BIOGRAPHICAL SKETCH

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NAME: Christina R. Bourne

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

POSITION TITLE: Associate Professor

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
University of Oklahoma, Norman OK	BS	05/1997	Biochemistry
Oklahoma Medical Research Foundation and OU Health Sciences Center, Oklahoma City OK	PhD	10/2003	Biochemistry, Mol Biol and Structural Biology
OU Health Sciences Center, Oklahoma City OK	Postdoctoral Fellow	10/2007	Structural Virology

A. Personal Statement

I have more than 20 years of experience in biochemistry and structural biology, including 15 years working in microbiology and antibacterial development. My research interests focus on targeting drug-resistant and chronic bacterial infections, and I am especially motivated to develop innovative new methods and novel targets to control bacterial growth.

I have built my independent research program to study Toxin Antitoxin systems (publications a-c), including a strong mentoring philosophy that shapes a productive team. These are challenging proteins to produce and work with, and my team has gained significant expertise. We have identified a protective effect to anti-gyrase antibiotics, including fluoroquinolones, mediated by a chromosomal ParE-type toxin (publication a). An important finding from this work was the concentration-dependence of toxin phenotypes, introducing a new concept in the field - that toxin effects can be attenuated by concentration and exposure time. This strongly suggests that chromosomally-encoded TA systems could be integrated into pro-survival pathways in bacterial cell physiology. We have also compared the toxicities of different ParE toxins following over-expression in *E. coli.* This has allowed for the first time a direct comparison within the family (publication b). We have also focused on the interaction of the ParE toxin with its cognate ParD antitoxin, and recently identified a key position that can greatly weaken the kinetics of interaction (publication c). This demonstrates a feasible strategy for manipulation of these systems to impact bacterial cell growth.

Our current investigations build from our previously funded work in relating structure to function of ParE toxins, and has expanded through our current funding from the Department of Defense to formulate a central hypothesis of the structure-function relationship of how different sequence motifs found in ParE toxins differentially interact with and inhibit DNA gyrase.

a. Muthuramalingam M, White JC, Murphy, T., Ames, J.R., **Bourne C.R.** The toxin from a ParDE toxin-antitoxin system found in *Pseudomonas aeruginosa* offers protection to cells challenged with anti-gyrase antibiotics. Mol. Microbiol. 2019 Feb; 111(2):441-54. PMID: 30427086; PMCID: PMC6368863.

b. Ames, J.R., Muthuramalingam M, Murphy, T., Najar F.Z., **Bourne C.R.** Expression of different ParE toxins results in conserved phenotypes with distinguishable classes of toxicity. Microbiol. Open. 2019 July; e902. PMID: 31309747; PMCID: PMC6813445.

c. Snead, K.S., Moore, L., **Bourne, C.R.** ParD antitoxin hotspot alters a disorder-to-order transition upon binding to its cognate ParE toxin, lessening its interaction affinity and increasing its protease degradation kinetics. ACS Biochemistry 2021 Dec; PMID: 34914378; PMCID: *in progress.*

Ongoing and completed projects that I would like to highlight:

d. U.S. Army, Department of Defense W81XWH2010121 (PI: C. Bourne) 02/20 – 02/23

"Unlocking the potential of bacterial ParE toxins: developing a blueprint for co-opting molecular time bombs that impact bacterial cell survival"
This project is examining the phenotypic outcomes for four human bacterial pathogens when their native chromosomal ParE toxins are over-expressed within the native host cells. A proof-of-concept study design will assess the efficiency of antitoxin removal from these ParE systems in an *E. coli* host.

e. Oklahoma Center for the Advancement of Science HR17-099 (PI: C. Bourne) 07/17 – 3/21

"Targeting bacterial cell metabolism by manipulating toxin-antitoxin systems"
The goal of this project was to identify a strategy to interrupt the interactions of a chromosomally encoded ParE gyrase-inhibiting toxin with its cognate ParD antitoxin. We characterized a novel mechanism of weakening the interaction of toxin with antitoxin by perturbing the dynamics of antitoxin association and increasing the off-rate of interaction by 1000-fold. This proof-of-principle study demonstrated that increased off-rates could promote greatly increased antitoxin degradation, thereby providing a novel therapeutic intervention strategy.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021 - *current* Associate Professor, U. of Oklahoma, Dept. of Chemistry and Biochemistry, Norman, OK
2021 – (*2023)* U. of Oklahoma, Dept. of Chemistry and Biochemistry, Executive Committee Member (elected)
Member, User Review Committee, National Center for CryoEM Access and Training (NCCAT)
2021 - *current*
2017 - *current* Member (Chair, effective 2021), Advisory Committee, OU Biomolecular Structure Core Facility
2015 - *current* Member, OU Institutional Biosafety Committee
2014 - 2021 Assistant Professor, U. of Oklahoma, Dept. of Chemistry and Biochemistry, Norman, OK
2011 - 2013 Member (Chair, 2012-2013) BEI Resources Scientific Focus Group for Biodefense and High Containment Bacteria
2007 – 2013 Associate Research Scientist, Oklahoma State University, Center for Veterinary Health Sciences, Stillwater, OK
2005 – 2007 American Cancer Society Mary Horton Postdoctoral Fellow, University of Oklahoma Health Sciences Center, Oklahoma City, OK
2003 Adjunct Instructor, Oklahoma City Community College, Science Division, Oklahoma City, OK
1997 - 1998 Associate Research Technician, Oklahoma Medical Research Foundation, Dept. of Crystallography, Oklahoma City, OK

Other Experience and Professional Memberships

Ad Hoc manuscript reviewer (limited to the previous 4 years): *ACS Medicinal Chemistry, ACS Omega, Frontiers in Microbiology, Frontiers in Genetics, Genes, Journal of Biochemistry, mBio, Medicinal Research Reviews, Microorganisms, Molecular Microbiology, Nature Reviews in Microbiology, Nucleic Acids Research, Protein Science, Structure, Toxins*
Proposal reviews (limited to previous 4 years): French National Research Agency, BBSRC, US Army Research Office, NIH Special Emphasis Panel ZRG1 BST-M, University of Missouri Research Board, University of Central Oklahoma

Member, American Crystallographic Association (2001-present), American Society for Biochemistry and Molecular Biology (2003-present), American Society for Microbiology (2008-present), American Association for the Advancement of Science(2017-present)

2021 - *current* Member, Editorial Board, *Frontiers in Microbiology* specialty section Microbial Physiology and Metabolism
2014 - 2017 Member, Editorial Board, *Scientific Reports*
2011 - 2017 Member, Editorial Advisory Board, *Journal of Molecular Recognition*
2015 Tech to Trek guest promoting science careers to young women, Southwestern Okla State Uni.
2015 Participant, BioCAT Advanced SAXS Training Course, Argonne National Laboratory
2000, 2014 Participant, RapiData X-ray Diffraction Data Collection and Structure Solving at Brookhaven National Laboratory, Upton, NY
2012 - 2013 Mentor, Oklahoma State University Women's Mentorship Program

2010	Guest Scientist, Community outreach program “Born To Do Science”
2009	Participant, MolSoft2009 Workshop on Modern Drug Target Crystallography and Structure Based Drug Discovery, San Diego, CA

Honors

2020	Nancy L. Mergler Faculty Mentor Award for Undergraduate Research
2020	Peggy Cotter Branch Travel Award, American Society of Microbiology
2018	OK - Louis Stokes Alliance for Minority Participation (LSAMP) Outstanding Faculty Mentor Award (Norman campus)
2014, 2015	VPR Summer Faculty Fellowship, University of Oklahoma
2005	Mary Horton Postdoctoral Fellowship, American Cancer Society
2005	Travel Grant, US National Committee for Crystallography
2003	Pauling Poster Prize, American Crystallographic Association
2001	Ludo Frevel Crystallography Scholarship, International Centre for Diffraction Data

C. Contributions to Science

1. **Toxin Antitoxin systems as targets to control bacterial growth:** I joined the field of Toxin Antitoxin (TA) systems when I started my independent position at OU. My team has worked to characterize and compare the extensive interaction interfaces between the toxin and antitoxin proteins with an aim of manipulating them to alter bacterial growth. An early contribution was a critical assessment of antitoxin half-life, culminating in a review article examining the evidence for protease degradation of these molecules (publication f). The shortened half-life of antitoxins also appears relevant to purified samples, and we have deduced an intrinsic degradation specifically at the toxin-binding region (g). Through our studies we also characterized RNase-type toxins, and identified a promiscuous nuclease activity and species-specific toxicity for the YoeB type (h, i).

   f. Muthuramalingam M, White JC, **Bourne CR.** Toxin-Antitoxin Modules Are Pliable Switches Activated by Multiple Protease Pathways. Toxins (Basel). 2016 Jul 9;8(7)PubMed PMID: 27409636; PubMed Central PMCID: PMC4963847.

   g. Snead, K.J., **Bourne C.R**. Intrinsic degradation of the Type-II antitoxin ParD from *Pseudomonas aeruginosa*. *bioRxiv* 2021 March; doi: 10.1101/2021.03.29.437564.

   h. Ames, J.R., McGillick, J., Murphy, T., Reddem, E., **Bourne, C.R.** Identifying a molecular mechanism that imparts species-specific toxicity to YoeB toxins. Front. Micro. 2020 May; 11:(article)959. PMID: 32528435; PMCID: PMC7256200.

   i. McGillick, J., Ames, J.R., Murphy, T., **Bourne C.R.** A YoeB toxin cleaves both RNA and DNA. 2021 Sci. Reports *11:3592.* PMID: 33574407 PMCID: PMC7878887.

2. **New inhibitors of bacterial biosynthetic folate pathway:** I carried out screening, biochemical assays, and structural biology for inhibitors of whole bacterial (including Select Agent) cell growth, and I expanded a commercial screening platform by developing novel analysis methodology (publication j). I crystallized and solved the structures of the dihydrofolate (DHFR) from three different bacteria (publication k, l). I carried out extensive SAR studies to characterize a series of inhibitors derived from the structure of the antibiotic trimethoprim, including whole cell MIC measurements, *in vitro* enzyme activity inhibition, and three-dimensional structure determinations. These studies have been continued and expanded in my independent lab at OU (publication m).

   j. **Bourne CR**, Wakeham N, Bunce RA, Nammalwar B, Berlin KD, Barrow WW. Classifying compound mechanism of action for linking whole cell phenotypes to molecular targets. J Mol Recognit. 2012 Apr;25(4):216-23. PubMed PMID: 22434711; PubMed Central PMCID: PMC3703735.

   k. **Bourne CR**, Wakeham N, Nammalwar B, Tseitin V, Bourne PC, Barrow EW, Mylvaganam S, Ramnarayan K, Bunce RA, Berlin KD, Barrow WW. Structure-activity relationship for enantiomers of potent inhibitors of *B. anthracis* dihydrofolate reductase. Biochim Biophys Acta. 2013 Jan;1834(1):46-52. PubMed PMID: 22999981; PubMed Central PMCID: PMC3530638.

   l. **Bourne CR**, Wakeham N, Webb N, Nammalwar B, Bunce RA, Berlin KD, Barrow WW. The structure and competitive substrate inhibition of dihydrofolate reductase from *Enterococcus faecalis* reveal

restrictions to cofactor docking. Biochemistry. 2014 Feb 25;53(7):1228-38. PubMed PMID: 24495113; PubMed Central PMCID: PMC3985486.

m. Muddala, P.N., White, J.C., Nammalwar, B., Pratt, I., Thomas, L.M., Bunce, R.A., Berlin, K.D., **Bourne, C.R.** Inhibitor design to target a unique feature in the folate pocket of *Staphylococcus aureus* dihydrofolate reductase. 2020 Eur. J. Med. Chem. 200:112412. Pubmed PMID: 32502861.

3. **A new strategy for antiviral therapy using misdirection of capsid assembly:** As a post-doc I contributed to validating a novel approach to anti-viral therapies by altering the assembly pathway of the Hepatitis B virus capsid assembly. Using biophysical measurements and biochemical assays, we determined this compound mis-directed HBV assembly (publication n) and I identified a lab-derived genotype that could mimic these effects (publication o). I was awarded a fellowship from the American Cancer Society to pursue structural studies, and these resulted in identifying the binding pocket for these compounds, contributed to structure-guided compound modifications, and subsequently tested derivatized compounds to validate the compound orientation (publications p, q). This work is on-going in the lab and start-up company (Assembly Biosciences) of Dr. Adam Zlotnick (postdoc supervisor).

   n. Stray SJ, **Bourne CR**, Punna S, Lewis WG, Finn MG, Zlotnick A. A heteroaryldihydropyrimidine activates and can misdirect hepatitis B virus capsid assembly. Proc Natl Acad Sci U S A. 2005 Jun 7;102(23):8138-43. PubMed PMID: 15928089; PubMed Central PMCID: PMC1149411.

   o. **Bourne CR**, Katen SP, Fulz MR, Packianathan C, Zlotnick A. A mutant hepatitis B virus core protein mimics inhibitors of icosahedral capsid self-assembly. Biochemistry. 2009 Mar 3;48(8):1736-42. PubMed PMID: 19196007; PubMed Central PMCID: PMC2880625.

   p. **Bourne CR**, Finn MG, Zlotnick A. Global structural changes in hepatitis B virus capsids induced by the assembly effector HAP1. J Virol. 2006 Nov;80(22):11055-61. PubMed PMID: 16943288; PubMed Central PMCID: PMC1642186.

   q. **Bourne C**, Lee S, Venkataiah B, Lee A, Korba B, Finn MG, Zlotnick A. Small-molecule effectors of hepatitis B virus capsid assembly give insight into virus life cycle. J Virol. 2008 Oct;82(20):10262-70. PubMed PMID: 18684823; PubMed Central PMCID: PMC2566253.

4. **Structure and function of human antibodies:** My graduate work focused on mechanisms of protein crystal growth and their application to the structural properties of human antibodies. I participated in studies conducted on flight missions STS-95 and STS-107 to evaluate the effect of microgravity on protein crystal quality (publication r). One sample produced a very large crystal, and the subsequent structure determination revealed improved diffraction properties (publication s). Other work identified an inherent proteolytic capacity of a subset of neoplastic-derived human IgM antibodies (publications t, u), a revolutionary finding that is still an active area of research, for example in the Ramsland lab at RMIT, Melbourne, AU.

   r. Alverado UR, **DeWitt CR**, Shultz BB, Ramsland PA, Edmundson AB. A method for growing protein crystals in capillary tubes. J Cryst Growth 2001; 233:407-414.

   s. Terzyan SS, **Bourne CR**, Ramsland PA, Bourne PC, Edmundson AB. Comparison of the three-dimensional structures of a human Bence-Jones dimer crystallized on Earth and aboard US Space Shuttle Mission STS-95. J Mol Recognit. 2003 Mar-Apr;16(2):83-90. PubMed PMID: 12720277.

   t. Ramsland PA, Upshaw JL, Shultz BB, **DeWitt CR**, Chissoe WF, Raison RL, Edmundson AB. Interconversion of different crystal forms of Fabs from human IgM cryoglobulins. J Cryst Growth 2001; 232:204-214.

   u. Ramsland PA, Terzyan SS, Cloud G, **Bourne CR**, Farrugia W, Tribbick G, Geysen HM, Moomaw CR, Slaughter CA, Edmundson AB. Crystal structure of a glycosylated Fab from an IgM cryoglobulin with properties of a natural proteolytic antibody. Biochem J. 2006 May 1;395(3):473-81. PubMed PMID: 16422668; PubMed Central PMCID: PMC1462693.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/10usXwuC15FAk/bibliography/47974641/public/?sort=date&direction=descending