

BIOGRAPHICAL SKETCH

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NAME: Jaiswal, Siddhartha

POSITION TITLE: Assistant 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)	Completi on Date MM/YYYY Y	FIELD OF STUDY
Stanford University, Stanford, CA	B.S.	06/2000	Biological Sciences
Stanford University, Stanford, CA	M.D./Ph.D.	06/2010	Immunology
Massachusetts General Hospital, Boston, MA	Residency/Fellowship	06/2014	Clinical Pathology and Transfusion Medicine
Harvard Medical School, Boston, MA	Postdoctoral Fellow	08/2017	Hematology

A. Personal Statement

I am a recent faculty recruit to Stanford University in the Department of Pathology, where my lab focuses on understanding the biology of the aging hematopoietic system. My thesis work at Stanford focused on understanding the role of the innate immune signaling ligand, CD47, in macrophage tumor immunosurveillance. This work formed the rationale for the therapeutic targeting of CD47 in human cancer, which is currently in clinical trials at Stanford and elsewhere.

I subsequently completed residency and fellowship training in pathology at the Massachusetts General Hospital and Harvard Medical School. As a post-doctoral fellow, I identified a common, pre-malignant state for blood cancers by reanalysis of large sequencing datasets. This condition, termed "clonal hematopoiesis", is characterized by the presence of stem cell clones harboring certain somatic mutations, primarily in genes involved in epigenetic regulation of hematopoiesis. Clonal hematopoiesis is prevalent in the aging population and increases the risk of not only blood cancer, but also cardiovascular disease and overall mortality. Understanding the biology of these mutations and how they contribute to the development of cancer and other age-related diseases is the current focus of work in my lab.

B. Positions and Honors**Positions and Employment**

2013-2017 Post-doctoral fellow, Division of Hematology, Brigham and Women's Hospital, Boston, MA
2014-2017 Graduate Assistant in Pathology, Massachusetts General Hospital, Boston, MA
2017-present Assistant Professor of Pathology, Stanford University School of Medicine, Stanford, CA

Honors

2000 Graduated with honors, Stanford University
2000 Firestone Medal for Excellence in Research, Stanford University
2014 Paul E. Strandjord Young Investigator Award, ACLPS
2016 Burroughs Wellcome Fund Career Award for Medical Scientists
2016 BroadIgnite Scholar

C. Contribution to Science

1. **Discovery of a common, pre-malignant state in blood:** Genomics studies have identified several recurrent driver mutations in hematologic malignancies. At the time I began my fellowship, it was unknown whether such somatic mutations occurred in the healthy population, or whether carrying such mutations had clinical consequences apart from malignancy. To answer these questions, I performed a study in which I analyzed whole exome sequencing data from blood cell DNA of over 17,000 subjects not known to have hematologic disorders. Surprisingly, I found that the same mutations that are frequently found in myeloid malignancies were also common in the healthy elderly, with at least 10% of those 70 or older harboring such a mutation. The presence of these mutations was associated with a 10-fold increased risk of developing a hematologic malignancy. These findings may spur the development of therapies to prevent the development of hematologic cancers at a pre-malignant stage.
 - a. **Jaiswal S**, Fontanillas P, Flannick J, Manning A, Grauman PV, ... Ebert BL. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488-98. doi: 10.1056/NEJMoa1408617. PubMed PMID: 25426837; PMCID: 4306669
 - b. Steensma DP, Bejar R, **Jaiswal S**, Lindsley RC, Sekeres MA, Hasserjian RP, Ebert BL. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood*. 2015;126(1):9-16. doi: 10.1182/blood-2015-03-631747. PubMed PMID: 25931582; PMCID: PMC4624443
 - c. Kahn JD, Miller PG, Silver AJ, Sellar RS, Bhatt S, ... **Jaiswal S***, Ebert BL*. PPM1D truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. *Blood*. 2018. Epub 2018/06/30. doi: 10.1182/blood-2018-05-850339. PubMed PMID: 29954749

2. **Understanding the role of clonal hematopoiesis in non-malignant diseases of aging:** In addition to increasing the risk of future malignancy, I found that clonal hematopoiesis also increased the risk of all-cause mortality, type 2 diabetes, stroke, and heart attack. The association between clonal hematopoiesis and coronary heart disease was validated in several additional human cohorts, and shown to have a causal role in a mouse model. Mutations that were found in clonal hematopoiesis also increased expression of inflammatory genes in macrophages, implicating this mechanism for the increased risk of coronary heart disease. This work has opened a new branch of study that links somatic mutations in blood cells to non-malignant disorders such as atherosclerosis.
 - a. **Jaiswal S**, Natarajan P, Silver AJ, Gibson CJ, Bick AG, ... Kathiresan S*, Ebert BL*. Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. *N Engl J Med*. 2017;377(2):111-21. doi: 10.1056/NEJMoa1701719. PubMed PMID: 28636844
 - b. Jan M, Ebert BL, **Jaiswal S**. Clonal hematopoiesis. *Semin Hematol*. 2017;54(1):43-50. doi: 10.1053/j.seminhematol.2016.10.002. PubMed PMID: 28088988.
 - c. Natarajan P, **Jaiswal S**, Kathiresan S. Clonal Hematopoiesis: Somatic Mutations in Blood Cells and Atherosclerosis. *Circ Genom Precis Med*. 2018;11(7):e001926. Epub 2018/07/11. doi: 10.1161/CIRCGEN.118.001926. PubMed PMID: 29987111; PMCID: PMC6082163

3. **Uncovering leukemia evasion of innate immunity:** Immune evasion is increasingly regarded as an important hallmark of cancer progression. Most studies have focused on the adaptive immune response against tumor cells. For my graduate thesis, I discovered a novel mechanism of tumor evasion from the innate immune system. Our lab first noted CD47 to be one of the most highly up-regulated genes in both mouse models of acute myeloid leukemia and in humans with the disease. My work found that CD47, via its interaction with the macrophage inhibitory receptor SIRP-alpha, acts as a "don't eat me" signal on leukemic cells to prevent phagocytosis. This mechanism is also utilized by normal hematopoietic stem cells as a protective response from macrophages during systemic

inflammation. This work is currently the basis for Phase I clinical trials targeting CD47 in hematologic malignancies and solid tumors.

- a. **Jaiswal S***, Traver D*, Miyamoto T, Akashi K, Lagasse E, Weissman IL. Expression of BCR/ABL and BCL-2 in myeloid progenitors leads to myeloid leukemias. *Proc Natl Acad Sci U S A*. 2003;100(17):10002-7. doi: 10.1073/pnas.1633833100. PubMed PMID: 12890867; PMCID: 187741
- b. **Jaiswal S**, Jamieson CH, Pang WW, Park CY, Chao MP, Majeti R, Traver D, van Rooijen N, Weissman IL. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell*. 2009;138(2):271-85. doi: 10.1016/j.cell.2009.05.046. PubMed PMID: 19632178; PMCID: 2775564
- c. Majeti R, Chao MP, Alizadeh AA, Pang WW, **Jaiswal S**, Gibbs KD, Jr., van Rooijen N, Weissman IL. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. *Cell*. 2009;138(2):286-99. doi: 10.1016/j.cell.2009.05.045. PubMed PMID: 19632179; PMCID: 2726837
- d. Chao MP, **Jaiswal S**, Weissman-Tsukamoto R, Alizadeh AA, Gentles AJ, ... Weissman IL. Calreticulin is the dominant pro-phagocytic signal on multiple human cancers and is counterbalanced by CD47. *Sci Transl Med*. 2010;2(63):63ra94. doi: 10.1126/scitranslmed.3001375. PubMed PMID: 21178137; PMCID: 4126904

* Denotes equal contribution

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