OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: PUFALL, MILES

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-7022-6916

Position Title: Associate Professor Department of Biochemistry and Molecular Biology

Organization and Location: University of Iowa, Iowa City, Iowa, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of California - San Francisco, San Francisco, CA, USA	Postdoctoral Fellow	07/2005	06/2011	Mentor: Keith Yamamoto
University of Utah, Salt Lake City, UT, USA	DOCTOR OF PHILOSOPHY	06/1998	06/2005	Oncological Sciences
American University, Washington, DC, USA	MASTER OF SCIENCE	01/1996	06/1999	Toxicology
Oberlin College, Oberlin, OH, USA	BACHELOR OF ARTS	08/1985	05/1989	Chemistry

Appointments and Positions

2011 - present	Associate Professor Department of Biochemistry and Molecular Biology, University of Iowa, Iowa City, Iowa, United States
2026 - present	Professor of Biochemistry and Molecular Biology, University of Iowa, Iowa City, Iowa, United States
2018 - 2026	Associate Professor of Biochemistry and Molecular Biology, University of Iowa, Iowa City, Iowa, United States
2011 - present	Associate Professor Department of Biochemistry and Molecular Biology, University of Iowa, Iowa City, Iowa, United States
2011 - present	Professor of Biochemistry and Molecular Biology, University of Iowa, Iowa City, Iowa, United States
2011 - 2018	Assistant Professor of Biochemistry, University of Iowa, Iowa City, Iowa, United States
2005 - 2011	Post Doctoral Fellow, University of California - San Francisco, San Francisco, California, United States
1996 - 1998	Project Manager, TechLaw, Inc., Chantilly, Virginia, United States

Products

Products Closely Related to the Proposed Project

1. Zimmerman JAO, Fang M, Pufall MA. PI3Kδ Inhibition Potentiates Glucocorticoids in B-lymphoblastic Leukemia by Decreasing Receptor Phosphorylation and Enhancing Gene Regulation. Cancers (Basel). 2023 Dec 27;16(1) PubMed Central PMCID: PMC10778422.
2. Pisano M, Sun F, Cheng Y, Parashar D, Zhou V, Jing X, Sompallae R, Abrudan J, Zimmermann M, Mathison A, Janz S, Pufall M. IL6Myc mouse is an immunocompetent model for the development of aggressive multiple myeloma. Haematologica. 2023 July 13; 108(12):3372-3383. Available from: https://haematologica.org/article/view/haematol.2022.282538 DOI: 10.3324/haematol.2022.282538
3. Poulard C, Kim H, Fang M, Kruth K, Gagnieux C, Gerke D, Bhojwani D, Kim Y, Kampmann M, Stallcup M, Pufall M. Relapse-associated AURKB blunts the glucocorticoid sensitivity of B cell acute lymphoblastic leukemia. Proceedings of the National Academy of Sciences. 2019 February 07; 116(8):3052-3061. Available from: https://pnas.org/doi/full/10.1073/pnas.1816254116 DOI: 10.1073/pnas.1816254116
4. Kruth K, Fang M, Shelton D, Abu-Halawa O, Mahling R, Yang H, Weissman J, Loh M, Müschen M, Tasian S, Bassik M, Kampmann M, Pufall M. Suppression of B-cell development genes is key to glucocorticoid efficacy in treatment of acute lymphoblastic leukemia. Blood. 2017 June 01; 129(22):3000-3008. Available from: https://ashpublications.org/blood/article/129/22/3000/36066/Suppression-of-Bcell-development-genes-is-key-to DOI:

10.1182/blood-2017-02-766204

5. Zimmerman J, Fang M, Doumbia B, Neyman A, Cha J, Thomas M, Hall B, Wu M, Wilson A, Pufall M. Deacylcortivazol-like pyrazole regioisomers reveal a more accommodating expanded binding pocket for the glucocorticoid receptor. RSC Medicinal Chemistry. 2021; 12(2):203-212. Available from: https://xlink.rsc.org/?DOI=D0MD00278J DOI: 10.1039/D0MD00278J

Other Significant Products Highlighting Contributions to Science

1. Spector BM, Santana JF, Pufall MA, Price DH. DFF-ChIP: a method to detect and quantify complex interactions between RNA polymerase II, transcription factors, and chromatin. Nucleic Acids Res. 2024 Oct 14;52(18):e88. PubMed Central PMCID: PMC11472042.
2. Zhang L, Rube H, Vakulskas C, Behlke M, Bussemaker H, Pufall M. Systematic in vitro profiling of off-target affinity, cleavage and efficiency for CRISPR enzymes. Nucleic Acids Research. 2020 May 21; 48(9):5037-5053. Available from: https://academic.oup.com/nar/article/48/9/5037/5823200 DOI: 10.1093/nar/gkaa231
3. Zhang L, Martini G, Rube H, Kribelbauer J, Rastogi C, FitzPatrick V, Houtman J, Bussemaker H, Pufall M. SelexGLM differentiates androgen and glucocorticoid receptor DNA-binding preference over an extended binding site. Genome Research. 2018 January; 28(1):111-121. Available from: http://genome.cshlp.org/lookup/doi/10.1101/gr.222844.117 DOI: 10.1101/gr.222844.117
4. Meijsing SH, Pufall MA, So AY, Bates DL, Chen L, Yamamoto KR. DNA binding site sequence directs glucocorticoid receptor structure and activity. Science. 2009 Apr 17;324(5925):407-10. PubMed Central PMCID: PMC2777810.
5. Wasserman HI, Chi B, Bohm KA, Duan M, Sahay H, Safi A, Crawford G, Mao P, Wyrick JJ, Pufall M, Gordân R. High-throughput characterization of transcription factors that modulate UV damage formation and repair at single-nucleotide resolution. Res Sq. 2025 Dec 10; PubMed Central PMCID: PMC12776441.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

Research Security Training Requirement for Federal Award Personnel: In accordance with Section 10634 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19234), each individual identified as a senior/key person must certify that they have completed the requisite research security training that meets the requirements specified in Item 2 of Important Notice No. 149 within 12 months prior to proposal submission.

Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: PUFALL, MILES

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-7022-6916

Position Title: Associate Professor Department of Biochemistry and Molecular Biology

Organization and Location: University of Iowa, Iowa City, Iowa, United States

Personal Statement

Research Goals and Expertise: The goal of my lab is to understand how cellular signals rewire gene regulatory programs by altering transcription factor function, with a primary focus on the Steroid Hormone Receptor family. We combine functional genomic, informatic, biophysical, and chemical approaches to determine how these receptors integrate signals to drive gene expression changes and phenotypic outcomes. We have synthesized novel glucocorticoids, developed assays to distinguish the activities of related compounds, and pioneered the integration of shRNA screening with gene expression, mutational data, and relapse-associated misregulation. These efforts have clarified how glucocorticoids induce cell death in B-cell precursor acute lymphoblastic leukemia (B-ALL), how resistance emerges, and how new or existing drug targets can restore sensitivity. This work has led to the identification of two new combination chemotherapies now in clinical trials. Building on this foundation, we are currently applying our approaches to conservative treatment of endometrial atypical hyperplasia and endometrial cancer with synthetic progesterones (progestins). Our goal is to understand how progestins act, why they sometimes fail, and how their efficacy can be enhanced. This research addresses a critical need, as endometrial cancer incidence and mortality are rising while most other cancers are declining. I am the PI of a project and part of the leadership team on an NCI Program Project Grant (P01), and an Investigator on a Department of Defense Translational Team Science Award. Related to transcription factor function, our other main area of expertise is understanding how proteins bind DNA. We have developed methods (SelexGLM, SEAM-seq) to comprehensively measure intrinsic specificity as well as the effect of DNA aberrations on specificity. I am currently the co-PI of an NSF grant supporting this work.

Training Experience: Training the next generation of scientists has always been a priority throughout my career. I have mentored three postdoctoral fellows, two MD fellows (one K12), four graduate students, and dozens of undergraduates, many of whom have advanced to tenure-track faculty, industry, or advanced training programs (PhD, MD, MD/PhD). I have also built innovative training programs across career stages, including a classroom-based undergraduate research experience (MP2BK), a practical data science and bioinformatics course for students with no coding background, a computational bootcamp for faculty and postdocs (CTAB), and a virtual summer course introducing high school students to cancer research (RUMC-SHE). I am also currently the Director of the Cancer Biology Program.

Honors

2017	Donald D. Dorfman Award, Holden Comprehensive Cancer Center
2010	Howard Temin NIH Pathway to Independence Award, National Cancer Institute
2006	Leukemia and Lymphoma Society Post-Doctoral Fellowship, Leukemia and Lymphoma Society
2005	James W. Prahl Memorial Award, Outstanding Contributions by a Graduate Student at the University of Utah in Biological or Biomedical Sciences, University of Utah
2002	NIH Multidisciplinary Cancer Research Training Grant, University of Utah
1999	NIH Biological Chemistry Training Grant, University of Utah
1998	Leo Schubert Award, Teaching Assistant of the Year, Department of Chemistry, American University
1997	Graduated with Distinction, American Unviersity
1996	Graduate Merit Fellowship, American University

Contributions to Science

1. **Allosteric Tuning of Transcription Factor Activity:** Transcription factors regulate associated genes by binding to specific sequences in response to cellular signals such as post-translational modification. Using Ets-1, an oncogene and founding member of the ETS family of proteins, my work demonstrated that transcription factors were not only switched on and off by post-translational modifications, but could be fine-tuned at the level of DNA binding (PMID: 15994560). This tailoring of

activity was directed by multiple phosphates being added to an intrinsically disordered region of the protein. Surprisingly, despite remaining disordered, these phosphates damped the conformational transitions required for high-affinity binding. This work created a new paradigm for how proteins function, one in which a well-structured state was not required to perform work. Reciprocally, binding to DNA sequences changes the structure of transcription factors. In my work on the glucocorticoid receptor, I showed that DNA can serve as a sequence-specific allosteric ligand to change recruitment of coregulators and regulatory activity (PMID: 19372434; PMID: 23728292). This has profound implications for understanding how transcription factors are regulated at specific genes and by polymorphisms and mutations in bound DNA sequences.

2. **DNA-Binding Specificity:** Transcription factors bind to specific genomic loci to regulate associated genes. They are recruited to these loci via their DNA-binding domains, which recognize and read specific DNA sequences. How cellular signals and mutations change the sequence preferences of transcription factors is not clear. To better understand this, we have developed high-resolution techniques to measure the DNA-binding specificity of transcription factors. These techniques result in energetic models, called position-specific affinity matrices, that quantify the contribution to the free energy of binding of any base pair throughout the DNA-binding footprint. Through these models, we can accurately predict the affinity of a transcription factor for any sequence. Further, we can quantify the effect of mutations or post-translational modifications on that preference. We have made two main contributions to this field. First, we developed a new method, SelexGLM, that is able to generate accurate models over a large footprint (PMID: 29196557). Previous methods were limited to ~12 bp, which prevented measurement of over half of all transcription factors. This enabled accurate distinction of nuclear hormone receptors, which were previously thought to bind identically. It also enabled measuring the specificity of non-transcription factors with interesting DNA-binding properties, including CRISPR enzymes. This technique has been refined in a new method, No Read Left Behind, by our collaborators. Second, we combine unbiased measurement of specificity with activity measurements to understand the effect of specificity on protein function. This combination allowed us to generate models for the efficiency of off-target cleavage of CRISPR enzymes and to discover that CasX is vastly more specific than Cas9 and Cas12a (PMID: 32315032).

3. **Steroid Treatment of Cancers:** In addition to B-ALL, other cancers are also treated with steroid hormones. We have brought our expertise in functional genomics and specificity to two of these: multiple myeloma and endometrial cancer. Multiple myeloma has several different treatment options, each of which includes glucocorticoids, which are cytotoxic and enhance the efficacy of other treatments. In collaboration with the Janz lab at the Medical College of Wisconsin, we helped to establish the IL6/Myc mouse model of multiple myeloma as an excellent genetic model to study glucocorticoid resistance (PMID: 37439384). Endometrial cancer incidence and mortality are increasing, likely in part due to increasing obesity and its resulting hormonal changes. Treatment with synthetic progesterones (progestins) has shown promise in early-stage disease. We are collaborating with labs at the University of New Mexico, the University of Kansas Medical Center, and the Huntsman Cancer Institute at the University of Utah to understand the mechanism of progestins, to determine which among the >20 FDA-approved progestins is most effective, and to enhance progestin efficacy by overcoming sources of resistance.

4. **Transcription Factor Integration of Cellular Signals:** We have fundamentally contributed to the understanding of how transcription factors integrate cellular signals to regulate genes. These signals include post-translational modifications, co-regulatory proteins, chromatin, and the sequence of DNA itself. To understand how transcription factors integrate these signals, I have studied B-cell acute lymphoblastic leukemia (B-ALL). B-ALL is the most common childhood cancer, and while it is now largely treatable, every effective regimen relies on glucocorticoids, which carry significant side effects. Glucocorticoids act canonically through the glucocorticoid receptor (GR), a ligand-activated transcription factor that regulates the genes driving leukemic cell death. To improve their efficacy while limiting these side effects, my lab set out to identify the signals impinging on GR that can be targeted specifically in B-ALL to increase potency. Using functional genomics, we defined which GR-regulated genes drive cell death and which signaling pathways modulate GR activity. Across a series of papers, we showed that GR integrates B-cell receptor and cell-cycle signaling to control not only apoptotic programs but B-cell developmental genes, killing B-ALL cells (PMID: 28424165; PMID: 30733284; PMID: 38201570), and that this logic exposes targetable vulnerabilities within the network (PMID: 30305606). Fundamentally, this is a basic science contribution, a systematic enumeration of the inputs and outputs of a single transcription factor and of how it converts its signaling environment into a gene regulatory program, both properly and aberrantly. Thus, by pursuing how GR works, rather than how to drug it, that we have found where it can be targeted, turning deep basic understanding into translational opportunities.

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