JIMMY A. BLAIR, PH.D.

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CHEMICAL BIOLOGY INVESTIGATOR

Medicinal & Synthetic Chemist • Protein Biochemist • X-ray Crystallographer

Enthusiastic chemical biology investigator and leader from the bench, currently directing an independent research team of undergraduates focused on developing novel antibiotics using structure-based drug design. Excellent scientific communication, collaboration, and team-building skills. Major areas of expertise include small-molecule inhibitor and chemical probe synthesis, protein biochemistry and assay development, recombinant protein expression and purification, structural biology including structure-based drug design and structure-guided protein engineering, and cell biology.

PROFESSIONAL EXPERIENCE

Williams College • Williamstown, MA • 2012 – present
Assistant Professor, Department of Chemistry

- Directed an undergraduate research program to develop novel antibiotics that inhibit bacterial histidine kinases.
    - Discovered and developed 3,4-diaryl pyrazole histidine kinase inhibitors, measured their selectivity among histidine kinases, and demonstrated their broad-spectrum antimicrobial effects.
    - Characterized the binding mode of 3,4-diaryl pyrazoles to the PhoQ histidine kinase using X-ray crystallography, revealing the key molecular interactions necessary to target histidine kinases.
    - Synthesized novel 1,4-diaryl triazole histidine kinase inhibitors using "click chemistry."
    - Designed assays to measure kinase activity, including a radioactive ^{32}P-ATP dot-blot assay for histidine phosphorylation and a ThermoFluor thermal shift assay to measure ligand binding to histidine kinases.
- Managed a budget of $149,986 for research and teaching.
- Managed and trained 19 undergraduate researchers; five attended graduate school; 13 attended medical school.
- Equipped a biophysical chemistry teaching laboratory for up to 50 students, which involved choosing, purchasing, and deploying ~$10,000 of equipment and supplies.
- Taught across the Chemistry Department curriculum in the organic chemistry and biological chemistry courses, including *Introductory Organic Chemistry* (CHEM 156); *Intermediate Organic Chemistry* (CHEM 251); *Chemical Biology—Discoveries at the Interface* (CHEM 326); and *Biophysical Chemistry* (CHEM 367).
- Developed an upper-level undergraduate course in *Chemical Biology* (CHEM 326) and laboratory experiments in *Biophysical Chemistry* (CHEM 367).
- Managed undergraduate lab teaching assistants and graders for *Organic* and *Biophysical Chemistry* courses.
- Taught 860 students over 11 semesters in class sizes ranging from seven to 130 students.

Stanford University • Stanford, CA • 2008 – 2012
NIH Postdoctoral Fellow • Department of Developmental Biology • Advisor: Lucy Shapiro, Ph.D.

- Designed and directed a project that solved the X-ray crystal structure of ChpT, an essential, novel phosphotransferase in the bacterium *Caulobacter crescentus*.
- Designed and analyzed biochemical and cellular assays to determine molecular-level protein-protein interactions of ChpT with its signaling partners.
- Established and managed a collaboration with staff scientists at SLAC National Laboratory; together, we solved two X-ray crystal structures of *Caulobacter* signaling proteins.
- Trained a physical chemist postdoc in molecular cloning and protein purification; our work led to solving the crystal structure of an essential pseudo-kinase.

PROFESSIONAL EXPERIENCE (CONTINUED)

University of California, Berkeley • Berkeley, CA • 2002 – 2008
Graduate Student Researcher • Department of Chemistry • Advisor: Kevan Shokat, Ph.D.

- Rationally designed and synthesized chemical tool molecules, based upon irreversible protein kinase inhibitors, to measure in-cell activity of key protein kinases involved in cancer; characterized covalent binding to engineered kinases using intact protein mass spectrometry and X-ray crystallography.
- Solved four co-crystal structures of c-Src kinase with inhibitors that potently inhibit both tyrosine and phosphoinositide kinases, revealing key chemical motifs that enable inhibition of kinase families sharing little structural similarity; these data helped establish design principals for development of a clinical candidate.
- Managed and assisted a team that solved the first co-crystal structures of irreversible inhibitors bound to tyrosine kinases (engineered c-Src-S349C and wild-type EGFR).
- Mentored two graduate rotation students in synthetic chemistry and cell biology techniques; together, we designed affinity probes for protein tyrosine kinases.

Carleton College • Northfield, MN • 2007
Visiting Instructor • Department of Chemistry

- Taught one term of Introductory Organic Chemistry laboratory to 82 students and managed nine undergraduate teaching assistants.

EDUCATION

Ph.D. in Chemistry • 2008
University of California, Berkeley • Advisor: Kevan Shokat, Ph.D.
Dissertation: *Chemical genetic tools to measure and regulate cellular kinase activity*

B.A. in Chemistry • *magna cum laude* • 2002
Carleton College • Northfield, MN • Advisor: David Alberg, Ph.D.
Senior independent study: *Synthesis of macrocyclic-epoxide, mechanism-based inhibitors of trypanothione reductase*

AWARDS AND GRANTS

2016 – 2018	The Hellman Fellows Fund • $19,986 *Designer antibiotics: crystallography-guided histidine kinase drug design*
2009 – 2011	National Institutes of Health National Research Service Award Postdoctoral Fellowship • $97,684 *Dissection of Phospho-signaling that Controls the* Caulobacter *Cell Cycle* • Grant #5F32AI082915-02
2002	Distinction in the Major & Distinction in the Integrative Exercise • Carleton College
2002	Outstanding Achievement in Chemistry • American Institute of Chemists
2002	Sigma Xi Honor Society
1993	Eagle Scout • Boy Scouts of America

SKILLS & TECHNICAL EXPERTISE

***Synthetic & medicinal chemistry*:** small-molecule synthesis of bioactive inhibitors, affinity probes, and tool compounds; evaluation of structure-activity relationships and drug-like properties; chemical characterization by 1D and 2D NMR, LC-MS, and IR; normal and reverse phase purification including automated purification methods on CombiFlash and HPLC instruments; solution and solid phase peptide synthesis

SKILLS & TECHNICAL EXPERTISE (CONTINUED)

***Biochemistry*:** recombinant protein expression and purification from *E. coli*; affinity capture, anion exchange, and gel filtration chromatography on ÄKTA instruments; SDS PAGE and western blot protein analysis; limited proteolysis protein analysis; intact protein MS; design of coupled-enzyme ATPase assays & radioactive (^{32}P) phosphotransfer assays in 96-well format; design of ThermoFluor thermal shift assays using BioRad RT-PCR; assay design on SpectraMax and BioTek plate readers; data analysis and curve fitting with GraphPad Prism software

***Molecular biology*:** PCR and primer design; site-directed mutagenesis; cloning from bacterial genomic DNA; gene construction for recombinant protein expression including restriction enzyme, Gibson assembly, and LIC techniques

X-ray crystallography: crystal formation and optimization; data collection and processing; model building of co-crystal structures complexed with small-molecule inhibitors; experience with the following crystallography software packages: CCP4, COOT, PHENIX, PyMOL, UCSF Chimera; and OpenEye Scientific's AFITT, OEDocking, and OMEGA

***Cell biology*:** bacterial cell biology in *C. crescentus*; multi-color fluorescence and phase-contrast microscopy; flow cytometry analysis of DNA content; MIC cell growth assays; standard tissue culture of mouse fibroblast cell lines

***Instrumentation*:** NMR (Bruker & Varian); LC-MS (Agilent & Bruker); Multimode plate reader (BioTek & SpectraMax); BioRad CFX96 RT-PCR; ÄKTA Pure FPLC; CombiFlash automated chromatography; GE Typhoon FLA flatbed imager; Epifluorescence microscopes (Leica & Nikon)

PUBLICATIONS

1. Vo, C. D.*; Shebert, H. L.*; Zikovich, S.*; Dryer, R. A.*; Huang, T. P.*; Moran, L. J.*; Cho, J.*; Wassarman, D. R.*; Falahee, B. E.*; Young, P. D.*; Gu, G. H.*; Heinl, J. F.*; Hammond, J. W.*; Jackvony, T. N.*; Frederick, T. E.; **Blair, J. A.** Repurposing Hsp90 inhibitors as antibiotics targeting histidine kinases. *Bioorganic & Medicinal Chemistry Letters* **2017**, *27*, 5235–5244. * Williams College student collaborators.

2. Mann, T. H.; Childers, W. S.; **Blair, J. A.**; Eckart, M. R.; Shapiro, L. A cell cycle kinase with tandem sensory PAS domains integrates cell fate cues. *Nature Communications* **2016**, *7*, 11454.

3. Stott, K. V.; Wood, S. M.; **Blair, J. A.**; Nguyen, B. T.; Herrera, A.; Mora, Y. P.; Cuajungco, M. P.; Murray, S. R. (p)ppGpp modulates cell size and the initiation of DNA replication in *Caulobacter crescentus* in response to a block in lipid biosynthesis. *Microbiology* **2015**, *161*, 553–564.

4. Childers, W. S.; Xu, Q.; Mann, T. H.; Mathews, I. I.; **Blair, J. A.**; Deacon, A. M.; Shapiro L. Cell fate regulation governed by a repurposed bacterial histidine kinase. *PLoS Biology* **2014**, *12*, e1001979.

5. **Blair, J. A.**; Xu, Q.; Childers, W. S.; Mathews, I. I.; Kern, J. W.; Eckart, M.; Deacon, A. M.; Shapiro, L. Branched signal wiring of an essential bacterial cell-cycle phosphotransfer protein. *Structure* **2013**, *21*, 1590–1601.

6. Barkovich, K. J.; Hariono, S.; Garske, A. L.; Zhang, J.; **Blair, J. A.**; Fan, Q.-W.; Shokat, K. M.; Nicolaides, T.; Weiss, W. A. Kinetics of Inhibitor Cycling Underlie Therapeutic Disparities between EGFR-Driven Lung and Brain Cancers. *Cancer Discovery* **2012**, *2*, 450–457.

PUBLICATIONS (CONTINUED)

7. Amin, D. N.; Sergina, N. V.; Ahuja, D.; McMahon, M.; **Blair, J. A.**; Wang, D.; Hann, B.; Koch, K. M.; Shokat, K. M.; Moasser, M. M. Resiliency and vulnerability in the HER2-HER3 tumorigenic driver. *Science Translational Medicine* **2010**, *2*, 16ra7.

8. Wong, C. H.; Baehner, F. L.; Spassov, D. S.; Ahuja, D.; Wang, D.; Hann, B.; **Blair, J.**; Shokat, K. M.; Welm, A. L.; Moasser, M. M. Phosphorylation of the SRC epithelial substrate Trask is tightly regulated in normal epithelia but widespread in many human epithelial cancers. *Clinical Cancer Research* **2009**, *15*, 2311–2322.

9. Apsel, B.; **Blair, J. A.**; Gonzalez, B.; Nazif, T. M.; Feldman, M. E.; Aizenstein, B.; Hoffman, R.; Williams, R. L.; Shokat, K. M.; Knight, Z. A. Targeted polypharmacology: discovery of dual inhibitors of tyrosine and phosphoinositide kinases. *Nature Chemical Biology* **2008**, *4*, 691–699.

10. **Blair, J. A.**; Rauh, D.; Kung, C.; Yun, C.-H.; Fan, Q.-W.; Rode, H.; Zhang, C.; Eck, M. J.; Weiss, W. A.; Shokat, K. M. Structure-guided development of affinity probes for tyrosine kinases using chemical genetics. *Nature Chemical Biology* **2007**, *3*, 229–238.

11. Sergina, N. V.; Rausch, M.; Wang, D.; **Blair, J.**; Hann, B.; Shokat, K. M.; Moasser, M. M. Escape from HER-family tyrosine kinase inhibitor therapy by the kinase-inactive HER3. *Nature* **2007**, *445*, 437–441.

PRESENTATIONS

1. **Blair, J. A.** *Discovery of broad-spectrum antibiotics targeting histidine kinases from repurposed and new scaffolds*. Poster: ChemBio in the Hub Symposium, Novartis, Cambridge, MA. October 2018.

2. **Blair, J. A.** *Repurposing cancer drugs as antibiotics: Development of Hsp90 inhibitors as inhibitors of bacterial histidine kinases*. Talk: Department of Biochemistry and Molecular Pharmacology, UMass Medical School. December 2016.

3. **Blair, J. A.** *Hsp90 inhibitors as lead molecules for histidine kinase inhibition: Toward novel antibiotics*. Poster: 251st ACS National Meeting, San Diego, CA. March 2016.

4. **Blair, J. A.** *Developing histidine kinase inhibitors: Antibiotic drug discovery at Williams*. Talk: Biological Chemistry Seminar Series, Wesleyan University. March 2015.

5. **Blair, J. A.** *Building a key from scratch*. Talk: Bronfman Science Lunch Speaker Series, Williams College. April 2013.

6. **Blair, J. A.** *The ChpT crystal structure reveals key features for recognition of its three cognate proteins*. Talk: The Fourth *Caulobacter* Meeting, McGill University, Montreal, Canada. May 2012.

7. **Blair, J. A.** *Structural clues to understanding the* Caulobacter crescentus *cell cycle*. Talk: JCSG 10th Annual Meeting, The Scripps Research Institute. April 2012.

8. **Blair, J. A.** *The hunt for regulators of an essential histidine kinase in* Caulobacter. Talk: 3D Club, Department of Developmental Biology, Stanford University. May 2010.

PRESENTATIONS (CONTINUED)

9. **Blair, J. A.** *Designed to report: A kinase affinity probe quantifies EGFR inhibition in cells*. Talk: Chemical Biology in the Bay Area Meeting, University of California, Berkeley. January 2008.

10. **Blair, J. A.** *Harnessing the power of chemical genetics: Rationally-designed affinity probes for tyrosine kinases report EGFR inhibition in cells*. Talk: Department of Chemistry, Carleton College. October 2007.

11. **Blair, J. C. A.** and Alberg, D. G. *Trypanothione reductase inhibition: Synthesis of mechanism-based inhibitors*. Poster: 223rd ACS National Meeting, Orlando, FL. April 2002.

PROFESSIONAL ACTIVITIES

2014 – Present	Member, American Chemical Society
2012 – Present	Member, Williams College Biochemistry & Molecular Biology (BIMO) Program Committee
2018	Reviewer, *Molecular & Cellular Proteomics*
2016 – 2017	Member, Williams College Honor and Discipline Committee; also served in 2014 – 2015
2016	Panelist, *Careers at Liberal Arts Colleges*, Harvard Chemical Biology Program Retreat
2016	Reviewer, *ACS Chemical Biology*
2014	Reviewer, *ACS Chemical Biology* & *Journal of Visualized Experiments*
2013 – 2014	Member, Williams College Science Executive Committee & Divisional Research Funding Committee
2013	External reviewer, South Carolina EPSCoR/IDeA GEAR:RE program
2008 – 2009	Reviewer, *Cancer Research*

INTERESTS

2017	Member, Williams College Ultimate Frisbee Fall Intramural Champions, Team Avocado
2017	Invited speaker, The Latke-Hamentaschen Debate, Williams College Jewish Association
2003 – 2004	President, Cal Cycling, University of California, Berkeley cycling team
1998 – 2002	NCAA Division III athlete in cross-country, track & field, Carleton College
	Landscape & travel photographer • Alpine skier, cyclist & runner • Home coffee roaster