Yang K, Wright PE, **Fraser JS#**. Automated identification of functional dynamic contact networks from X-ray crystallography. *Nature Methods*. 2013. PMCID: PMC3760795.
c. Herzik Jr. MA, **Fraser JS**, Lander GC. A multi-model approach to assessing local and global cryo-EM map quality. **Preprint** on BioRxiv. 2017. http://dx.doi.org/10.1101/128561
d. **Fraser JS**, Clarkson MW, Degnan SC, Erion R, Kern D, Alber T. Hidden alternative structures of proline isomerase essential for catalysis. *Nature*. 2009; 462(7273):669-73. PMCID: PMC2805857.

2. **Creating multi-temperature X-ray data collection methods to inform mechanistic studies**. We recognized that the standard practice of cryocooling crystals could distort protein conformations. In both larger surveys and isolated mechanistic studies, we have demonstrated the value of room temperature data collection for revealing the structural basis of protein conformational dynamics, leading to new insights into the enzymes PTP1B, CypA, H-Ras, and DHFR, and increasing connections to dynamics studies from NMR and simulations. Additionally, we have identified how temperature can bias small molecule discovery, leading some fragment sites inaccessible at cryogenic temperatures, and the positioning of crucial water molecules in the flu ion channel M2.
   a. **Fraser JS**, van den Bedem H, Samelson AJ, Lang PT, Holton JM, Echols N, Alber T. Accessing protein conformational ensembles by room-temperature X-ray crystallography. *Proceedings of the National Academy of Sciences*. 2011. PMCID: PMC3182744.
   b. Thomaston JL, Alfonso-Prieto M, Woldeyes RA**, Fraser JS**, Klein ML, Fiorin G, DeGrado WF. High-resolution structures of the M2 channel from influenza A virus reveal dynamic pathways for proton stabilization and transduction. *Proceedings of the National Academy of Sciences*. 2015. PMCID: PMC4655559.
   c. Biel JT, Thompson MC, Cunningham CN, Corn JE, **Fraser JS.** Flexibility and design: conformational heterogeneity along the evolutionary trajectory of a redesigned ubiquitin. *Structure*. 2017. PMCID: PMC5415430.
   d. Keedy DA*, Kenner LR*, Warkentin M*, Woldeyes RA*, Thompson MC, Brewster AS, Van Benschoten AH, Baxter EL, Hopkins JB, Uervirojnangkoorn M, McPhillips SE, Song J, Alonso-Mori R, Holton JM, Weis WI, Brunger AT, Soltis SM, Lemke H, Gonzalez A, Sauter NK, Cohen AE, van den Bedem H, Thorne RE**, Fraser JS**. Mapping the Conformational Landscape of a Dynamic Enzyme by XFEL and Multitemperature Crystallography. *eLife*. 2015. PMCID: PMC4721965.

3. **Developing new X-ray diffuse scattering and X-FEL experiments to probe correlated motions in proteins**. A major limitation of most biophysical techniques is the inability to directly reveal correlations in motions between distinct regions of macromolecules. Diffuse scattering has the potential to reveal these motions; however, we currently lack the ability to collect, integrate, and refine diffuse scattering data. We are tackling each of these problems directly with collaborators: Michael Wall, Nicholas Sauter, Tom Terwilliger, and Paul Adams. Our long-term goal is to increase the information content of every X-ray diffraction experiment to reveal atomic level coupling at high resolution and improved models of grouped flexibility at low resolution. We are also taking advantage of the new capabilities of next-generation X-ray free electron laser (X-FEL) light sources to perform radiation damage-free imaging of proteins. Our long term goal is to watch how protein conformational ensembles respond when perturbed by rapid temperature jumps using the X-FEL.
   a. Van Benschoten AH, Liu L, Gonzalez A, Brewster AS, Sauter NK, **Fraser JS#**, Wall ME. Measuring and modeling diffuse scattering in protein X-ray crystallography. *Proceedings of the National Academy of Sciences*. 2016. PMCID: PMC4839442.
   b. Wall ME, Van Benschoten AH, Sauter NK, Adams PD, **Fraser JS**, Terwilliger TC. Conformational dynamics of a crystalline protein from microsecond-scale molecular dynamics simulations and diffuse X-ray scattering. *Proceedings of the National Academy of Sciences*. 2014. PMCID: PMC4273327.
   c. Van Benschoten AH, Afonine PV, Terwilliger TC, Wall ME, Jackson CJ, Sauter NK, Adams PD, Urzhumtsev A, **Fraser JS#**. Predicting X-ray Diffuse Scattering from Translation Libration Screw Structural Ensembles. *Acta Crystallographica D*. 2015. PMCID: PMC4528799

d. Thomaston JL, Woldeyes RA, Nakane T, Yamashita A, Tanaka T, Koiwai K, Brewster AS, Barad BA, Chen Y, Lemmin T, Uervirojnangkoorn M, Arima T, Kobayashi J, Masuda T, Suzuki M, Sugahara M, Sauter NK, Tanaka R, Nureki O, Tono K, Joti Y, Nango E, Iwata S, Yumoto F, **Fraser JS**, DeGrado WF. XFEL structures of the influenza M2 proton channel: Room temperature water networks and insights into proton conduction. *Proceedings of the National Academy of Sciences*. 2017. PMCID: PMC5754760

4. **Identifying unifying concepts between systems and structural biology**. With Nevan Krogan, we have articulated the similarities in genetic epistasis and thermodynamic measurements and applied these insights to large-scale studies of point mutants and posttranslational modifications. This framework forms the basis for the UCSF graduate course that I direct, PUBS (Physical Underpinnings of Biological Systems), which uses deep sequencing to determine the context dependence of fitness effects of mutations. The class is taught through project-based learning where incoming students perform all library preparations, load samples directly on the MiSeq, and write all their own code to process sequencing data.
    a. Beltrao P, Albanèse V, Kenner LR, Swaney DL, Burlingame A, Villén J, Lim WA, **Fraser JS**, Frydman J, Krogan NJ. Systematic functional prioritization of protein posttranslational modifications. *Cell*. 2012. PMCID: PMC3404735
    b. Braberg H, Jin H, Moehle EA, Chan YA, Wang S, Shales M, Benschop JJ, Morris JH, Qiu C, Hu F, Tang LK, **Fraser JS**, Holstege FC, Hieter P, Guthrie C, Kaplan CD, Krogan NJ. From structure to systems: high-resolution, quantitative genetic analysis of RNA polymerase II. *Cell*. 2013. PMCID: PMC3932829
    c. **Fraser JS**[#], Gross JD, Krogan NJ. From systems to structure: bridging networks and mechanism. *Mol Cell*. 2013. PMCID: PMC3558917
    d. Mavor D, Barlow KA, Thompson S, Barad BA, Bonny AR, Cario CL, Gaskins G, Liu Z, Deming L, Axen SD, Caceres E, Chen W, Cuesta A, Gate R, Green EM, Hulce KR, Ji W, Kenner LR, Mensa B, Morinishi LS, Moss SM, Mravic M, Muir RK, Niekamp S, Nnadi CI, Palovcak E, Poss EM, Ross TD, Salcedo E, See S, Subramaniam M, Wong AW, Li J, Thorn KS, Conchúir SÓ, Roscoe BP, Chow ED, DeRisi JL, Kortemme T, Bolon DN, **Fraser JS**[#]. Determination of Ubiquitin Fitness Landscapes Under Different Chemical Stresses in a Classroom Setting. *eLife*. 2016. PMCID: PMC4862753
5. **Determining structures of protein mediating microbial-host interactions**. I have a longstanding interest in microbiology, beginning from my undergraduate work with Alan Davidson (Toronto) on bacteriophage structure prediction that lead to the surprising discovery of a class of mobile immunoglobulin domains. I have collaborated with the Zusman lab (UC Berkeley) to determine the structure of FrzS, a key signaling regulator of Myxococcus xanthus, with the Fischbach lab (UCSF) to determine how the gut microbiome produces the neurotransmitter tryptamine, and with the Tawfik lab (Weizmann Institute, Israel) to determine the role of epistasis in restricting antibiotic resistance mutations. We are expanding this interest to include the interaction of human enzymes in degrading chitin molecules, which can cause inflammation in the context of allergy and asthma, and the hijacking of the proline isomerase CypA in lentiviral evolution.
    a. **Fraser JS**, Yu Z, Maxwell KL, Davidson AR. Ig-like domains on bacteriophages: a tale of promiscuity and deceit. *J Mol Biol.* 2006. PMID: 16631788.
    b. Williams BB, Van Benschoten AH, Cimermancic P, Donia MS, Zimmermann M, Taketani M, Ishihara A, Kashyap PC, **Fraser JS**, Fischbach MA. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. *Cell Host Microbe*. 2014. PMCID: PMC4260654
    c. Kane JR, Stanley DJ, Hultquist JF, Johnson JR, Mietrach N, Binning JM, Jónsson SR, Barelier S, Newton BW, Johnson TL, Franks-Skiba KE, Li M, Brown WL, Gunnarsson HI, Adalbjornsdóttir A, **Fraser JS**, Harris RS, Andrésdóttir V, Gross JD, Krogan NJ. Lineage-Specific Viral Hijacking of Non-canonical E3 Ubiquitin Ligase Cofactors in the Evolution of Vif Anti-APOBEC3 Activity. *Cell Reports*. 2015. PMCID: PMC4613747.
    d. Dellus-Gur E, Elias M, Caselli E, Prati F, Salverda ML, de Visser JA, **Fraser JS**[#], Tawfik DS. Negative epistasis and evolvability in TEM-1 β-lactamase - The thin line between an enzyme's conformational freedom and disorder. *J Mol Biol*. 2015. PMCID: PMC4718737.

Complete List of 50 Publications in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40891283/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

Packard Fellowship for Science and Engineering Fraser (PI) 11/01/14 – 10/31/19
The David and Lucile Packard Foundation
The major goal of this project is to create and apply methods to examine non-Bragg (diffuse) scattering to define and study the importance of conformational dynamics in protein function.

NSF 11-522 Snell (PI) 09/01/13 – 09/01/23
NSF - OIA - SCI & TECH CTRS
Biology with X-ray Lasers
The major goal of this center is to encourage the development of methods for biophysics using the newly developed x-ray free electron lasers (X-FEL). We participate by generating samples for X-FEL diffraction and comparing the resulting data to room temperature synchrotron datasets.

LFR-17-476732 Fraser (PI) 03/01/17 – 02/29/20
UC Lab Fees Research Program
Macromolecular movements by simulation and diffuse scatter
The goal of this project is to validate X-ray diffuse scattering data with molecular dynamics simulations. Fraser is the overall project director, overseeing coordination between sites (UCSD, UCI, UCR, LANL).

MCB 1714915 Herschlag (PI) 08/01/17 – 07/31/21
NSF
Collaborative Research: Systematic Investigation of the Structure, Dynamics, and Energetics of Hydrogen Bonds and the Protein Interior Using Ketosteroid Isomerase and Model Systems
The goal of this project is to determine the biophysical and mechanistic basis for enzyme catalysis.

R01 GM0517315 Holton (PI) 07/01/17 – 06/30/22
NIH/NIGMS
Eliminating Critical Systematic Errors In Structural Biology With Next-Generation Simulation
The goal of the project is to use simulations to explore systematic errors to enable improved modeling.

P30 GM0519206 Adams (PI) 07/01/17 – 06/30/22
NIH/NIGMS
ALS Efficiently Networking Advanced Beam Line Experiments (ALS-ENABLE)
Fraser administers the project as Deputy Director of Macromolecular Crystallography and performs outreach. Fraser is the deputy project director, overseeing the crystallography component of the project.

R01 GM123159 Fraser (MPI)/van den Bedem 12/01/17 – 11/31/21
NIH/NIGMS
Resolving ensemble averaged conformations by multi-temperature x-ray crystallography
The objective of this research program is to experimentally access and computationally model multi-scale heterogeneity in allosteric protein-ligand complexes.

Completed Research Support

R21 GM110580 Fraser (PI) 04/01/14-03/31/17
NIH/NIGMS
Model Comparison in Structural Biology
This project created new metrics for determining the precision and accuracy of protein conformations.

DP5 OD009180 Fraser (PI) 09/01/11 – 08/31/17
NIH/OSC
The Impact of Mutation on the Conformations and Recognition of Ubiquitin
This project used deep mutational scanning and biophysical characterization to study variants of Ubiquitin.

BIOGRAPHICAL SKETCH

NAME: Seiple, Ian Bass

eRA COMMONS USER NAME: ibseiple

POSITION TITLE: Assistant Professor In Residence

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of California, Berkeley	B.S.	05/2006	Chemistry
The Scripps Research Institute	Ph.D.	06/2011	Chemistry
Harvard University	Postdoc	07/2015	Chemistry

A. Personal Statement

I seek to apply modern chemical synthesis to prevailing biological challenges by synthesizing small molecule drug candidates, generating novel chemical libraries, and developing tools to study biological pathways (see seiplegroup.ucsf.edu for more details). A primary push in my laboratory is the development of robust platforms for the discovery and synthesis of antibiotic candidates that have potential to combat multidrug-resistant bacterial infections. These platforms are informed by structural binding data, known resistance pathways, and pharmacological considerations; they are enabled by the strategic application of modern chemical synthesis.

Laboratory mentoring is a central reason why I want to remain in academics. I have conducted the majority of my research on teams of 3-6 researchers, and I have played a leadership role in each of these teams. This has provided me the opportunity to directly mentor more than a dozen graduate and undergraduate students over the past eight years, many of whom had no prior experience in research. My nascent laboratory offers training in complex molecule synthesis as well as opportunities for multidisciplinary expansion that will be facilitated by the highly collaborative environment at UCSF. I aim to provide attentive mentorship when necessary, but my goal is for every researcher who trains in my laboratory to develop confidence as an independent investigator.

I am fully committed to serving as a mentor both to individual students in my laboratory as well as the broader student body at UCSF. Although there was not a teaching requirement for my graduate program (nor at my postdoctoral position), I have actively sought experience with teaching throughout my training. At UCSF, I co-instruct the graduate course Chemistry 244, which introduces students to advanced organic reaction mechanisms. I also serve as a lecturer for PCOL131 (antibiotics and chemotherapy), during which I introduced School of Pharmacy students to protein synthesis inhibitors. Finally, I founded the Synthesis Journal Club, a biweekly seminar designed to keep students and other researchers up to date with current chemistry literature (the first of its kind at UCSF, attended by 20+ students).

The four publications below provide a picture of the breadth of my research, including complex molecule synthesis, methods development, and medicinal chemistry. My research is also expanding to include a significant anticancer component (publications to come).

a. Li Q, Seiple IB. Modular, scalable synthesis of group A streptogramin antibiotics. J Am Chem Soc. 2017 139, 13304-13307. PMID: 28902996.

b. Yao Y, Cai L, Seiple IB. Synthesis, structural reassignment, and antibacterial evaluation of 2,18-seco-lankacidinol B. Angew Chem Int Ed. 2018 57:13551-13554. PMID: 30133094

c. Seiple IB, Zhang Z, Jakubec P, Langlois-Mercier A, Wright PM, Hog DT, Yabu K, Allu SR, Fukuzaki T, Carlsen PN, Kitamura Y, Zhou X, Condakes ML, Szczypinski FT, Green WD, Myers AG. A platform for the discovery of new macrolide antibiotics. Nature. 2016 533:338-345. PMID: 27193679

d. Seiple IB, Su S, Young IS, Nakamura A, Yamaguchi J, Jørgensen L, Rodriguez RA, O'Malley DP, Gaich T, Köck M, Baran PS. Enantioselective total syntheses of (-)-palau'amine, (-)-axinellamines, and

(-)-massadines. J Am Chem Soc. 2011 Sep 21; 133(37):14710-26. PMID: 21861522. PMCID: PMC3173569

B. Positions and Honors

Positions and Employment

2014-2015 Consultant, Macrolide Pharmaceuticals
2015-present Assistant Professor, Pharmaceutical Chemistry, University of California, San Francisco
2015-present Member, UCSF Cardiovascular Research Institute

Other Experience and Professional Memberships

2015-present American Association for the Advancement of Science, Member
2016-present Graduate Fellowship Review Board Member, National Science Foundation
2016-present Royal Society of Chemistry, Reviewer
2017-present American Chemical Society, Member and Reviewer
2017-present Nature Publishing Group, Reviewer

Honors

2002 Valedictorian of 2002 Graduating Class, Newbury Park High School
2002 Robert C. Byrd Undergraduate Fellowship, University of California, Berkeley
2002 Dean's List, University of California, Berkeley
2006 Merck Index Award for Undergraduate Research, University of California, Berkeley
2006 Dean's Fellowship, The Scripps Research Institute
2008 GRFP Predoctoral Fellowship, National Science Foundation
2008 Best Chemistry Lecture, 2008 Scripps Symposium, The Scripps Research Institute
2009 Excellence in Chemistry Award, Roche
2009 Japan Global Center of Excellence Featured Speaker, Tohoku University
2010 Graduate Fellowship, Bristol–Myers Squibb
2011 Ruth L. Kirschstein National Research Service Award Individual Postdoctoral Fellowship, National Institutes of Health
2015 UCSF Program for Breakthroughs in Biomedical Research, New Frontier Research Award
2016 UCSF Catalyst Award for Translational Research
2017 UC Cancer Research Coordinating Committee Award
2018 NIH NIGMS Maximizing Investigators' Research Award (MIRA)
2018 Beckman Young Investigator's Award
2018 Packard Fellowship in Science and Engineering

C. Contributions to Science

1. I worked with a team of several colleagues to develop scalable, modular platform for the synthesis of novel macrolide antibiotics with the goal of overcoming multidrug-resistant bacterial infections. We developed a route to novel antibiotics that proceeds in as few as 10 steps and up to 42% overall yield. We utilized this platform to produce over 300 novel macrolide antibiotic candidates, many of which show promising activity against Gram-positive and Gram-negative bacteria (including multidrug-resistant strains). This work led to the development of a glycine aldol methodology that provides access to beta-hydroxyamino acids as single stereoisomers, and to the founding of Macrolide Pharmaceuticals, a company that uses our technology to develop new macrolide antibiotics (and has produced over 800 macrolides to date).
    a. Seiple IB, Zhang Z, Jakubec P, Langlois-Mercier A, Wright PM, Hog DT, Yabu K, Allu SR, Fukuzaki T, Carlsen PN, Kitamura Y, Zhou X, Condakes ML, Szczypinski FT, Green WD, Myers AG. A platform for the discovery of new macrolide antibiotics. Nature. 2016 533,338-345. PMID: 27193679
    b. Seiple, I. B.; Hog, D. T.; Myers, A. G. Practical Protocols for the Preparation of Highly Enantioenriched Silyl Ethers of (R)-3-Hydroxybutan-2-one, Building Blocks for the Synthesis of Macrolide Antibiotics. Synlett. 2015; 1(27):57-60.
    c. Wright PM, Seiple IB, Myers AG. The evolving role of chemical synthesis in antibacterial drug discovery. Angew Chem Int Ed Engl. 2014 Aug 18; 53(34):8840-69. PMCID: PMC4536949

d. Seiple IB, Mercer JA, Sussman RJ, Zhang Z, Myers AG. Stereocontrolled synthesis of syn-ß-Hydroxy-a-amino acids by direct aldolization of pseudoephenamine glycinamide. Angew Chem Int Ed Engl. 2014 Apr 25; 53(18):4642-7. PMCID: PMC4191905

2. A primary focus of my career has been the development of fully synthetic routes to dimeric natural products belonging to the pyrrole–imidazole family, most of which were originally isolated from rare marine sponges. My coworkers and I developed the first route to palau'amine, the most synthetically challenging pyrrole–imidazole alkaloid that was shown to be a potent human proteasome inhibitor. I also played a major role in the synthesis of related family members, including the axinellamines and the massadines. In addition to providing the first laboratory syntheses of these rare marine natural products, our efforts resulted in the discovery of several new methodologies, including oxidations with silver(II) picolinate and catalyst- free aminations of aminobromoimidazoles. This project enabled follow-up investigations on the bioactivity of palau'amine, which was identified as a moderately potent human proteasome inhibitor.
   a. Seiple IB, Su S, Young IS, Nakamura A, Yamaguchi J, Jørgensen L, Rodriguez RA, O'Malley DP, Gaich T, Köck M, Baran PS. Enantioselective total syntheses of (-)-palau'amine, (-)-axinellamines, and (-)-massadines. J Am Chem Soc. 2011 Sep 21; 133(37):14710-26. PMCID: PMC3173569
   b. Seiple IB, Su S, Young IS, Lewis CA, Yamaguchi J, Baran PS. Total synthesis of palau'amine. Angew Chem Int Ed Engl. 2010 Feb 1; 49(6):1095-8. PMCID: PMC3367661
   c. O'Malley DP, Yamaguchi J, Young IS, Seiple IB, Baran PS. Total synthesis of (+/-)-axinellamines A and B. Angew Chem Int Ed. 2008; 47(19):3581-3. PMID: 18357612
   d. Yamaguchi J, Seiple IB, Young IS, O'Malley DP, Maue M, Baran PS. Synthesis of 1,9-dideoxy-pre-axinellamine. Angew Chem Int Ed. 2008; 47(19):3578-80. PMID: 18357598

3. Heterocycles are ubiquitous in small molecule therapeutics, and efficient methods to functionalize them are in great demand. Selective functionalization of nitrogen-containing heterocycles was a persistent challenge in our synthesis of the pyrrole–imidazole alkaloids, and indeed is a challenge to synthesis in general. I discovered that aryl- and alkylboronic acids could be used as radical precursors using silver catalysis under extremely mild, oxidative conditions (ambient temperature under air). The resulting radicals react rapidly with electron-deficient heterocycles and quinones, providing arylated and alkylated products. I also played a role in the development of a similar method to generate trifluoromethyl radicals under metal-free conditions, and showed their utility in the reaction with several electron-rich and electron-poor heterocycles without the need for prior functionalization. This project enabled a completely new approach to the functionalization of medicinally relevant molecules, and has already been applied by pharmaceutical companies to the expansion of chemical libraries and to the large-scale synthesis of drug candidates.
   a. Seiple IB, Su S, Rodriguez RA, Gianatassio R, Fujiwara Y, Sobel AL, Baran PS. Direct C-H arylation of electron-deficient heterocycles with arylboronic acids. J Am Chem Soc. 2010 Sep 29; 132(38):13194-6. PMCID: PMC2946225
   b. Fujiwara Y, Domingo V, Seiple IB, Gianatassio R, Del Bel M, Baran PS. Practical C-H functionalization of quinones with boronic acids. J Am Chem Soc. 2011 Mar 16; 133(10):3292-5. PMCID: PMC3964812
   c. Ji Y, Brueckl T, Baxter RD, Fujiwara Y, Seiple IB, Su S, Blackmond DG, Baran PS. Innate C-H trifluoromethylation of heterocycles. Proc Natl Acad Sci U S A. 2011 Aug 30; 108(35):14411-5. PMCID: PMC3167544

Complete List of Published Work in MyBibliography:

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/ian.seiple.1/bibliography/48886709/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

On-going Research Support

UC CRCC Award Seiple (PI) 01/01/2018-01/01/2019
UC Cancer Research Coordinating Committee
Synthesis of Novel Lankacidin Microtubule Stabilizers
This grant supports the development of a platform for the synthesis of lankacidins from a pool of simple, readily available chemical building blocks. The proposed research will provide an avenue to modify lankacidins to improve their antitumor activity. This project also offers great potential to advance understanding of

microtubule stabilization by providing access to novel chemical probes.
Role: PI

IRG-17-180-19 (Seiple) Seiple (PI) 02/01/18 - 01/01/19
American Cancer Society
Amino Acid N-Carboxyanhydrides as Precursors to Anticancer Cyclic Peptides
Herein we propose a method for the cyclization of linear peptides into cyclic peptides that relies on the strategic application of amino acid N-carboxyanhydrides (NCAs). Our method would enable macrocyclization to proceed without added chemical reagents and with carbon dioxide as the only byproduct.

P0528276 (Seiple) Seiple (PI) 09/01/2018 - 08/31/2022
Arnold and Mabel Beckman Foundation
Platforms for the generation of new classes of antibiotics
The major goals of this project are to use modern chemical synthesis to solve prevailing biological challenges. One of our primary objectives is to develop new strategies to overcome infections caused by multidrug-resistant bacteria. Innovation in this area is in dire need as infections emerge that are resistant to all current therapies.

R35GM128656 (Seiple) Seiple (PI) 09/01/2018 - 08/31/2023
NIH-NIGMS MIRA
Platforms for the Synthesis of Bacterial Protein Synthesis Inhibitors

Due to the continually increasing prevalence of multidrug-resistant bacterial infections and the paucity of antibiotics in the pipeline, there is a pressing need for new methods to bolster the armamentarium of antimicrobial therapeutics. This proposal will leverage innovations in chemical synthesis to develop antibiotic candidates using as templates natural and synthetic molecules that inhibit the bacterial ribosome.
Synthesis of Struturally Complex Therapeutics

P0530654 (Seiple) Seiple (PI) 11/01/2018 - 10/31/2023
David and Lucile Packard Foundation
Synthesis of Struturally Complex Therapeutics

Despite significant advances in drug discovery over the past century, an abundance of disease-associated biological targets remain challenging or impossible to drug with traditional small molecule therapeutics. Large, structurally complex molecules have shown promise in engaging these targets, but often have poor drug-like properties and are inherently challenging to optimize. The goal of this project is to overcome these two major limitations using modular synthesis and binding-induced hybridization.

Completed Research Support

F32GM099233 Seiple (PI, postdoc) 09/01/2011-08/29/2014
National Institutes of Health
Preparation of a Solid-Phase Polyketide Synthase Mimic
This project supported my work on polyketides of the erythromycin family of antibiotics (macrolides). While the initial grant strategy did not come to fruition, the project was fruitful, and resulted in the first scalable synthesis of macrolide antibiotics (broadly defined).
Role: PI-Postdoctoral Fellow

Program for Breakthrough Biomedical Research Seiple (PI) 02/01/2016-01/31/2017
Platform for the Discovery of Novel Pleuromutilin Antibiotics
A versatile platform for the discovery of fragments of pleuromutilin antibiotics was developed. This technology has the potential to transform this class to be suitable for systemic use in humans and to enable continual,

dynamic structural modifications to combat microbial resistance. Our route provides access to the core pharmacophore of pleuromutilins in only 7 steps, enabling future structural optimization informed by co-crystal structures.
Role: PI

UL1 TR001872 Seiple (PI) 12/01/2016-06/29/2018
NIH/UCSF Catalyst
A Platform for the synthesis of Antibiotics that Target the Peptidyl Transferase Center of Bacterial Ribosomes
This project aims to develop syntheses of several classes of antibiotics that target the peptidyl transferase center of the bacterial ribosome. Building block-based routes to each of these classes will be employed to generate analogs that will be tested for efficacy against panels of pathogenic bacteria, including several multidrug-resistant strains.
Role: PI