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: Deaconescu, Alexandra M.

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

POSITION TITLE: Assistant professor (tenure-track)

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
Cooper Union for the Advancement of Science and Art, New York, NY	BENG	05/2001	Chemical Engineering
The Rockefeller University, New York, NY	PHD	06/2007	Molecular Biophysics and Biochemistry
Brandeis University/HHMI, Waltham, MA	Postdoctoral Fellow	12/2012	Structural Biology (advisor: Dr. Niko Grigorieff)
Janelia Farm HHMI Research Campus, Ashburn, VA	Research Associate	06/2013	Structural Biology (advisor: Dr. Niko Grigorieff)

A. Personal Statement

The long-term goal of my research program is to understand at atomic resolution the mechanistic underpinnings of stress responses. These are essential for survival in all organisms, and often rely on the interplay between cellular pathways used to control genome integrity and transcriptional programs. My interests stem from my previous studies of transcription and DNA repair ATPases. As such, the work proposed here centers on the regulation of RpoS, a promoter specificity subunit and the master regulator of the general stress response in γ–proteobacteria, and Mfd, a widely conserved bacterial transcription-repair coupling factor involved in a specific stress response to DNA damage. The proposal builds upon my previous experience, and aims to decipher, structurally and functionally, how these key factors regulate transcription, promote the preferential repair of active genes, mediate adaptive mutagenesis and the acquisition of antibiotic resistance. **My aim is to develop an atomic resolution understanding of the macromolecular interactions that are being sculpted during these general and specific stress responses and how these processes lead to elevated mutation rates and accelerated molecular evolution.** This work has direct relevance for antibiotic development via anti-evolution drugs and the dissection of cellular mechanisms involved in bacterial virulence.

My overall experimental approach is rooted in my training in biochemistry and techniques that can probe macromolecular structure across resolution ranges, including X-ray crystallography, single-particle electron microscopy and small-angle X-ray scattering. I have recently collaborated with investigators of complementary expertise, such as biomolecular NMR [Dorothy Kern (Brandeis University)], cytoskeleton biology [Antonina Roll-Mecak (NIH), Bruce Goode (Brandeis University)] as well as molecular genetics [Susan Gottesman (NIH) and Irina Artsimovitch (Ohio State University)], single-molecule biophysics [Michelle Wang (Cornell University)] and the biochemistry of unfoldases [Sue Wickner (NIH)]. Due to the interdisciplinary nature of my research, my lab offers, in my view, a good training environment for students and postdoctoral researchers of diverse interests, aspirations, and backgrounds.

B. Positions and Honors

Positions

1999	Summer Undergraduate Research Fellow of the American Chemical Society, The Cooper Union for the Advancement of Science and Art (Mentor: Dr. Robert Topper)
2000	Summer Undergraduate Research Fellow, The Rockefeller University (Stephen Burley Lab) Collaborator: William Studier (Brookhaven National Laboratory)
9/2001-10/2006	Graduate Fellow, The Rockefeller University (PhD Thesis Advisor: Dr. Seth Darst) Collaborators: N. Savery (University of Bristol) and Ann Hochschild (Harvard University)
11/2006 -12/2012	Postdoctoral Fellow, HHMI and Brandeis University (Nikolaus Grigorieff Laboratory)
	Collaborators: Bruce Goode (Brandeis University), Antonina Roll-Mecak (NIH-NINDS), Irina Artsimovitch (Ohio State University)
1/2013 -12/2013	Research Specialist I, HMMI (Niko Grigorieff Laboratory)
1/2014 -present	Assistant Professor (Tenure-track), Department of Molecular Cell Biology and Biochemistry, Brown University

Peer-Review

2010-present	Ad hoc reviewer for *Nature Structural & Molecular Biology, EMBO Journal, FEMSLE Microbiology Reviews*, *PNAS, Journal of Biological Chemistry, PLOS ONE, Structure, eLife, Nucleic Acids Research, Structure, eLife*
2012-present	Grant proposal reviewer for *The National Research Council of Romania, Association for International Cancer Research, KAUST, PRESTIGE Marie Curie Postdoctoral Fellowship Program (European Union Seventh Framework FP7 Programme), Breast Cancer Now, Israel Science Foundation, The Netherlands Organization for Science Research, NIH*

Honors

1997-2001	Full-Tuition Scholarship from The Cooper Union, New York, NY
1998-2001	National Dean's List
1999	American Chemical Society (Petroleum Research Fund) Undergraduate Research Fellowship
2000	Undergraduate Summer Research Fellowship, The Rockefeller University
2000	Elected Membership to The Tau Beta Pi National Engineering Honor Society
2001	Certificate in Leadership in Engineering (LEAP), Honors Level, The Cooper Union
	The Herbert B. Baldwin Prize for excellence in Chemical Engineering, The Cooper Union for the Advancement of Science and Art
2004	*RU Abroad* Travel Fellowship from The Rockefeller University
2005	Travel Grant to the Murnau Conference on Macromolecular Recognition, German Society for Biochemistry and Molecular Biology
2006	Scholarship, International School of Crystallography at Ettore Majorana Centre, Erice, Italy (declined)
2006	Scholarship, Frontiers in Structural Biology Keystone Research Symposium

2008-2010	**Damon Runyon Cancer Research Foundation Postdoctoral Fellowship**
2008	Full Scholarship to the Osaka University Global COE and IBRO-APRC Summer School, Japan's Ministry of Education, Culture, Sports, Science and Technology and International Brain Research Organization
2010	Scholarship, International School of Crystallography at Ettore Majorana Centre, Erice, Italy
2012	W.M. Keck Postdoctoral Fellowship, The W.M. Keck Foundation and the Gulf Coast Research Consortium/Computational Cancer Biology Program (declined)
2013	**Howard Hughes Medical Institute Award in Quantitative Biology**
2014	Medical Research Award, Rhode Island Foundation
2016, 2021	**Salomon Faculty Research Award (Brown University)**
2018	**Seed Award for Cryo-EM Instrumentation (Brown University)**

C. Contribution to Science

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/18yer6bKcee5q/bibliography/public/

1. My long-standing scientific interest has been the mechanisms linking DNA repair and transcription as exemplified by diverse pathways of transcription-coupled nucleotide excision repair (TCR). Using X-ray crystallography, I determined the first structure of an intact transcription-repair coupling factor (the Mfd protein) from any organism. This study has served as a starting point in the field for a program of rational mutagenesis and further studies for identifying contact surfaces for its binding partners (RNA polymerase, UvrA and DNA) as well as mechanisms of regulation. My subsequent work on this system has presented the first experimental evidence for bacterial transcription-repair coupling factors directly participating in sensing DNA lesions, and suggesting that the prevalent damage recognition model in the field ("by proxy, solely by RNA polymerase) needs further reconsideration. We have recently presented the first structure of a substrate-bound bacterial transcription-repair coupling factor Mfd together with a detailed mechanistic analysis of its DNA binding and translocation activity that suggest new principles for design of an Mfd-based anti-evolution drug that could act as a broad-spectrum antibiotic in combination therapies. **Work in this area has been highlighted by Molloy, S. *Nature Rev. Microbiology* (2006) 4, 240-241, Faculty of 1000, the Scientific Bulletin of the Advanced Photon Source (Argonne National Laboratory), The Cornell Chronicle and a Rockefeller University (2006) and Cornell University (2018) press release. Part of this work resulted from NIGMS support.**

    a. Brugger C, Zhang C, Suhanovsky M, Kim D, Sinclair-Davis A, Lyumkis D, **Deaconescu AM**. Molecular Determinants of dsDNA Translocation by the Transcription-Repair Coupling and Evolvability Factor Mfd, in press at *Nature Communications.* 2020 Jul 27; 11(1):3740. PMID: 32719356 PubMed Central PMCID: PMC7385628. Supported by GM121975 and P20GM103430

    b. Le TT, Yang Y, Tan C, Suhanovsky MM, Fulbright RM Jr, Inman JT, Li M, Lee J, Perelman S, Roberts JW, **Deaconescu AM**, Wang MD. Mfd Dynamically Regulates Transcription via a Release and Catch-Up Mechanism. *Cell*. 2018 Jan 11;172(1-2):344-357.e15. PubMed PMID: 29224782; PubMed Central PMCID: PMC5766421. Supported by P20GM103430

    c. **Deaconescu AM**, Sevostyanova A, Artsimovitch I, Grigorieff N. Nucleotide excision repair (NER) machinery recruitment by the transcription-repair coupling factor involves unmasking of a conserved intramolecular interface. *Proc Natl Acad Sci U S A*. 2012 Feb 28;109(9):3353-8. PubMed PMID: 22331906; PubMed Central PMCID: PMC3295266.

d. **Deaconescu AM**, Chambers AL, Smith AJ, Nickels BE, Hochschild A, Savery NJ, Darst SA. Structural basis for bacterial transcription-coupled DNA repair. *Cell*. 2006 Feb 10;124(3):507-20. PubMed PMID: 16469698.

2. Given my long-standing interest in the DNA damage response, I have recently extended my efforts to understanding the transcriptional reprogramming mediated by the bacterial promoter specificity subunit RpoS (σ^S), the master regulator of the stress response. RpoS is subjected to tight regulation, including by ATP-dependent proteolysis. I have undertaken a systematic structural study of the regulation of RpoS turnover by the ClpXP adaptor, RssB as well as its multiple recently-discovered stress-specific inhibitors, collectively coined anti-adaptors, and joined efforts with the groups of Susan Gottesman (NIH) and Sue Wicker (NIH) to carry out complementary *in vivo* characterization. This work has already provided the first structural study of a ClpXP RpoS adaptor/anti-adaptor pair, which has direct relevance for biofilm formation. This underlies 80% of all bacterial infections. In very recent work presented as a preprint on BioRxiv, we have also determined the structural basis for RssB regulation by phosphorylation. **Work in this area has been highlighted in a Brown University press release (2019). This work resulted from NIGMS support.**

a. Dorich V, Brugger C, Tripathi A, Hoskins JR, Tong S, Suhanovsky MM, Sastry A, Wickner S, Gottesman S, **Deaconescu AM**. Structural basis for inhibition of a response regulator of σ^S stability by a ClpXP antiadaptor. *Genes Dev*. 2019 Jun 1;33(11-12):718-732. PubMed PMID: 30975721; PubMed Central PMCID: PMC6546054. Supported by GM121975.

b. Schwartz J, Son J, Brugger C, **Deaconescu AM**. Phospho-dependent Signaling by the Atypical Response Regulator and ClpXP Adaptor RssB. bioRxiv 2021.01.11.426222; doi: https://doi.org/10.1101/2021.01.11.426222. Supported by GM121975.

3. Through a collaboration with the Roll-Mecak lab (NINDS/NIH), I have carried out biochemical and structural studies by small-angle X-ray scattering and transmission electron microscopy to reveal the mechanism of action of two distinct tubulin post-translational modification enzymes (TTL, a tubulin tyrosine ligase and TAT, a tubulin acetyltransferase). These studies presented the first structural information on any tubulin post- translational modification enzyme, and explained their substrate specificity (tubulin versus microtubule or vice versa), their ability to modulate the partitioning of monomeric and polymeric tubulin as well as their role in serving as an enzymatic timer for microtubule lifetimes in cells. We also showed that the microtubule severing enzyme spastin contributes the amplification of microtubule arrays by incorporation of tubulin heterodimers at the sites of severing nanodamage, resolving a long-standing apparent paradox in the field. Recent additional work in collaboration with the Kern Lab (Brandeis University/HHMI) has also dissected the role of Tau and the Pin 1 proline isomerase in microtubule assembly. **Work in this area has been previewed by Kull & Sloboda, *Cell* (2014) 157(6): 1255-12256, highlighted in *ACS Chemical Biology*** (Dahlmann HA, 2014), ***Science*** (Hurtley S, 2018) and ***Developmental Cell*** (Akhmanova A, 2018; Stavoe AKH & Holzbaur ELF, 2018), an **NIH press release**, **recommended by Faculty of 1000 and featured on several news outlets, including EurekAlert!, and Nanowerk. Part of this work resulted from NIGMS support.**

a. Vemu A, Szczesna E, Zehr EA, Spector JO, Grigorieff N, **Deaconescu AM**, Roll-Mecak A. Severing enzymes amplify microtubule arrays through lattice GTP-tubulin incorporation. *Science*. 2018 Aug 24;361(6404)PubMed PMID: 30139843; PubMed Central PMCID: PMC6510489. Supported by GM121975.

b. Szyk A, **Deaconescu AM**, Spector J, Goodman B, Valenstein ML, Ziolkowska NE, Kormendi V, Grigorieff N, Roll-Mecak A. Molecular basis for age-dependent microtubule acetylation by tubulin acetyltransferase. *Cell*. 2014 Jun 5;157(6):1405-15. PubMed PMID: 24906155; PubMed Central PMCID: PMC4726456.

c. Szyk A, **Deaconescu AM**, Piszczek G, Roll-Mecak A. Tubulin tyrosine ligase structure reveals adaptation of an ancient fold to bind and modify tubulin. *Nat Struct Mol Biol*. 2011 Oct 23;18(11):1250-8. PubMed PMID: 22020298; PubMed Central PMCID: PMC3342691.

d. Kutter S, Eichner T**, Deaconescu AM**, Kern D. Regulation of Microtubule Assembly by Tau and not by Pin1. J Mol Biol. 2016 May 8;428(9 Pt A):1742-59. PubMed PMID: 26996940.

4. Together with the laboratory of B. Goode (Brandeis University) and G. Gundersen (Columbia University), I have uncovered a novel role as an actin nucleator for adenomatous polyposis coli (APC), a well-known tumor suppressor and microtubule-stabilizing factor. We showed that the C-terminal region of APC, commonly mutated in colorectal cancer, potently nucleates actin *in vitro* and *in vivo,* using a unique mechanism involving dimerization and synergy with the distinct actin nucleator mDia. **Work in this area has been highlighted in Leslie, M. J Cell Biol (2010) 189(7):1055 and evaluated as a "must read" by Faculty of 1000.**

a. Okada K, Bartolini F, **Deaconescu AM**, Moseley JB, Dogic Z, Grigorieff N, Gundersen GG, Goode BL. Adenomatous polyposis coli protein nucleates actin assembly and synergizes with the formin mDia1. J Cell Biol. 2010 Jun 28;189(7):1087-96. PubMed PMID: 20566685; PubMed Central PMCID: PMC2894447.