

BIOGRAPHICAL SKETCH

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NAME: Ross Lawrence Levine, M.D.

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

POSITION TITLE: Deputy Physician-In-Chief, Translational Research, Memorial Hospital; Chief, Molecular Cancer Medicine Service (HOPP); Member, HOPP/Leukemia Service; Professor of Medicine, Weill Cornell Medicine; Laurence Joseph Dineen Chair in Leukemia Research; Program Member, CCSG

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
Harvard University	A.B.	June 1994	Biology
Johns Hopkins School of Medicine	M.D.	May 1999	Medicine

A. Personal Statement

The goal of our research is to improve our understanding of the genetic basis of myeloid malignancies, and to use this knowledge to improve outcomes for patients with these disorders. Our efforts are focused on the role of JAK-STAT signaling in malignant transformation and in the effects of mutations in epigenetic modifiers in clonal hematopoiesis, MDS, MPN, and AML. Moreover, as a physician scientist, our lab has a specific interest in translating this knowledge back to the clinic and in participating in the preclinical and clinical evaluation of targeted therapies for leukemia patients. As Deputy Physician-In-Chief, Translational Research, Memorial Hospital I lead MSK translational research initiatives and programs.

I serve as a member of the Executive Committee of the Tri-Institutional M.D.-Ph.D. Program. I have mentored 8 graduate students, including 2 MD-PhD students, I currently have 1 pre-doctoral trainee and 4 who have graduated and continued in related research careers. I also have 8 post-doctoral currently in training and 14 who have graduated and continued in related research careers. I have a long-standing commitment to an inclusive training environment and to supporting students from underrepresented backgrounds, including those with a disability and/or from disadvantaged backgrounds. I also am fully committed to training in Rigor & Reproducibility, Responsible Conduct of Research, career development, and a timely time to degree.

B. Positions, Scientific Appointments, and HonorsPositions and Employment:

1997-1998 Howard Hughes Medical Institute Research Training Fellowship
 1999-2002 Intern/Resident, Department of Medicine, Massachusetts General Hospital
 2002-2006 Fellow, Department of Hematology/Oncology, Dana-Farber/Partners
 2003-2006 Fellow in Medicine, Brigham and Women's Hospital Supervisor: D. Gary Gilliland, Ph.D. M.D.,
 2006-2007 Instructor in Medicine, Harvard Medical School/Dana-Farber Cancer Institute Supervisor: D. Gary Gilliland, Ph.D. M.D.,
 2007-2011 Assistant Member, Memorial Sloan Kettering Cancer Center, Assistant Professor of Medicine, Weill Cornell Medical College
 2011-2014 Associate Member, Memorial Sloan Kettering Cancer Center
 2011-2015 Associate Professor of Medicine, Weill Cornell Medical College
 2014- Member, Memorial Sloan Kettering Cancer Center, tenure, full time
 2015- Professor of Medicine, Weill Cornell Medical College
 2015- Center for Epigenetics Research, MSKCC

2016-2020 Director, MSK Center for Hematologic Malignancies
2016- Executive Committee, Tri-Institutional M.D.-Ph.D. Program
2019- Chief, Molecular Cancer Medicine Service, Human Oncology and Pathogenesis Program
2022- Deputy Physician-In-Chief, Translational Research, Memorial Hospital

Honors:

2021 Memorial Sloan Kettering Award for Excellence in Mentoring
2018 Dameshek Prize, American Society of Hematology
2017 American Association of Physicians
2014 Pershing Square Sohn Prize for Cancer Research
2013 Laurence Joseph Dineen Chair in Leukemia Research
2013 Interurban Clinical Club (NYC Councilor)
2012 Leukemia and Lymphoma Society Scholar
2011 Boyer Award for Clinical Research, Memorial Sloan Kettering Cancer Center
2011 William Osler Young Investigator Award, Interurban Clinical Club
2011 American Society of Clinical Investigation
2007-2011 Geoffrey Beene Junior Chair
2007 Howard Hughes Medical Institute Early Career Award
2006 American Society of Hematology Basic Research Fellow Award
2006 American Society of Clinical Oncology Young Investigator Award
2006 Doris Duke Charitable Foundation Clinical Scientist Development Award
1999 Alpha Omega Alpha, Johns Hopkins University
1994 Harvard University, *magna cum laude*

National/International Committees

2012-2019 Medical and Scientific Advisory Board, Leukemia and Lymphoma Society
2015- ASH Task Force on Precision Medicine
2017- Chair, Mark Foundation for Cancer Research Scientific Advisory Board
2017- ASH Committee on Scientific Affairs (Chair 2019-2021)

Scientific Meeting Chair/Committee

2013 Chair FASEB Conference on Hematologic Malignancies
2012- Co-Chair ESH Meeting on Myeloproliferative Neoplasms
2015-2022 American Society of Hematology Annual Meeting Program Committee (2016 Scientific Program co-chair)
2017-8 Co-Chair, AACR Annual Meeting (Chair of Education Program)
2018- Chair, AACR Molecular Biology for Clinical Oncologists Workshop

C. Contributions to Science

1. Molecular Pathogenesis of MPN: We have a long-standing interest in MPN molecular pathogenesis, including the role of mutations in the JAK-STAT pathway and in epigenetic regulators in MPN pathogenesis.

- a. Rampal R., Ahn J., Abdel-Wahab O., Nahas M., Wang K., Lipson D., Otto G., Yelensky R., Hricik T., McKenney A., Chung Y.R., Pandey S., van den Brink M., Armstrong S., Dogan A., Intlekofer A., Manshouri T., Park C. Vertovsek S., Rapaport F., Stephens P., Miller V., **Levine R.L.** Genomic and Functional Analysis of Leukemic Transformation of Myeloproliferative Neoplasms. *Proc Natl Acad Sci U S A.* 2014 Dec 16;111(50):E5401-10. PMID: PMC4273376
- b. Kleppe M., Spitzer M.H., Li S., Hill C.E. Dong L., Papalexi E., De Groote S., Bowman R.L., Keller M., Koppikar P., Rapaport F.T., Feldstein-Teruya J., Gandara J., Mason C.E., Nolan G.P., **Levine R.L.** Jak1 Integrates Cytokine Sensing to Regulate Hematopoietic Stem Cell Function and Stress Hematopoiesis. *Cell Stem Cell*, 2017 Oct 5;21(4):489-501. PMID: PMC5847260

2. Development of Targeted Therapies for MPN Patients: We have credentialed targeted therapies for MPN patients in murine models and primary patient samples. This includes JAK inhibitors, which are now approved, and BRD4 inhibitors, which are in trials worldwide based on our work and which have shown clinical efficacy.

- a. Meyer S.C., Keller MD, Chiu S., Koppikar P., Guryanova O.A., Rapaport F., Xu K., Manova K., Pankov D., O'Reilly R.J., Kleppe M., McKenney A.S., Shih A.H., Shank K., Ahn J., Papalexi E., Spitzer B., Socci N., Viale A., Mandon E., Ebel N., Andraos R., Rubert J., Dammassa E., Romanet V., Dölemeyer A., Zender M., Heinlein M., Rampal R., Weinberg R.S., Hoffman R., Sellers W.R., Hofmann F., Murakami M., Baffert F., Gaul C., Radimerski T.*, and **Levine R.L.*** CHZ868, a Type II JAK2 Inhibitor, Reverses Type I JAK Inhibitor Persistence and Demonstrates Efficacy in Myeloproliferative Neoplasms. *Cancer Cell*, 2015 Jul 13;28(1):15-28. PMID: PMC4503933
- b. Kleppe M., Koche R., Zou L., van Galen P. Hill C.E., Dong L., DeGroot S., Papalexi E., Hanasoge Somasundara A.V., Cordner K., Keller M., Farnoud N., Medina J., McGovern E., Reyers J., Roberts S., Witkin M., Rapaport F., Teruya-Feldstein J., Qi J., Rampal R., Bernstein B.E., Bradner J.E.*, **Levine R.L.*** Dual Targeting of Oncogenic Activation and Inflammatory Signaling Increases Therapeutic Efficacy in Myeloproliferative Neoplasms. *Cancer Cell*. 2018 Jan 8;33(1):29-43. PMID: PMC5760343.
- c. Pastore F., Bhagwat N., Pastore A., Radziskeuskaya A., Karzai A., Krishnan A., Li B., Bowman R.L., Xiao W., Viny A.D., Zouak A., Park Y.C., Cordner K.B., Braunstein S., Maag J.L.V., Grego A., Mehta J., Wang M., Lin H., Durham B.H., Koche R.P., Rampal R.K., Helin K., Scherle P., Vaddi K., Levine R.L. PRMT5 inhibition modulates E2F1 methylation and gene regulatory networks leading to therapeutic efficacy in JAK2V617F mutant MPN. *Cancer Discovery*. 2020 Jul 15. PMID: PMC7642059

3. Role of Mutations in Epigenetic Modifiers in MDS/AML Pathogenesis and Therapy: We have investigated the role of novel mutations in epigenetic modifiers in patient samples and model systems which have allowed us to delineate novel mechanisms of transformation by these mutations in epigenetic modifiers.

- a. Shih A., Jiang Y., Maydan C., Shank K., Pandey S., Barreyo L., Antony-Debre I., Viale A., Socci N., Sun Y., Robertson A., Cavatore M., Stanchina E., Hricik T., Rapaport F., Woods B., Wei C., Hatlen M., Baljevic M., Nimer S.D., Tallman M., Paietta E., Cimmino L., Aifantis I., Steidl U., Mason C., Melnick A.*, **Levine R.L.*** Mutational Cooperativity Linked to Combinatorial Epigenetic Gain of Function in Acute Myeloid Leukemia. *Cancer Cell*, 2015 Apr 13;27(4):502-15, PMID: PMC4518555
- b. LaFave L.M., Béguelin W., Koche R., Teater M., Spitzer B., Chramiec A., Papalexi E., Keller M., Hricik T., Konstantinoff K., Micol J.B., Durham B., Knutson S.K., Campbell J.E., Blum G., Shi X., Doud E., Krivtsov A., Chung Y.R., Khodos I., DeStanchina E., Ouerfelli O., Adusumilli P., Thomas P.M., Kelleher N.L., Luo M., Keilhack H., Abdel-Wahab O., Melnick A., Armstrong S.A., and **Levine R.L.** Bap1 loss leads to EZH2-dependent transformation. *Nature Medicine*. 2015 Nov;21(11):1344-9. PMID: PMC4636469
- c. Shih A.H., Meydan C., Shank K., Garrett-Bakelman F.E., Ward P.S., Intlekofer A., Nazir A., Stein E., Knapp K., Glass J., Travins J., Straley K., Gliser C., Mason C., Yen K., Thompson C.B., Melnick A.*, **Levine R.L.*** Combination Targeted Therapy to Disrupt Aberrant Oncogenic Signaling and Reverse Epigenetic Dysfunction in IDH2- and TET2-Mutant Acute Myeloid Leukemia. *Cancer Discovery*, 2017, May;7(5):494-505. PMID: PMC5413413
- d. Viny AD, Bowman RL, Liu Y, Lavall^oe VP, Eisman S, Xiao W, Durham B, Navitskaya A, Park J, Braunstein S, Alija B, Karzai A, Csete IS, Witkin M, Azizi E, Baslan T, Ott CJ, Pe'er D, Dekker J, Koche R, Levine RL. Cohesin members Stag1 and Stag2 display distinct roles in chromatin accessibility and topological control of HSC self-renewal and differentiation. *Cell Stem Cell* 2019 Nov 7;25(5):682-696. PMID: PMC6842438

4. Genetic Studies in Clonal Hematopoiesis and AML: We performed mutational profiling of AML patients, including in large, clinical trial cohorts to develop robust prognostic schema. We identified TET2 mutations as a common somatic event in clonal hematopoiesis, which has now been extended to show that mutations in leukemia genes are common events in aging subjects without overt hematologic malignancies.

- a. Patel J.P. Gönen, M. Figueroa, M.E., Fernandez, H., Sun, Z., Racevskis, J., Van Vlierberghe, P., Dolgalev, I., Thomas, S., Aminova, O., Huberman, K., Cheng, J., Viale, A., Socci, N., Heguy, A., Cherry, A., Vance, G., Higgins, R.R., Ketterling, R., Gallagher, R.E., Litzow, M., van den Brink, M.R.M., Lazarus, H.M., Rowe, J., Luger S., Ferrando, A., Paietta, E., Tallman, M.S., Melnick, A., Abdel-Wahab, O., and **Levine, R.L.** Prognostic and Therapeutic Relevance of Integrated Genetic Profiling in AML *New England Journal of Medicine*. 2012, Mar 22;366(12):1079-89. PMID: PMC3545649
- b. Busque L., Patel J.P., Figueroa, M.E., Vasanthakumar A., Provost S., Hamilou Z., Mollica L., Li J., Viale, A., Heguy, A., Hassimi M., Socci N., Bhatt P.K., Gönen, M., Mason C.E., Melnick, A., Godley

- L.A., Brennan C., Abdel-Wahab, O., and **Levine, R.L.** Recurrent Somatic TET2 Mutations in Normal Elderly Individuals with Clonal Hematopoiesis. *Nature Genetics*, 2012 Nov; 44(11):1179-81. PMCID: PMC3483435
- c. Coombs C.C., Zehir A., Devlin S.M., Kishtagari A., Syed A., Jonsson P., Hyman D.M., Solit D.B., Robson M.E., Baselga J., Arcila M.E., Ladanyi M., Tallman M.S., **Levine R.L.***, Berger M.F.*. Therapy-Related Clonal Hematopoiesis in Patients with Non-hematologic Cancers Is Common and Associated with Adverse Clinical Outcomes. *Cell Stem Cell*. 2017 Aug 9. pii: S1934-5909(17)30289-8. PMCID: PMC5591073
- d. Miles L.A.*, Bowman R.L.*, Merlinsky T.R., Csete I.S., Ooi A., Durruthy-Durruthy R., Bowman M., Famulare C., Patel M.A., Mendez P., Ainali C., Demaree B., Delley C.L., Abate A.R., Manivannan M., Sahu S., Goldberg A.D., Bolton K., Zehir A., Rampal R., Carroll M.P., Meyer S.E., Viny A.D., **Levine R.L.** Single cell mutation analysis of clonal evolution in myeloid malignancies. *Nature*, 2020 Nov;587(7834):477-482. PMID: 33116311; PMCID: PMC7677169

5. Development of Animal Models of Myeloid Malignancies: We have used conditional murine knockout and knock-in approaches to develop novel, murine MPN, MDS and AML models.

- a. Moran-Crusio K.*, Reavie L.* Shih A.*, Abdel-Wahab O.A. Ndiaye-Lobry D., Lobry C., Figueroa M., Vasanthakumar A. Patel J., Zhao X., Perna F., Pandey S., Madzo J., Song C., Dai Q., He C., Ibrahim S., Beran M., Zavadil J., Nimer S.D., Melnick A., Godley L., Aifantis I.*, and **Levine R.L.*** Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. *Cancer Cell*, 12 July 2011, 20:1-14. PMCID: PMC3194039 ^{co-first authors} *co-corresponding authors
- b. Viny A.D., Ott C.J., Spitzer B., Rivas M., Meydan C., Papalexli E., Yelin D., Shank K., Reyes J., Chiu A., Romin Y., Boyko V., Thota S., Maciejewski J.P., Melnick A., Bradner J.E., **Levine R.L.** Dose-dependent role of the cohesin complex in normal and malignant hematopoiesis. *Journal of Experimental Medicine*. 2015 Oct 19; 212(11):1819-32. PMCID: PMC4612085
- c. Guryanova O.A., Shank K., Spitzer B., Luciani L., Koche R., Garrett-Bakelman F.E., Chezi Gangel, Durham B., Mohanty A., Hoermann G., Pronier E., Rivera S.A., Chramiec A.G., Lennart Bastian, Keller M.D., Tovbin D., Loizou E., Weinstein A.R., Rodriguez Gonzalez A.A., Lieu Y., Rowe J.M., Pastore F., McKenney A.S., Krivtsov A.V., Sperr W.R., Cross J., Tallman M.S., Arcila M.E., Abdel-Wahab O., Armstrong S.A., Kubicek S., Staber P.B., Gönen M., Paietta E.M., Melnick A.M., Nimer S.D., Mukherjee S.*, **Levine R.L.*** DNMT3A R882 mutations promote anthracycline resistance in acute myeloid leukemia through impaired nucleosome remodeling. *Nature Medicine*, 2016 Dec;22(12):1488-1495. PMCID: PMC5359771

Complete List of Published Work

<http://www.ncbi.nlm.nih.gov/sites/myncbi/ross.levine.1/bibliography/40949909/public/?sort=date&direction=ascending>