BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Kathleen M. Sakamoto

eRA COMMONS USER NAME (credential, e.g., agency login): Sakamoto2

POSITION TITLE: Shelagh Galligan Professor of Pediatrics

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
Williams College, Williamstown, MA	B.A.	06/1979	Biology, Cum Laude
University of Cincinnati College of Medicine, Cincinnati, OH	M.D.	06/1985	Medicine
Children's Hospital Los Angeles, Los Angeles, CA		06/1988	Pediatrics
Children's Hospital Los Angeles, Los Angeles, CA and Mattel Children's Hospital, University of California, Los Angeles		06/1991	Hematology/Oncology Fellowship
California Institute of Technology, Pasadena, CA	Ph.D.	01/2004	Biology

A. Personal Statement

Since 1993, my research interest has been gene regulation and signal transduction pathways in normal and aberrant hematopoiesis. Following my postdoctoral fellowship with Dr. Judith Gasson (UCLA), my lab characterized GM-CSF signaling at the molecular level and identified the transcription factor CREB as a target of cytokine signaling in AML cells. During my thesis work in the laboratory of Ray Deshaies, Ph.D. at Caltech, I developed a new approach to target cancer-causing proteins for ubiquitination and degradation known as Protacs (also known as "degraders"). This technology resulted in a clinical trial for this year. Over the past decade, we have studied novel therapies to treat a variety of hematologic diseases, including acute myeloid leukemia (AML) and Diamond Blackfan Anemia (DBA). We described CREB as a proto-oncogene in myeloid leukemogenesis and are developing small molecules to inhibit CREB for the treatment of acute leukemia. In collaboration with Shuo Lin, Ph.D. at UCLA, we developed zebrafish models to study DBA and myelodysplastic syndromes. I currently have a Department of Defense (Idea grant) to study the role of Nemo-like Kinase in the Pathogenesis of DBA. We have recently published studies on signaling pathways related to FOXM1, TNFalpha, and MMP9 during human erythropoiesis. I have been the P.I. of the first NIH T32 training grants funded at UCLA and at Stanford in the Division of Pediatric Hematology/Oncology. I have also served on grant review committees for NIH, ACS, Leukemia and Lymphoma Society, Alex's Lemonade Stand Foundation, Pediatric Cancer Research Foundation, Bear Necessities/Rally Foundation, St. Baldrick's Foundation, Hyundai Hope on Wheels, and American Society of Hematology (Scholar award, Bridge grant, RTAF award, Honors award, and MMSAP award programs).

B. Positions and Honors

Positions and Employment

1991-1993 Clinical Instructor, Department of Pediatrics, UCLA School of Medicine
1993-2011 Assistant to Full Professor of Pediatrics and Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA

2005-2011 Chief, Division of Hematology-Oncology, Mattel Children's Hospital, David Geffen School of Medicine at UCLA
2006-2011 Co-Associate Director, Signal Transduction Program Area, Jonsson Comprehensive Cancer Center, UCLA
2006-2011 Vice-Chair of Research, Mattel Children's Hospital UCLA
2011 Co-Chair, UCLA CTSI Committee on Maternal, Child, and Adolescent Health
2011-current Professor of Pediatrics, Stanford University School of Medicine.
2011-2014 Chief, Division of Hematology/Oncology/Stem Cell Transplant/Cancer Biology at the Bass Cancer Center, Stanford School of Medicine, Lucile Packard Children's Hospital
2014-2020 Member and Chair, Appointments and Promotions Committee, Stanford University School of Medicine
2013-present Member, Maternal Child Health Research Institute Executive Committee, Stanford University

Certification

1986 Diplomate, National Board of Medical Examiners
1989 Diplomate, American Board of Pediatrics (recertified 1999, 2006, 2016)
1994 Diplomate, American Board of Pediatrics, Hematology-Oncology (recertified 1999, 2006, 2016)

Honors

1992 STOP CANCER/Jonsson Comprehensive Cancer Center Career Development Award
1994 American Society of Pediatric Hematology-Oncology Young Investigator Award
1996 Western Society for Pediatric Research, Junior Faculty Ross Award in Research
1999 Leukemia and Lymphoma Society of America Fellow, Special Fellow, and Scholar Awards
2005-2009 Member, NIH Hematopoiesis Study Section
2005-2016 Member, Translational Research Program Grant Review Committee for the Leukemia and Lymphoma Society of America
2006 Benjamin Franklin High School Wall of Fame Award
2007-present Member, St. Baldrick's Foundation Scientific Review Committee
2008 "Meet-the-Expert" on Transcription Factors and AML, American Society of Hematology meeting
2008-2010 Board of Trustees, American Society of Pediatric Hematology-Oncology
2009 Fernbach Distinguished Visiting Professor Lectureship, Texas Children's Cancer Center, Baylor College of Medicine
2011 Chair, ASH Scientific Subcommittee on Myeloid Biology
2010-2016 Member, NIDDK-D study section for training grants (K awards and T32)
2011 Brent Ely Visiting Professor in Pediatric Oncology, University of Colorado and Children's Hospital Denver
2012 Shelagh Galligan Endowed Chair
2013 Invited speaker, Swerling Symposium "Seminars in Oncology," Dana Farber Cancer Institute
2013 Jason Bennette Memorial Lectureship, Cohen Children's Hospital, Long Island, NY.
2015 Steven Rosen Endowed Lectureship, Northwestern University School of Medicine
2016 Pediatric Cancer Research Foundation Memorial Lecture Honoree
2016-2019 Ad hoc reviewer for NIH BMCT, MCH and F32 study sections
2016 Chair, Scientific Review Committee, Bear Necessities and Rally Foundation
2018 ASH coordinating reviewer for Chemical Biology session
2017-2020 Chair, Physician Scientist Special Interest Group, American Society of Pediatric Hematology/Oncology
2019 UCLA Specialized Training and Research (STAR) Program Alumni Achievement Award
2020-2023 NIDDK Council and NIDDK Strategic Plan Working Group

C. Contribution to Science

1. Mechanisms of Bone Marrow Failure: We first demonstrated that RPS19 morpholinos injected embryos recapitulated the DBA phenotype in zebrafish. We further showed that RPS19-deficiency in zebrafish and human hematopoietic cells results in increased TNFalpha, decreased gata-1 expression, and suppression of erythropoiesis. Our results also suggested that inhibitors of TNFalpha could rescue the defects in erythropoiesis caused by RPS19-deficiency and this was mediated in a p38 MAP kinase-dependent pathway. We recently described the novel role of Nemo-like kinase in the pathogenesis of DBA.

a. Bibikova E, Youn MY, Danilova N, Ono-Uruga Y, Konto-Ghiorghi Y, Ochoa R, Narla A, Glader B, Lin S, and **KM Sakamoto.** TNF-mediated inflammation represses GATA1 and activates p38 MAP kinase in RPS19-deficient hematopoietic progenitors. Blood, 124(25):3791-8, 2014.
b. Youn M, Huang H, Chen C, Kam S, Wilkes MC, Chae HD, Sridhar KJ, Greenberg PL, Glader B, Narla A, Lin S* and **KM Sakamoto***. MMP9 Inhibition increases erythropoiesis in RPS14-deficient del(5q) MDS models through suppression of TGF-beta pathways. Blood Adv, 3:2751-2763, 2019. *co-senior authors.
c. Wilkes MC, Siva K, Chen J, Varetti G, Dever DP, Nishimura T, Chae H, Youn MY, Narla A, Glader B, Nakauchi H, Porteus MH, Repellin CE, Gazda TH, Lin S, Serrano M, Flygare J and **KM Sakamoto**. Diamond Blackfan Anemia is Mediated by Hyperactive Nemo-Like Kinase. Nat Commun, July 3, 2020.
d. Wilkes MC, Siva K, Varetti G, Mercado J, Wentworth EP, Perez C, Saxena M, Km S, Kapur S, Chen J, Narla A, Glader B, Lin S, Serrano M, Flygare J and **KM Sakamoto**. Metformin-induced Suppression of NLK improves Erythropoiesis in Diamond Blackfan Anemia through Induction of miR26a, Exp Hematol, *in press.*

2. CREB in Normal Hematopoiesis and Leukemogenesis: We were the first to demonstrate that CREB is overexpressed in human AML cells. We generated a CREB transgenic mouse model in which CREB was overexpressed in myeloid progenitors. These mice developed MDS/MPN but not AML. This paper demonstrated that CREB is a bonafide proto-oncogene. We also demonstrated that CREB overexpression is associated with an increased risk of relapse and decreased event-free survival, which has since been validated by Giuseppi Basso (University of Padova) and Steven Kornblau (MD Anderson). We also showed that CREB cooperates with Sox4 to transform myeloid progenitor cells to AML.
a. Shankar D, Cheng JC, Kinjo K, Wang J, Federman N, Moore TB, Gill A, Rao N, Landaw EM, and **KM Sakamoto.** The role of CREB as a proto-oncogene in Hematopoiesis and in Acute Myeloid Leukemia. Cancer Cell, 7:351-362, 2005.
b. Sandoval S, Kraus C, Cho EC, Cho M, Bies J, Landaw EM, Wolff L, and **KM Sakamoto**. Sox4 cooperates with CREB in Myeloid Transformation, Blood, 120: 155-165, 2012.
c. Chae HD, Mitton BA, and **KM Sakamoto**. Replication factor C3 is a CREB Target Gene that Enhances G1/S Transition of AML cells and Self-renewal of Hematopoietic Stem and Progenitor Cells. Leukemia, 29: 1379-1389, 2015.
d. Kim PG, Nakano H, Das PP, Chen MJ, Rowe RG, Chou SS, Ross SJ, **Sakamoto KM**, Zon LI, Schlaeger TM, Orkin SH, Nakano A, and Daley GQ. Flow-induced protein kinase A-CREB pathway acts via BMP signaling to promote HSC emergence. J Exp Med, 212: 633-648, 2015.

3. CREB and Immunity/Infectious disease: In this paper, we showed that CREB transgenic mice had an increased incidence of abscess formation. We found that CREB overexpression affects the innate immune response primarily through deregulation of inflammatory cytokines and increasing NADPH oxidase activity.
a. Wen AY, **Sakamoto KM**, and Miller LS. The Role of the Transcription Factor CREB in Immune Function. J Immunol, 185:6413-9, 2010.
b. Wen AY, Landaw EM, Ochoa R, Cho M, Chao A, Lawson, and **KM Sakamoto**. Increased Abscess Formation and Defective Chemokine Regulation in CREB Transgenic Mice. PLoS ONE, 8:(2)e55866, 2013.
c. Francois S, Sen N, Mitton B, Xiao X, **Sakamoto KM**, and Arvin A. Varicella-Zoster Virus Activates CREB and Inhibition of the pCREB-p300/CBP-interaction inhibits Viral Replication *in vitro* and Skin Pathogenesis *in vivo*. J Virology, Jul 20, 2016.

4. Novel Approaches to Treat Leukemia: We described that CREB is a target for therapy and are developing small molecules to inhibit CREB:CBP interaction and CREB function in addition to other novel approaches to treat acute leukemia.
a. Mitton B, Chae HD, Hsu K, Dutta R, Aldana-Masangkay G, Ferrari R, Davis K, Tiu BC, Kaul A, Lacayo N, Dahl G, Xie F, Li BX, Breese MR, Landaw EM, Nolan G, Pellegrini M, Romanov S, Xiao X, and **KM Sakamoto.** Small molecule inhibition of cAMP response element binding protein in human acute myeloid leukemia cells. Leukemia, 30:2302-2311, 2016.
b. Chae HD, Cox N, Dahl GV, Lacayo NJ, Davis KL, Capoliccio S, Smith M, and **KM Sakamoto**. Niclosamide Suppresses Acute Myeloid Leukemia Cell Proliferation Through Inhibition of CREB-Dependent Signaling Pathways. Oncotarget, 9:4301-4317, 2017 (published as a Priority Paper).

c. Chae HD, Cox N, Capolicchio S, Lee JW, Norikoshi N, Kam S, Ng A, Edwards J, Butler TL, Chan J, Lee Y, Potter G, Capece M, Liu C, Wakatsuki S, Smith M and **KM Sakamoto**. Salicylamide as a potential treatment for acute myeloid leukemia through inhibition of the CREB pathway. Bioorg Med Chem Letters, 29:2307-2315, 2019.
d. Chae HD, Dutta R, Tiu B, Hoff F, Accordi B, Serafin V, Youn MY, Huang M, Sumarsono N, Davis KL, Lacayo NJ, Pigazzi M, Horton TM, Kornblau SM and **KM Sakamoto**. RSK Inhibitor BI-D1870 Inhibits Acute Myeloid Leukemia Cell Proliferation by Targeting Mitotic Exit. Oncotarget, 11:2387-2403, 2020

5. Development of Protacs for Cancer Therapy: In collaboration with Raymond Deshaies, Ph.D. (Caltech) and Craig Crews, Ph.D. (Yale), we were the first to demonstrate that cancer-causing proteins could be targeted for ubiquitination and degradation in cancer. We demonstrated this with purified proteins and in cells.

a. **Sakamoto KM**, Crews CM, Kim KB, Kumagai A, Mercurio F, Deshaies RJ. Protac: chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation. Proc Natl Acad Sci U S A, 98(15):8554-9, 2001.
b. **Sakamoto KM,** Kim KB, Verma R, Ransick A, Stein B, and Deshaies RJ. Development of Protacs to target cancer-promoting proteins for ubiquitination and degradation. Mol Cell Proteomics, 2003 2:1350-8. Epub 2003 Oct 2.
c. Rodriguez-Gonzalez A, Cyrus K, Salcius M, Kim KB, Crews CM, Deshaies RJ, and **KM Sakamoto**. Targeting Steroid Hormone Receptors for Ubiquitination and Degradation in Breast and Prostate Cancer, Oncogene, 27:7201-11, 2008.
d. Yu HH and **KM Sakamoto**. Redirecting the Cellular Waste Disposal Machinery to Target Transcription. Nuclear Receptors: The Art and Science of Modular Design and Discovery (Editor, Mostafa Badr), *in press.*

For complete list of 140 publications on Pubmed see URL (under Sakamoto KM)
http://www.ncbi.nlm.nih.gov/pubmed/?term=kathleen+sakamoto

6. Patent applications based on discoveries in the Sakamoto lab

"Proteolysis Targeting Chimeric Pharmaceutical" (Raymond Deshaies, Craig Crews, and Kathleen Sakamoto), Ref. No. CIT3284

"Inhibitors of CREB:CBP Interaction for Treatment of Acute Myeloid Leukemia" (Kathleen Sakamoto, Mark Smith, Bryan Mitton, Hee-Don Chae). Ref. No. 16/081,396.

"Small molecules to target Nemo-like Kinase for treatment of bone marrow failure syndromes" (Kathleen Sakamoto, Mark Wilkes). S20-270 U.S. Provisional Application No.: 63/046,877 (STAN-1769PRV)

"Protein double-shell nano structures for guiding drug discovery" (Soichi Wakatsuki, Wah Chiu, Naoki Horikoshi, Kathleen Sakamoto). (STAN-S20-404).

D. Research Support

Ongoing Research Support

R01DK107286
National Institutes of Health (NIDDK) 09/1/16-08/31/21
Signaling Pathways in MDS
Sakamoto, PI
-The goal of this project is to characterize inflammatory signaling pathways that mediate RPS14-induced anemia in MDS.

BM180024 07/1/19-06/30/21
Department of Defense New Idea Grant
The Role of Nemo-Like Kinase in Diamond Blackfan Anemia
Sakamoto, PI
- The goal is to study Nemo-Like Kinase in Diamond Blackfan Anemia models

Research Grant 01/1/19-12/31/20
Diamond Blackfan Anemia Foundation
Targeting Nemo-Like Kinase for the Treatment of DBA
Sakamoto, PI and Wilkes, co-investigator
- The goal is to study the effects of NLK inhibition in combination with known therapies for DBA in murine and human DBA models *in vitro*.

T32DK098132 04/1/14-03/31/25

National Institutes of Health (NIDDK)
Training in Pediatric Nonmalignant Hematology and Stem Cell Biology
Sakamoto, PI
- The goal is to train postdoctoral fellows in nonmalignant hematology and stem cell biology.

Translational Research Grant 01/1/19-12/31/21
Pediatric Cancer Research Foundation
Targeted Inhibition of CREB for the Treatment of Pediatric Acute Myeloid Leukemia
Sakamoto, PI
- The goal is to develop more potent CREB inhibitors for the treatment of pediatric AML.

Research Grant 12/31/18-6/30/21
Hyundai Hope on Wheels
The Role of RSK in the Pathogenesis of Pediatric AML and as a Target for Therapy
Sakamoto, PI
- The goal is to study the role of RSK in the pathogenesis of AML and as a target for therapy.

Translational Research Program 07/1/19-06/30/22
Leukemia & Lymphoma Society
Niclosamide for the Treatment of Relapsed/Refractory Pediatric Acute Myeloid Leukemia
Sakamoto, PI and Lacayo, co-PI
- The goal is to study the use of niclosamide for the treatment of relapsed/refractory pediatric AML.

Cure Childhood Cancer 08/1/19-07/31/21
Phase I clinical trial with Niclosamide for the Treatment of Relapsed/Refractory Pediatric AML.
Sakamoto, PI
- To conduct a Phase I clinical trial for treatment of relapsed pediatric AML.