BIOGRAPHICAL SKETCH

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NAME: Yoshimi, Akihide

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

POSITION TITLE: Section Head

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	START DATE MM/YYYY	END DATE MM/YYYY	FIELD OF STUDY
<Education>				
Faculty of Medicine, The University of Tokyo, Tokyo, Japan	MD	04/1997	03/2003	Medicine
Graduate School of Medicine, The University of Tokyo, Tokyo, Japan	PhD	04/2007	03/2011	Hematology and Oncology
<Work History>				
The University of Tokyo Hospital, Tokyo, Japan	Resident	06/2003	05/2004	Internal medicine
The Kanto Medical Center NTT, Tokyo, Japan	Resident	06/2004	03/2005	Internal Medicine
The Kanto Medical Center NTT, Tokyo, Japan	Senior Resident	04/2005	05/2006	Hematology and Oncology
The University of Tokyo Hospital, Tokyo, Japan	Senior Resident	06/2006	12/2007	Hematology and Oncology
The University of Tokyo Hospital, Tokyo, Japan	Assistant Professor	04/2011	05/2015	Hematology and Oncology
Memorial Sloan Kettering Cancer Center, New York, NY	Visiting Investigator	07/2015	07/2018	Hematology and Oncology
Memorial Sloan Kettering Cancer Center, New York, NY	Leukemia & Lymphoma Society Special Fellow	07/2018	06/2020	Hematology and Oncology
Memorial Sloan Kettering Cancer Center, New York, NY	Senior Research Scientist	08/2018	06/2020	Hematology and Oncology
National Cancer Center Research Institute, Tokyo, Japan	Section Head	07/2020	08/2022	Oncology
Kitasato University School of Science, Kanagawa, Japan	Visiting Professor	04/2022	present	Oncology
National Cancer Center Research Institute, Tokyo, Japan	Chief	09/2022	present	Oncology

A. Personal Statement

After my early research experience on the role of key transcription factors in leukemogenesis at the University of Tokyo, Japan, I joined Dr. Abdel-Wahab's group at Memorial Sloan Kettering Cancer Center to study the role of mutant RNA splicing factors in the pathogenesis and therapy of leukemias and clarified the mechanisms of co-operativity between mutant IDH2 and SRSF2 in myeloid leukemias (Ref. 1) and MYC activation in *SF3B1* mutant CLL (Ref. 2). I also established novel xenograft models of MDS/MPN overlap syndromes with or without splicing factor mutations (Ref. 4), which are robust and genetically faithful enough to perform pre-clinical tests of a novel clinical-grade spliceosomal inhibitor (Ref. 3). I started my own lab at National Cancer Center Japan and I am

working on the pathogenic roles of aberrant RNA processing in cancers as well as 3D structure of ALK family receptors (Ref. 5) and potential oncogenic roles of orphan receptors.

1. **Yoshimi A**, Lin KT, Wiseman DH, Rahman MA, Pastore A, Intlekofer AM, Wang B, Lee SC, Micol JB, Zhang XJ, Botton S, Penard-Lacronique V, Stein E, Cho H, Miles RE, Inoue D, Albrecht TR, Somervaille TCP, Thompson CB, Levine RL, Dvinge H, Bradley RK, Wagner EJ, Krainer AR, Abdel-Wahab O. Coordinated Alterations in RNA Splicing and Epigenetic Regulation Drive Leukemogenesis. ***Nature***. 2019 Oct 2;574:273-277. PMID: 31578525
2. Liu Z*, **Yoshimi A*,#**, Wang J, Cho H, Lee SCW, Ki M, Bitner L, Chu T, Mato AR, Ruvolo P, Fabbri G, Pasqualucci L, Abdel-Wahab O, Rabadan R#. Mutations in the RNA splicing factor SF3B1 promote tumorigenesis through MYC stabilization. ***Cancer Discov***. 2020 Jul;10(6):806-821. PMID: 32188705. (*equal contribution; #co-corresponding)
3. Seiler M*, **Yoshimi A***, Darman R*, Chan B, Keaney G, Thomas M, Agrawal AA, Caleb B, Csibi A, Sean E, Fekkes P, Karr C, Klimek V, Lai G, Lee L, Kumar P, Lee SC, Liu X, Mackenzie C, Meeske C, Mizui Y, Padron E, Park E, Pazolli E, Peng S, Prajapati S, Taylor J, Teng T, Wang J, Warmuth M, Yao H, Yu L, Zhu P, Abdel-Wahab O, Smith PG, Buonamici S. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. ***Nat Med***. 2018 May 24;497-504. PMID: 29457796. (*equal contribution)
4. De Munck S, Provost M, Kurikawa M, Omori I, Mukohyama, J, Felix J, Bloch Y, Abdel-Wahab O, Bazen F, **Yoshimi A**, Savvides SN. Structural basis of cytokine-mediated activation of ALK family receptors. ***Nature***. 2021 Dec;600(7887):143-147. PMID: 34646012.
5. Shiraishi Y, Okada A, Omori I, Chiba K, Iida N, Yamauchi H, Kosaki K, **Yoshimi A**. Systematic identification of intron retention associated variants from massive publicly available transcriptome sequencing data. ***Nat Commun***. accepted

B. Positions and Honors

Positions and Employment

2003 - 2004	Junior resident, The University of Tokyo Hospital, Tokyo, Japan
2004 - 2006	Junior/Senior resident, The Kanto Medical Center NTT, Tokyo, Japan
2006 - 2007	Senior resident, The University of Tokyo Hospital, Tokyo, Japan
2011 - 2015	Clinical fellow, The University of Tokyo Hospital, Tokyo, Japan
2015 - 2018	Visiting investigator, Memorial Sloan Kettering Cancer Center, New York, NY, USA
2018 - 2020	Senior Research Scientist, Memorial Sloan Kettering Cancer Center, New York, NY, USA
2020 - 2022	Section Head, Cancer RNA Research Unit, National Cancer Center Research Institute, Tokyo, Japan
2022 -	Visiting Professor, Kitasato University School of Science
2022 -	Chief, Division of Cancer RNA Research, National Cancer Center Research Institute, Tokyo, Japan

Other Experience and Professional Memberships

2003 -	Member, The Japan Society of Internal Medicine (JSIM)
2006 -	Member, The Japanese Society of Hematology (JSH)
2009 -	Member, Japanese Cancer Association (JCA)
2011 -	Certifying Hematology Specialist, JSH
2013 -	Supervisory Doctor, JSH
2013 -	Supervisory Doctor, JSIM
2019 -	Member, American Society of Hematology (ASH)
2020 -	Councilor, JSH
2022 -	Councilor, JCA

Selected Honors and Grants

2009 – 2011	Research Fellowship for Young Scientist, The Japan Society for the Promotion of Science (JSPS)
2010	Keystone Symposia Scholarship, Keystone Symposia
2010	Encouraging Prize, Japanese Society of Hematology
2012 - 2014	Grant-in-Aid for Young Scientists (B), JSPS
2012	The 8th Young Hematologist Award, Kyowa Hakko-Kirin Co., Ltd
2013	Special Award for Young Researchers, Japan Leukemia Research Fund
2014 - 2015	Grant-in-Aid for Young Scientists (B), JSPS
2015	Japan Cancer Association (JCA) Incitement Award
2016 - 2017	Postdoctoral Fellowship for Research Abroad, JSPS
2016 - 2017	AAMDSIF Research Award, Aplastic Anemia & MDS International Foundation
2017 - 2017	LSLF Research Award, Lauri Strauss Leukemia Foundation
2017	ASH Abstract Achievement Award, American Society of Hematology (ASH)
2018 - 2020	Leukemia & Lymphoma Society (LLS) Special Fellow Award, LLS
2018	ASH Abstract Achievement Award, ASH
2019	AACR Scholar -in-Training Award, American Association for Cancer Research
2019	FASEB Hematologic Malignancies Conference Travel Award, FASEB
2020	LLS CDP Special Fellow Achievement Award, LLS
2020	ASH Year's Best
2020 - 2022	Home-Returning Researcher Development Research, JSPS
2020 - 2022	The Japan-Canada Joint call for Strategic International Collaborative Research Program (SICORP), Japan Agency for Medical Research and Development (AMED)
2021 - 2024	Grants-in-Aid for Scientific Research (A), JSPS
2021 - 2024	Science and Technology Platform Program for Advanced Biological Medicine, AMED
2022 - 2024	Fusion Oriented Research for Disruptive science and Technology, Japan Science and Technology Agency (JST)
2022 - 2024	P-PROMOTE, AMED
2022 - 2024	ASH Global Research Award
2022	Japan Bioindustry Association (JBA) Award
2022	JCA-Mauvernay Award

C. Contribution to Science

1. In 2020, I started my own laboratory named Cancer RNA Research Unit at National Cancer Center Japan (and the lab has been promoted to Division of Cancer RNA Research in 2022). My lab is studying to understand and target aberrant RNA processing in cancers, especially focusing on recurrent mutations in genes encoding splicing factors and splicing-associated variants that induce aberrant splicing in the genes themselves.

    a. De Munck S, Provost M, Kurikawa M, Omori I, Mukohyama, J, Felix J, Bloch Y, Abdel-Wahab O, Bazen F, **Yoshimi A**, Savvides SN. Structural basis of cytokine-mediated activation of ALK family receptors. ***Nature***. 2021 Dec;600(7887):143-147. PMID: 34646012.
    b. Shiraishi Y, Okada A, Omori I, Chiba K, Iida N, Yamauchi H, Kosaki K, **Yoshimi A**. Systematic identification of intron retention associated variants from massive publicly available transcriptome sequencing data. ***Nat Commun***. accepted.
    c. Liu Z*, **Yoshimi A***,#, Wang J, Cho H, Lee SCW, Ki M, Bitner L, Chu T, Mato AR, Ruvolo P, Fabbri G, Pasqualucci L, Abdel-Wahab O, Rabadan R#. Mutations in the RNA splicing factor SF3B1 promote transformation through MYC stabilization. ***Cancer Discov***. 2020 Jul;10(6):806-821. PMID: 32188705. (*equal contribution; #co-corresponding)

d. Yamauchi H, Nishimura K, **Yoshimi A**. Aberrant RNA splicing and therapeutic opportunities in cancers. ***Cancer Sci***. 2022 Feb;113(2):373-381. PMID: 34812550.

e. Hai Y, Kawachi A, He X, **Yoshimi A**. Pathogenic Roles of RNA-Binding Proteins in Sarcomas. ***Cancers (Basel)***. 2022 Aug 5;14(15):3812. PMID: 35954475.

2. In 2015, I joined Dr. Omar Abdel-Wahab's group at Memorial Sloan Kettering Cancer Center (MSKCC) to study the role of mutant RNA splicing factors in the pathogenesis and therapy of myeloid leukemias. I identified that (1) mutations in *SRSF2* and *IDH2* frequently co-occur in myeloid leukemias due to mutual interaction between mutant IDH2-mediated DNA methylation and mutant SRSF2-mediated mis-splicing, and (2) mutations in *SF3B1* activates MYC pathway via stabilization of MYC protein.

   a. **Yoshimi A**, Lin KT, Wiseman DH, Rahman MA, Pastore A, Intlekofer AM, Wang B, Lee SC, Micol JB, Zhang XJ, Botton S, Penard-Lacronique V, Stein E, Cho H, Miles RE, Inoue D, Albrecht TR, Somervaille TCP, Thompson CB, Levine RL, Dvinge H, Bradley RK, Wagner EJ, Krainer AR, Abdel-Wahab O. Coordinated Alterations in RNA Splicing and Epigenetic Regulation Drive Leukemogenesis. ***Nature***. 2019 Oct 2;574:273-277. PMID: 31578525

   b. Liu Z*, **Yoshimi A***,#, Wang J, Cho H, Lee SCW, Ki M, Bitner L, Chu T, Mato AR, Ruvolo P, Fabbri G, Pasqualucci L, Abdel-Wahab O, Rabadan R#. Mutations in the RNA splicing factor SF3B1 promote transformation through MYC stabilization. ***Cancer Discov***. 2020 Jul;10(6):806-821. PMID: 32188705. (*equal contribution; #co-corresponding)

   c. Inoue D, Chew GL, Liu B, Michel BC, Pangallo J, D'Avino AR, Hitchman T, North K, Lee SC, Bitner L, Block A, Moore AR, **Yoshimi A**, Escobar-Hoyos L, Cho H, Penson A, Lu SX, Taylor J, Chen Y, Kadoch C, Abdel-Wahab O, Bradley RK. Spliceosomal disruption of the non-canonical BAF complex in cancer. ***Nature***. 2019 Oct 9;574:432-436. PMID: 31597964.

   d. Lee SC, Dvinge H, Kim E, Cho H, Micol JB, Chung YR, Durham BH, **Yoshimi A**, Kim YJ, Thomas M, Lobry C, Chen CW, Pastore A, Taylor J, Wang X, Krivtsov A, Armstrong SA, Palacino J, Buonamici S, Smith PG, Bradley RK, Abdel-Wahab O. Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal proteins. ***Nat Med***. 2016 Jun;22(6):672-8. PMID: 27135740.

3. Since I joined Dr. Abdel-Wahab's group at MSKCC, I established novel patient-derived xenograft (PDX) models for chronic myelomonocytic leukemias where mutations in splicing factors are frequently identified (> 50%), to perform pre-clinical studies of a novel clinical grade spliceosomal inhibitor. The novel PDX models are extremely robust and could be widely used for pre-clinical tests of a variety of drugs.

   a. Seiler M*, **Yoshimi A***, Darman R*, Chan B, Keaney G, Thomas M, Agrawal AA, Caleb B, Csibi A, Sean E, Fekkes P, Karr C, Klimek V, Lai G, Lee L, Kumar P, Lee SC, Liu X, Mackenzie C, Meeske C, Mizui Y, Padron E, Park E, Pazolli E, Peng S, Prajapati S, Taylor J, Teng T, Wang J, Warmuth M, Yao H, Yu L, Zhu P, Abdel-Wahab O, Smith PG, Buonamici S. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. ***Nat Med***. 2018 May;24(4):497-504. PMID: 29457796. (*equal contribution)

   b. Cimmino L, Dolgalev I, Wang Y, **Yoshimi A**, Martin GH, Wang J, Ng V, Xia B, Witkowski MT, Mitchell-Flack M, Grillo I, Bakogianni S, Ndiaye-Lobry D, Martín MT, Guillamot M, Banh RS, Xu M, Figueroa ME, Dickins RA, Abdel-Wahab O, Park CY, Tsirigos A, Neel BG, Aifantis I. Restoration of TET2 Function Blocks Aberrant Self-Renewal and Leukemia Progression. ***Cell***. 2017 Sep 7;170(6):1079-1095.e20. PMID: 28823558.

   c. **Yoshimi A**, Balasis ME, Vedder A, Feldman K, Ma Y, Zhang H, Lee SC, Letson C, Niyongere S, Lu SX, Ball M, Taylor J, Zhang Q, Zhao Y, Youssef S, Chung YR, Zhang XJ, Durham BH, Yang W, List AF, Loh ML, Klimek V, Berger MF, Stieglitz E, Padron E, Abdel-Wahab O. Robust patient-derived xenografts of MDS/MPN overlap syndromes capture the unique characteristics of CMML and JMML. ***Blood***. 2017 Jul 27;130(4):397-407. PMID: 28576879.

d. Wang E, Lu SX, Pastore A, Chen X, Imig J, Lee SC, Hockemeyer K, Ghebrechristos YE, **Yoshimi A**, Inoue D, Ki M, Cho H, Bitner L, Kloetgen A, Lin KT, Uehara T, Owa T, Tibes R, Krainer AR, Abdel-Wahab O, Aifantis I. Targeting an RNA-binding Splicing Network in Acute Myeloid Leukemia. ***Cancer Cell***. 2019 Mar 18;35(3):369-384.e7. PMID: 30799057.

4. While working at the University of Tokyo Hospital, I identified recurrent *CDC25C* mutations in patients with familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML). FPD/AML is an autosomal dominant disorder which is characterized by inherited thrombocytopenia and a lifelong risk of development of hematological malignancies. I conducted a nationwide survey to collect samples from patients and performed a NGS study in 56 pedigrees, which identified *CDC25C* as the most recurrently mutated gene in FPD/AML patients.

   a. **Yoshimi A**, Toya T, Kawazu M, Ueno T, Tsukamoto A, Iizuka H, Nakagawa M, Nannya Y, Arai S, Harada H, Usuki K, Hayashi Y, Ito E, Kirito K, Nakajima H, Ichikawa M, Mano H, Kurokawa M. Recurrent CDC25C mutations drive malignant transformation in FPD/AML. ***Nat Commun***. 2014 Aug 27;5:4770. PMID: 25159113.

   b. **Yoshimi A**, Toya T, Nannya Y, Takaoka K, Kirito K, Ito E, Nakajima H, Hayashi Y, Takahashi T, Moriya-Saito A, Suzuki K, Harada H, Komatsu N, Usuki K, Ichikawa M, Kurokawa M. Spectrum of clinical and genetic features of patients with inherited platelet disorder with suspected predisposition to hematological malignancies: a nationwide survey in Japan. ***Ann Oncol***. 2016 May;27(5):887-95. PMID: 26884589.

   c. Takaoka K, Kawazu M, Koya J, **Yoshimi A**, Masamoto Y, Maki H, Toya T, Kobayashi T, Nannya Y, Arai S, Ueno T, Ueno H, Suzuki K, Harada H, Manabe A, Hayashi Y, Mano H, Kurokawa M. A germline HLTF mutation in familial MDS induces DNA damage accumulation through impaired PCNA polyubiquitination. ***Leukemia***. 2019 Jul;33(7):1773-1782. PMID: 30696947.

   d. Sakurai M, Kasahara H, Yoshida K, **Yoshimi A**, Kunimoto H, Watanabe N, Shiraishi Y, Chiba K, Tanaka H, Harada Y, Harada H, Kawakita T, Kurokawa M, Miyano S, Takahashi S, Ogawa S, Okamoto S, Nakajima H. Genetic basis of myeloid transformation in familial platelet disorder/acute myeloid leukemia patients with haploinsufficient RUNX1 allele. ***Blood Cancer J***. 2016 Feb 5;6:e392. PMID: 26849013.

5. When I worked at the University of Tokyo Hospital, I identified mechanisms of EVI1-induced epigenetic, transcriptional, and signaling abnormalities in myeloid malignancies. EVI1 is essential for proliferation of hematopoietic stem cells and implicated in the development of myeloid disorders. I demonstrated that EVI1 directly represses PTEN transcription by recruiting polycomb repressive complexes, which leads to activation of AKT/mTOR signaling. Dependence of EVI1-expressing leukemic cells on AKT/mTOR signaling provided the first example of therapeutic strategies for leukemias with activated EVI1.

   a. **Yoshimi A**, Goyama S, Watanabe-Okochi N, Yoshiki Y, Nannya Y, Nitta E, Arai S, Sato T, Shimabe M, Nakagawa M, Imai Y, Kitamura T, Kurokawa M. Evi1 represses PTEN expression and activates PI3K/AKT/mTOR via interactions with polycomb proteins. ***Blood***. 2011 Mar 31;117(13):3617-28. PMID: 21289308.

   b. Watanabe-Okochi N, **Yoshimi A**, Sato T, Ikeda T, Kumano K, Taoka K, Satoh Y, Shinohara A, Tsuruta T, Masuda A, Yokota H, Yatomi Y, Takahashi K, Kitaura J, Kitamura T, Kurokawa M. The shortest isoform of C/EBPβ, liver inhibitory protein (LIP), collaborates with Evi1 to induce AML in a mouse BMT model. ***Blood***. 2013 May 16;121(20):4142-55. PMID: 23547050.

   c. Arai S, **Yoshimi A**, Shimabe M, Ichikawa M, Nakagawa M, Imai Y, Goyama S, Kurokawa M. Evi-1 is a transcriptional target of mixed-lineage leukemia oncoproteins in hematopoietic stem cells. ***Blood***. 2011 Jun 9;117(23):6304-14. PMID: 21190993.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/akihide.yoshimi.1/bibliography/public/