BIOGRAPHICAL SKETCH

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NAME: Rebecca Wagner Alexander

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

POSITION TITLE: Professor of Chemistry

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	Completion Date	FIELD OF STUDY
University of Delaware	Honors B.S.	05/1990	Chemistry
University of Pennsylvania	PhD	05/1996	Biological Chemistry
Massachusetts Institute of Technology	Postdoctoral	06/1997	Biochem/Molec. Biol.
The Scripps Research Institute	Postdoctoral	08/1999	Chemical Biology

A. Personal Statement

Scientific expertise: This project aims to investigate the three-dimensional structure and enzymatic activities of an aminoacyl-tRNA synthetase from the human pathogen *Mycoplasma penetrans*. This enzyme has an N-terminal appended domain that confers an apparently novel activity to the canonical tRNA aminoacylation function of the core enzyme methionyl-tRNA synthetase (MetRS). I have extensive experience with the basic molecular biochemical techniques used in this study. We have worked with MetRS from other organisms (primarily *E. coli* but also *B. cenocepacia*) and are experienced in studying mechanisms of tRNA aminoacylation using mutagenic structure-function analysis, pre-steady-state kinetics, and computational modeling of protein and RNA dynamics. While I currently hold a full-time administrative post in the Office of the Dean of the College at Wake Forest University, I have been able to maintain an active research lab with excellent collaborations and technical support.

Exposing students to meritorious research: I am enthusiastically committed to providing meaningful research experiences for young scientists at all levels (high school through postdoctoral). WFU provides students the best combination of a liberal arts education and research participation mentored by externally funded scholars. Since 2000, I have mentored 72 undergraduates and 5 high school students, including 5 minority students and 47 women. My lab currently has 2 graduate students and 6 undergraduates, including 1 minority student and 4 women. Students participate in local, regional, and national/international conferences, such as WFU's Undergraduate Research Day, the RNA Society of NC's Symposium on RNA Biology, the international tRNA Conference, and the International Symposium on Aminoacyl-tRNA Synthetases. Undergraduates have gone on to PhD programs at the Scripps Research Institute, Johns Hopkins University, Notre Dame University, and other highly ranked graduate programs. Students have also matriculated into medical school at UNC-Chapel Hill, WFU, and the University of Alabama at Birmingham and MD-PhD programs at the Universities of Iowa and Pennsylvania.

B. Positions and Honors

Positions and Employment

1990 - 1996	Research Assistant, University of Pennsylvania
1991 - 1994	NSF Predoctoral Fellow, University of Pennsylvania
1996 - 1997	NIH Postdoctoral Fellow, Massachusetts Institute of Technology
1997 - 1999	NIH Postdoctoral Fellow, The Scripps Research Institute
2000 - 2007	Assistant Professor of Chemistry, Wake Forest University
2007 - 2013	Associate Professor of Chemistry, Wake Forest University

2008 - 2014	Co-Director, Undergraduate Research and Creativity Center, Wake Forest University
2000 - present	Associate, Dept. of Cancer Biology, Wake Forest University School of Medicine
2004 - present	Member, Ctr. for Structural Biology, Wake Forest University School of Medicine
2010 - present	Co-Director, Center for Molecular Signaling and Communication, Wake Forest University
2012 - present	Affiliate, Department of Biochemistry, WFSOM
2013 - present	Professor, Department of Chemistry, Wake Forest University
2016 - present	Director of Academic Programming for Wake Downtown, Wake Forest University
2020 - present	Associate Dean for Research and Community Engagement, Wake Forest University

Other Experience and Professional Memberships

1994 - present	American Association for the Advancement of Science
2000 - present	American Chemical Society
2000 - present	RNA Society
2000 - 2016	RNA Society of North Carolina steering committee
2002	Panel Member, Molecular Biochemistry, NSF
2005, 2007-2008	Panel Member, Genetic Mechanisms of Cancer, American Cancer Society
2005	Panel Member, Post-transcriptional Modifications, NSF
2009 - 2011	Panel Member, RNA Mechanisms of Cancer, American Cancer Society
2011 - 2012	Panel Member, Structural Biochemistry, NSF

Honors

1989-1990	Quesita Drake Scholarship, University of Delaware
1990	Merck Award, University of Delaware
1990	Phi Beta Kappa, University of Delaware
1990-1991	Harrison Fellowship, University of Pennsylvania
1995-1996	Dissertation Fellowship, University of Pennsylvania
2005	Saguiv Hadari Junior Faculty Leave, Wake Forest University
2008-2011	Robert P. and Debra Lee Faculty Fellow, Wake Forest University
2009-2010	Reynolds Research Leave, Wake Forest University
2014-2017	F.M. Kirby Family Faculty Fellow, Wake Forest University

C. Contributions to Science

1. As an NSF predoctoral fellow with Barry Cooperman at the University of Pennsylvania, I investigated aspects of E. coli ribosome structure using photoaffinity cross-linking tags to map the organization of ribosomal proteins and RNA in the era before high resolution structures were available. Our low-resolution data provided initial indications of protein arrangement in the three-dimensional ribosome environment.

   Rosen, K.V., Alexander, R.W., Wower, J., and Zimmermann, R.A. (1993) Mapping the central fold of transfer RNA_2^{fMet} in the P-site of the *Escherichia coli* ribosome. *Biochemistry* 32: 12802-12811. PMID: 8251501

   Alexander, R.W., Muralikrishna, P., and Cooperman, B.S. (1994) Ribosomal components neighboring the conserved 518-533 loop of 16S rRNA in 30S subunits. *Biochemistry* 33: 12109-12118. PMID: 7918432

   Muralikrishna, P., Alexander, R.W., and Cooperman, B.S. (1997) Placement of the α-sarcin loop within the 50 S subunit: Evidence derived using a photolabile oligodeoxynucleotide probe. *Nucleic Acids Res.* 25:4562-4569. PMID: 9358167

   Alexander, R.W., and Cooperman, B.S. (1998) Ribosomal proteins neighboring 23 S rRNA nucleotides 803-811 within the 50 S subunit. *Biochemistry* 37:1714-1721. PMID: 9484243

   Wang, R., Alexander, R.W., van Loock, M., Vladimirov, S., Bukhtiyarov, Y., Harvey, S.C., and Cooperman, B.S. (1999) Three-dimensional placement of the conserved 530 loop of 16 S rRNA and of its neighboring components in the 30 S subunit. *J. Mol. Biol.* 286:521-540. PMID: 9973568

2. As an NIH postdoctoral fellow with Paul Schimmel at MIT and The Scripps Research Institute (La Jolla), I laid the foundation for my independent career. I used *E. coli* methionyl-tRNA synthetase (MetRS) as a model for long-range signaling between the enzyme's anticodon-binding domain

Alexander, R.W., Nordin, B.E., and Schimmel, P. (1998) Activation of microhelix charging by localized helix destabilization. *Proc. Natl. Acad. Sci. USA* 95:12214-12219. PMID: 9770466

Alexander, R.W., and Schimmel, P. (1999) Evidence for breaking domain-domain functional communication in a synthetase-tRNA complex. *Biochemistry* 38, 16359-16365. PMID: 10587461

Alexander, R.W., and Schimmel, P. (2001) Domain-domain communication in aminoacyl-tRNA synthetases. *Prog. Nucl. Acid Res. Mol. Biol.* 69: 317-349. PMID: 11550797

Alexander, R.W., and Tamura, K. (2004) Peptide synthesis through evolution. *Cell. Mol. Life Sci.* 61:1317-1330. PMID: 15170510

3. Since becoming an independent investigator, I have continued to probe the enzymology of aminoacyl-tRNA synthetases, using both experimental and computational approaches. In particular my lab has been interested in how methionyl-tRNA synthetase (MetRS) recognizes the $tRNA^{Met}$ anticodon, a key determinant for attachment of methionine to its cognate tRNA, despite the ~50Å separation between anticodon binding site and catalytic active site. Using molecular dynamics simulations, we demonstrated that intrinsic motions of *E. coli* MetRS are correlated between these distal sites even in the absence of tRNA. We have also turned our attention to aspects of translational accuracy and the organismal strategies used to ensure or loosen error-free protein synthesis. In the publications below, WFU graduate students are in bold and undergraduates are underlined.

Budiman, M.E., Knaggs, M.H., Fetrow, J.S., and Alexander, R.W. (2007) Using molecular dynamics to map interaction networks in an aminoacyl-tRNA synthetase. *Proteins: Structure, Function, and Bioinformatics* 68: 670-689. PMID: 17510965

Jones, T.E., Brown, C.L, Geslain, R., Alexander, R.W. and Ribas de Pouplana, L. (2008) An operational RNA code for faithful assignment of ATG triplets to methionine. *Molecular Cell* 29: 401-407. PMID: 18280245

Banerjee, P., Warf, M.B., and Alexander, R.W. (2009) Effect of a domain-spanning disulfide on aminoacyl-tRNA synthetase activity. Biochemistry 48: 10113-10119. PMID: 19772352

Alexander, R.W., Eargle, J., and Luthey-Schulten, Z. (2010) Experimental and computational determination of tRNA dynamics. FEBS Letters 584: 376-386. PMID: 19932098

Banerjee R., Reynolds N.M., Yadavalli S.S., Rice C., Roy H., **Banerjee P.,** Alexander R.W., and Ibba M. (2011) Mitochondrial aminoacyl-tRNA synthetase single-nucleotide polymorphisms that lead to defects in refolding but not aminoacylation. *J. Mol. Biol.* 410: 280-293. PMID: 21601574

Jones T.E., Alexander R.W., and Pan T. (2011) Misacylation of specific nonmethionyl tRNAs by a bacterial methionyl-tRNA synthetase. *Proc. Natl. Acad. Sci. USA* 108: 6933-6938. PMID: 21482813

Casina, V.C., Lobashevsky, A.A., McKinney, W.E., Brown, C.L., and Alexander, R.W. (2011) Role for a conserved structural motif in assembly of a class I aminoacyl-tRNA synthetase active site. *Biochemistry* 50: 763-769. PMID: 21175197

Jones, T.E., Ribas de Pouplana, L., and Alexander, R.W. (2013) Evidence for late resolution of the AUX codon box in evolution. *J. Biol. Chem.* 288:19625-19632. PMID: 23696642

Godwin, R.C., Macnamara, L.M., Alexander, R.W., and Salsbury, F.R. Jr. (2018) Structure and dynamics of $tRNA^{Met}$ containing core substitutions. *ACS Omega* 3: 10668–10678. PMID: 30288458

Muraski, M., **Nilsson, E.**, *Weekley, B.*, **Sharma, S.B.**, Alexander, R.W. (2020) A novel aminoacyl-tRNA synthetase appended domain can supply the core synthetase with its amino acid substrate. *Genes* 11:1320-1331. PMID: 33171705

A full list of publications in my bibliography is available at
https://www.ncbi.nlm.nih.gov/myncbi/1Pig7LFEzbTk7/bibliography/public/

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

Ongoing Research Support

NSF MCB-1818131; Role: PI 08/01/18 – 07/31/23
Collaborative Proposal: Role of tRNA base modifications in genetic code accuracy and cellular fitness

This project, in collaboration with Vaughn Cooper (University of Pittsburgh School of Medicine) investigates the unusual finding of evolved mutants in *Berkholderia cenocepacia* tRNA isoleucine lysidine synthetase that enhance bacterial fitness in nutrient-limited conditions while diminishing enzyme activity.

Completed Research Support

NSF MCB-1052402; Role: PI 03/01/11-02/28/14

Dissecting catalytic features of diverse methionyl-tRNA synthetase enzymes

This study used pre-steady-state kinetics, computational simulations, and mutagenic structure-function analysis to elucidate mechanistic features of three methionyl-tRNA synthetase enzymes.

NSF MCB-0448243; Role: PI 6/15/05-6/14/11

CAREER: Dissecting interdomain communication in methionyl-tRNA synthetase

This project probed tRNA-induced conformational change in *E. coli* MetRS using experimental and computational approaches, and demonstrated that protein flexibility is important for tRNA aminoacylation, a key peptide motif contributes in a structure-specific but not sequence-specific manner to tRNA aminoacylation, and that motions of the protein's anticodon binding domain are correlated with movement in peptide motifs up to 80 Å away.