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

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Hargreaves, Diana

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0003-3724-3826

Position Title: Professor, Molecular and Cell Biology Laboratory

Organization and Location: Salk Institute for Biological Studies, La Jolla, California, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
Stanford University, Stanford, California, United States	Postdoctoral Fellow	05/2009	08/2015	Developmental Biology
Yale University, New Haven, Connecticut, United States	Doctor of Philosophy (PHD)	08/2002	05/2009	Immunobiology
Haverford College, Haverford, Pennsylvania, United States	Bachelor of Science (BS)	08/1996	05/2000	Chemistry/Biochemistry

Appointments and Positions

2025 - present	Professor, Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, California, United States
2026 - present	Adjunct Professor, UCSD Division of Biological Sciences, La Jolla, California, United States
2024 - present	Co-PI, Salk Cancer Center T32 Training Grant, Salk Institute for Biological Studies, La Jolla, California, United States
2022 - 2026	Adjunct Associate Professor, UCSD Division of Biological Sciences, La Jolla, California, United States
2021 - present	Program Leader and Executive Committee Member, Salk Institute for Biological Studies -Salk Cancer Center, La Jolla, California, United States
2021 - 2025	Associate Professor, Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, California, United States
2015 - 2022	Adjunct Assistant Professor, UCSD Division of Biological Sciences, La Jolla, California, United States
2015 - 2021	Assistant Professor, Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, California, United States
2009 - 2015	Postdoctoral Candidate with Dr. Gerald Crabtree, HHMI, Stanford University School of Medicine, Stanford, California, United States
2002 - 2009	Doctoral Candidate with Dr. Ruslan Medzhitov, HHMI, Yale University School of Medicine, New Haven, Connecticut, United States
2000 - 2002	Research Assistant I and II with Dr. Jason Cyster, HHMI, University of California San Francisco, San Francisco, California, United States
1999 - 2000	HHMI Scholar and Bachelor's Thesis Candidate, Haverford College, Haverford, Pennsylvania, United States

Products

Products Closely Related to the Proposed Project

1. Liao J, Ho J, Burns M, Dykhuizen EC, Hargreaves DC. Collaboration between distinct SWI/SNF chromatin remodeling complexes directs enhancer selection and activation of macrophage inflammatory genes. Immunity. 2024 Aug 13;57(8):1780-1795.e6. PubMed Central PMCID: PMC11324393.
2. Maxwell MB, Hom-Tedla MS, Yi J, Li S, Rivera SA, Yu J, Burns MJ, McRae HM, Stevenson BT, Coakley KE, Ho J, Gastelum KB, Bell JC, Jones AC, Eskander RN, Dykhuizen EC, Shadel GS, Kaech SM, Hargreaves DC. ARID1A suppresses R-loop-mediated STING-type I interferon pathway activation of anti-tumor immunity. Cell. 2024 Jun 20;187(13):3390-3408.e19. PubMed Central PMCID: PMC11193641.
3. McDonald B, Chick BY, Ahmed NS, Burns M, Ma S, Casillas E, Chen D, Mann TH, O'Connor C, Hah N, Hargreaves DC,

Kaech SM. Canonical BAF complex activity shapes the enhancer landscape that licenses CD8(+) T cell effector and memory fates. Immunity. 2023 Jun 13;56(6):1303-1319.e5. PubMed Central PMCID: PMC10281564.

4. Loo CS, Gatchalian J, Liang Y, Leblanc M, Xie M, Ho J, Venkatraghavan B, Hargreaves DC, Zheng Y. A Genome-wide CRISPR Screen Reveals a Role for the Non-canonical Nucleosome-Remodeling BAF Complex in Foxp3 Expression and Regulatory T Cell Function. Immunity. 2020 Jul 14;53(1):143-157.e8. PubMed Central PMCID: PMC7341821.
5. Kelso TWR, Porter DK, Amaral ML, Shokhirev MN, Benner C, Hargreaves DC. Chromatin accessibility underlies synthetic lethality of SWI/SNF subunits in ARID1A-mutant cancers. Elife. 2017 Oct 2;6 PubMed Central PMCID: PMC5643100.

Other Significant Products Highlighting Contributions to Science

1. Gatchalian J, Malik S, Ho J, Lee DS, Kelso TWR, Shokhirev MN, Dixon JR, Hargreaves DC. A non-canonical BRD9-containing BAF chromatin remodeling complex regulates naive pluripotency in mouse embryonic stem cells. Nat Commun. 2018 Dec 3;9(1):5139. PubMed Central PMCID: PMC6277444.
2. Kadoch C, Hargreaves DC, Hodges C, Elias L, Ho L, Ranish J, Crabtree GR. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. Nat Genet. 2013 Jun;45(6):592-601. PubMed Central PMCID: PMC3667980.
3. Dykhuizen EC, Hargreaves DC, Miller EL, Cui K, Korshunov A, Kool M, Pfister S, Cho YJ, Zhao K, Crabtree GR. BAF complexes facilitate decatenation of DNA by topoisomerase IIα. Nature. 2013 May 30;497(7451):624-7. PubMed Central PMCID: PMC3668793.
4. Hargreaves DC, Horng T, Medzhitov R. Control of inducible gene expression by signal-dependent transcriptional elongation. Cell. 2009 Jul 10;138(1):129-45. PubMed Central PMCID: PMC2828818.
5. Foster SL, Hargreaves DC, Medzhitov R. Gene-specific control of inflammation by TLR-induced chromatin modifications. Nature. 2007 Jun 21;447(7147):972-8. PubMed PMID: 17538624.

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: Hargreaves, Diana

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Position Title: Professor, Molecular and Cell Biology Laboratory

Organization and Location: Salk Institute for Biological Studies, La Jolla, California, United States

Personal Statement

The overall goal of my research program is to understand the role of SWI/SNF (aka BAF) chromatin remodeling complexes in differentiation and disease relating to cancer and inflammation. As a postdoctoral researcher, I performed a meta-analysis of cancer exome sequences to determine that SWI/SNF complex genes are mutated in ~20% of all human cancers, with 8-60% of gastrointestinal and gynecologic cancers having a mutation in the ARID1A subunit. As an independent researcher, my laboratory has shown that ARID1A regulates chromatin accessibility at enhancer regulatory elements, with associated effects on histone modifications and gene expression. Further, we have found that ARID1A deletion or chemical inhibition leads to DNA replication stress, which primes interferon-response genes and tumor immunity through a cGAS/STING-dependent mechanism. We determined that type I interferon is required for the enhanced responsiveness of ARID1A-deficient tumors to immune checkpoint blockade (ICB). Our findings provide the molecular basis for the sensitivity of ARID1A mutant cancers to ICB observed clinically. Finally, we identified a new BAF variant, referred to as the noncanonical BAF (ncBAF) complex, and defined the role of SWI/SNF complex variants (known as cBAF, ncBAF, and PBAF) in CD8 T cells and macrophages using molecular and biochemical techniques, as well as state-of-the-art functional genomics and epigenomics.

I have been serving as Co-PI of Salk's T32 Cancer Heterogeneity, Immunity and Microenvironment (CHIME) since 2024. I have also served as primary mentor, co-mentor, and steering committee member for the T32 CHIME Award for over 8 years. I am a program leader in the Salk Cancer Center, co-leading the Genome Stability, Epigenetics, and Aging in Cancer (GEA) Program, and play a key leadership role in executive decisions as a member of the Salk Cancer Center Executive Committee. I teach a lecture in the Salk Cancer Center course and serve as a faculty reviewer for the grant writing workshops taken by the T32 CHIME fellows. Informally, I have advised several former T32 trainees in their academic job search, and attended practice seminars and chalk talks, which contributed to the initiative to formalize these activities under the T32. I currently oversee the training of 6 graduate students and postdoc and serve as a member of the UCSD Biological Sciences Admissions Committee and the UCSD T32 Pathways in Biological Sciences (PiBS) Executive Committee. Of my past trainees, all are in scientific research as graduate students, postdocs or biotech researchers. My mentorship focuses on rigorous training in experimental technique and analysis, fellowship and grant writing, manuscript preparation, public speaking, collaborations and networking. I encourage career advancement into the academic and biomedical research fields and support my trainees in identifying opportunities and transitioning to the next career stage. I have trained several Salk Summer Undergraduate Research Fellows (SURF) fellows, served as a HHMI-Gilliam mentor, and received mentorship training to ensure that I continue to cultivate a supportive work environment for scientific research. I am committed to providing my advice and experience as a member of the External Advisory Board (EAB) for the University of Kentucky's Interdisciplinary Research Training in Cancer Biology T32 CA165990.

Honors

2025	V Foundation All-Star Translational Award, V Foundation for Cancer Research
2023	American Cancer Society Early Career Researcher of the Year Award, American Cancer Society
2020	American Cancer Society Research Scholar Award, American Cancer Society
2020	HHMI-Gilliam Fellowship Mentor, HHMI
2019	Pew-Stewart Scholar for Cancer Research, The Pew Charitable Trusts
2018	Recipient of the Richard Heyman and Anne Daigle Endowed Developmental Chair, Heyman and Anne E. Daigle
2018	Maximizing Investigators' Research Award for Early Stage Investigators (R35), The National Institute of General Medical Sciences
2016	V Scholar Award, V Foundation for Cancer Research
2015	R00 Pathway to Independence Award, National Cancer Institute
2014	K99 Pathway to Independence Award, National Cancer Institute

2013	Ann Schreiber Research Training Program of Excellence Award, Ovarian Cancer Research Fund
2010	Helen Hay Whitney Foundation Postdoctoral Fellowship, Helen Hay Whitney Foundation

Contributions to Science

1. Defined SWI/SNF tumor suppressor mechanisms linking genome instability, innate immune signaling, and cellular state transitions. My work established that SWI/SNF complex subunits are mutated in approximately 20 percent of human cancers and identified ARID1A as a highly recurrent tumor suppressor in gynecologic and gastrointestinal malignancies. We demonstrated that ARID1A loss alters chromatin accessibility at enhancer elements and creates specific dependencies on paralogous SWI/SNF subunits. These studies provided a mechanistic basis for targeting strategies in ARID1A mutant cancers. More recently, we discovered that ARID1A loss induces DNA replication stress and R-loop accumulation, resulting in cytosolic nucleic acid sensing and activation of a cGAS-STING dependent type I interferon program. This response represents a stress-state-dependent signaling axis that links chromatin remodeling defects to innate immune activation. We further showed that type I interferon signaling is required for the enhanced sensitivity of ARID1A deficient tumors to immune checkpoint.
   Selected publications:
   a.) Kadoch C, Hargreaves DC et al., Nature Genetics, 2013.
   b.) Dykhuizen EC, Hargreaves DC et al., Nature, 2013.
   c.) Kelso TWR et al., eLife, 2017.
   d.) Maxwell MB et al., Cell, 2024.

2. Discovered and characterized functionally distinct SWI/SNF complex variants with context-specific roles in transcriptional and immune cell fate control. I identified a noncanonical BRD9-containing BAF complex and demonstrated that SWI/SNF complexes exist as functionally distinct variants with unique genomic targeting and regulatory interactions. We showed that these variants exert opposing and context-dependent effects on transcriptional programs, particularly in immune cell differentiation. Using genome-wide CRISPR screens and epigenomic profiling, we defined variant-specific requirements for regulatory T cell function, macrophage activation, and CD8 T cell effector and memory differentiation. These studies established that chromatin remodeling outcomes are highly context dependent and shaped by both SWI/SNF composition and cellular state.
   Selected publications:
   a.) Gatchalian J et al., Nature Communications, 2018.
   b.) Loo C-S, Gatchalian J et al., Immunity, 2020.
   c.) McDonald B, Chick BY et al., Immunity, 2023.
   d.) Liao J, et al. Immunity, 2024.

3. Defined chromatin-based control of inflammatory and interferon-stimulated gene programs in innate immune cells. My laboratory has shown that SWI/SNF complexes are dynamically recruited to regulatory elements during inflammatory signaling and that variant-specific SWI/SNF activity governs enhancer selection, chromatin accessibility, and interferon-stimulated gene expression. In macrophages, we demonstrated cooperative and antagonistic functions of canonical and noncanonical SWI/SNF complexes in shaping inflammatory transcriptional responses. These findings established core principles by which chromatin remodeling integrates signaling inputs with transcriptional outputs.
   Selected publications:
   a.) Liao J et al., Immunity, 2024.

4. Established chromatin structure as a determinant of inducible gene expression kinetics and inflammatory memory. Earlier in my career, I demonstrated that inducible inflammatory genes are distinguished by their basal chromatin states, which determine transcriptional kinetics and stimulus specificity. We showed that signal-dependent transcriptional elongation and nucleosome remodeling are key regulatory steps controlling inflammatory gene activation and adaptation. This work provided a conceptual foundation for understanding how chromatin architecture constrains or permits stress-induced transcriptional programs.
   Selected publications:
   a.) Foster SL, Hargreaves DC et al., Nature, 2007.
   b.) Hargreaves DC et al., Cell, 2009

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