BIOGRAPHICAL SKETCH

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

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

POSITION TITLE: **Director of Children's Research Institute at UT Southwestern; 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
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 in the hematopoietic system and the role these mechanisms play in cancer. 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. Given that self-renewal mechanisms change with age and that cancers often arise from mutations that inappropriately activate self-renewal pathways, this potentially explains why the mechanisms that are competent to cause cancer also change with age. In terms of cell-extrinsic mechanisms, we have identified the location and cellular composition of hematopoietic stem cell niches in adult bone marrow and spleen, and have started to identify new mechanisms by which the niche regulates stem cell maintenance. We also study the mechanisms that regulate the self-replication of cancer cells and how these mechanisms compare to the self-renewal of developmentally-related stem cells, particularly focusing on melanoma and leukemia. For example, we discovered that distant metastasis is limited by oxidative stress and that successfully metastasizing melanoma cells undergo reversible metabolic changes that allow them to cope with oxidative stress. In recent years, we have expanded the scope of our studies to discover metabolic mechanisms that regulate stem cell and cancer cell function. We developed a metabolomic approach that can be used to study rare cell populations and discovered that hematopoietic stem cells (HSC) take up more ascorbate (vitamin C) than other hematopoietic cells and that ascorbate is required to regulate HSC function and to suppresses the development of leukemia by promoting Tet demethylase activity.

Studies of particular relevance to this proposal:

1. Signer, R.A.J., J.A. Magee, A. Salic, S.J. Morrison. 2014. Haematopoietic stem cells require a highly regulated protein synthesis rate. **Nature** 509:49-54. PMC4015626
2. Inra, C.N., B.O. Zhou, M. Acar, M.M. Murphy, J. Richardson, Z. Zhao, S.J. Morrison. 2015. A perisinusoidal niche for extramedullary hematopoiesis in the spleen. **Nature** 527:466-471. PMID26570997
3. 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
4. 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, S.J. Morrison. 2017. Ascorbate regulates haematopoietic stem cell function and suppresses leukaemogenesis. **Nature** 549: 476-481. PMID28825709

B. Positions and Honors

Positions and Employment

1986 – 1990 President and Director of Endogro Systems Inc.
1991 – 1996 Graduate student in the laboratory of Dr. Irving L. Weissman, Stanford University

1996 – 1999 Postdoctoral scholar in the lab of Dr. David J. Anderson, Caltech
1999 – 2004 Assistant Professor, Department of Internal Medicine, University of Michigan
2000 – present Investigator, Howard Hughes Medical Institute
2004 – 2008 Associate Professor, Department of Internal Medicine, University of Michigan
2005 – 2011 Director, University of Michigan Center for Stem Cell Biology
2005 – 2011 Henry Sewall Professor of Medicine, University of Michigan
2008 – 2011 Professor, Department of Internal Medicine, University of Michigan
2008 – 2011 Research Professor, Life Sciences Institute, University of Michigan
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
2016 – present Kathryne and Gene Bishop Distinguished Chair in Pediatric Research

Honors and Awards (since 2000)

2000 – 2003 Searle Scholar
2002 Named to TR100 list: MIT Technology Review Magazine's list of 100 young innovators
2003 Wired Magazine Rave Award for Science
2003 Presidential Early Career Award for Scientists & Engineers, White House
2004 Dean's Award for Basic Science, University of Michigan Medical School
2006 Detroit News Michiganian of the Year
2007 Pfizer Young Michigan Biomedical Investigator of the Year Award
2007 McCulloch and Till Award, International Society for Hematology & Stem Cells
2008 American Association of Anatomists Harland Winfield Mossman Award
2009 MERIT Award, National Institute on Aging, National Institutes of Health
2012 Roy M. Huffington Distinguished Lecture, Baylor College of Medicine
2015 President, International Society for Stem Cell Research
2016 Keynote Address, Keystone Symposium on Stem Cells and Cancer
2017 Malkin-Kraft Lecturer, Northwestern University
2017 Sol Sherry Lecture, International Society for Hemostasis and Thrombosis
2018 Keynote Address, AACR Special Conference on Metabolism and Cancer
2018 Lubomir S. Hnilica Lecture, Frontiers in Biochemistry, Vanderbilt University
2018 Elected member, National Academy of Medicine
2018 Keynote Address, American Society of Cell Biology Annual Meeting
2019 Scientist in Residence, University of Duisburg-Essen
2019 Emily Frederick DiMaggio Lecture, Dana-Farber Cancer Institute
2019 Enrico Mihich Lecture, Pezcoller Foundation Symposium

Editorial Boards

2006 – 2015 Faculty of 1000, Section Head "Stem cells & Regeneration"
2006 – present Cell Stem Cell
2010 – present Journal of Experimental Medicine
2011 – present EMBO Journal
2011 – 2017 Current Opinion in Cell Biology
2012 – present Cancer Cell
2012 – present eLife (Senior Editor)
2012 – present EMBO Reports
2012 – present Stem Cell Reports
2014 – present Cancer Discovery

C. Contributions to science

1. 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 self-renewal. We went on to develop assays to study self-renewal in hematopoietic stem cells (HSCs) and neural stem cells and to identify a series of key regulators. We discovered that networks of proto-oncogenes and tumor suppressors that control cancer cell proliferation also regulate stem cell self-renewal, but that these networks do not generically regulate the proliferation of all cells. Restricted progenitor

proliferation does not require many of the mechanisms that regulate stem cell self-renewal. Each time we identified a self-renewal regulator we learned something new about how self-renewal occurs by examining the downstream mechanisms. While many of the components of the self-renewal networks were first discovered as a result of their function in cancer cells, these networks evolved to regulate normal tissue homeostasis. Their ability to promote neoplastic proliferation when over-activated by mutations reflects the ability to cancer cells to hijack stem cell self-renewal mechanisms. The approaches we have taken to study self-renewal have been widely adopted by many laboratories.

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. 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
c. Signer, R.A.J., J.A. Magee, A. Salic, S.J. Morrison. 2014. Haematopoietic stem cells require a highly regulated protein synthesis rate. **Nature** 509:49-54. PMC4015626
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, S.J. Morrison. 2017. Ascorbate regulates haematopoietic stem cell function and suppresses leukaemogenesis. **Nature** 549: 476-481. PMID28825709

2. Melanoma tumorigenesis and metastasis: We showed that melanomas have high frequencies of phenotypically diverse tumorigenic cells and do not exhibit a hierarchical organization into tumorigenic and non-tumorigenic cells, suggesting that melanoma does not follow the cancer stem cell model (a, b). We found that melanomas from patients exhibit reproducible differences in their rates of spontaneous metastasis in NSG mice that are predictive of differences in distant metastasis in patients (c). Stage III melanomas that form distant metastases in patients also metastasize widely in NSG mice (efficient metastasizers) while stage III melanomas that did not form distant metastases in patients metastasize more slowly in NSG mice (inefficient metastasizers). Efficient metastasizers often give rise to circulating melanoma cells in the blood of NSG mice while inefficient metastasizers do not, suggesting that the capacity survive in the blood limits distant metastasis. We found that metastasizing melanoma cells experience oxidative stress in the blood and in visceral organs beyond what they experience in established subcutaneous tumors. Anti-oxidants promote distant metastasis in NSG mice, demonstrating that oxidative stress limits distant metastasis. Successfully metastasizing melanoma cells undergo reversible metabolic changes that increase their capacity to withstand oxidative stress, including increased dependence upon NADPH-generating enzymes in the folate pathway (d). Folate pathway inhibition reduces metastatic tumor burden without inhibiting the growth of subcutaneous tumors. We hypothesize that oxidative stress limits distant metastasis in multiple solid cancers.
   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. Quintana, E., E. Piskounova, M. Shackleton, D. Weinberg, U. Eskiocak, D.R. Fullen, T.M., and S.J. Morrison. 2012. Human melanoma metastasis in NSG mice correlates with clinical outcome in patients. **Science Translational Medicine** 4,159ra149. PMID23136044
   d. 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** 527:186-9. PMC4644103

3. 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 while stem cells in most adult tissues are quiescent most of the time. Stem cells in young adult tissues retain robust regenerative capacity but this declines over time in aging tissues. These temporal changes in stem cell properties are evolutionarily conserved, but the underlying mechanisms are poorly understood. 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

4. The extrinsic mechanisms by which the niche regulates hematopoietic stem cell maintenance: The nature of the HSC niche in the bone marrow is a paradigm for understanding the cell-extrinsic mechanisms that maintain stem cells through adult life in mammalian tissues. We discovered that most HSCs in adult bone marrow are associated with sinusoidal blood vessels throughout the bone marrow and are maintained by factors that are secreted by endothelial cells and Leptin Receptor-expressing perivascular stromal cells. Conditional deletion of *Scf* from both endothelial cells and LepR+ stromal cells eliminates all quiescent and serially transplantable HSCs from adult bone marrow, eventually leading to hematopoietic failure. The LepR+ perivascular stromal cells are also highly enriched for skeletal stem cells, which serve as the main source of bone and adipocytes formed in adult bone marrow. We have also identified long-range factors that extrinsically regulate HSC function, showing that estrogen promotes the proliferation of HSCs and the expansion of erythropoiesis during pregnancy.
   a. Zhou, B.O., R. Yue, M. M. Murphy, J.G. Peyer, 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. Nakada, D., H. Oguro, B. Levi, N. Ryan, A. Kitano, Y. Saitoh, M. Takeichi, G. Wendt, and S.J. Morrison. 2014. Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. **Nature** 505:555-558. PMC4015622
   c. Inra, C.N., B.O. Zhou, M. Acar, M.M. Murphy, J. Richardson, Z. Zhao, S.J. Morrison. 2015. A perisinusoidal niche for extramedullary hematopoiesis in the spleen. **Nature** 527:466-471. PMC4838203
   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

5. The identification and characterization of neural stem cells in the central and peripheral nervous systems: We identified markers and developed techniques to prospectively identify and purify by flow cytometry uncultured stem cells from the central and peripheral nervous systems. This made it possible to directly study the properties of these cells and to better understand their physiological functions. In the PNS, this led to the discovery that neural crest stem cells persist much later than expected during fetal development and undergo multilineage differentiation in multiple regions of the developing PNS. Intrinsic differences in the sensitivity of neural crest stem cells to lineage determination factors in different regions of the developing PNS regulate their acquisition of different fates in different locations. In the CNS, we discovered that neurosphere-initiating cells are highly mitotically active progenitors rather than quiescent neural stem cells. Instead, we have shown that the quiescent stem cells that persist long-term in the mouse forebrain and that regenerate the SVZ after injury are not competent to form colonies in existing culture conditions.

a. Morrison, S.J., P.M. White, C. Zock, and D.J. Anderson. 1999. Prospective identification, isolation by flow cytometry and in vivo self-renewal of multipotent mammalian neural crest stem cells. **Cell** 96:737-749 PMID10089888
b. Bixby, S., G.M. Kruger, J.T. Mosher, N. Joseph, and S.J. Morrison. 2002. Cell-intrinsic differences between neural stem cells from different regions of the peripheral nervous system regulate the generation of neural diversity. **Neuron** 35:643-656 PMID12194865
c. Joseph, N.M., S. He, E. Quintana, Y-G. Kim, G. Núñez, and S.J. Morrison. 2011. Enteric glia are multipotent in culture but primarily form glia in the adult rodent gut. **Journal of Clinical Investigation** 121:3398-3411. PMC3163971
d. Mich, J.K., R.A.J. Signer, D. Nakada, A. Pineda, R.J. Burgess, T.Y. Vue, J.E. Johnson, S.J. Morrison. 2014. Prospective identification of functionally distinct stem cells and neurosphere-initiating cells in adult mouse forebrain. **eLIFE** 10.7554/eLife.02669. PMC4038845

All of our papers can be found at the following URL:
http://www.ncbi.nlm.nih.gov/sites/myncbi/sean.morrison.1/bibliography/40441875/public/?sort=date&direction=ascending

D. Ongoing Research Support

001823 (PI, Morrison) 09/01/00 – 08/31/20
Howard Hughes Medical Institute
Funding is not associated with a specific project

R37 AG02494514 (PI, Morrison) 08/01/04 – 05/31/20
NIH/NIA (MERIT Award)
"The Regulation of Stem Cell Aging"
To test if the Bmi-1 polycomb protein is required to maintain adult neural stem cells, neurogenesis, and neurological function during aging by opposing the age-related increases in $p16^{Ink4a}$ and $p19^{Arf}$ expression.

RP180778 (PI, Morrison) 08/31/18 – 08/30/22
Cancer Prevention and Research Institute of Texas
"Metabolic enablers of melanoma progression – MIRA"
This is a multi-investigator grant that funds work in the laboratories of Sean Morrison, Ralph DeBerardinis, and Prashant Mishra to study the metabolic mechanisms that regulate melanoma disease progression, including pathways that regulate oxidative stress resistance during metastasis (Morrison lab), intraoperative isotope tracing to characterize melanoma metabolism in humans (DeBerardinis lab), and effects of mitochondrial heterogeneity on metastasis (Mishra lab).

R01 DK11875-02A1 (Morrison) 04/01/19 – 03/31/24
NIH – National Institutes of Health
The Metabolic Regulation of Hematopoietic Stem Cell Function
To determine whether ascorbate (vitamin C) depletion, which is common among people in Western countries, promotes hematopoietic regeneration or clonal hematopoiesis and to identify the mechanisms by which ascorbate regulates hematopoiesis.

U01 CA228608-01A1 (PI, Morrison) 09/05/19 – 09/04/24
NCI – National Cancer Institute
"The Metabolic Regulation of Melanoma Metastasis"
The goal of this project is to compare patient-derived xenograft and patient-derived organoid assays to study the regulation of oxidative stress in melanoma cells.