

BIOGRAPHICAL SKETCH

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NAME: Hur, Sun

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

POSITION TITLE: Oscar M. Schloss, MD Professor

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)	Completion Date MM/YYYY	FIELD OF STUDY
Ewha Women's University, Seoul	B.S.	06/2001	Physics (with minor in Chemistry)
University of California, Santa Barbara, CA	Ph.D.	06/2003	Physical Chemistry
University of California, San Francisco, CA	Post-doctoral	08/2008	Structural biology

A. Personal Statement

My research focuses on the molecular mechanisms of self vs non-self discrimination by the immune system. Our mechanistic work on a family of immune receptors, RIG-I-like receptors (RLRs), revealed how the innate immune system detects viral RNA during infection and how RNA detection is coupled to antiviral signal activation. Our work also led to the identification of endogenous RNAs that can inappropriately activate RLRs under pathologic conditions, linking dysregulated RLR function to immune disorders.

More recently, we started exploring transcriptional regulatory mechanisms that underlie T cell self-tolerance and global immune homeostasis. We have been focusing on two transcription factors, Aire and FoxP3, that are involved in negative selection of self-reactive T cells and development of immune-suppressive regulatory T cells, respectively. We found that both proteins form homo-multimers and that these multimeric assemblies are the keys to the cognate site recognition and their transcriptional regulatory functions.

Central to my research program is a focus on mechanistic understanding of protein-nucleic acid interactions in immunity. My scientific journey has progressed from physics during college to computational chemistry in my PhD, followed by structural biology and biochemistry in my postdoctoral fellowship, and now an interdisciplinary approach centered around immunology in my own lab. I am also committed to training the next generation of scientists by fostering a collaborative lab environment that values diverse perspectives and backgrounds.

B. Positions, Scientific Appointments and Honors**Positions and Employment**

2021-present	Investigator, Howard Hughes Medical Institute, Boston, MA
2020-present	Oscar M. Schloss, MD Professor, Department of Pediatrics at Harvard Medical School, Boston, MA
2019-present	Professor at Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School, Boston, MA
2019-present	Senior Investigator, Program in Cellular and Molecular Medicine, Children's Hospital Boston, Boston, MA
2012-2019	Investigator, Program in Cellular and Molecular Medicine, Children's Hospital Boston, Boston, MA
2014-2019	Associate Professor at Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School, Boston, MA
2008-2014	Assistant Professor at Department of Biological Chemistry and Molecular Pharmacology at Harvard Medical School, Boston, MA

2003–2008 Post-Doctoral Fellow at Department of Biochemistry and Biophysics in University of California, San Francisco.

Honors & Awards (since 2008)

2024 Elected member, American Academy of Arts & Sciences
2023 Elected fellow, American Academy of Microbiology
2022 Dorothy Crowfoot Hodgkin Award, Protein Society
2021 Paul Marks Prize, Memorial Sloan Kettering Cancer Center
2021 Investigator, Howard Hughes Medical Institute
2021 Finalist for Blavatnik National Awards in Life Sciences
2020 Finalist for Blavatnik National Awards in Life Sciences
2020 Oscar M. Schloss, MD Professorship, Harvard University
2019 Richard A. and Susan F. Smith President's Innovation Award, Boston Children's Hospital
2019 NIH Director's Pioneer award
2017 Judy Lieberman Chair in Structural Biology, Boston Children's Hospital
2015 Vilcek Prize for Creative Promise in Biomedical Science
2015 Burroughs Wellcome Investigator in Pathogenesis of Infectious Disease
2015 Investigatorship, Boston Children's Hospital
2013 Career Development Award, Boston Children's Hospital
2012 Milton Fund Award, The William F. Milton Fund
2010 Pew Scholar in Biomedical Science, The Pew Charitable Trusts
2009 New Investigator Award, Massachusetts Life Science Center

Keynote lectures

2024 RNA Biology in Host-Pathogen Interaction
2023 International Conference on Nucleic Acid Immunity
2023 PCGI/MFCIIR Symposium, University of Pennsylvania
2021 Life Science Institute Symposium, University of Michigan
2020 HIV Consortium CRNA Annual Retreat
2018 New England Bioscience Society Annual Conference
2016 NIAMS Annual Retreat, NIH
2015 GRK1721 winter school, LMU, Max Planck and Technical University of Munich, Germany

Other Professional Experience

2025 – Editorial Board, Immunity & Inflammation
2025 Co-organizer, Keystone meeting, RNA-mediated regulation of immunity
2024 Co-organizer, International Conference on Nucleic Acid Immunity
2024 Co-organizer, Cold Spring Harbor Asia, Immune Tolerance
2024 – Executive Committee & Treasurer, International Society of Nucleic Acid Immunity
2024 – Scientific Advisor, Cartesian Therapeutics
2023 Co-organizer, Keystone meeting, Immunity and Aging
2023 – Selection Committee, Rosenstiel Award, Brandeis
2023 – Scientific Advisor, Pew Scholar program
2023 – Scientific Advisor, Harvard CFAR consortium
2023 – Scientific Advisor, Odyssey Therapeutics
2022 – 2024 Scientific Advisor, CJ CheilJedang
2019 – Executive Committee, Harvard Virology Graduate Program
2019 – Faculty Advisor, New England Bioscience Society
2020 – 2022 Scientific Advisor, IFM Therapeutics
2019 – 2022 Scientific Advisor, Silicon Therapeutics & Pharmavant 8, Inc
2017 – 2021 Standing member in MSFC study section, NIH
2014 – 2017 Consultant, Pfizer Research (Inflammation & Remodeling)

C. Contribution to Science

1. **Viral dsRNA recognition by MDA5** MDA5 is a conserved innate immune receptor that recognizes viral RNAs during infection and activates the interferon signaling pathway to establish the antiviral immune

response. My laboratory discovered that MDA5 assembles into filamentous oligomers along dsRNA^a, and that it regulates filament stability through dynamic instability in a manner dependent on dsRNA length^b. This kinetic mechanism underlies MDA5's ability to discriminate between self and non-self RNAs^{a,b}. We were the first to reconstitute the MDA5 signaling process using purified components, including the downstream adaptor molecule MAVS^c, and to determine the crystal structure of the MDA5:RNA complex^c. These studies established a framework for understanding MDA5 and other innate immune receptors that recognize foreign nucleic acids^d.

- a. Peisley, A., Lin, C., Wu, B., Orme-Johnson, M., Liu, M., Walz, T., **Hur S.** Cooperative Assembly and Dynamic Disassembly of MDA5 Filaments for Viral dsRNA Recognition. *Proc. Natl. Acad. Sci. U.S.A.* (2011), 108, 21010-5. PMID: PMC3248507
- b. Peisley A*, Jo MH*, Lin C, Wu B, Orme-Johnson M, Walz T, Hohng S, **Hur S.** Kinetic Mechanism for Viral dsRNA Length Discrimination by MDA5 Filament. *Proc. Natl. Acad. Sci. U.S.A.* (2012), 109: E3340-9. PMID: PMC3523859
- c. Wu B, Peisley A, Richards C, Yao H, Zeng X, Lin C, Chu F, Walz T, **Hur S.** Structural Basis for dsRNA recognition, filament formation and antiviral signaling by MDA5. *Cell* (2013). 152: 276-89. PMID: 23273991.
- d. Ablasser A*, and **Hur S***, Regulation of cGAS- and RLR-mediated nucleic acid immunity, *Nat. Immunol. Rev.*, (2020), 21:17-29. (* co-corresponding authors).

2. Viral dsRNA recognition by RIG-I Our work has also provided mechanistic insights into functions of another viral RNA receptor, RIG-I, a paralog of MDA5. We found that RIG-I, like MDA5, forms a filament along long dsRNA, but the mechanism of RIG-I filament assembly differs significantly from that of MDA5^a. These differences explain how RIG-I and MDA5 differentially recognize viral RNAs and partition their functions as non-redundant viral RNA receptors. We further demonstrated that filament formation of the RIG-I RNA-binding promotes oligomerization of its signaling domain (CARD), enabling the recruitment and activation of the downstream adaptor MAVS^b. By determining the crystal structure of the RIG-I CARD oligomer in complex with MAVS, we addressed the long-standing question of how RIG-I activates MAVS, and showed that a similar mechanism applies to MDA5^b. In addition, we uncovered a novel effector-like functions of RIG-I-like receptors (RLRs), their ATP-driven filament dynamics can displace viral proteins pre-bound to dsRNA, highlighting a previously unappreciated antiviral mechanism^c. Finally, we identified common dsRNA byproducts of *in vitro* transcription that can readily activate RLRs and other dsRNA sensors, and offered a simple solution to remove the immunogenic RNA byproducts^d, an important issue in RNA therapeutics.

- a. Peisley A*, Wu B*, Yao H, Walz T and **Hur S.**, RIG-I forms signaling-competent filaments in an ATP-dependent and ubiquitin-independent manner. *Mol. Cell*, (2013), 51, 573-83. PMID: 23993742. Non-NIH support.
- b. Wu B, Peisley A, Tetrault D, Li Z, Egelman EH, Magor, KE, Walz T, Penczek PA and **Hur S.** Molecular imprinting as a signal activation mechanism of the viral RNA sensor RIG-I. *Mol. Cell*, (2014), 55:511-23 PMID: 25018021. PMID:4142144.
- c. Yao H, Dittmann M, Peisley A, Hoffmann H-H, Gilmore RH, Schmidt T, Schmidt-Burgk J, Hornung V, Rice CM and **Hur S.** ATP-dependent effector-like functions of RIG-I like receptors. *Mol. Cell*, (2015), 58:541-8. PMID:4427555
- d. Mu X, Greenwald E, Ahmad S, and **Hur S.**, An origin of the immunogenicity of *in vitro* transcribed RNA. *Nucleic Acid Research*, (2018) 46: 5239–5249. PMID:6007322

3. Regulatory mechanisms of dsRNA biology My laboratory, in collaboration with Dr. Yanick Crow, found that mutations in MDA5 can cause auto-inflammatory diseases^a, specifically Aicardi-Goutières syndrome, a monogenic model for Systemic Lupus Erythematosus (SLE). We found that these mutations stabilize MDA5 filaments on cellular dsRNAs, specifically those derived from inverted repeat Alu retroelements (IR-Alus), which are abundant in the 3'UTRs of many transcripts^b. This work demonstrated the importance of MDA5 filament dynamic instability in self-RNA tolerance, and laid the foundation for understanding disease pathogenesis driven by the aberrant activation of other nucleic acid sensors. More recently, we explored additional dsRNA-sensing pathways, particularly the dsRNA-dependent kinase PKR. We demonstrated that

stress granules (SGs)—cytoplasmic condensates formed upon PKR activation—play critical roles in preventing excessive inflammation during infection and autoinflammatory conditions^c. Furthermore, we identified the dsRNA-binding protein PACT as a key homeostatic regulator of PKR. PACT limits PKR's diffusion along dsRNA, suppressing its in-trans autophosphorylation and consequent activation by cellular dsRNAs, such as those formed by IR-Alus^d.

- a. Rice GI*, del Toro Duany Y*, Jenkinson EM, Forte GMA, Anderson BH, Ariaudo G, Bader-Meunier B, Baildam EM, Battini R, Beresford MW, Casarano M, Chouchane M, Cimaz R, Collins AE, Cordeiro NJV, Dale RC, Davidson JE, De Waele L, Desguerre I, Faivre L, Fazzi E, Isidor B, Lagae L, Latchman AR, Lebon P, Li C, Livingston JH, Lourenco CM, Mancardi MM, Masurel-Paulet A, McInnes IB, Menezes MP, Mignot C, O'Sullivan J, Orcesi S, Picco PP, Riva E, Robinson RA, Rodrigues D, Salvatici E, Scott C, Szybowska M, Tolmie JL, Vanderver A, Vanhulle C, Vieira JP, Webb K, Whitney RN, Williams SG, Wolfe LA, Zuberi SM, **Hur S**[^] and Crow YJ[^], Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. *Nature Genetics* (2014), 46:503-9. PMID: PMC4004585 (* co-first authors, [^] co-corresponding authors)
- b. Ahmad S*, Mu X*, Yang F*, Greenwald E, Park JW, Jacob E, Zhang C-Z and **Hur S**., Breaching self-tolerance to Alu duplex RNA underlies MDA5-mediated inflammation. *Cell*, (2018), 172:797-810
- c. Paget M, Cadena C, Ahmad S, Wang H, Jordan TX, Kim E, Zhang Q, Koo B, Lyons S, Ivanov P, tenOever B, Mu X and **Hur S**., Stress granules are shock absorbers that prevent excessive innate immune response to dsRNA, *Mol Cell*, (2023), 83: 1180-1196, PMID: 37028415
- d. Ahmad S.*, Zou T.*, Hwang J.*, Zhao L.*, Wang X., Davydenko A., Buchumenski I., Zhuang P., Fishbein AR., Capcha-Rodriguez D., Orgel A., Levanon EY., Myong S., Chou J.[^], Meyerson M.[^], **Hur S**., PACT prevents aberrant activation of PKR by endogenous dsRNA without sequestration. *BioRxiv*, <https://doi.org/10.1101/2024.10.23.619951>

4. Ubiquitin and E3 ligases in Innate Immunity Ubiquitin plays an important role in activation and regulation of many innate immune signaling pathways. In particular, both RIG-I and MDA5 require K63-linked poly-Ub chains for downstream signal activation. To understand the underlying mechanism, we determined the crystal structure of RIG-I in complex with K63-linked poly-Ub^a, demonstrating that Ub functions as a molecular glue to stabilize the active, oligomeric state of RIG-I signaling domain (CARD). We further demonstrated that, unlike the prevailing model, ubiquitination of RIG-I is mediated by the E3 ligase RIPLET, not TRIM25, and that RIPLET utilizes bivalency to selectively recognize the filamentous form of RIG-I. This ensures that antiviral signaling is activated only in the presence of cognate viral RNAs^b. We next showed that a similar mechanism applies to MDA5, but with a distinct E3 ligase, TRIM65^c. Our cryo-EM structures of RIG-I and MDA5 filaments in complex with the cognate E3 ligase support that these E3 ligases co-evolved with the receptors for the close coordination of their functions^c.

- a. Peisley A, Wu B, Xu H, Chen ZJ and **Hur S**., Structural basis for ubiquitin-mediated antiviral signal activation by RIG-I. *Nature*, (2014), 509:110-4. PMID: 24590070. PMC Journal in process.
- b. Cadena C, Ahmad S, Xavier A, Willemsen J, Park S, Park JW, Oh SW, Fujita T, Hou F, Binder M, & **Hur S**, Ubiquitin-dependent and -independent roles of E3 ligase RIPLET in innate immunity, *Cell*, (2019) 177(5):1187-1200 PMID: 31006531
- c. Kato K, Ahmad S, Zhu Z, Young JM, Mu X, Park S, Malik H and **Hur S**., Structural analysis of RIG-I-like receptors reveals ancient rules of engagement between diverse RNA helicases and TRIM ubiquitin ligases, *Mol Cell*, 2021, 81(3), 599-613 PMID: 33373584

5. Transcriptional regulators for T cell tolerance My lab recently initiated studies on transcription factors (TFs) in the adaptive immune system. Our work on Aire, a TF essential for clonal deletion of self-reactive T cells, revealed that Aire forms filamentous polymers for its transcriptional activity^a and that this activity is tightly regulated to assemble active transcriptional hubs at correct target sites^{a,b}. Specifically, we identified chromatin anchoring as a novel mechanism to suppress aberrant polymerization of Aire, and demonstrated that target-bound coactivators (CBP/P300) recruit Aire and nucleate its polymerization at specific sites^b. Our work on FoxP3, a lineage-defining TF for regulatory T cells (Tregs), challenged the conventional view of FoxP3 as a simple domain-swap dimer^c. We discovered that FoxP3 adopts multiple distinct oligomeric forms depending on

DNA sequence. In particular, FoxP3 forms higher-order multimers on TnG repeat microsatellites, and uses its multimeric architecture to bridge DNA and form chromatin loops in Tregs^d. This highlights FoxP3 as a rare example of a TF with architectural functions in genome organization. Together, our work on Aire and FoxP3 highlights a novel class of transcription factors where nucleic acid-dependent protein multimerization plays a central role in target recognition and transcriptional regulation.

- a. Huoh YS, Wu B, Park S, Bansal K, Greenwald E, Mathis D, **Hur S**, Dual functions of Aire multimerization in the transcriptional regulation of T cell tolerance, *Nat. Comm.*, (2020), 11(1):1625. PMID: PMC7118133
- b. Huoh YS*, Zhang Q*, Torner R, Baca SC, Arthanari H, **Hur S**, Mechanism for controlled assembly of transcriptional condensates by Aire. *Nature Immunology*, (2024);25(9):1580-1592. PMID: 39169234
- c. Leng F*, Zhang W*, Ramirez RN, Leon J, Zhong Y, van der Veecken J, Rudensky AY, Benoist C, **Hur S**, The transcription factor FoxP3 can fold into two dimerization states with divergent implications for regulatory T cell function and immune homeostasis. *Immunity*, (2022), 55(8):1354-69. PMID: 35926508
- d. Zhang W*, Leng F*, Wang X, Ramirez RN, Park J, Benoist C, **Hur S**, FoxP3 recognizes microsatellites and bridges DNA through multimerization. *Nature*, (2023), 624: 433-441. PMID: 38030726

Complete List of Published Work:

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47550710/?sort=date&direction=ascending>