BIOGRAPHICAL SKETCH

NAME: Akiko Shimamura, M.D., Ph.D.

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

POSITION TITLE: Professor of Pediatrics, Harvard Medical School; Samuel E. Lux IV, Chair in Hematology/Oncology; Director Bone Marrow Failure and MDS Program

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Princeton University, Princeton, NJ	AB	06/1983	Biochemistry
Johns Hopkins Hospital, Baltimore, MD, USA	First year of medical school	06/1984	Medicine
University of Rochester, Rochester, NY, USA	MD, PHD	05/1991	Medicine and Biology
Johns Hopkins Hospital, Baltimore, MD, USA		06/1994	Pediatrics Residency
Dana-Farber Cancer Institute/Boston Children's Hospital, Boston, MA, USA		06/1997	Pediatric Hematology Oncology Fellowship

A. Personal Statement

I am a physician scientist in the field of pediatric hematology and oncology. My research focuses on bone marrow failure (BMF) and genetic predisposition to myelodysplastic syndrome (MDS). Specifically, my laboratory conducts patient-oriented research on the molecular mechanisms regulating hematopoiesis, marrow failure, and clonal evolution. I am also the principal investigator for Bone Marrow Failure translational studies spanning both laboratory research and clinical trials. I direct the BMF and MDS Program at Dana Farber/Boston Children's Cancer and Blood Disorders Center. I co-organized (with Dr. David Williams) the North American Pediatric Aplastic Anemia Consortium. I chaired the Germline Genetics Subcommittee of the ASH Precision Medicine Task Force. The goals of my research are to investigate the molecular and genetic mechanisms causing bone marrow failure and MDS-predisposition and to develop effective strategies for surveillance, treatment and prevention. I developed and direct the North American Shwachman Diamond Syndrome Registry which includes clinical data and clinically annotated biological samples. I also oversee a BMF/MDS clinical database and sample repository since 2001. We developed one of the earliest clinical genetic panels for bone marrow failure and identified novel causative genes. We recently identified somatic acquired mutations predictive of disease evolution in the MDS- predisposition syndrome, Shwachman Diamond Syndrome and studied functional and biological consequences. I also design and conduct clinical trials translating findings from the laboratory to the treatment of bone marrow failure.

B. Positions and Honors

Positions and Employment

1997 - 2003	Instructor in Pediatrics, Harvard Medical School
2000 - 2007	Director, Bone Marrow Failure Clinic, Boston Children's Hospital
2003 - 2007	Assistant Professor of Pediatrics, Harvard Medical School
2007 - 2015	Associate Professor of Pediatrics, University of Washington
2007 - 2015	Director, Bone Marrow Failure and MDS Clinic, Seattle Children's Hospital
2008 - 2014	Associate Member, Fred Hutchinson Cancer Research Center
2014 - 2015	Full Member, Fred Hutchinson Cancer Research Center
2015	Professor of Pediatrics, University of Washington School of Medicine
2015 - Present	Director, Bone Marrow Failure and MDS Program, Dana Farber/Boston Children's Cancer and Blood Disorders Center
2016- 2018	Associate Professor of Pediatrics, Harvard Medical School
2017-Present	Samuel E. Lux IV Chair in Hematology/Oncology
2018-Present	Professor of Pediatrics, Harvard Medical School

Other Experience and Professional Memberships

2006 - Present	Scientific Advisory Board, Shwachman Diamond Syndrome Foundation
2008 – Present	Director, North American Shwachman Diamond Syndrome Registry
2009 - Present	Scientific Advisory Board, Severe Chronic Neutropenia International Registry
2013 - 2015	National Institutes of Health, Permanent Member, Molecular and Cellular Hematology (rotated off due to move to Boston)
2017 – Present	Editorial Board, *Blood*
2017 - Present	Medical and Scientific Advisory Board, MDS Foundation
2019 - Present	Scientific Advisory Board, *DADA2* Foundation
2019 - Present	Medical Advisory Board, *RUNX1* Research Program

Honors

2013	Rare Disease Research Hall of Fame, National Organization for Rare Diseases (NORD)
2014	Nominee, RARE Tribute, Champions of Hope
2015	EWOG-MDS Award, EWOG-MDS
2020	Frank A. Oski Memorial Lectureship Award, American Society of Pediatric Hematology/Oncology

C. Contribution to Science

1. **Genetics of inherited marrow failure and MDS**

The study of inherited and acquired mutations informs our understanding of the molecular pathways regulating hematopoiesis and clonal evolution. Timely diagnosis of inherited marrow failure/MDS is critical to inform medical management and to guide choice of family donors for bone marrow transplant. Using whole exome sequencing, we identified novel genetic causes of bone marrow failure and leukemia predisposition. Genetic diagnosis informs clinical management and treatment. We were among the first to develop a multiplexed next-generation sequencing panel for BMF/MDS to demonstrate that a significant number of BMF and MDS patients (5-15%) have cryptic, clinically unsuspected, genetic causes. Our panel was the earliest multiplexed BMF/MDS germline genetic panel available as a clinical test utilizing next-gen sequencing.

Zhang MY, Keel SB, Walsh T, Lee MK, Gulsuner S, Watts AC, Pritchard CC, Salipante SJ, Jeng MR, Hofmann I, Williams DA, Fleming MD, Abkowitz JL, King MC, **Shimamura A**. Genomic analysis of bone marrow failure and myelodysplastic syndromes reveals phenotypic and diagnostic complexity. Haematologica. 2015. 100(1):42-8. PMCID: PMC4540357

Zhang, MY, Churpek, JE, Walsh, T, Lee, MK, Keel, SB, Loeb, KR, Gulsuner, S, Pritchard, CC, Forouhar, M, Gyurkocza, B, Schwartz, BS, Neistadt, B, Marquez, R, Mariani, C, Coats, S, Hofmann, I, Lindsley, RC, Williams, DA, Abkowitz, JL, Horwitz, MS, Godley, LA, King, MC, and **Shimamura, A**. Germline *ETV6* Mutations in Familial Thrombocytopenia and Hematologic Malignancy. Nature Genetics. 2015. 47(2): 180-185. PMCID: PMC4540357

Keel SB, Scott A, Sanchez-Bonilla M, Ho PA, Gulsuner S, Pritchard CC, Abkowitz JL, King MC, Walsh T, **Shimamura A.** Genetic features of myelodysplastic syndrome and aplastic anemia in pediatric and young adult patients. Haematologica. 2016 Nov;101(11):1343-1350. PMID: 27418648

Seo A, Ben-Harosh M, Sirin M, Stein J, Dgany O, Kaplelushnik J, Hoenig M, PannickeU, Lorenz M, Schwarz K, Stockklausner C, Walsh T, Gulsuner S, Lee MK, Sendamarai A, Sanchez-Bonilla M, King MC, Cario H, Kulozik AE, Debatin KM, Schulz A, Tamary H, **Shimamura A.** Blood 2017. Bone marrow failure unresponsive to bone marrow transplant is caused by mutations in *THPO*. Blood 2017. 30(7):875-880. PMID: 28559357

2. **Ribosomal disorders in marrow failure and malignancy**

Mutations in the SBDS gene cause Shwachman-Diamond syndrome (SDS) which is characterized by marrow failure and leukemia predisposition. Work from our lab demonstrated that the SBDS protein was found in the nucleolus and associated with the 60S ribosomal subunits but not the mature 80S ribosome (Blood, 2007), and affected the association of the 40S and 60S ribosomal subunits. We were the first to demonstrate that loss of SBDS expression resulted in mitotic spindle instability. We extended these studies to ribosomal pathways in multiple myeloma. We utilized IPS cells to model marrow failure and MDS in SDS and identified potential therapeutic targets which we validated with primary patient marrow. We also worked with Dr. Ingber to model SDS in a bone marrow organoid system. These studies contributed to our understanding that ribosome

homeostasis, previously relegated to a housekeeping function, also affects hematopoiesis and clonal evolution.

Austin, K.M., Gupta, M.L., Coats, S.A. Tulpule, A., Mostoslavsky, G., Balazs, A.B., Mulligan, R.C., Daley, G. Q., Pellman, D., and **Shimamura, A.** Mitotic spindle destabilization and genomic instability in Shwachman-Diamond Syndrome. Journal of Clinical Investigation, 2008 Apr;118(4):1511-8. PMCID: PMC2263145.

Burwick, N, Coats, SA, Nakamura, T, and **Shimamura, A.** Impaired Ribosomal Subunit Association in Shwachman-Diamond Syndrome. Blood 2012. 120(26):5143-52. PMCID: PMC3537309

Ruiz-Gutierrez M, Vargel Bölükbaşi Ö, Alexe G, Kotini AG, Ballotti K, Joyce CE, Russell DW, Stegmaier K, Myers K, Novina CD, Papapetrou EP, **Shimamura A.** Therapeutic discovery for marrow failure with MDS predisposition using pluripotent stem cells. JCI Insight. 2019 Par 30; 5, pii: 125157. doi: 10.1172/jci.insight.125157. PMID: PMID:31039138.

Chou DB, Frismantas V, Milton Y, David R, Pop-Damkov P, Ferguson D, MacDonald A, Vargel Bölükbaşı Ö, Joyce CE, Moreira Teixeira LS, Rech A, Jiang A, Calamari E, Jalili-Firoozinezhad S, Furlong BA, O'Sullivan LR, Ng CF, Choe Y, Marquez S, Myers KC, Weinberg OK, Hasserjian RP, Novak R, Levy O, Prantil-Baun R, Novina CD, **Shimamura** A, Ewart L, Ingber DE. On-chip recapitulation of clinical bone marrow toxicities and patient-specific pathophysiology. Nat Biomed Eng. 2020 Jan 27. doi: 10.1038/s41551-019-0495-z PMID: 31988457

3. **Clinical phenotyping and treatment of marrow failure disorders**

Disease registries have been instrumental for the study of rare disorders. To this end, I organized and direct the North American Shwachman-Diamond syndrome registry, whose mission is to understand the natural history and molecular pathophysiology of SDS to improve diagnosis, medical management, and treatment. We found that the clinical phenotype of SDS was much broader than previously recognized and that many patients with SDS lack typical clinical stigmata. We also found that outcomes of AML are abysmal in patients with SDS due to both high treatment-related toxicities and resistant disease, thus providing a strong rationale for the development of novel treatments. I also co-organized the North American Pediatric Aplastic Anemia Consortium, a working group that reported presenting features and outcomes of the largest cohort of pediatric patients with aplastic anemia treated with immunosuppressive therapy. These studies are important because they inform the medical management of marrow failure patients.

Myers, KC, Bolyard, AA, Otto, B, Jones, A, Wong, TE, Harris, RE, Davies, SM, Dale, DC, **Shimamura, A.** Variable clinical presentation of Shwachman-Diamond Syndrome: Update from the North American Shwachman-Diamond Syndrome Registry. J Pediatr. 2014. 164(4):866-70. PMCID: PMC4077327

Rogers ZR, Nakano TA, Olson TS, Bertuch AA, Wang W, Gillio A, Coates TD, Chawla A, Castillo P, Kurre P, Gamper C, Bennett CM, Joshi S, Geddis AE, Boklan J, Nalepa G, Rothman JA, Huang JN, Kupfer GM, Cada M, Glader B, Walkovich KJ, Thompson AA, Hanna R, Vlachos A, Malsch M, Weller EA, Williams DA, **Shimamura A.** Immunosuppressive therapy for pediatric aplastic anemia: A North American Peditaric Aplastic Anemia Consortium Study. Haematologica. 2019. Apr 4. pii: haematol.2018.206540. doi: 10.3324/haematol.2018.206540. [Epub ahead of print] PMID: 30948484

Furutani E, Shah AS, Zhao Y, Andorsky D, Dedeoglu F, Geddis A, Zhou Y, Libermann TA, Myers KC, **Shimamura A**. Inflammatory manifestations in patients with Shwachman-Diamond syndrome: a novel phenotype. Am J Med Genet. 2020 Apr 15. doi: 10.1002/ajmg.a.61593. PMID: 32293785

Myers KC*, Furutani E*, Weller E, Siegele B, Galvin A, Arsenault V, Alter BP, Boulad F, Bueso-Ramos C, Burroughs L, Castillo P, Connelly J, Davies SM, DiNardo CD, Hanif I, Ho RH, Karras N, Manalang M, McReynolds LJ, Nakano TA, Nalepa G, Norkin M, Oberley MJ, Orgel E, Pastore YD, Rosenthal J, Walkovich K, Larson J, Malsch M, Elghetany MT, Fleming MD, **Shimamura A.** Clinical features and outcomes of patients with Shwachman Diamond Syndrome and myelodysplastic syndrome or acute myeloid leukaemia: a multicenter, retrospective cohort study. Lancet Haematol. 2020. 7(3): *e238-e246.* PMID: 31879230 *equal contribution

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/akiko.shimamura.1/bibliography/40669793/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1RC2DK122533-01 **Shimamura** (PI) 7/1/2019 – 6/30/2024
Systems Biology of Bone Marrow Failure and MDS for Precision Medicine
The objective of this multi-PI study is to integrate genomics, transcriptomics, epigenomics, and clinical phenomes to elucidate the molecular mechanisms driving bone marrow failure and MDS and to inform personally tailored medical treatment.
Role: PI

5U01HL134812-03 **George Daley** (PI) 06/01/2018-05/31/2023
National Heart, Lung, and Blood Institute
Stem cells for therapeutics discovery in genetic blood disorders
This multi-PI, multi-center component of the Progenitor Cell Translation Consortium will screen and validate genes and small molecules as novel therapeutics and move them into clinical trials.
Role: Project PI

Research Award **Shimamura** (PI) 03/01/2018-02/28/2021
Fanconi Anemia Research Fund
Pilot Study of Metformin for Patients with Fanconi Anemia
Aim: Pilot clinical trial of metformin to treat bone marrow failure in Fanconi anemia combined with biological correlative studies to assess the effect of metformin on hematopoiesis and DNA damage.
Role: PI

P01 HL048546-21A1) **Grompe** (PI) 09/01/2016 - 08/31/2021
National Heart, Lung and Blood Institute, National Institutes of Health
Pathophysiology and Treatment of Fanconi Anemia
Project 3 (P01 HL048546-21A1) **Shimamura** (Project PI)
Preclinical Studies of Marrow Failure and Clonal Evolution in Fanconi Anemia
Project 3 will evaluate the effects of small molecule compounds on hematopoiesis in Fanconi anemia and translate these findings to the clinic.
Role: Project 3 PI
Core D (P01 HL048546-21A1)
Clinical Sample Processing Core **Armant** (Project PI)
The Fanconi Anemia Repository, Core D will collect and maintain a bank of clinically annotated biological resources necessary to support this program project grant.
Role: Co-Investigator

R34 HL133384-01 **Williams** (PI) 04/1/2017 - 03/31/2021
National Heart, Lung and Blood Institute, National Institutes of Health
Feasibility study randomizing IST vs URD BMT for children with aplastic anemia
The goal of this pilot clinical trial is to determine the feasibility of randomizing children with acquired aplastic anemia to either immunosuppression therapy (current standard of care) versus a highly matched unrelated donor hematopoietic stem cell transplant.
Role: Co-Investigator

R01 HL150669 **Bauer** (PI) 12/20/2019 - 11/30/2023
National Heart, Lung and Blood Institute
Rectifying splicing mutations in blood disorders by gene editing.
The goal is to develop innovative gene editing methods that can repair the abnormal genes that cause beta-thalassemia and Shwachman-Diamond syndrome to restore their normal processing.
Role: Co-Investigator

OVERLAP

None