BIOGRAPHICAL SKETCH

NAME: **Saghi Ghaffari, M.D.-Ph.D.**

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

POSITION TITLE: **Professor with Tenure, Department of Cell, Developmental & Regenerative Biology and Oncological Sciences at Icahn School of Medicine at Mount Sinai**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Paris, XII, Paris, France	M.D.	April 1989	Medicine
University of Paris, XI, Paris, France	M.Sc.	Sep. 1992	Statistics, Computer Science, Epidemiology
University of British Columbia Vancouver, Canada	Ph.D.	Dec. 1996	Normal and Malignant Human Hematopoietic Stem Cells
Whitehead Institute for Biomedical Research, Cambridge, MA	Post-Doc	1996-2002	Erythropoiesis, EpoR Signaling, Signal Transduction

A. Personal Statement

My laboratory investigates mechanisms governing hematopoietic stem and progenitor cell (HSPC) fate and how their dysregulation contributes to malignant transformation and stem cell aging. As a physician-scientist, I pursue fundamental biological questions with translational potential for hematologic disorders. I am deeply committed to education and mentorship and have trained more than 40 trainees from diverse backgrounds, many of whom have obtained independent funding and pursued scientific careers in academia or industry. Our work pioneered the identification of the longevity factors FOXO3 and FOXO1 as key regulators of adult hematopoietic and embryonic stem cells respectively. This work supported by the first NIH grant investigating FOXO in mammalian stem cells established FOXO3 as a critical regulator of hematopoietic stem cells (HSCs), erythropoiesis and redox homeostasis. Building on more than two decades of research, we now focus on organelle biology and metabolism, particularly lysosomes and mitochondria, and their roles in HSPC function and disease. Using mitochondrial-based approaches, we identified deeply quiescent and potent subsets of mouse and human HSCs. We subsequently discovered that lysosomes play fundamental roles in HSC potency, quiescence, metabolism, and aging beyond their established functions in autophagy and degradation. These findings have led to ongoing efforts in enhancing HSC function for transplantation, rejuvenating aging HSCs, and therapeutically targeting leukemic stem cells. In parallel, we established mitochondria as dynamic regulators of erythroid maturation and enucleation. Our overarching goal is to translate these discoveries into new strategies for stem cell transplantation and regenerative medicine**.** These integrated research directions provide a foundation for current work in my laboratory funded by NCI and NHLBI.

Ongoing and recently completed projects to highlight include:

5R01 HL161567-03 Ghaffari (PI) 02/15/22 – 1/31/26 (NCE)
Leveraging mitochondrial heterogeneity to investigate lysosomal regulation of human HSC quiescence

5R01 CA205975-08 Ghaffari (PI) 09/01/16 - 08/31/27
Elucidation of the contribution of lysosomal-mitochondrial communication in regulating leukemic stem cells

5R01 HL136255-07 Ghaffari (PI) 01/01/17 - 12/31/26
FOXO3 Regulation of Normal and Stress Erythropoiesis

B. Positions, Scientific Appointments, and Honors

2017-	Professor with Tenure, Department of CDRB – now Stem Cell Biology and Regenerative Medicine (SCBRM) - Icahn School of Medicine at Mount Sinai, New York, NY
2020 -	Professor with Tenure, Department of Oncological Sciences, ISMMS, New York, NY
2010-2017	Associate Professor, Cell, Developmental and Regenerative Biology, and Department of Medicine, Division of Hematology/Oncology, Mount Sinai School of Medicine, New York, NY
2016	Member, Faculty Search Committee, Black Family Stem Cell Institute
2016-2018	Co-Organizer, Stem Cell Advocacy Group, New York State
2006-2010	Assistant Professor, Developmental and Regenerative Biology, Mount Sinai School of Medicine
2009-2014	Co-Director Icahn School of Medicine at Mount Sinai Summer Undergraduate Research Program
2009-	Member, Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY
2005-	Member, Black Family Stem Cell Institute, Mount Sinai School of Medicine, New York, NY
2005-2013	Member, Admission Committee, Medical Scientist Training Program (MSTP, M.D.-Ph.D.), Graduate School of Biological Sciences
2006-2013	Director, Advanced Signal Transduction, PhD Students, MSSM
2003-2010	Assistant Professor, Department of Gene and Cell Medicine, Mount Sinai School of Medicine, New York, NY
2011	Member, Committee for M.D./Ph.D. Innovation
2012	Member, Faculty Search Committee, Tisch Cancer Institute
2014	Member, Advisory Board, NIGMS T32 Training grant (Marek Mlodzik, PI)
1999	Instructor, Molecular Mechanisms of Human Leukemia, Advanced Undergraduate Seminar Course, Massachusetts Institute of Technology, Cambridge, MA
1997- 2002	Clinical Scientist (Harvey Lodish Laboratory), Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge MA
1996-1997	Post-doctoral Fellow (George Daley Laboratory and Harvey Lodish Laboratory) Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge MA
1991 -1996	Graduate Student (Connie Eaves Laboratory), Terry Fox Laboratory, British Columbia Cancer Agency and University of British Columbia, Vancouver, B.C., Canada
1989 -1991	Clinical Research Associate, Centre National de Transfusion Sanguine, Paris, France
1986 -1989	Medical Resident, Paris, France

Honors

2026	Contributor, Book Chapter on “Metabolism” to “Hematology: Principles and Practice” [Ron Hoffman, Edward Benz, and Vijay Sankaran, Editors]
2026-	Member, Awards Nomination Committee, Department of SCBRM
2023-2026	Member, Appointment, Promotion and Tenure Committee, ISMMS, New York, NY
2023-2024	Visiting Professor (*Invited*), Single Cell Transciptomic/Inflammation Studies, Institut Imagine, Hôpital Necker-Enfants Malades, Paris, France
2024-2025	Member, ASH Bridge Grant Study Section
2026-	Co-organizer, ISMMS-Imagine Symposium
2024	Reviewer, French National Research Agency, CE13-Cellular Biology, Developmental Biology and Evolution, Paris, France
2023	Nominated, Scientific Committee on Blood Disorders in Childhood; Scientific Committee on Stem Cells and Regenerative Medicine; Scientific Committee on Hematopoiesis, ASH
2023	Reviewer, National Medical Research Council International Expert Panel, Ministry of Health Singapore
2022	Speaker and Chair, Executive Summary, Large Population Genomic Studies and Red Cell Disorders, Scientific Program on Red Cell Biology, American Society of Hematology
2021-2022	Appointed Chair, Scientific Committee on Red Cell Biology, American Society of Hematology
2020-2021	Appointed Vice Chair, Scientific Committee on Red Cell Biology, American Society of Hematology
2022-2024	Reviewer, Distinguished Scholar Awards Study Section, Mount Sinai Health System
2021	Member, ASH Scholar Awards Study Section
2020-2023	Member, National Medical Research Council International Expert, Ministry of Health Singapore

2017-2021 Appointed Member, Scientific Committee on Red Cell Biology, American Society of Hematology
2016 Speaker, "Mitochondria and Metabolism in Stem Cell Maintenance and Aging", American Society of Hematology Scientific Program, 58th annual meeting, San Diego, CA
2018 Co-organizer, Symposium in Memory and Celebration of Ihor R. Lemischka, PhD
2016 Co-organizer and Co-Chair, NIH-NHLBI Dyserythropoiesis Workshop, Bethesda, MD
2013 Coordinator Abstract Review (Hematopoietic Stem and Progenitor Biology), 55th Annual Meeting of the American Society of Hematology, New Orleans, LA
2013 Independent Expert, Site Visit Panel, Leukaemia & Lymphoma Research, U.K
2009 Roche Foundation for Anemia Research (RoFAR) Award
2008-2010 Hirschl/Weill-Caulier Trust Research Award
2006-2009 Research Scholar, American Cancer Society
2004-2006 Career Enhancement Award, NHLBI
1998-2003 NIH Mentored Clinician Scientist Career Award, National Cancer Institute (K08)
1998-2001 Leukemia Lymphoma Society Fellowship Award (*declined*)
1991-1996 Terry Fox Physician-Scientist Fellowship of the National Cancer Institute of Canada

Boursière du Gouvernement Français (Recipient of a French Government Scholarship), Institut National des Sciences Appliquées (INSA), Lyon, France – one of two students nationally selected through a competitive examination among top students in Mathematics, Physics, and Chemistry in Iran.

NIH Committees (*past ten years*)

Member, NIH NIDDK (KUH)-Fellowship Review Panel (2012-2019); Reviewer, ZHL1 CSR-P M2 NIH Special Emphasis Panel [SEP] (2016); ZDK1 GRB-D M2 NIH SEP (2016); ZRG1 F10A NIH Physiology, Pathobiology Cardiovascular and Respiratory Systems (2016); ZDK1 GRB-9 M3 NIH SEP (2017); ZCA1 RTRB-U (O1) R NIH NCI SEP (2017); ZCA1 SRB-K (M2) NIH NCI SEP (2018); ZAI1 JA-1 (S3) NIH NIAID SEP (2019); NIDDK SEP (2020); NIH/NIAID SEP (2020); ZDK1 GRB-G (01) L NIDDK-KUH-Fellowship Review Panel (2020); ZRG1 CVRS-S955, NIH Lasker Award Panel (2021); Member, NIH NIDDK (KUH)-Fellowship Review Panel (2021-); ZDK1 GRB-J M1 High Impact Panel (2022); NHLBI ZHL1 PPG-L (O1) 1 (2022); NHLBI PPG Study Section (2023); Member, DDK-G Study Section (2022-2025); NIH NIDDK ZRG1 F12B-G 20 L (07/2025)

Distinct Professional Activities (*2001-*) Ad hoc reviewer for Blood, Blood Advances, Cell Reports, Cell Stem Cell, Developmental Cell, e-Life, EMBO Journal, EMBO Reports, Experimental Hematology, Genes and Development, Journal of Clinical Investigation, Journal of Biological Chemistry, Leukemia, Nature, Nature Aging, Nature Cell Biology, Nature Communications, Nature Immunology, Nature Medicine, PNAS, Science.

Selected Editorial Responsibilities (*since 2017*) Editorial Board Member, Cells (2020-) Co-Editor, "Mitochondria in Stem Cells", Frontiers in Cell, Developmental; Biology (2020) Editor, "Forkhead Transcription Factors in Development and Disease" Current Topics; Developmental Biology, Volume 127, Elsevier (2018); Editorial Board Member, Experimental; Hematology (2017), Editorial Advisory Board Member, Life Science Alliance (EMBOpress, Rockefeller University Press, CSHL Press, 2017) Associate Editor Member, Frontiers in Physiology, Red Blood Cell Section (2022-); Editorial Board Member, Stem Cell Advances (2026-)

Selected (*Since 2022*) Invited Speaker at Meetings, Seminars and Presentations

2027 JSH-ASH Joint Symposium *Plasticity, Memory, and Reversibility in Hematopoiesis and Disease*, Fukuoka Japan (*accepted invitation*)
2027 Invited lecturer "Connie Eaves Memorial Lecture" International Conference on Stem Cells, Chania, Crete, Greece (*accepted invitation*)
2027 Invited Chair, Gordon Research Conference on Red Cells, Newport RI (*accepted invitation*)
2027 Erythroblastic anemia, Garden Network, Palermo, Italy (*accepted invitation*)
2026 AI in hematological disorders – Garden Network, Webinar, Italy (*accepted invitation*)
2026 3rd International Vexas Workshop, Milan, Italy (*accepted invitation*)
2026 University of Edinburgh, Edinburgh, UK
2026 University of Tokyo, Hematopoietic Stem Cell Symposium, New York
2026 Cell Death Society annual conference, Paris, France
2025 Gordon Red Cell Research Conference, Newport RI

2024 MRC Weatherall Institute of Molecular Medicine, Oxford University, Oxford UK
2024 Hemoglobin Switching Conference, Puerto Rico, United States
2024 Fourth International Erythrocyte Biology Conference, Henan (*accepted invitation*)
2024 Ludwig Distinguished Seminar, Ludwig Institute for Cancer Research, Lausanne Switzerland
2024 Seminar *Imagine*, Institut Imagine, Hôpital Necker-Enfants Malades, Paris, France
2023 Seminar Series, Department of Genetics, Yale School of Medicine, New Haven, CT
2023 Herman B Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, IN
2023 Gordon Red Cell Research Conference, Newport RI
2022 Blood Research Seminar, Department of Medicine, Division of Hematology, Oncology, UNC, Chapel Hill
2022 Hemoglobin Switching Conference, Crete, Greece

C. Contributions to Science (H Index: 45; > 9100 Citations; Google Scholar)

1. FOXOs are critical transcriptional regulators of stem cell potency

Our laboratory was the first to identify FOXOs – specifically **FOXO3** [Yalcin et al., *JBC*, 2008; *EMBO J.*, 2010] and **FOXO1** [Zhang et al., *Nature Cell Biology*, 2011] – as **essential, non-redundant regulators** of stem cell potency in both embryonic and adult hematopoietic stem cells. These discoveries, reported in the context of an NIH grant specifically focused on FOXO regulation of mammalian stem cells, established FOXOs as one of the few transcription factor families with a critical role in maintaining stem cell potency across developmental stages, from embryonic to adult stem cells [highlighted in *Cell Stem Cell*, 2011].

a) Zhang X., Yalcin S., Lee D.F.,….Lemischka I., Keller G. and **S. Ghaffari**. FOXO1 is an essential regulator of pluripotency in human embryonic stem cells. **Nature Cell Biology** 13 (9): 1092 – 99, 2011, Jul 31. doi: 10.1038/ncb2293. ***Highlight in "Cell Stem Cell: 9 (3), p181, 2011"***. PMCID: PMC4053529 ***> 330 Citations***

b) Yalcin S, Zhang X., Marinkovic D., Luciano J.P., Sarkar A., Brugnara C., Vercherat C., Taneja R.and **S. Ghaffari**. Foxo3 is essential for the regulation of ATM and oxidative stress-mediated homeostasis of hematopoietic stem cells. **Journal of Biological Chemistry,** 283:25692-25705, 2008. ***> 300 Citations***

c) Rimmelé P., C. Bigarella, Izac B., R., Dieguez-Gonzalez, M. Donovan, C. Brugnara, D. Sinclair and **S. Ghaffari**. SIRT1 controls hematopoietic stem cell longevity and lineage specification **Stem Cell Reports**, 3 (1): 44-59, 2014. ***> 190 Citations***

d) Rimmelé P.*, Liang R.*, Bigarella C.L.*, Chipuk J.E., Sadek H., Zhang C.C. and **S. Ghaffari.** FOXO3 is essential for mitochondrial function in hematopoietic stem cells. **EMBO Reports,** July 24, 2015. [Epub ahead of print]; Sep;16(9):1164-76, 2015 (***Highlight in Cell News- ASCB***). PMCID: PMC4576984. ***150 Citations***

2. Lysosomes are key regulators of hematopoietic stem cell dormancy

My laboratory recently discovered that lysosomes are key regulators of HSC quiescence, potency, and metabolism through a slow lysosomal degradation process that is distinct from canonical autophagy**.** These findings challenge the long-standing paradigm of autophagy-mediated regulation of HSCs and reveal a previously unrecognized mechanism by which lysosomes directly control HSC dormancy and function.

a) Liang R. Arif T., Menon V., Lin M., Benson D., Papatsenko, D., **S. Ghaffari**. Restraining lysosomal activity preserves hematopoietic stem cell quiescence and potency. **Cell Stem Cell,** 2020 Mar 5;26(3):359-376.e7. ***Previewed in Luis et al., Cell Stem Cell 26(3):299-301;*** PMCID: PMC8075247 ***~ 290 Citations***

b) **S. Ghaffari**. Lysosomal regulation of metabolism in quiescent hematopoietic stem cells: more than just autophagy. **Cell Stem Cell**, 28(3):374-377, 2021 (***Invited Forum).***

c) T Arif, J Qiu, H Khademian, A Lohithakshan, A Menon, V Menon, ...M.M. Ménager, **S. Ghaffari** Reversing lysosomal dysfunction restores youthful state in aged hematopoietic stem cells. **Cell Stem Cell** VOL 32, 12, P1904-1922; 2025, Dec 4. ***20 Citations***

3. Mitochondrial activity identifies distinct functional subsets of hematopoietic stem and erythroid cells

By leveraging a mitochondrial-based approach, we discovered, discrete subpopulations with unique unanticipated properties in highly purified phenotypically-defined populations of erythroid cells and HSCs.

a) Liang R. Arif T., Menon V., Lin M., Benson D., Papatsenko, D., **S. Ghaffari**. Restraining lysosomal activity preserves hematopoietic stem cell quiescence and potency. **Cell Stem Cell,** 2020 Mar 5;26(3):359-376.e7. ***Previewed in Luis et al., Cell Stem Cell 26(3):299-301;*** PMCID: PMC8075247 ***~ 290 Citations***

b) Liang R., Menon V., Qiu J., Arif T., Renuse S., Lin M., Nowak R., Hartmann B., Tzavaras B., Benson D.L., Chipuk J.E., Fribourg M., Pandey A., Fowler V., and **S. Ghaffari.** Mitochondrial localization and moderated activity are key to murine erythroid enucleation. **Blood Advances**, May 25;5(10):2490-2504. 2021 doi: 10.1182/bloodadvances.2021004259. PMCID: PMC8152511.

c) Qiu J., Gjini J., Arif T., Moore K., Lin M., and **S. Ghaffari.** Using mitochondrial activity to select for potent human hematopoietic stem cells. **Blood Advances.** 2021 Mar 23;5(6):1605-1616.

d) Filippi M.D. and **S. Ghaffari**. Mitochondria in the maintenance of hematopoietic stem cells: *New Perspectives and Opportunities* **Blood** 2019 Feb 26. pii: blood-2018-10-808873 (***Invited Review).*** PMCID: PMC6497515. ***> 220 Citations***

4. Glycolysis Is a Major Source of Energy in Activated but Not Quiescent HSCs

We recently demonstrated that, contrary to the long-held view in hematopoiesis, glycolysis serves as a major source of energy in activated, but not quiescent, HSCs. These findings challenge the prevailing paradigm of HSC metabolism and provide new insights into the metabolic regulation of HSC activation and function. This metabolic model was predicted in our earlier review (Bigarella et al., *Development* 2014) ***> 790 Citations***

a) Liang R., Arif T., Kalmykova S., Kasianov A., Lin M., Menon V., Qiu J., Bernitz J.M., Moore K., Lin F., Benson D.L., Tzavaras N., Mahajan M., Papatsenko D., and **S. Ghaffari.** Restraining Lysosomal Activity Preserves Hematopoietic Stem Cell Quiescence and Potency. **Cell Stem Cell,** 2020 Mar 5;26(3):359-376.e7. ***Previewed in Luis et al., Cell Stem Cell 26(3):299-301;*** PMCID: PMC8075247 ***~ 290 Citations***

b) Arif T., Qiu J., Khademian H., Lohithakshan A., Menon A., Menon V., ... Ménager M.M., **S. Ghaffari** Reversing lysosomal dysfunction restores youthful state in aged hematopoietic stem cells. **Cell Stem Cell 2025, Dec 4.** ***20 Citations***

c) Qiu JJ, **S. Ghaffari**. Mitochondrial Deep Dive into Hematopoietic Stem Cell Dormancy: Not Much Glycolysis but Plenty of Sluggish Lysosomes **Exp. Hematology Oct: 114:1-8, 2022 (*Invited Review*)**

d) Qiu J., Menon V., Tzavaras N., Liang R., and **S. Ghaffari**. A protocol for identifying and analyzing quiescent mouse and human hematopoietic stem cells using flow cytometry and confocal imaging **STAR Protocols** 2022 Dec 16;3(4):101828 (***Cell Press, Invited Protocol***)

5. Redox signaling regulation of hematopoietic stem cells and primary erythropoiesis

Our work was the first to demonstrate that redox signaling is a physiological regulator of erythropoiesis and among the first to establish its role in hematopoietic stem cells, identifying FOXO3 as a key mediator. Together with subsequent work from others, we established the FOXO3-mediated redox pathway as a central mechanism maintaining hematopoietic homeostasis. This work was reviewed in Bigarella et al., *Development* (2014), which has received ***> 790 Citations***).

a) Yalcin S, Zhang X., Marinkovic D., Luciano J.P., Sarkar A., Brugnara C., Vercherat C., Taneja R. and **S. Ghaffari.** Foxo3 is essential for the regulation of ATM and oxidative stress-mediated homeostasis of hematopoietic stem cells. **Journal of Biological Chemistry**, (283): 25692-25705, 2008. ***> 300 Citations***

b) Marinkovic D., Zhang X., Yalcin S., Brugnara C., Huber T., and **S. Ghaffari.** Foxo3 is required for the regulation of oxidative stress in erythropoiesis, **Journal of Clinical Investigation,** 117 (8): 2133-2144, 2007 ***[Highlighted in Commentary: JCI, 107 (8): 2075-2077, 2007]; > 400 Citations***

c) Yalcin S, Marinkovic D., Mungamuri SK, Zhang X., Tong W., and **S. Ghaffari.** Oxidative stress-mediated amplification of AKT/mTOR signaling pathway leads to myeloproliferative syndrome in Foxo3$^{-/-}$ mice. **EMBOJ,** 29(24):4118-31, 2010. PMCID: PMC3018793. ***> 170 Citations***

d) Liang R., Camprecios G., McGrath K., Novak R., Zhang X., Bieker J., Papatsenko D., Ma'yanA., Bresnick E., Fowler V., Palis J., and **S. Ghaffari**. A systems approach identifies essential FOXO3 functions at key steps of terminal erythropoiesis. **PLoS Genetics,** Oct 9;11 (10): e1005526, 2015.

e) Liang R., Lin M., Menon V., Qiu J., Arif T., Breda L., Rivella S. and **S. Ghaffari**. Elevated P21 (CDKN1A) mediates β-thalassemia erythroid apoptosis but its loss does not improve β-thalassemic erythropoiesis. **Blood Advances** 2023 Nov 28;7(22):6873-6885.

Patent: Methods of Culturing Quiescent Hematopoietic Stem Cells and Treatment Methods; Patent Cooperation Treaty Application filed on 11/18/2021 (PCT/US2020/034574) – **Patent application being processed to be Granted (07/2026; (*Inventors: Saghi Ghaffari, Raymond Liang*)**

Complete list of work: https://www.ncbi.nlm.nih.gov/myncbi/1h9BhtpPr7i5J/bibliography/public/