BIOGRAPHICAL SKETCH

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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
University of Cincinnati College of Medicine, Cincinnati, OH	M.D.	06/1985	Medicine
California Institute of Technology, Pasadena, CA	Ph.D.	01/2004	Biology
Children's Hospital Los Angeles, Los Angeles, CA	Postdoctoral	6/1998	Pediatrics
Children's Hospital Los Angeles, Los Angeles, CA and Mattel Children's Hospital, University of California, Los Angeles	Clinical Fellowship	6/2001	Hematology/Oncology

A. Personal Statement

Since 1993, my research interest has been gene regulation and signal transduction pathways in normal and aberrant hematopoiesis. During my postdoctoral fellowship under the mentorship of Dr. Judith Gasson (UCLA), I characterized GM-CSF signaling at the molecular level and identified the transcription factor CREB as a target of cytokine signaling in AML cells. A first author publication in Molecular and Cellular Biology (1994) resulted from this work. Since then, I have been studying the role of CREB during myeloid leukemogenesis and am developing small molecules to inhibit CREB for the treatment of acute leukemia. Publications in Cancer Cell (2005), Blood (2008), Leukemia (2016), and Bioorgan Med Chem Letters (2019) resulted from these studies. As a result of this work, I have written a Phase I clinical trial with niclosamide for relapsed/refractory pediatric AML. New drugs are being developed at Stanford in collaboration with Soichi Wakatsuki, Ph.D. (SLAC) and Ron Dror, Ph.D. (Computer Science). Two patents resulted from this work: 1) 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 and 2) Protein double-shell nano structures for guiding drug discovery (Soichi Wakatsuki, Wah Chiu, Naoki Horikoshi, Kathleen Sakamoto) (STAN-S20-404). This 16-year emphasis on molecular characterization of CREB in AML serves as the foundation for this proposal aimed at understanding the primary kinase, pp90RSK, which phosphorylates CREB to provide new insights into CREB signaling pathways and the potential for translating these discoveries to the clinic.

In addition to my work on CREB regulation in AML, my lab has also built on my graduate work under Ray Deshaies, Ph.D. at Caltech, where I developed a new approach to target cancer-causing proteins for ubiquitination and degradation known as Protacs (also known as "degraders"), published in Proc Natl Acad Sci (2001), Molecular and Cellular Proteomics (2003), Science (2004), and Oncogene (2008). This work resulted in a patent: Proteolysis Targeting Chimeric Pharmaceutical (Raymond Deshaies, Craig Crews, and Kathleen Sakamoto), Ref. No. CIT3284. This technology is currently in clinical trials. We are also collaborating with Cytosolve, Inc. to understand the systemic architecture of AML and microenvironment (Cancers, 2021).

We are also studying the pathogenesis and treatment of pediatric CML. We have performed bulk RNA-seq and transcriptomic profiling of pediatric CML stem cells in comparison to adult CML stem cells. Analysis of

pediatric CML cells by single cell RNA-seq is in progress. We also studied the late effects of tyrosine kinase inhibitors in pediatric CML patients and patterns of surveillance for late effects of BCR-ABL tyrosine kinase inhibitors in pediatric Philadelphia chromosome positive leukemias (BMC Cancer, 2021).

Ongoing Research Support

R01 DK107286
Sakamoto (PI)
09/01/16-08/31/22
Signaling Pathways in MDS

Leukemia & Lymphoma Society -Translational Research Program (R6518-23)
Sakamoto (PI)
07/01/19-06/30/22 (renewal until 6/30/24)
Niclosamide for the Treatment of Relapsed/Refractory Pediatric Acute Myeloid Leukemia

Pediatric Cancer Research Foundation - Translational Research Grant
Sakamoto (PI)
01/01/22-12/31/24
Targeting Mitochondrial Pathways in Pediatric AML

California Institute of Regenerative Medicine (12475)
Sakamoto (PI)
11/01/21-10/31/23
Small molecules to inhibit Nemo-like Kinase for the Treatment of Diamond Blackfan Anemia

Citations:

1. Shankar D, Cheng JC, Kinjo K, Wang J, N, Moore TB, Gill A, Rao N, EM, and **Sakamoto KM.** (2005).The role of CREB as a proto-oncogene in Hematopoiesis and in Acute Myeloid Leukemia. Cancer Cell, 7:351-362. PMID: 15837624
2. Mitton B, Chae HD, Hsu K, Dutta R, Aldana-Masangkay G, Ferrari R, Davis K, Tiu BC, Kaul A, S N, Dahl G, Xie F, Li BX, Breese MR, Landaw EM, Nolan G, Pellegrini M, Romanov S, Xiao X, and **Sakamoto KM**. (2016). Small molecule inhibition of cAMP response element binding protein in human acute myeloid leukemia cells. Leukemia, 30:2302-2311. PMID: 27211267
3. 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**. (2020) RSK Inhibitor BI-D1870 Inhibits Acute Myeloid Leukemia Cell Proliferation by Targeting Mitotic Exit. Oncotarget, 11:2387-2403. PMID: 32637030
4. Zhang K, Horikoshi N, Li S, Pintilie GD, Powers AS, Chae HD, Khan YA, Suomivuori CM, Dror RO, **Sakamoto KM***, Chiu W*, and S Wakatsuki*. (2022) Achieving Near-atomic Resolution Cryo-EM Structure of an 11-kDa Flexible Protein to Guide Drug Discovery. ACS Central Science, 8:214-222. *Co-senior authors. PMID: 35233453

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2019-present	Director of Scholarship, Division of Pediatric Hematology/Oncology, Stanford University
2013-2022	Member, Child Health Research Institute Executive Committee, Stanford University
2019-2020	Chair, Appointments and Promotions Committee, Stanford University School of Medicine
2014-2019	Member, Appointments and Promotions Committee, 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
2011-current	Professor of Pediatrics, Stanford University School of Medicine.
2011	Co-Chair, UCLA CTSI Committee on Maternal, Child, and Adolescent Health
2006-2011	Vice-Chair of Research, Mattel Children's Hospital UCLA
2006-2011	Co-Associate Director, Signal Transduction Program Area, Jonsson Comprehensive Cancer Center, UCLA

2005-2011 Chief, Division of Hematology-Oncology, Mattel Children's Hospital, David Geffen School of Medicine at UCLA
1993-2011 Assistant to Full Professor of Pediatrics and Pathology & Laboratory Medicine, David Geffen School of Medicine at UCLA
1991-1993 Clinical Instructor, Department of Pediatrics, UCLA School of Medicine

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

Honors
2021-present Alex's Lemonade Stand Foundation Scientific Review Board
2020-present NIDDK Council
2020-present DOD/CDMRP Bone Marrow Failure Research Program Panel Member
2019 UCLA Specialized Training and Research (STAR) Program Alumni Achievement Award
2017-2020 Chair, Physician Scientist Special Interest Group, American Society of Pediatric Hematology/Oncology
2018, 2021 ASH coordinating reviewer or Chair for Chemical Biology session
2016-2019 Ad hoc reviewer for NIH BMCT, MCH and F32 study sections
2016 Pediatric Cancer Research Foundation Memorial Lecture Honoree
2015 Steven Rosen Endowed Lectureship, Northwestern University School of Medicine
2013 Jason Bennette Memorial Lectureship, Cohen Children's Hospital, Long Island, NY.
2013 Invited speaker, Swerling Symposium "Seminars in Oncology," Dana Farber Cancer Institute
2012 Shelagh Galligan Endowed Chair
2011 Brent Ely Visiting Professor in Pediatric Oncology, University of Colorado and Children's Hospital Denver
2010-2016 Member, NIDDK-D study section for training grants (K awards and T32)
2011 Chair, ASH Scientific Subcommittee on Myeloid Biology
2009 Fernbach Distinguished Visiting Professor Lectureship, Texas Children's Cancer Center, Baylor College of Medicine
2008-2010 Board of Trustees, American Society of Pediatric Hematology-Oncology
2008 "Meet-the-Expert" on Transcription Factors and AML, American Society of Hematology meeting
2007-present Member, St. Baldrick's Foundation Scientific Review Committee
2006 Benjamin Franklin High School Wall of Fame Award
2005-2016 Member, Translational Research Program Grant Review Committee for the Leukemia and Lymphoma Society of America
2005-2009 Member, NIH Hematopoiesis Study Section
1999 Leukemia and Lymphoma Society of America Fellow, Special Fellow, and Scholar Awards
1996 Western Society for Pediatric Research, Junior Faculty Ross Award in Research
1994 American Society of Pediatric Hematology-Oncology Young Investigator Award
1992 STOP CANCER/Jonsson Comprehensive Cancer Center Career Development Award

C. Contribution to Science

1. **Signaling pathways in normal hematopoiesis and leukemogenesis**: We were the first to demonstrate that the transcription factor CREB is activated downstream of GM-CSF and overexpressed in human AML cells. We generated a CREB transgenic mouse model in which CREB was overexpressed in myeloid progenitors, which led to MDS/MPN but not AML. Our work showed 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. This work led to development of CREB inhibitors and studies on the CREB kinase, pp90RSK.
   a. Sandoval S, Kraus C, Cho EC, Cho M, Bies J, Landaw EM, Wolff L, and **KM Sakamoto**. (2012). Sox4 cooperates with CREB in Myeloid Transformation, Blood, 120: 155-165. PMID: 22627767
   b. Chae HD, Mitton BA, and **KM Sakamoto**. (2015). 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. PMID: 25541153

c. Youn MY, Gomes JO, Mark K and **KM Sakamoto**. (2021). RSK Isoforms in Acute Myeloid Leukemia, Biomedicines, 9(7):726. PMID: 34202904
d. Ayyadurai S, Deonikar P, Mclure K and **Sakamoto KM**. (2022). A Systems Architecture of Acute Myeloid Leukemia. Cancers, 14:756. PMID: 35159023

2. **Novel approaches to study and treat leukemia:** We are developing small molecules and peptides that could inhibit the interaction of CREB and its binding partner CBP. Development of drugs to target CREB could lead to more effective and less toxic therapies for acute leukemia. The identification of niclosamide as a derivative of the CREB inhibitor XX-650-23 has resulted in a Phase I clinical trial to repurpose niclosamide for the treatment of relapsed/refractory pediatric AML. In addition, we have taken a new CryoEM approach with Soichi Wakatsuki (SLAC/Structural Biology) and Ron Dror (Computer Science) to develop new molecules that target CREB:CBP interaction. In collaboration with Kara Davis, we developed new ways to analyze mass cytometry.
   a. Chae HD, Cox N, Dahl GV, Lacayo NJ, Davis KL, Capoliccio S, Smith M, and **Sakamoto KM**. (2017). Niclosamide Suppresses Acute Myeloid Leukemia Cell Proliferation Through Inhibition of CREB-Dependent Signaling Pathways. Oncotarget, 9:4301-4317 (published as a Priority Paper). PMID: 29435104
   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**. (2017). Small molecule inhibition of cAMP response element binding protein in human acute myeloid leukemia cells. Leukemia, 30:2302-2311. PMID: 27211267
   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**. (2019). SAR optimization studies on modified salicylamides as a potential treatment for acute myeloid leukemia through inhibition of the CREB pathway. Bioorg Med Chem Letters, 29:2307-231. PMID: 31253529
   d. Lo YC, Keys T, Jager A, Sarno J, Domizi P, Majeti R, **Sakamoto KM**, Lacayo N, Mullighan C, Waters J, Sahaf B, Bendall S, and KL Davis. (2022). CytofIn enables integrated analysis of public mass cytometry datasets using generalized anchors. Nature Commun, 13:934. PMID: 35177627

3. **Immune function and leukemia:** We showed that CREB transgenic mice had an increased incidence of abscess formation and CREB overexpression affects the innate immune response primarily through deregulation of inflammatory cytokines and increasing NADPH oxidase activity. These studies advanced the field of transcriptional regulation in immune function. We also collaborated with Dr. Swaminathan on immunotherapy project and ALL.
   a. Wen AY, **Sakamoto KM**, and Miller LS. (2010). The Role of the Transcription Factor CREB in Immune Function. J Immunol, 185:6413-9. PMID: 21084670
   b. Wen AY, Landaw EM, Ochoa R, Cho M, Chao A, Lawson, and **Sakamoto KM**. (2013). Increased Abscess Formation and Defective Chemokine Regulation in CREB Transgenic Mice. PLoS ONE, 8:(2)e55866. PMID: 23405224
   c. Francois S, Sen N, Mitton B, Xiao X, **Sakamoto KM**, and Arvin A. (2016). 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, 90:8686-97. PMID: 27440893
   d. Duault C, Kumar A, Khani AT, Lee SJ, Yang L, Huang M, Manning B, Hurtz C, Ghoda L, Mcdonald T, Lacayo NJ, **Sakamoto KM**, Carroll M, Marcucci G, Yu J, Caligiuri MA, Maecker HT, and S Swaminathan. (2021). Activated Natural Killer Cells with Impaired Cytolytic Potential Predict Poor Clinical Prognosis in High-risk B- and T-cell Acute Lymphoblastic Leukemia. Blood, 138:1465-1480. Epub ahead of print. PMID: 34077953

4. **Molecular Pathogenesis of Chronic Myeloid Leukemia:** We studied the transcriptomic differences between pediatric and adult CML and the clonal diversity and heterogeneity of pediatric CML using single cell RNA-seq. We are also investigating the long-term effects of TKI in pediatric CML patients.
   a. Smith S, Hijiya N and **KM Sakamoto**. (2021). Pediatric CML. Curr Onc Rep, 23:40. PMID: 33718985
   b. Smith SM, Sabnis HS, Lewis RW, Effinger KE, Bergsagel J, Patterson B, Mertens A, **Sakamoto KM**, Schapira L, and SM Castellano. (2021). Patterns of Surveillance for late effects of BCR-ABL tyrosine kinase inhibitors in pediatric Philadelphia chromosome positive leukemias. BMC Cancer, 21:474. PMID: 33926411

c. Youn MY, Smith SM, Chae HD, Lee AG, Murphy LC, Donato M, Sweet-Cordero A, Abidi Parveen, Bittencourt H, Lacayo N, Dahl G, Aftandilian C, Davis K, Matthews JA, Kornblau SM, Huang M, Sumarsono N, Redell MS, Fu CH, Chen IM, Alonzo T, Eklund EA, Gotlib JR, Khatri P, Hijiya N and **KM Sakamoto**. (2021). Comparison of the Transcriptomic Signatures in Pediatric and Adult CML. Cancers, 13:6263. PMID: 34944883
d. Ford M, Aftandilian C, Mauro M, **Sakamoto KM***, Hijiya N*. (2022) Management of Chronic Myeloid Leukemia in Children and Young Adults. Current Hematologic Malignancy Reports (Springer) Aug 3. *co-senior authors.

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 breast and prostate cancer.
   a. **Sakamoto KM**, Crews CM, Kim KB, Kumagai A, Mercurio F, Deshaies RJ. (2001). 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. PMID: 11438690
   b. **Sakamoto KM,** Kim KB, Verma R, Ransick A, Stein B, and Deshaies RJ. (2003). Development of Protacs to target cancer-promoting proteins for ubiquitination and degradation. Mol Cell Proteomics, 2003 2:1350-8. Epub 2003 Oct 2. PMID: 14525958
   c. Verma R, Peters NR, D'Onofrio M, Tochtrop G, **Sakamoto KM**, Varadan R, Zhang M, Coffino P, Fushman D, Deshaies RJ, King RW. (2004) Ubistatins inhibit proteasome-dependent degradation by binding the ubiquitin chain. Science, 306:117-20. PMID: 15459393
   d. Rodriguez-Gonzalez A, Cyrus K, Salcius M, Kim KB, Crews CM, Deshaies RJ, and **Sakamoto KM**. (2008). Targeting Steroid Hormone Receptors for Ubiquitination and Degradation in Breast and Prostate Cancer, Oncogene, 27:7201-11. PMID: 18794799

6. **Pathogenesis and Treatment of Bone Marrow Failure Syndromes:** Diamond Blackfan Anemia (DBA) is a congenital bone marrow syndrome resulting from ribosome insufficiency. We first demonstrated that Ribosomal Protein S19 (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 also reported that Nemo-like Kinase is hyperactivated and a target for DBA therapy despite the underlying ribosomal mutation. Novel approaches to treat DBA resulted from these studies.
   a. 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***. (2019). MMP9 Inhibition increases erythropoiesis in RPS14-deficient del(5q) MDS models through suppression of TGF-beta pathways. Blood Adv, 3:2751-2763. ***co-senior authors.** PMID: 31540902
   b. 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**. (2020) Metformin-induced Suppression of NLK improves Erythropoiesis in Diamond Blackfan Anemia through Induction of miR26a, Exp Hematol, Sep 12, 2020. PMID: 3292695
   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**. (2020). Diamond Blackfan Anemia is Mediated by Hyperactive Nemo-Like Kinase. Nat Commun, 11: 3344., PMID: 32620751
   d. Wilkes MC, Jung K, Lee BE, Saxena M, Sathianathen R, Varetti G, Mercado J, Perez C, Flygare J, Serrano M, Narla A, Glader B, **Sakamoto KM**. (2021). The Active Component of Ginseng, Ginsenoside Rb improves erythropoiesis in models of Diamond Blackfan Anemia by targeting Nemo-like Kinase. J Biol Chem, Jul 20. PMID: 34298020

For complete list of 154 publications on Pubmed see URL (under Sakamoto KM)
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