BIOGRAPHICAL SKETCH

NAME: **Sean J. Morrison, Ph.D.**

POSITION TITLE: **Director, Children's Research Institute at UT Southwestern Medical Center; Investigator, Howard Hughes Medical Institute**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Dalhousie University, Halifax, Canada	B.Sc.	05/1991	Biology and Chemistry
Stanford University, Palo Alto, CA	Ph.D.	06/1996	Immunology
California Institute of Technology, Pasadena, CA	Fellow	08/1999	Neurobiology

A. Personal Statement

We study the intrinsic and extrinsic mechanisms that regulate stem cell self-renewal (particularly in the hematopoietic system) and the role these mechanisms play in cancer (particularly leukemia and melanoma). Self-renewal is the process by which stem cells divide to make more stem cells, perpetuating stem cells throughout life to regenerate tissues. We discovered a series of key regulators that distinguish stem cell self-renewal from the proliferation of restricted progenitors in the same tissues. We also identified ways in which self-renewal mechanisms change with age, conferring temporal changes in stem cell properties that match the changing growth and regeneration demands of tissues. This may explain why the mechanisms that are competent to cause cancer also change with age. In terms of cell-extrinsic mechanisms, we identified the location and cellular composition of hematopoietic stem cell (HSC) niches in adult bone marrow and spleen, and discovered the Leptin Receptor$^+$ perivascular stromal cells that are the major source of factors required for HSC maintenance in the bone marrow. The LepR$^+$ cells also include the skeletal stem cells that are the major source of osteoblasts and adipocytes in adult bone marrow. We have shown that HSCs are metabolically distinct from restricted progenitors in vivo and depend upon metabolic regulation for epigenetic control and leukemia suppression. We discovered that distant metastasis by melanoma cells is limited by oxidative stress and that successfully metastasizing melanoma cells undergo reversible metabolic changes to cope with oxidative stress. We proposed that "pro-oxidant" therapies that exacerbate oxidative stress in cancer cells could be used to inhibit cancer progression.

1. Kiel, M.J., O.H. Yilmaz, T. Iwashita, C. Terhorst, and S.J. Morrison. 2005. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. **Cell** 121: 1109-1121. PMID 15989959
2. Ding, L., T.L. Saunders, G. Enikolopov, and S.J. Morrison. 2012. Endothelial and perivascular cells maintain hematopoietic stem cells. **Nature** 481:457-462. PMC3270376
3. Agathocleous M., C.E. Meacham, R.J. Burgess, E. Piskounova, Z. Zhao, G.M. Crane, B.L. Cowin, E. Bruner, M.M. Murphy, W. Chen, G.J. Spangrude, Z. Hu, R.J. DeBerardinis, and S.J. Morrison. 2017. Ascorbate regulates haematopoietic stem cell function and suppresses leukaemogenesis. **Nature** 549: 476-481. PMID 28825709
4. Shen, B., A. Tasdogan, J.M. Ubellacker, J. Zhang, E.D. Nosyreva, L. Du, M.M. Murphy, S. Hu, Y. Yi, N. Kara, X. Liu, S. Guela, Y. Jia, V. Ramesh, C. Embree, E.C. Mitchell, Y.C. Zhao, L.A. Ju, H. Zhao, G.M. Crane, Z. Zhao, R. Syeda, and S.J. Morrison. 2021. A mechanosensitive peri-arteriolar niche for osteogenesis and lymphopoiesis. **Nature** 591:438-444. PMID 33627868

B. Positions, Scientific Appointments, and Honors

2016 – present Kathryne and Gene Bishop Distinguished Chair in Pediatric Research
2011 – present Director, Children's Research Institute, University of Texas Southwestern Medical Center

2011 – present	Professor, Children's Research Institute, UT Southwestern Medical Center
2011 – present	Mary McDermott Cook Chair in Pediatric Genetics, Department of Pediatrics, UTSW
2008 – 2011	Research Professor, Life Sciences Institute, University of Michigan
2008 – 2011	Professor, Department of Internal Medicine, University of Michigan
2005 – 2011	Henry Sewall Professor of Medicine, University of Michigan
2005 – 2011	Director, University of Michigan Center for Stem Cell Biology
2004 – 2008	Associate Professor, Department of Internal Medicine, University of Michigan
2000 – present	Investigator, Howard Hughes Medical Institute
1999 – 2004	Assistant Professor, Department of Internal Medicine, University of Michigan
1996 – 1999	Postdoctoral scholar in the lab of Dr. David J. Anderson, Caltech
1991 – 1996	Graduate student in the laboratory of Dr. Irving L. Weissman, Stanford University
1986 – 1990	President and Director of Endogro Systems Inc.

Honors and Awards

2020	Excellence in Postdoctoral Mentoring Award, Postdoctoral Association at UT Southwestern
2020	Philip Levine Memorial Lecture, Rockefeller University
2020	Elected member, National Academy of Sciences
2019	Emily Frederick DiMaggio Lecture, Dana-Farber Cancer Institute
2018	Keynote Address, American Society of Cell Biology Annual Meeting
2018	Elected member, National Academy of Medicine
2018	Lubomir S. Hnilica Lecture, Frontiers in Biochemistry, Vanderbilt University
2018	Keynote Address, AACR Special Conference on Metabolism and Cancer
2017	Malkin-Kraft Lecturer, Northwestern University
2017	Sol Sherry Lecture, International Society for Hemostasis and Thrombosis
2016	Keynote Address, Keystone Symposium on Stem Cells and Cancer
2015	President, International Society for Stem Cell Research
2012	Roy M. Huffington Distinguished Lecture, Baylor College of Medicine
2009	MERIT Award, National Institute on Aging, National Institutes of Health
2008	American Association of Anatomists Harland Winfield Mossman Award
2007	McCulloch and Till Award, International Society for Hematology & Stem Cells
2006	Detroit News Michiganian of the Year
2004	Dean's Award for Basic Science, University of Michigan Medical School
2003	Wired Magazine Rave Award for Science
2003	Presidential Early Career Award for Scientists & Engineers, White House
2002	Named to TR100 list: MIT Technology Review Magazine's list of 100 young innovators
2000 – 2003	Searle Scholar
1997 – 1999	American Cancer Society, California Division, Junior and Senior Postdoctoral Fellowships
1996 – 1998	Natural Sciences and Engineering Research Council Postdoctoral Fellowship
1991 – 1996	Howard Hughes Institute Predoctoral Fellowship in Biological Sciences
1991	Dalhousie University Medal in Biology
1986	Young Canadians Award for Excellence in Science

Editorial boards

2014 – present	Cancer Discovery
2012 – present	Stem Cell Reports
2012 – present	EMBO Reports
2012 – 2018	eLife (Senior Editor)
2012 – 2020	Cancer Cell
2011 – present	EMBO Journal
2010 – present	Journal of Experimental Medicine
2006 – present	Cell Stem Cell

C. Contributions to Science

Stem cell self-renewal is regulated by networks of proto-oncogenes and tumor suppressors: When I started my laboratory in 1999 virtually nothing was known about the molecular mechanisms that regulate stem cell self-renewal. We developed assays to study self-renewal in hematopoietic stem cells (HSCs) and neural stem cells

and identified a series of key regulators, revealing several important principles. First, stem cell self-renewal is mechanistically distinct from restricted progenitor proliferation. Second, many self-renewal mechanisms are conserved across stem cells in different tissues. Third, these mechanisms comprise networks of proto-oncogenes and tumor suppressors that are dysregulated in cancer: cancer cells tend to hijack stem cell self-renewal mechanisms to enable tumorigenesis. Fourth, these networks change over time, conferring temporal changes in stem cell properties that match the changing growth and regeneration demands of tissues. Fifth, tumor suppressor expression increases with age in stem cells, suppressing the development of cancer but also reducing stem cell function and tissue regenerative capacity during aging. Finally, stem cells are metabolically distinct from restricted progenitors in vivo and depend upon metabolic regulation for epigenetic control and cancer suppression.

a. Molofsky, A.V., R. Pardal, T. Iwashita, I.K. Park, M.F. Clarke, and S.J. Morrison. 2003. *Bmi-1* dependence distinguishes neural stem cell self-renewal from progenitor proliferation. **Nature** 425:962-967. PMC2614897
b. Yilmaz, O.H., R. Valdez, B. Theisen, W. Guo, D. Ferguson, H. Wu, and S.J. Morrison. 2006. Pten dependence distinguishes haematopoietic stem cells from leukaemia-initating cells. **Nature** 441:475-482. PMID 16598206
c. Li, Q., N. Bohin, T. Wen, V. Ng, J. Magee, S.C. Chen, K. Shannon, and S.J. Morrison. 2013. Oncogenic Nras has bimodal effects on stem cells that sustainably increase competitiveness. **Nature** 504:143-147. PMC4128640
d. Agathocleous M., C.E. Meacham, R.J. Burgess, E. Piskounova, Z. Zhao, G.M. Crane, B.L. Cowin, E. Bruner, M.M. Murphy, W. Chen, G.J. Spangrude, Z. Hu, R.J. DeBerardinis, and S.J. Morrison. 2017. Ascorbate regulates haematopoietic stem cell function and suppresses leukaemogenesis. **Nature** 549:476-481. PMID28825709

The regulation of temporal changes in stem cell properties, including stem cell aging: Stem cells must undergo temporal changes in their properties throughout life to match the changing growth and regeneration demands of tissues. Stem cells in fetal tissues proliferate rapidly to support the growth of fetal tissues while stem cells in most adult tissues are quiescent most of the time. While stem cells in young adult tissues retain robust regenerative capacity, this declines over time in aging tissues. We discovered that networks of heterochronic gene products regulate temporal changes in stem cell properties between fetal and adult stages as well as during stem cell aging. For example, *Hmga2* expression declines while *let-7* expression and *Ink4a* expression increase with age, reducing stem cell frequency and function in multiple tissues. By deleting *Ink4a* from mice, we partially rescued the decline in stem cell function with age and enhanced the regenerative capacity of aging tissues. Networks of proto-oncogenes and tumor suppressors thus change throughout life to balance tissue regeneration with tumor suppression: proto-oncogenic signals dominate during fetal development when tissue growth is rapid but cancer risk is low, and tumor-suppressor mechanisms are amplified during aging when cancer risk is high. This provides one explanation for why regenerative capacity declines during aging in tissues that contain stem cells.

a. Molofsky, A.V., S.G. Slutsky, N.M. Joseph, S. He, R. Pardal, J. Krishnamurthy, N. Sharpless, and S.J. Morrison. 2006. Increasing p16 *Ink4a* expression decreases forebrain progenitor function and neurogenesis during ageing. **Nature** 443: 448-452. PMC2586960
b. Kim, I., T.L. Saunders, and S.J. Morrison. 2007. Sox17 dependence distinguishes the transcriptional regulation of fetal from adult hematopoietic stem cells. **Cell** 130: 470-483. PMC2577201
c. Nishino, J., I. Kim, K. Chada, and S.J. Morrison. 2008. Hmga2 promotes neural stem cell self-renewal in young, but not old, mice by reducing p16 Ink4a and p19*Arf* expression. **Cell** 135: 227-239. PMC2582221
d. Nishino, J., K. Sunjung, Y. Zhu, H. Zhu, and S.J. Morrison. 2013. A network of heterochronic genes including Imp1 regulates temporal changes in stem cell properties. **eLIFE** 2:e00924. 10.7554. PMC3817382

The niche for hematopoietic stem cells: We have identified a series of cell-extrinsic mechanisms that regulate the maintenance of hematopoietic stem cells (HSCs). We were the first to propose that HSCs reside in perivascular niches after discovering SLAM family markers that enhanced the purification of mouse HSCs and enabled their localization in the bone marrow and spleen (a). We showed that most HSCs reside adjacent to sinusoidal blood vessels in the bone marrow and spleen (a, b, c). We discovered the Leptin Receptor^{+} perivascular stromal cells that express the highest levels of niche factors in the bone marrow (d) and showed that these cells and endothelial cells are the major sources of known factors required for HSC maintenance in

bone marrow (d, e). We also showed that the niche changes in response to injury, with adipocytes becoming a major source of factors for HSC regeneration after myeloablation.

a. Kiel, M.J., O.H. Yilmaz, T. Iwashita, C. Terhorst, and S.J. Morrison. 2005. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. **Cell** 121: 1109-1121. PMID 15989959
b. Ding, L., T.L. Saunders, G. Enikolopov, and S.J. Morrison. 2012. Endothelial and perivascular cells maintain hematopoietic stem cells. **Nature** 481:457-462. PMC3270376
c. Ding, L. and S.J. Morrison. 2013. Haematopoietic stem cells and early lymphoid progenitors occupy distinct bone marrow niches. **Nature** 495:231-235. PMC3600153
d. Acar, M., K.S. Kocherlakota, M.M. Murphy, J.G. Peyer, H. Oguro, C.N. Inra, C.J. Jaiyeola, Z. Zhao, K. Luby-Phelps, and S.J. Morrison. 2015. Deep imaging of bone marrow shows non-dividing stem cells are mainly perisinusoidal. **Nature** 526:126-130. PMC4850557

The identification and regulation of skeletal stem cells in adult bone marrow: The Leptin Receptor$^+$ cells that we discovered as a key component of the niche for hematopoietic stem cells (HSCs) include the skeletal stem cells that are the main source of new osteoblasts and adipocytes that form in adult bone marrow (a). These cells are normally quiescent in adult bone marrow but are activated by diverse injuries, including fractures and myeloablation, to increase their production of osteoblasts and adipocytes in the bone marrow (a, b). Most, but not all, of the osteoblasts that make an enduring contribution to fracture repair and all of the adipocytes that accumulate after myeloablation or during aging in the bone marrow arise from these Leptin Receptor$^+$ cells. We discovered a new bone-forming growth factor that is synthesized by Leptin Receptor$^+$ cells and that is required for the maintenance of adult skeletal bone mass: Osteolectin/Clec11a (c). Osteolectin acts by binding to $\alpha 11\beta 1$ integrin on the surface of Leptin Receptor$^+$ cells and promoting their differentiation into mature osteoblasts. Conditional deletion of either *Osteolectin* or *α11 integrin* from Leptin Receptor$^+$ cells leads to accelerated bone loss in adult mice, identifying a new regulatory mechanism for the control of adult skeletal bone mass. Importantly, the Leptin Receptor$^+$ cells arise in the bone marrow around the time of birth but are initially very rare and make little contribution to the formation of growth of the skeleton but are critical for the maintenance of the skeleton during adulthood.

a. Zhou, B.O., R. Yue, M. M. Murphy, J.G. Peyer, and S.J. Morrison. 2014. Leptin-receptor-expressing mesenchymal stromal cells represent the main source of bone formed by adult bone marrow. **Cell Stem Cell** 15:154-168. PMC4127103
b. Zhou, B.O., H. Yu, R. Yue, Z. Zhao, J. Rios, O. Naveiras, and S.J. Morrison. 2017. Bone marrow adipocytes promote the regeneration of stem cells and hematopoiesis by secreting SCF. **Nature Cell Biology** 19:891-903 PMID: 28714970
c. Yue, R., B.O. Zhou, and S.J. Morrison. 2016. Clec11a/Osteolectin is an osteogenic growth factor that promotes the maintenance of the adult skeleton. **eLIFE** 5:e18782. PMID 27976999
d. Shen, B., A. Tasdogan, J.M. Ubellacker, J. Zhang, E.D. Nosyreva, L. Du, M.M. Murphy, S. Hu, Y. Yi, N. Kara, X. Liu, S. Guela, Y. Jia, V. Ramesh, C. Embree, E.C. Mitchell, Y.C. Zhao, L.A. Ju, H. Zhao, G.M. Crane, Z. Zhao, R. Syeda, and S.J. Morrison. 2021. A mechanosensitive peri-arteriolar niche for osteogenesis and lymphopoiesis. **Nature** 591:438-444. PMID 33627868

Melanoma tumorigenesis and metastasis: We developed a xenograft assay in which single melanoma cells from patients could form tumors (a). This showed that cells with tumor-forming potential are abundant and phenotypically diverse in melanoma, demonstrating that the cancer stem cell model does not apply to some cancers (b). Melanomas also spontaneously metastasize in this xenograft model, creating for the first time an assay in which metastasis could be studied in vivo. We have used this assay to study the metastatic potential of melanomas from more than 150 patients so far and observe that metastatic potential in this xenograft assay correlates with metastatic behavior in patients: stage III melanomas that form distant metastases in patients also metastasize widely in NSG mice (efficient metastasizers) while stage III melanomas that do not form distant metastases in patients metastasize more slowly in NSG mice (inefficient metastasizers). We used this xenograft model to characterize the mechanisms that regulate distant metastasis, discovering that cancer cells experience a dramatic increase in oxidative stress during metastasis, leading to the death of most metastasizing cells (c). The rare melanoma cells that survive during metastasis undergo reversible metabolic changes that confer oxidative stress resistance (c). In fact, intrinsic metabolic differences among melanomas confer differences in metastatic potential (d). We proposed that “pro-oxidant” therapies that exacerbate oxidative stress in cancer cells could be used to inhibit cancer progression (c, d).

a. Quintana, E., M. Shackleton, M. Sabel, D.Fullen, T.M. Johnson, and S.J. Morrison. 2008. Efficient tumor formation by single human melanoma cells. **Nature** 456:593-598. PMC2597380
b. Quintana, E., M. Shackleton, D.R. Fullen, M.S. Sabel, T.M. Johnson, and S.J. Morrison. 2010. Phenotypic heterogeneity among tumorigenic melanoma cells from patients that is reversible and not hierarchally organized. **Cancer Cell** 18: 510-523. PMC3031091
c. Piskounova, E., M. Agathocleous, Z. Hu, S. Mann, Z. Zhao, A.M. Leitch, T.M. Johnson, R.J. DeBerardinis, and S.J. Morrison. 2015. Oxidative stress inhibits distant metastasis by human melanoma cells. **Nature** 527:186-91. PMC4644103
d. Tasdogan, A., B. Faubert, V. Ramesh, J.M. Ubellacker, B. Shen, A. Solmonson, M.M. Murphy, Z. Gu, W. Gu, M. Martin, T. Mathews, S.Y. Kasitinon, T. Vandergriff, Z. Zhao, D. Schadendorf, R.J. DeBerardinis, and S.J. Morrison. 2020. Metabolic heterogeneity confers differences in melanoma metastatic potential. **Nature** 577:115-120. PMID: 31853067

All of our papers can be found at the following URL:
https://www.ncbi.nlm.nih.gov/myncbi/sean.morrison.1/bibliography/public/