BIOGRAPHICAL SKETCH

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NAME: Conn, Graeme Leslie

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

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Edinburgh, UK	B.Sc.	05/1993	Chemistry
University of Edinburgh, UK	Ph.D.	10/1996	Chemistry
Johns Hopkins University	Postdoc	12/1999	Structural Biology

A. Personal Statement

My role on this NCCAT screening proposal will be to provide necessary resources and mentorship at Emory to support Mr. Alejandro Oviedo in his sample (OAS3 and nc866 RNA) purification and cryo-EM specimen preparation for the proposed research activities at NYSBC. Alejandro and my other current trainees are primarily involved in projects investigating: ***i)*** ribosomal RNA, transfer RNA and protein methyltransferase enzymes related to bacterial resistance to antibiotics or virulence and/ or human health (supported by NIH/NIAID R01 AI088025 and NIH/NIGMS R01 GM130135); ***ii)*** bacterial efflux systems in studies that developed from our on-going work in the area of bacterial antibiotic resistance mechanisms and, ***iii)*** non-coding RNA structure and activity against proteins of the human innate immune response (Alejandro's specific project; supported by NIH/NIAID AI144067). Each of these projects involves team members using complementary biochemical, biophysical, and structural approaches (typically single-particle cryoEM) providing a supportive environment for Alejandro to complete his proposed studies of OAS3-RNA complexes. These efforts will also be supported by Emory's EM core (of which I am one of three Scientific Co-directors) as well as colleagues among Emory's major users of this facility. I also plan to support and encourage Alejandro to apply to participate in other training programs offered at NCCAT (or other national centers) to further enhance his training in cryo-EM.

Selected current research support (as noted above):

1. NIH/NIAID, R01 AI088025, *RNA modification and antibiotic resistance,* MPI–Conn*,Dunham (5/1/2010–4/30/2025).
2. NIH/NIGMS, R01 GM130135, *Mechanisms and biological functions of SPOUT methyltransferases*, MPI-Jackman*, Conn (09/14/2018–07/31/2023). [Pending admin review: renewal application has been recommended for funding by POe]
3. NIH/NIAID, R01 AI144067, *dsRNA regulation of the cytosolic innate immune system*, PI–Conn, CoI–Lowen, (3/12/2019–2/28/2028). [This award directly supports Alejandro's research project]

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020–present Co-scientific Director, Robert P. Apkarian Integrated Electron Microscopy Core, Emory University
2019–present Professor, Department of Biochemistry, Emory University School of Medicine, Atlanta, GA.
2008–2019 Associate Professor, Department of Biochemistry, Emory University School of Medicine, Atlanta, GA.
2007–2008 Senior Lecturer (equivalent to Associate Professor, *with tenure*), Faculty of Life Sciences, University of Manchester, UK.
2000–2007 Lecturer (equivalent to Assistant Professor, *tenure track*), Dept. Biomolecular Sciences, UMIST (2000-2004)/ Faculty of Life Sciences, University of Manchester, UK (2004-2007).

2000–2004 Wellcome Trust Independent Research Career Development Fellow, Dept. Biomolecular Sciences, UMIST, UK.
1999–2000 Wellcome Trust Postdoctoral Fellow, Dept. of Biomolecular Sciences, UMIST, UK.
1996–1999 Wellcome Trust Postdoctoral Fellow, Johns Hopkins University, Baltimore, MD.

Awards/Honors

2019 Researcher Appreciation Day recognition, Emory University School of Medicine.
2018 Hidden Gem award, Emory University School of Medicine.
2000–2004 Wellcome Trust Independent Research Career Development Fellowship.
1996–2000 Wellcome Trust International Traveling Prize Fellowship (Postdoctoral).
1993–1996 Royal Society of Edinburgh Caledonian Trust Scholarship (PhD).
1990–1994 1st, 3rd and 4th Year Undergraduate Class Prize (top ranked student), Department of Chemistry, University of Edinburgh, UK.
1990–1993 Faculty of Science and Engineering Bursary, University of Edinburgh, UK.

Other Experience, Service and Professional Memberships

2022-present Associate Editor, npj Antimicrobials and Resistance.
2019 NIH/NIAID ZAI1 LR-M (M1), Special Emphasis Panel (RFA-AI-18-025, Elucidating the Functional Roles of Non-Coding RNAs in Viral Infectious Diseases (R21).
2017-2019 Guest Editor, special topic "*Bacterial Mechanisms of Antibiotic Resistance: A Structural Perspective*", Frontiers in Molecular Biosciences.
2015-present NIH/ CSR F13, Fellowships: Infectious Diseases and Microbiology (five times total, most recently Nov 2020).
2014-present Frontiers in Molecular Biosciences, Reviewing Editor (Structural Biology).
2013-2014 Chair, Proteins and Crystallography Committee 2, American Heart Association.
2012 Co-chair, Proteins and Crystallography Committee 2, American Heart Association.
2012 'Recombinant and *in vitro* RNA synthesis: Methods and Protocols' (Editor), Methods in Molecular Biology series (Walker, J.M., series Editor), Humana Press.
2001-present *Ad hoc* grant reviewer/ study section: The Wellcome Trust, BBSRC (UK), American Heart Association, American Cancer Society, NIH/CSR (IMST-G 30 (S10 Shared Equipment review), ZRG1 BCMB-R 02 M, ZDC1 SRB-K17 (R03 review) and DP5 Director's Early Independence Award), American Heart Association and the Canadian Council for the Arts (Killam Research Fellowship).
2001-present Manuscript reviewer: *Nature Methods, Nature Protocols, PNAS, J.Mol. Biol.*, *Nucleic Acids Res.*, *J. Biol. Chem., BioTechniques*, *Biochemistry*, *Cell. Mol. Life Sci., Chem. Senses*, *Biol. Cell., J. Biotechnology, Current Biology, Molecular Microbiology, FEMS Letters and PLoS-ONE, ChemBioChem., RNA-Journal of the RNA Society, Frontiers Microbiology, mBio.*
2000-present Biochemical Society UK (2003-2007), Association for Chemoreception Sciences (2003-2011), American Society for Microbiology (ASM; since 2008), American Association for the Advancement of Science (AAAS; since 2009), American Crystallographic Society (ACA; since 2010), The American Society for Biochemistry and Molecular Biology (ASBMB; since 2011), and the RNA Society (since 2017).

C. Contributions to Science

Complete List of Published Work in My NCBI (75 total publications): My Bibliography-Conn, G.L.
http://www.ncbi.nlm.nih.gov/sites/myncbi/graeme.conn.1/bibliography/40548662/public/?sort=date&direction=descending

Trainees (my lab) are highlighted in the references: **postdoctoral researchers** (bolded and underlined;) and *graduate students* (italicized and underlined; also: †rotation student only, #undergraduate); additionally, trainees from minorities underrepresented in the sciences are noted¶.

1. Bacterial ribosomal RNA modification and antibiotic resistance. Aminoglycoside antibiotics typically act by binding and inducing specific conformational changes in the ribosome "decoding center" that result in aberrant protein synthesis. Aminoglycosides have retained potent activity, leading to a reevaluation of their potential utility in the clinic in the face of increasing resistance to many first line drugs. Clinical aminoglycoside resistance typically arises through the action of aminoglycoside modifying enzymes, whereas drug-producing bacteria also use 16S rRNA methyltransferase enzymes to modify the ribosomal drug binding site, either at the N7 position of G1405 (m^7G1405) or the N1 position of A1408 (m^1A1408). Now, a serious threat to the future clinical usefulness of aminoglycosides has arisen from the acquisition and spread among human bacterial pathogens of these rRNA

methyltransferases. rRNA modification confers exceptionally high-level resistance and, combined, these modifications are capable of blocking the effects of *all* clinically useful aminoglycosides including the latest generation of drugs. Determining the structures of these enzymes and defining the features which govern their interactions with cosubstrate S-adenosyl-L-methionine (SAM) and 30S substrate, have been a major contribution from my lab. Our early work defined critical features for SAM binding and 30S recognition by Sgm (a drug producer m^7G1405 enzyme) and, subsequently, revealed the first structures of m^1A1408 enzymes with cosubstrate from both aminoglycoside-producing and human pathogenic bacteria. Next, in collaboration with Christine Dunham's group (Emory, Chemistry) we presented a breakthrough in the field with the determination of a first structure of a resistance methyltransferase (NpmA) bound to its 30S substrate (**ref. a**). This work was followed by a detailed mechanistic study to dissect the molecular basis of 30S recognition by NpmA. Together, these publications revealed the basis for the requirement of mature 30S as substrate, and the molecular details underpinning specific target recognition, including flipping of the target A1408 base into the NpmA active site. Our on-going studies include complementary studies of members of the clinically more prevalent m^7G1405 family (e.g. **ref. b,d**) as well as the dual (30S and 50S subunit) methyltransferase TlyA from *Mycobacterium tuberculosis* (e.g. **ref. c**), which is associated with mycobacterial resistance to the tuberactinomycin drugs capreomycin and viomycin. Our long-term goal is to exploit the understanding we develop of these methyltransferase enzymes and their target recognition mechanisms to facilitate development of specific inhibitors of these resistance determinants.

1a. **Dunkle, J.A**., *Vinal, K*., **Desai, P.M**., Zelinskaya, N., *Savic, M.*, **West, D.M.¶**, *Conn, G.L. and *Dunham, C.M. (2014). Molecular recognition and modification of the 30S ribosome by the aminoglycoside-resistance methyltransferase NpmA. *Proc. Natl. Acad. Sci. U.S.A.* **111**(17), 6275-6280. (*Co-corresponding author) [PMCID: PMC4035980]

1b. **Nosrati, M**., **Dey, D**., Mehrani, A., D. *Strassler, S.E*., Zelinskaya, N., Hoffer, E.D., Stagg, S.M., Dunham, C.M. and Conn, G.L. (2019). Functionally critical residues in the aminoglycoside resistance-associated methyltransferase RmtC play distinct roles in 30S substrate recognition. *J. Biol. Chem. 294, 17642-17653.* [PMCID-PMC6873201]

1c. *Laughlin, Z.T*., **Nandi, S**., **Dey, D**., Zelinskaya, N., **Witek, M.A**., Srinivas, P., Nguyen, H.A., *Kuiper, E.G*., Comstock, L.R., Dunham, C.M. and Conn, G.L. (2022) 50S subunit recognition and modification by the Mycobacterium tuberculosis ribosomal RNA methyltransferase TlyA. *Proc. Natl. Acad. Sci. U. S. A.*, **119**, e2120352119. [PMCID: PMC9168844]

1d. Srinivas, P., **Nosrati, M**., Zelinskaya, N., **Dey, D**., Comstock, L.R., Dunham, C.M.* and Conn, G.L.* (2023). 30S subunit recognition and G1405 modification by the aminoglycoside-resistance 16S ribosomal RNA methyltransferase RmtC, *Proc. Natl. Acad. Sci. USA,* **120**(25):e2304128120. doi: 10.1073/pnas.2304128120.). *Co-corresponding authors *Co-corresponding authors

2. Structure, activity, and substrate selection by the *P. aeruginosa* RND pump MexXY-OprM. My lab's work on the resistance-nodulation-cell division (RND) family efflux pumps represents a relatively new direction in our fundamental studies of bacterial antibiotic resistance. These studies originated from on-going *in silico* analyses of aminoglycoside antibiotic dynamics and interactions with *methylated* 30S ribosome subunits to understand how some drugs of this class appear to be able to "evade" the effects of RNA modification by the aminoglycoside-resistance 16S rRNA methyltransferases (see **Contribution 1** above). Our current focus is on *P. aeruginosa* MexXY-OprM which is unique in both its dependence on aminoglycosides for regulation of its expression and its ability to preferentially efflux these antibiotics leading to clinical resistance (e.g. in strains isolated from individuals with cystic fibrosis). Using phylogenetic analyses, computational molecular modeling of the MexXY-OprM complex, and *in silico* ligand docking in the MexY distal binding pocket (DBP) we proposed a novel hypothesis: that the physicochemical properties of the MexY DBP have evolved to prefer aminoglycosides over β-lactams via a "Goldilocks binding affinity" (**ref. a**). That is, substrates (aminoglycosides) must bind sufficiently tightly to be taken up by MexY but not too tightly, so as to impede movement through the transporter to the adaptor protein MexX. Supporting this novel concept, β-lactams are universally predicted to bind more tightly to MexY, and the converse is also true: aminoglycosides were predicted, without exception, to bind more tightly to MexB, of the homologous RND pump MexAB-OprM which exports β-lactams but not aminoglycosides. Future studies will experimentally test these ideas and define the structure and activity of the *P. aeruginosa* MexXY-OprM efflux system using biochemical, computational, microbiological, structural biology approaches with the long-term goal of developing novel efflux inhibitors to counter the antibiotic resistance the systems provide to pathogenic bacteria.

2a. **Dey, D.**, *Kavanaugh, L.G.* and Conn, G.L. (2020). Antibiotic substrate selectivity of *Pseudomonas*

aeruginosa MexY and MexB efflux systems is determined by a Goldilocks affinity. *Antimicrob. Agents Chemother.* **64**(8), e00496-20. [PMCID: PMC7526836]

3. EftM trimethylation of EF-Tu and its impact on *P. aeruginosa* physiology and pathology. In collaboration with Dr. Joanna Goldberg (Emory, Pediatrics) we showed that the activity of the *P. aeruginosa* methyltransferase EftM is regulated via a novel mechanism: direct thermoregulation of the protein's structure itself. EftM trimethylates lysine 5 (K5) of the translation factor EF-Tu in a manner we hypothesize mimics the phosphorylcholine modification which is important for host-cell adhesion and virulence of other opportunistic pathogens. Our first collaborative study was important because it provided a mechanistic basis for how *P. aeruginosa* may control expression of this modification (**ref. a**). Subsequent work revealed an additional contribution to regulation of EftM expression at the transcriptional level and also that EF-Tu modification K5 has no impact on its canonical role in translation, suggesting its purpose is potentially exclusive to the surface-localized role in host cell adhesion (**ref. b**). Finally, we recently completed a study revealing details of the molecular mechanism of EF-Tu recognition by EftM which appears to exploit strategies common to both Class I Rossmann fold and the eukaryotic SET domain methyltransferases (**ref. c**). This work sets the scene for future studies on EftM structure/ enzymatic mechanism (in particular the similarity of its active site to those of SET methyltransferases) that will provide a framework for future development of specific inhibitors of EF-Tu K5 trimethylation to impact *P. aeruginosa* virulence.

3a. Owings, J.P.*, Kuiper, E.G.*, Prezioso, S.M., Meisner, J., Varga, J.J., Zelinskaya, N., Dammer, E.B., Duong, D.M., Seyfried, N.T., Albertí, S., Conn, G.L. and Goldberg, J.B. (2016). *Pseudomonas aeruginosa* EftM is a thermoregulated methyltransferase. *J. Biol. Chem.* **291**(7), 3280-90 (*Co-first authors) [PMCID: PMC4751374]

3b. Prezioso, S.M., Duong, D.M., Kuiper, E.G., Deng, Q., Dammer, E.B., Seyfried, N.T., Albertí, S., Conn, G.L. and Goldberg, J.B. (2019). Methylation of elongation factor-Tu by the dual thermoregulated methyltransferase EftM does not impact its canonical function in translation. *Scientific Reports*, **9**(1):3553. [PMCID: PMC6401129]

3c. Kuiper, E.G.*, **Dey, D.***, LaMore, P.A., Owings, J. P., Prezioso, S. M., Goldberg, J. B., and Conn, G.L. (2019). Substrate recognition by the Pseudomonas aeruginosa EF-Tu methyltransferase EftM. *J. Biol. Chem.*, **294**, 20109-20121. [PMCID: PMC6937583] (*Co-first authors)

4. Non-coding RNA structure and regulation of proteins of the human innate immune system. My lab has long-standing interests in understanding the structure and activity of viral and cellular non-coding RNAs, and their mechanisms of regulation of the host cell innate immune system double-stranded (ds)RNA-sensors, dsRNA-activated protein kinase (PKR) and oligoadenylate synthetase 1 (OAS1). Our early work defined the stabilities and roles of the conserved domains within the adenovirus non-coding RNA, VA RNA_I, and more recently centered on nc886, a *cellular* ncRNA proposed to be an endogenous regulator of PKR. These studies have defined the nc886 RNA structure and revealed that only one conformer of nc886 can adopt a (currently undefined) tertiary structure that confers both potent inhibition of PKR and activation of a second dsRNA-sensing innate immune protein, OAS1, which has become the main current focus of our work in this area. In response to dsRNA, 2',5'-oligoadenylate synthetase (OAS) proteins produce 2',5'-linked oligoadenylate second messengers for which the only known target is the latent ribonuclease, RNase L. Activation of the OAS/RNase L pathway triggers a program of cellular and viral RNA degradation designed to halt protein synthesis in the infected cell. First, we reported the discovery of a novel *single-stranded* RNA motif (termed 3'-ssPy, or "*three prime spy*") that strongly potentiates OAS1 activation by a short model dsRNA duplex as well as structured viral and cellular non-coding RNAs (**ref. a**). Subsequently, we identified the role of a novel tertiary structure within nc886 in potent the activation of the OAS/RNase L pathway both *in vitro* and in the context of cellular innate immune signaling (**ref. b**). Our most recent studies have revealed that even for "simple" model dsRNAs there is a potentially complex interplay of RNA features that controls whether OAS1 becomes activated or not (e.g. **ref. c**,**d**) and we are currently working to fully define the "rules" that govern potent OAS1 activation by dsRNA and the impacts of motifs like 3'-ssPy.

4a. Vachon, V.K., Calderon, B.M.¶ and Conn, G.L. (2015). A novel RNA molecular signature for activation of 2'-5' oligoadenylate synthetase-1. *Nucleic Acids Res.* **43**(1), 544-552. [PMCID: PMC4288181]

4b. Calderon, B.M.¶ and Conn, G.L. (2018). A human cellular noncoding RNA activates the antiviral protein 2'–5'-oligoadenylate synthetase 1. *J. Biol. Chem.* ***293****, 16115-16124.* [PMCID: PMC6187638]

This article was an Editors' Pick for the October 12th, 2018 issue of *JBC*, see:

Dinman, J.D. (2018). Shapeshifting RNAs guide innate immunity. *J. Biol. Chem.* ***293****, 16125-12126.*

4c. *Schwartz, S.L.*, *Park, E.N.*[#], *Vachon, V.K.,* Danzy, S., Lowen, A.C. and Conn, G.L. (2020). Human OAS1 activation is highly dependent on both RNA sequence and context of activating RNA motifs. *Nucleic Acids Res*. **48**(13), 7520–7531. [PMCID PMC7367156]

4d. *Schwartz, S.L*., **Dey, D.**, *Tanquary, J.*[†], Bair, C.R., Lowen, A.C. and Conn, G.L. (2022) Role of helical structure and dynamics in oligoadenylate synthetase 1 (OAS1) mismatch tolerance and activation by short dsRNAs. *Proc. Natl. Acad. Sci. U. S. A.*, **119**, PMCID: PMC8784149.

5. Molecular bases of OAS IEIs. As part of a multinational interdisciplinary team, we recently reported the identification and mechanistic basis of a new IEI resulting from four distinct heterozygous mutations in the human *OAS1* gene which encodes the enzyme oligoadenylate synthetase 1 (OAS1; **ref. a**). The OAS family of proteins is responsible for sensing foreign (e.g. viral) double-stranded (ds)RNA and promoting an interferon-induced innate immune response. In humans, three catalytically active OAS proteins (OAS1-3) accomplish this by dsRNA-activated synthesis of 2',5'-linked oligoadenylate (2,5-A) second messengers which then activate the latent ribonuclease (RNase L). Our studies showed that the four OAS1 variants possess low-level gain-of-function (GoF) activity, i.e. 2,5-A synthesis in the *absence of dsRNA activation*, and thus result in a new IEI we termed OAS1-associated polymorphic auto-inflammatory immunodeficiency disorder (OPAID). Using computational modeling and molecular dynamics (MD) approaches, my group that showed each OAS1 GoF amino acid substitution results in similar changes in protein dynamics surrounding the active site, despite being distributed across one half of the protein. In our on-going work, we will next define the molecular basis for OAS1 GoF, including the mechanism of allosteric communication between the GoF sites and residues surrounding the active site. Defining these mechanisms also promises to significantly deepen our understanding of how OAS1 is regulated, both by dsRNA activators and by protein residue networks that limit aberrant activation in the absence of dsRNA. Recently, through our global IEI surveillance network we also identified a first heterozygous missense mutation in *OASL* leading to OASL gain-of-function activity and dysregulation of innate immune signaling. As noted in the NIAID Notice of Special Interest (NOSI) "*Investigations on Inborn Errors of Immunity/Primary Immunodeficiencies*" (NOT-AI-21-032), efforts to understand genetic defects leading to *even exceptionally rare IEIs* offer unparalleled potential for novel insights into the fundamental molecular and cellular mechanisms of immune system function. Our goal will therefore be to establish a foundation from which to exploit the OASL variant and its resultant IEI to define currently unappreciated interplay between innate immune sensing of DNA and RNA viruses via the OASL/ RIG-I and cGAS/ STING pathways.

5a. Magg, T., Okano, T., Koenig, L.M., Boehmer, D.F.R., *Schwartz, S.L*., Inoue, K., Heimall, J., Licciardi, F., Ley-Zaporozhan, J., Ferdman, R.M., Caballero-Oteyza, A., *Park, E.N.*[#], *Calderon, B.M.*[¶], **Dey, D.**, Kanegane, H., Cho, K., Montin, D., Reiter, K., Griese, M., Albert, M.H., Rohlfs, M., Gray, P., Walz, C., Conn, G.L., Sullivan, K.E., Klein, C., Morio, T. and Hauck, F. (2021) Heterozygous OAS1 gain-of-function variants cause an autoinflammatory immunodeficiency. *Science Immunology*, **6**.PMCID: PMC8392508.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
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NAME: Alejandro Oviedo

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

POSITION TITLE: Graduate Student

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
Texas State University San Marcos, TX	B.S.	08/2014	05/2018	Biochemistry
Texas State University San Marcos, TX	M.S.	08/2018	05/2020	Biochemistry
Emory University Atlanta, GA	Ph.D.	08/2020	In Progress	Biochemistry

A. Personal Statement

The goal of this application is to get accepted into the Grid Preparation and Screening (GPS) program at NCCAT. Utilizing the tools and expertise from this program would allow me to determine the correct concentration, grid type, and freezing conditions to prepare grids OAS3-RNA complexes for cryo-EM analysis. I hope to gain technical training that would allow me to expand on my project of finding the first structure of OAS3 bound to activating RNA.

The full length OAS3 structure has not been solved, leaving gaps in our understanding of its activation by dsRNA. Therefore, I plan to uncover the mechanism of activation by cellular and viral RNAs. I will share our findings with other researchers at conferences to grow our understanding of this important pathogen recognition receptor. I will also be able to use the training to educate other members of our lab on how to optimize sample and grid preparation.

I will rely on the abundance of RNA biologists and structural biologists in the Dept. of Biochemistry to help guide me as I work to understand and solve OAS3 activation by dsRNA. The Apkarian Integrated Electron Microscopy Core (IEMC) at Emory University will also be available to assist me as a process my dataset and ultimately solve the structure of my OAS3-RNA complexes.

B. Positions and Honors

Positions and Employment

2015-2017	Chemistry Supplemental Instruction Leader, Student Learning Assistance Center, Texas State University
2016-2018	Senior STEM Tutor, Student Support Services, Texas State University
2017	Chemistry Laboratory Instructor, Department of Chemistry & Biochemistry, Texas State University
2017-2018	Undergraduate Research Assistant in the laboratory of Dr. L. Kevin Lewis, Department of Chemistry & Biochemistry, Texas State University
2018-2020	Graduate Research Assistant in the laboratory of Dr. Liqin Du, Department of Chemistry & Biochemistry
2020-2021	Graduate Research Assistant, Biochemistry, Cell and Developmental Biology Program (BCDB), Laney Graduate School, Emory University
2021-Present	Graduate Research Assistant in the laboratory of Dr. Graeme Conn, Department of Biochemistry, Emory University

Other Experience

2019-2020	Founding Member of Texas State Biochemistry Journal Club, Texas State University
2020- 2022	Board Advisor for Latinx Graduate Student Association, Laney Graduate School, Emory University
2021-2023	Elected Student Representative BCDB Executive Committee, BCDB Program, Laney Graduate School, Emory University
2022-Present	President of Latinx Graduate Student Association, Laney Graduate School, Emory University

Honors & Awards

2018-2020	Scholar, South Texas Doctoral Bridge Program (R25 GM102783)
2020-Present	Fellow, Centennial Scholars Fellowship (Given to applicants who have demonstrated outstanding academic achievement)
2020-2022	Fellow, Initiative for Maximizing Student Diversity (IMSD) Fellowship (R25 GM125598)
06/2023	Poster Award, Gordon Research Seminar Nucleic Acids 2023
06/2023	Excellence in Biochemistry DEI Award

C. Contributions to Science

1. Dissertation Research: nc886 structure and mechanism of OAS activation.

My dissertation project in Dr. Graeme Conn's lab involves elucidating the mechanism of OAS1 and OAS3 activation by the higher order structure of the cellular RNA, nc886. This work will provide novel insights into cellular RNA regulation of two important innate immune dsRNA sensors, OAS1/OAS3. My proposal has been presented at the 19th Annual DSAC Student Research Symposium (see 1, below) sponsored by the Laney Graduate School of Emory University and the BCDB Recruitment Poster Session (see 2, below) to showcase research in the BCDB program for accepted recruits.

1. **Oviedo, A.,** Conn, G.L. (2022) Non-coding RNA 866 (nc886) structure and mechanism of oligoadenylate synthetase 1 (OAS1) activation. 19th Annual DSAC Student Research Symposium. Atlanta. GA. [Poster Presentation]
2. **Oviedo, A.,** Conn, G.L. (2022) Non-coding RNA 866 (nc886) structure and mechanism of oligoadenylate synthetase 1 (OAS1) activation. BCDB Recruitment Poster Session. Atlanta. GA. [Poster Presentation]

2. Undergraduate Research: Defects in HR and BER DNA repair pathways leads to high levels of G_2/M cells in *Saccharomyces cerevisiae.*

For my undergraduate research, I joined a DNA repair and yeast genetics lab under the mentorship of Dr. Kevin Lewis in the Department of Chemistry & Biochemistry at Texas State University. The highly complex process of maintaining genetic stability is an essential requirement for life, as accurate DNA replication is required to replicate cells in any life form. Even with error rates as low as 10^{-8} per base for polymerases with proofreading exonuclease activity, human cellular DNA still experiences 50,000-100,000 chemical modifications per cell per day from exposure to endogenous and exogenous DNA damaging agents. To study DNA repair pathways, we used the yeast model system of *Saccharomyces cerevisiae.* The Lewis laboratory had previously observed that DNA repair-deficient *rad52* haploid and diploid mutant cell cultures have high levels of distended, large-budded G_2 phase cells and long cell cycle transit times. That work demonstrated that the high G_2 phase cell phenotype of *rad52* cells was abolished when any of seven known DNA damage checkpoint genes were co-inactivated. My project extended these studies and sought to determine whether defects in other DNA repair pathways also lead to accumulation of large-budded cells and changes in doubling rates. Our findings revealed that mutants deficient in Nucleotide Excision Repair pathway (*rad2, rad7 and rad14*), Mismatch Repair pathway (*msh2, msh3 and msh6*) or Translesion synthesis (*rev1, rev3 and rev7*) do not have high levels of large-budded cells. By contrast, G_2/M cells were strongly elevated in mutant cultures defective in the Base Excision Repair pathway (*ogg1, ung1 and apn1*) during normal growth. Mutants of the Homologous Recombination (HR) pathway nucleases and other proteins affecting HR were analyzed using phase contrast microscopy for altered cell cycle distributions. Our results indicated that many mutants involved in the HR pathway have high levels of large-budded cells. The project proceeded with DAPI staining to distinguish G_2 vs M cells, testing DNA damage checkpoint gene double mutants, and analyzing cell cycle times. With the results I obtained, I presented a poster at the 2018 Experimental Biology (EB) conference in San Diego, California (see 1, below) and this experience opened my eyes to the opportunities available to me with a Ph.D.

1. **Oviedo, A.,** Valencia, S., Weis, M., and Lewis, LK. (2018) Defects in homologous recombination (HR) and base excision repair (BER), but not NER or MMR, lead to altered cell cycle phase distributions in *S. cerevisiae.* Experimental Biology, San Diego, CA. [Poster Presentation]

3. Master's Research: Characterizing potential differentiation agents in neuroblastoma.
I applied to the Biochemistry Master's program at Texas State University and was accepted into the South Texas Doctoral Bridge Program. There, I joined the lab of Dr. Liqin Du and worked on a collaborative project with Dr. Alexander Kornienko's organic synthesis laboratory. My Master's research focused on characterizing novel compounds for neuroblastoma differentiation therapy. Neuroblastoma is a childhood cancer that arises from neural crest precursor cells that fail to differentiate into mature neurons that make up the parasympathetic nervous system. Current differentiation therapy relies on 13-cis-retinoic acid, but approximately 50% of patients become resistant to further treatment. More insight into key genes and molecules that can induce differentiation in neuroblastoma cells is needed to develop new treatment approaches. Through a large-scale, high-throughput screen, Dr. Du's lab identified several novel differentiation-inducing compounds which hold the promise to be developed into differentiation agents to treat human neuroblastomas. My goal was to characterize the effects of three novel compounds in neuroblastoma cell lines with differing genetic backgrounds and to test whether these compounds have generic and more potent differentiation-inducing activity than 13-cis-retinoic acid. I used western blot analysis to detect neuronal differentiation markers, colony formation assays for proliferation, as well as cell viability assays to determine compound IC_{50} values. Two of the three compounds identified from the screen were validated as differentiation inducers in cell lines with different genetic backgrounds. In addition, I found that the heterogeneity of neuroblastoma causes varying responses to treatment with some cell lines showing sensitivity to treatment when others were resistant. We expect that chemical modifications to the validated compounds will improve their differentiation-inducing activity. Throughout my two years on this project, I was able to present my master's thesis results at multiple local (see 2 and 3, below) and national conferences (see 1, below). Becoming an expert in cell culture and western blotting, I was able to contribute to a project examining the network formed by PLAGL2, MYCN and miR-506-3p as an important mechanism in regulating neuroblastoma cell fate, determining neuroblastoma prognosis, and mediating the therapeutic function of retinoic acid. Dr. Du's lab published these results, and I am now the third author on this publication (see 4, below).

1. **Oviedo, A.,** Zhao, Z., Kornienko,A., and Du, L. (2019) Characterizing the Activity of Three Novel Differentiation-inducing Small Compounds in Neuroblastoma Cell Lines. ABRCMS, Anaheim, CA. [Poster Presentation]
2. **Oviedo, A.,** Zhao, Z., Kornienko,A., and Du, L. (2020) Characterizing the Activity of Three Novel Differentiation-inducing Small Compounds in Neuroblastoma Cell Lines. WiSE Conference, Texas State University. [Poster Presentation]
3. **Oviedo, A.,** Zhao, Z., Kornienko,A., and Du, L. (2020) Characterizing the Activity of Three Novel Differentiation-inducing Small Compounds in Neuroblastoma Cells. 3 Minute Thesis, Texas State University. [Oral Presentation]
4. Zhao, Z., Shelton, S.D., **Oviedo, A.,** Baker, A., Bryant, C. P., Omidvarnia, S., Du, L. (2020). The PLAGL2/MYCN/miR-506-3p interplay regulates neuroblastoma cell fate and associates with neuroblastoma progression. *J Exp Clin Cancer Res.* doi: 10.1186/s13046-020-1531-2 [**PMCID: PMC7036248**].

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

Texas State University (B.S.) GPA: 3.22

Year	Course	Grade	Year	Course	Grade
2014	Functional Biology Lab	A	2016	Calculus II	A
2014	General Chemistry I Lab	A	2016	Microbiology	B
2014	Functional Biology	B	2016	Descriptive Inorganic Chemistry	B
2014	University Seminar	A	2016	Principles of Biochemistry	B
2014	General Chemistry I	A	2016	Mechanics	B
2014	College Writing I	A	2016	Genetics	B
2014	Principles of American Government	A	2016	Organic Chemistry Lab II	B
2015	Organismal Biology Lab	A	2017	Vertebrate Physiology	B
2015	Organismal Biology	A	2017	Biochemical Techniques	B
2015	General Chemistry Lab II	A	2017	Analytical Biochemistry	C

2015	Organic Chemistry I	B	2017	Metabolism	B
2015	Calculus I	B	2017	Physical Chemistry Biochemistry	B
2015	Ethics & Society	A	2017	Undergraduate Research	A
2015	Introduction to Psychology	B	2017	Molecular Biology	C
2015	Fundamentals of Human Communication	A	2017	Advance Biochemistry Lab I	B
2015	History of the US to 1877	A	2017	Electricity & Magnetism	B
2015	General Chemistry II	B	2017	History of the US to Date	C
2015	Pre-Calculus Math	B	2018	Introduction to Fine Arts	B
2015	Functional American Government	A	2018	Immunology	C
2015	Organic Chemistry Lab I	A	2018	Medical Microbiology	B
2016	Organic Chemistry II	B	2018	Advance Biochemistry Lab II	B
2016	College Writing II	B	2018	US Literature Since 1865	A

Texas State University (M.S.) GPA: 3.88

Year	Course	Grade	Year	Course	Grade
2018	Cytology & Microscopic Technology	A	2019	Thesis	A
2018	Seminar In Chemistry	A	2019	Thesis	A
2018	Molecular Biology & Genetics	A	2019	Seminar In Chemistry	A
2018	Fundamentals of Research	A	2020	Current Topics in Biochemistry	A
2019	Seminar in Chemistry	A	2020	Nucleic Acids	A
2019	Physical Biochemistry	B	2020	Thesis	A
2019	Proteins	A			

Emory University (Ph.D.) GPA: 3.96

Year	Course	Grade	Year	Course	Grade
2020	Foundations in BCDB I	A-	2021	Jones Prg. In Ethics: Workshop	S
2020	Introductory Graduate Seminar	A	2021	Advanced Graduate Research	A
2020	Laboratory Rotations	A	2021	Advanced Graduate Research	A
2020	Current Topics in Bioscience (IMSD)	A	2021	Advanced Graduate Seminar	S
2020	Jones Prg. In Ethics: Core Class	S	2021	Current Topics in Bioscience (IMSD)	A
2021	Foundations in BCDB II	A-	2021	Hypothesis & Science Writing	A
2021	Introductory Graduate Seminar	A	2021	Graduate School Workshop	S
2021	Laboratory Rotations	A	2021	Teaching Assistantship	S
2021	Current Topics in Bioscience (IMSD)	A	2022	Advanced Graduate Research	A
2022	Advanced Graduate Seminar	S	2022	Current Topics in Bioscience (IMSD)	A
2022	Statistical Design	A	2022	Advanced Graduate Research	A
2022-2023	Advanced Graduate Seminar	S	2022-2023	Dissertation Research	A