BIOGRAPHICAL SKETCH

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NAME: Kathleen M. Sakamoto, M.D., Ph.D.

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.	06/79	Biology, Cum Laude
University of Cincinnati College of Medicine, Cincinnati, OH	M.D.	06/85	Medicine
California Institute of Technology, Pasadena, CA	Ph.D.	01/2004	Biology
Children's Hospital Los Angeles, Los Angeles, CA		06/88	Pediatrics
Children's Hospital Los Angeles, Los Angeles, CA and Mattel Children's Hospital, University of California, Los Angeles		6/91	Hematology/Oncology Fellowship

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. This technology will result in a clinical trial for cancer patients next year. Over the past decade, we studied novel therapies to treat a variety of hematologic diseases, including acute myeloid leukemia (AML) and Myelodysplastic Syndromes. 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 myelodysplastic syndromes. I have been funded by the NIH since 1993 and received a K08 award, NCI R29 grant, R01 and R21 grants from the NCI, NHLBI, and NIDDK. I received support from the Leukemia and Lymphoma Society (fellow, special fellow, and Scholar award), American Cancer Society (Scholar award), and Department of Defense (Idea grant). I have been the P.I. of the first NIH T32 training grants funded at UCLA and 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, RTAF, and MMSAP award programs).

1. Shankar D, Cheng JC, Kinjo K, Wang J, Federman N, Moore TB, Gill A, Rao N, Landaw EM, and **Sakamoto KM.** The role of CREB as a proto-oncogene in Hematopoiesis and in Acute Myeloid Leukemia. Cancer Cell, 7:351-362, 2005.
2. 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 **Sakamoto KM**. Small molecule inhibition of cAMP response element binding protein in human acute myeloid leukemia cells. Leukemia, 30:2302-2311, 2016.

3. Chae HD, Cox N, Dahl GV, Lacayo NJ, Davis KL, Capoliccio S, Smith M, and **Sakamoto KM**. Niclosamide Suppresses Acute Myeloid Leukemia Cell Proliferation Through Inhibition of CREB-Dependent Signaling Pathways. Oncotarget, 9:4301-4317, 2017 (published as a Priority Paper).
4. Danilova N, Wilkes M, Bibikova E, Youn MY, **Sakamoto KM***, and Lin S*. Innate Immune System Activation in Zebrafish and Cellular Models of Diamond Blackfan Anemia. Sci Rep, 8(1):5165, 2018. ***co-senior authors.**

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
2013-present	Member, Child Health Research Institute Executive Committee, Stanford University
2014-present	Member, Appointments and Promotions Committee, Stanford University School of Medicine

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.
2014	ASH abstract reviewer and session moderator for Hematopoiesis: Cytokines, Signal Transduction, Apoptosis, and Cell Cycle Regulation
2015	Steven Rosen Endowed Lectureship, Northwestern University School of Medicine
2016	Pediatric Cancer Research Foundation Memorial Lecture Honoree
2016-present	Ad hoc reviewer for NIH BMCT, MCH and F32 study sections
2016	Chair, Scientific Review Committee, Bear Necessities and Rally Foundation

2017 ASH abstract review committee for Red Cells and Erythropoiesis, Structure and Function, Metabolism, and Survival session
2018 ASH coordinating reviewer for Chemical Biology session
2017-present Chair, Physician Scientist Special Interest Group, American Society of Pediatric Hematology/Oncology
2020-present NIDDK Council

C. Contribution to Science

1. Novel Approaches to Treat Acute Leukemia: We described that CREB is a target for therapy and are developing small molecules and peptides to inhibit CREB:CBP interaction and CREB function in addition to other novel approaches to treat AML.

a. Mitton BM, Hsu K, Dutta R, Tiu BC, Cox N, Mclure KG, Chae HD, Smith M, Eklund EA, Solow-Cordero DE, and **Sakamoto KM**. Small Molecule Screen for Inhibitors of the Transcription Factor, CREB. Oncotarget, 7:8653-8662, 2016.
b. 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 **Sakamoto KM.** Small molecule inhibition of cAMP response element binding protein in human acute myeloid leukemia cells. Leukemia, 30:2302-2311, 2016.
c. Chae HD, Cox N, Dahl GV, Lacayo NJ, Davis KL, Capoliccio S, Smith M, and **Sakamoto KM**. Niclosamide Suppresses Acute Myeloid Leukemia Cell Proliferation Through Inhibition of CREB-Dependent Signaling Pathways. Oncotarget, 9:4301-4317, 2017 (published as a Priority Paper).
d. Duque-Alfonso J, Lin CH, Han K, Morgens DW, Jen EE, Weng Z, Jeong J, Wong SHK, Zhu L, Wei MC, Chae HD, Schrappe M, Cario G, Duyster J, Xiao X, **Sakamoto KM**, Bassick MC, and ML Cleary. Cancer Res, 78:6497-6508, 2018.

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 **Sakamoto KM.** 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 **Sakamoto KM**. 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. **Development of Protacs for Cancer Therapy:** In collaboration with Raymond Deshaies, Ph.D. (Caltech) and Craig Crews, Ph.D. (Yale), we demonstrated that cancer-causing proteins could be targeted for ubiquitination and degradation in breast and prostate 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. Verma R, Peters NR, D'Onofrio M, Tochtrop G, **Sakamoto KM**, Varadan R, Zhang M, Coffino P, Fushman D, Deshaies RJ, King RW. Ubistatins inhibit proteasome-dependent degradation by binding the ubiquitin chain. Science, 306:117-20, 2004.
   d. Rodriguez-Gonzalez A, Cyrus K, Salcius M, Kim KB, Crews CM, Deshaies RJ, and **Sakamoto KM**. Targeting Steroid Hormone Receptors for Ubiquitination and Degradation in Breast and Prostate Cancer, Oncogene, 27:7201-11, 2008.

5. **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.
   a. Bibikova E, Youn MY, Danilova N, Ono-Uruga Y, Konto-Ghiorghi Y, Ochoa R, Narla A, Glader B, Lin S, and **Sakamoto KM.** TNF-mediated inflammation represses GATA1 and activates p38 MAP kinase in RPS19-deficient hematopoietic progenitors. Blood, 124(25):3791-8, 2014.
   b. Youn M, Wang N, LaVasseur C, Bibikova E, Kam S, Glader B, **Sakamoto KM***, and Narla A*. Loss of FOXM1 promotes erythropoiesis through increased proliferation of erythroid progenitors. Haematologica, 102:826-834, 2017. ***co-senior authors.**
   c. Danilova N, Wilkes M, Bibikova E, Youn MY, **Sakamoto KM***, and Lin S*. Innate Immune System Activation in Zebrafish and Cellular Models of Diamond Blackfan Anemia. Sci Rep, 8(1):5165, 2018. ***co-senior authors.**
   d. 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, *under revision.*

For complete list of 131 publications on Pubmed see URL (under Sakamoto KM)
https://www.ncbi.nlm.nih.gov/pubmed/?term=sakamoto+km

Patents

1. "Proteolysis Targeting Chimeric Pharmaceutical (Protacs)" (Raymond Deshaies, Craig Crews, and Kathleen Sakamoto), Ref. No. CIT3284
2. "Inhibitors of CREB:CBP Interaction for Treatment of Acute Myeloid Leukemia" (Kathleen Sakamoto, Mark Smith, Bryan Mitton, Hee-Don Chae). U.S. Application Serial No. 16/081,396; European Application Serial No. 17764254.3

D. Research Support

Ongoing Research Support

R01DK107286
National Institutes of Health (NIDDK) 9/1/16-8/31/20
Signaling Pathways in MDS
Sakamoto, PI and Shuo Lin, co-PI
-The goal of this project is to characterize inflammatory signaling pathways that mediate RPS14-induced anemia in MDS.

R56DK112869-01A1 8/1/18-7/31/19
National Institutes of Health (NIDDK)
The Role of the Parathyroid Hormone Receptor in Osteoblast Support of Erythropoiesis.
Wu, PI and K. Sakamoto, co-Investigator
- The goal of this project is to define the role of the parathyroid hormone receptor in osteoblast support of erythropoiesis.

T32DK098132 4/1/14-3/31/20 (NCE)
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 1/1/19-12/31/21
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 7/1/17-6/30/19
Bear Necessities/Rally Foundation
CREB Inhibitors for Relapsed Acute Leukemia
Sakamoto, PI
- The goal is to develop small molecules to target CREB for treatment of relapsed acute leukemia.

Research Grant 1/1/18-7/31/20
Stanford Translation and Clinical Innovation Award
Sakamoto, PI
- The goal is to identify novel approaches to treat AML.

Research Grant 12/31/18-12/30/20
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.

Trans-interdisciplinary Grant 6/1/18-5/31/20
Maternal Child Health Institute at Stanford
Novel drugs to treat AML
Sakamoto, PI; Soichi Wakatsuki and Ron Dror (co-PIs)
- The goal is to develop new drugs to target CREB using structural chemistry and computational biology.

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

<u>Completed Research Support</u>
R13 CA 186539 5/1/14-5/31/18
National Institutes of Health (NHLBI/NCI)
Professional Development and Late Career Transitions in Pediatric Hematology/Oncology
Sakamoto, PI
-The goal is to support a workshop at the annual American Society of Pediatric Hematology/Oncology meeting to discuss late career transitions.