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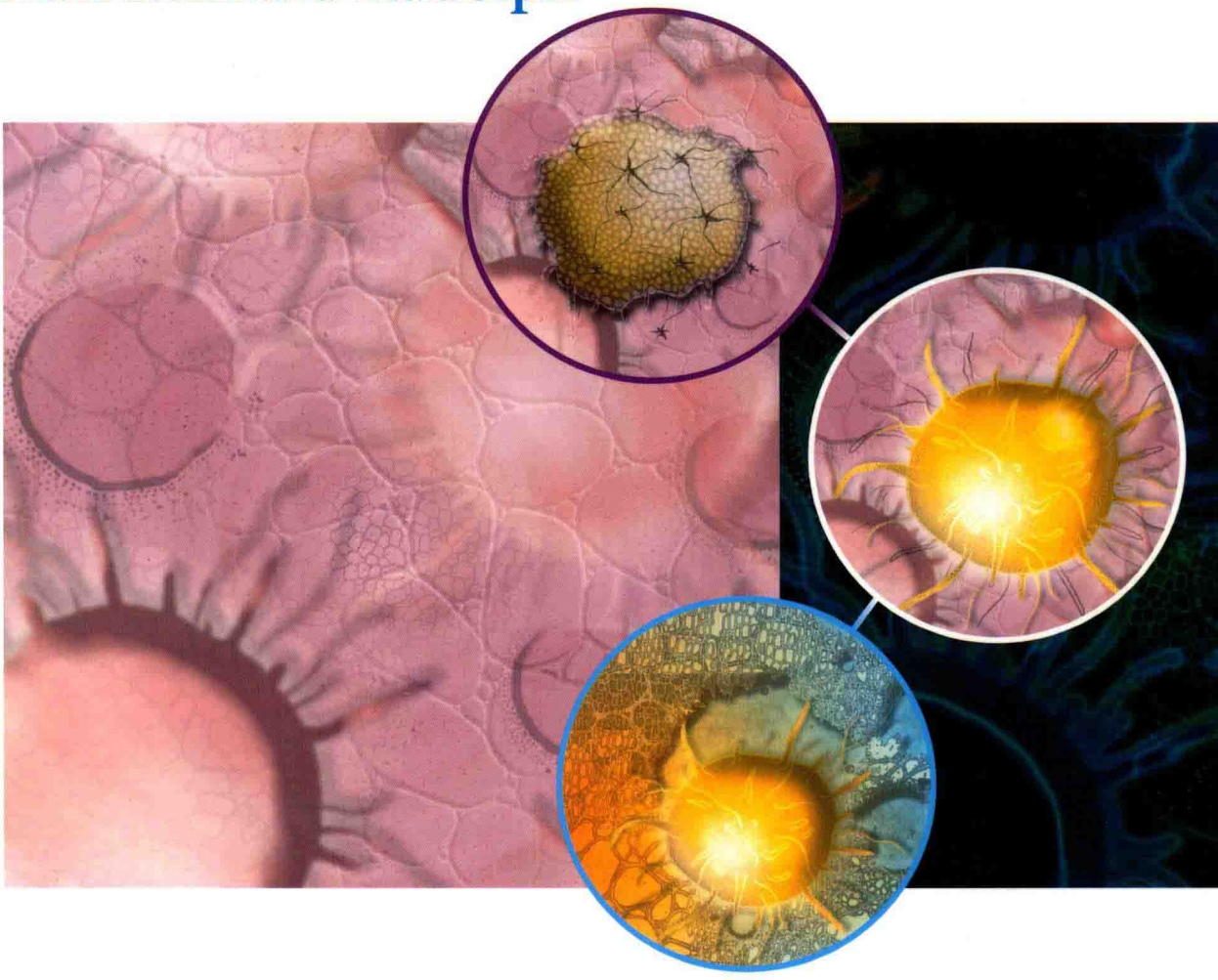
Molecular Mechanisms of Adult Stem Cell Aging

Editor
Karl Lenhard Rudolph



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Molecular Mechanisms of Adult Stem Cell Aging

Volume Editor

Karl Lenhard Rudolph Ulm

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Else Kröner-Fresenius Symposia

Vol. 1

Series Editor

S. Pahernik Heidelberg

Preface

This new book series features the proceedings of the Else Kröner-Fresenius Symposia, which is intended to cover clinically relevant topics at the forefront of biomedical research. They give experts in new or evolving fields of biomedicine the opportunity to critically analyze the most recent findings and outline future research strategies. Today's research is characterized by the accelerated generation of biological and medical data, the increasingly interdisciplinary nature of scientific approaches as well as efforts to integrate individual findings into complex system networks. These developments emphasize the need for new forums of discussion.

The research discussed at the first Else Kröner-Fresenius Symposium focuses on stem cell aging at the cellular and molecular levels. The understanding of stem cell aging in the context of other tissues and malignant tumors is highly relevant for current developments in biomedicine.

Decreasing capacity for tissue renewal is a fundamental feature of the physiological process of aging. Dr. Karl Lenhard Rudolph's research has contributed to our understanding of the molecular mechanisms by which the complex balance of tissue integrity is gradually altered in the process of tissue aging. He has shown that inhibition of telomere dysfunction can modulate the process of cellular senescence. The physiology, modulation and pathology of stem cell systems discussed at the first Else Kröner-Fresenius Symposium promise to eventually open new ways of restoring organ function lost by disease or physical trauma. A wide variety of organ systems, pathophysiological settings and experimental models were discussed at the meeting, integrating knowledge from diverse fields of research.

The Else Kröner-Fresenius-Stiftung thanks Dr. Rudolph for his inspiring scientific work and personal input for organizing together, with his young team, the first Else Kröner-Fresenius Symposium.

The Else Kröner-Fresenius-Stiftung

In 1983, Else Kröner (1925–1988) founded the Else Kröner-Fresenius-Stiftung, a non-profit-making foundation dedicated to promoting medical science and providing humanitarian aid. After her death in 1988, nearly her entire estate was transferred to the foundation for the pursuit of these aims. The symposia are published as part of

the foundation's commitment to the advancement of medical research and treatment.

In 1946, after the death of Dr. Eduard Fresenius, who founded the pharmaceutical company Fresenius in 1912, Else Kröner inherited the company. She also inherited the historic Hirsch Apotheke, which had been founded in Frankfurt am Main in the 15th century. Else Kröner decided to take responsibility for the Fresenius company, although it was in debt and all but 30 of the original 400 employees had to be laid off. She joined with her husband, Hans Kröner, to save and expand the company. While the company's mere survival had marked all of its activity to that point, entrepreneurial decisions in the 1950s ensured its successful development. Decades of growth followed, leading to an internationally competitive enterprise and market leader in many areas of health care. Else Kröner led the company until 1981. After the transformation of Fresenius into a stock company, she remained Chairman of the Supervisory Board until her death in 1988. The Fresenius Group is currently the leading global provider of dialysis and artificial nutrition as well as being a major private hospital management company in Germany.

Sascha Pahernik, Heidelberg
Member of the Scientific Commitee of
the Else Kröner-Fresenius-Stiftung
Series Editor

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Introduction

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Institute of Molecular Medicine and Max Planck Research Group on Stem Cell Aging, University of Ulm, Ulm, Germany

There is growing evidence that adult stem cells age. This process can result in alterations in stem cell number and function, leading to distinct phenotypic outcomes in different organ systems.

The molecular causes of stem cell aging remain to be defined. There is evidence that stem cell aging can involve cell intrinsic as well as extrinsic alterations that affect the stem cell niche or the macro-environment. In various organ systems, stem cells represent the most long-living population of cells retaining a capacity to proliferate and differentiate. The aging of adult stem cells likely plays a key role in the decline of organ maintenance and regenerative reserve during ag-

ing and at the end stage of chronic diseases. In addition, it may contribute to stem cell transformation and carcinogenesis.

Given the pivotal role of adult stem cells in aging, regeneration and cancer, the Else Kröner-Fresenius Stiftung decided to initiate a symposium focusing on adult stem cell aging. The symposium, in May 2009, brought together leading experts in the field in an atmosphere that fostered scientific exchange and open discussion on new models and future concepts. The meeting significantly contributed to scientific advancement in this emerging field of research, which should ultimately lead to the development of new therapies in aging, regeneration and cancer. This book represents a meeting report summarizing the current knowledge in the field of stem cell aging and reviewing the emerging topics discussed at the Else Kröner-Fresenius Symposium on the Molecular Mechanisms of Adult Stem Cell Aging.

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Speakers at the Symposium

Daniel Hartmann

Institute of Molecular Medicine and Max Planck Research Group on Stem Cell Aging, University of Ulm, Ulm, and Department of Surgery, Technical University Munich, Munich, Germany

Thomas Braun, MD

T.B. is director of the Department of Cardiac Development and Remodeling at the Max Planck Institute for Heart and Lung Research in Bad Nauheim (Germany) (www.mpi-bn.mpg.de). After finishing his medical studies in Göttingen and his medical thesis at the Institute of Human Genetics in Hamburg, he worked as a postdoc at the Department of Toxicology, University of Hamburg, in Hamburg (Germany), the Institute of Virology in Oxford (UK), the Medical Research Council in Cambridge (UK), the Whitehead Institute for Biomedical Research in Cambridge (USA) and as a group leader at the Department of Cellular and Molecular Biology, Braunschweig University of Technology, in Braunschweig (Germany). In 1993, he completed his PhD in cellular biochemistry and the German 'habilitation'. He has been associate professor at the Institute of Medical Radiology and Cell Research, Würzburg (Germany) and full professor and director of the Institute of Physiological Chemistry at the University of Halle-Wittenberg where he also served as vice dean for research in the Medical Faculty. Since 2004, he has been a scientific member and director at the Max Planck Institute in Bad Nauheim and full professor at the Department of Internal Medicine at the University of Giessen (Germany). He is an elected member of the German Academy of Natural Scientists, Leopoldina and St. Cross College, Oxford (UK).

T.B.'s research has two main focuses. The first is processes that lead to proliferation of organ-typical precursor cells and their coordinated differentiation during organ development and regeneration. The second is the development of pre-clinical models, which can be used to enable, improve and accelerate tissue regeneration, particularly in the heart. He has made several seminal contributions to the understanding of muscle development and regeneration that have had a major impact in the field. Key findings were the identification of the myogenic factor Myf-5, the analysis of the biological function of Myf-5, Myf-6 and MyoD in vivo, the discovery of the homeobox protein Lbx1 as a regulator of limb muscle precursor cell migration, the analysis of the role of FGFs for muscle cell migration and regeneration, the identification of Pax7 as a crucial regulator of muscle satellite cell survival and maintenance, the identification of new muscle-specific

transcriptional co-regulators and many other discoveries, including the recent identification of miRNAs as regulators of phenotype modulation of smooth muscle cells, which has a major impact on the understanding of the pathogenesis of arteriosclerosis.

Tao Cheng, MD

T.C. received his medical degrees and clinical training (internal medicine and hematology) from the Secondary Military Medical University, Shanghai (China). He did his postdoctoral fellowship (hematopoiesis and stem cell biology) at the Massachusetts General Hospital and Harvard Medical School with Dr. David Scadden. He is now an associate professor with tenure at the Department of Radiation Oncology and the director of stem cell biology and co-leader of the Cancer Stem Cell Program at the University of Pittsburgh Cancer Institute (http://bmg.mgb.pitt.edu). Prior to his current tenure, he was assistant professor of medicine at Harvard Medical School. He also holds an adjunct professorship at the Chinese Academy of Medical Sciences and Peking Union Medical College and is leading a national laboratory on experimental hematology in China (http://english.bjhb.gov.cn). He has received many awards, including the Young Faculty Scholar Award from the American Society of Hematology in 2002, a Chang-Jiang Scholarship from the Ministry of Education of China in 2007, and the Scholar Award from the Leukemia and Lymphoma Society of the USA in 2008.

T.C.'s research mainly concerns cell cycle control of stem cells and stem cell response to injury or disease. His focus is on (1) the roles of cell cycle regulators (mainly CDK inhibitors) in stem cell self-renewal, (2) the distinction between molecular mechanisms in leukemic stem cells versus normal hematopoietic stem cells, and (3) stem cell protection in transplant recipients or under pathological conditions.

James DeGregori, PhD

J.D. is a professor in the Department of Biochemistry and Molecular Genetics and director of the Molecular Biology Program at the University of Colorado Denver School of Medicine (www.uchsc.edu/molbio). He received his PhD from the Massachusetts Institute of Technology in 1993 under the mentorship of H. Earl Ruley. From 1993 to 1997 he was a postdoctoral fellow with Joseph Nevins at Duke University Medical Center. His honors include being named a V Foundation Scholar and a Leukemia and Lymphoma Society Scholar.

Studies to better understand the conditions that foster the initiation of leukemias and lymphomas are currently a major thrust of the DeGregori lab. The lab has developed an evolution-based model for cancer development, 'Adaptive Oncogenesis', and is currently exploring how reduced progenitor cell fitness resulting from carcinogen exposure, irradiation, inadequate diet or aging can select for adaptive oncogenic events and thereby promote the expansion and fixation of oncogenically initiated cells. In particular, current studies are focused on how the reduced fitness of lymphoid progenitor cells in aged individuals can increase the selection for oncogenic events such as Bcr-Abl, leading to increased leukemogenesis.

Gerald de Haan, PhD

G.d.H. is a professor of molecular stem cell biology at the Department of Cell Biology, University Medical Center Groningen in the Netherlands (www.rug.nl/umcg). He received his PhD in 1995 and was a postdoctoral fellow in the lab of Gary Van Zant at the University of Kentucky until 1998. He was awarded a fellowship by the Royal Netherlands Academy of Arts and Sciences to establish his own lab in Groningen, and received a VICI grant from the Netherlands Organization for Scientific Research.

G.d.H.'s research interests relate to the molecular understanding of self renewal of hematopoietic stem cells. These include the identification of genes that regulate self renewal, hematopoietic stem cell expansion, development of leukemia, and studies on hematopoietic stem cell aging. In earlier studies, G.d.H.'s group was able to show how hematopoietic stem cell turnover is correlated with mouse lifespan. Genetic studies have identified genomic loci that control these parameters, and more recently genome-wide expression studies have resulted in the construction of gene networks that underlie stem cell turnover and functioning. In addition, his lab studies the involvement of epigenetic modifications during hematopoietic stem cell aging.

Ronald A. DePinho, MD

R.A.D. is director of the Belfer Institute Center for Applied Cancer Science at the Dana-Farber Cancer Institute, and is professor of medicine and genetics at Harvard Medical School; he is an American Cancer Society research professor, and member of the Institute of Medicine of the National Academies (http://research4.dfci.harvard.edu/DePinho). He founded and directs the Belfer Institute, which is a novel integrated program for cancer drug discovery and development. R.A.D. serves on numerous advisory boards in the public and private sector and is founder, director and advisor of several biotechnology companies and advises many pharmaceutical companies as well as the US government on various national efforts such as the human cancer genome project. He has received numerous awards including the Melini Award for Biomedical Excellence, the ACSI Stanley J. Korsmeyer Award, the AACR Clowes Award, the Harvey Society Lectureship, the Helsinki Medal, and the Albert Szent-Gyorgyi Prize.

The DePinho laboratory has utilized molecular, cellular and organismal approaches to dissect complex human disorders including cancer and aging. R.A.D. illuminated how the fundamental confluence of telomere dysfunction, impaired DNA damage signaling, and age- or disease-accelerated epithelial renewal conspire to drive the benign to malignant transition in carcinomas, the most common cancers, as well as in aging-related degenerative diseases. These studies revealed how such cancers acquire complex translocations and recurrent amplifications/deletions needed to drive malignancy. Building on these discoveries, he created many engineered cancer models, including those with telomere dysfunction with which he defined fundamental mechanisms underlying cancer's hallmark feature of genome instability and harnessed such systems in human cancer gene discovery. He defined the extent to which telomeres influence the normal aging process and metabolism and established the essentiality of telomeres and FoxOs in stem cell homeostasis in the aged. He provided the first genetic evidence that premature aging and degenerative phenotypes of Werner and Ataxia-Telangiectasia syndromes are driven by the impact of these deficiencies on telomere maintenance. Notably, he showed that end-stage liver cirrhosis, a leading cause of death worldwide, is precipitated by telomere depletion. R.A.D. also made fundamental contributions on many fronts, including the use of inducible cancer models establishing the concept of tumor maintenance and their use in drug response and diagnostics, the genetic analysis of tumor suppressors, and the discovery of co-activated receptor tyrosine kinases in all solid tumors – a paradigm that now guides receptor tyrosine kinase inhibitor combination trials.

Kenneth Dorshkind, PhD

K.D., professor and vice chair for research in the Department of Pathology and Laboratory Medicine at the David Geffen School of Medicine at the University of California, Los Angeles, earned his doctorate in biological structure at the University

of Washington, Seattle in 1980 and then completed a postdoctoral fellowship at the Ontario Cancer Institute in Toronto. He serves as director of the Hematopoietic Malignancies Program in the Jonsson Comprehensive Cancer Center (www.cancer.ucla.edu) and as academic associate director of the UCLA Broad Stem Cell Research Center (www.stemcell.ucla.edu). Work in the Dorshkind laboratory is supported by multiple grants from the National Institutes of Health.

Research in the Dorshkind laboratory is focused on the analysis of lymphocyte development during embryogenesis and senescence. One aim is to compare and contrast B cell progenitors that emerge during fetal life with those that are generated in postnatal bone marrow. Emerging data from his laboratory indicate that the first wave of B cell development in the fetus generates B-1 B cell progenitors, which are effectors of innate immunity. The other main goal of the laboratory is to determine the basis for declines in lymphocyte development with age. It is known that lymphoid progenitors exhibit severe growth defects during aging while myelopoiesis is relatively unperturbed. Recent data generated in his laboratory have demonstrated that the preferential expression of the p16Ink4a and Arf tumor suppressor proteins in aged lymphoid progenitors contributes to their reduced growth and survival and makes the aged progenitors refractory to transformation. Down-regulation of p16Ink4a and Arf reversed the senescent phenotype but restored susceptibility to transformation. These data have provided a molecular explanation for lymphoid lineage aging and support the hypothesis that aging and cancer resistance are linked processes.

Toren Finkel, MD, PhD

T.F. is currently the chief of the Translational Medicine Branch of the National Heart Lung and Blood Institute in Bethesda, Md. (USA). He received his undergraduate degree in physics and his MD and PhD degree from Harvard Medical School in 1986. Following a residency in internal medicine at the Massachusetts General Hospital, he completed a fellowship in cardiology at Johns Hopkins Medical School. In 1993, he accepted a position within the Intramural Research Program of the National Institutes of Health in Bethesda. In 2001, he became the chief of the Cardiology Branch and in 2007, he became chief of the newly formed Translational Medicine Branch within the NHLBI (http://dir.nhlbi.nih.gov).

T.F.'s current research interests include (1) the role of reactive oxygen species in aging and the contribution of stem/progenitor cell dysfunction in age-related diseases, (2) the role of mammalian sirtuins in both aging and metabolism, and (3) the mTOR pathway in aging and energy signal transduction. His work is supported by National Institutes of Health intramural funds and from a Senior Scholar award from the Ellison Medical Foundation.

Hartmut Geiger, PhD

H.G. holds the leadership position of the KFO142: 'Molecular and Cellular Aging – From Mechanisms to Clinical Perspective' in the Division of Dermatology and Allergic Diseases at University of Ulm (www.uni-ulm.de/klinik/derma/e/index_e.html), and an adjunct associate professor position in the Division of Experimental Hematology and Cancer Biology at Cincinnati Children's Hospital Medical Center (www.cincinnatichildrens.org). After obtaining his PhD at the Max Planck Institute of Immunobiology in Freiburg (Germany), H.G. moved to the laboratory of Gary Van Zant at the University of Kentucky in Lexington, Ky. (USA) to study the genetic regulation of hematopoietic stem cells. He was subsequently appointed assistant professor and in 2008 associate professor at the Divi-

sion of Experimental Hematology at Cincinnati Children's Hospital Medical Center.

H.G. was appointed to his current leadership position of the KFO142 in 2008. His research focuses on hematopoietic stem cell biology, with a special emphasis on molecular pathways of stem cell aging and alterations of stem cell niche interaction upon aging.

Margaret A. Goodell, PhD

M.A.G. received her doctorate from the University of Cambridge in England and underwent postdoctoral training at MIT and Harvard Medical School. M.A.G. has been on the faculty at Baylor College of Medicine in Houston, Tex. (USA) (www.bcm.edu/db) since 1997, and is the director of the college's Stem Cells and Regenerative Medicine Center (www.bcm.edu/star). She is a member of the Center for Cell and Gene Therapy, and the Departments of Pediatrics, Molecular and Human Genetics, and Immunology. She has served on the board of the International Society for Stem Cell Research (2005–2008) and the International Society for Experimental Hematology (2009–2012). She serves on several editorial boards including *PLoS Biology*, *Cell Stem Cell*, and *Blood*, and as a reviewer for multiple journals and grant-awarding agencies. She received the DeBakey Award for Excellence in Research at Baylor College in 2004 and the Stohlman Scholar Award from the Leukemia and Lymphoma Society in 2006. In 2007, she was awarded the Vivian L. Smith Chair in Regenerative Medicine at Baylor College.

M.A.G. developed the innovative side population method for the isolation of hematopoietic stem cells from mouse bone marrow, which is now widely used and has been applied to identify candidate stem cells from multiple tissues and species. She now directs a laboratory of about 20 students and postdoctoral fellows focusing on the fundamental mechanisms that regulate hematopoietic stem cells. She has shown that aging has a broad impact on the function and gene expression of mouse stem cells, and is currently studying the specific roles of a variety of genes in stem cell aging.

D. Leanne Jones, PhD

D.L.J. is in the Laboratory of Genetics at the Salk Institute for Biological Studies in La Jolla, Calif. (USA) (www.salk.edu). After completing her PhD in microbiology and molecular genetics at Harvard Medical School with Dr. Karl Münger, she engaged in postdoctoral studies with Philip Ingham at the Medical Research Council Centre for Development and Biomedical Genetics in Sheffield (UK), and then with Margaret Fuller in the Department of Developmental Biology at Stanford University School of Medicine in Palo Alto, Calif. (USA). She started her own research group at the Salk Institute in 2004. D.L.J. has received several research awards including ones from the Ellison Medical Foundation, American Cancer Society, and the California Institute for Regenerative Medicine.

D.L.J.'s research focuses on the molecular mechanisms underlying the manner in which aging affects stem cells, the stem cell environment (niche) and the relationship between the two. Using *Drosophila* spermatogenesis as a model system for studying the aging of adult stem cells, her lab has found that significant changes to the stem cell niche occur, which are accompanied by a concomitant loss of stem cells. An aging-related decline in the expression of key stem cell self-renewal factors normally produced by supporting niche cells revealed that stem cell niches are highly dynamic, rather than static structures. These studies suggest genetic programs are in place to regulate maintenance of a functional stem cell niche over time. Therapeutic strategies that manipulate the size and activity of stem cell niches will complement stem cell transplantation in regenerative medicine and the treatment of cancer.

Zhenyu Ju, MD, PhD

Z.J. heads the Max Planck Partner Research Group on Stem Cell Aging at the Institute of Laboratory Animal Sciences, Chinese Academy of Medical Sciences (www.cnilas.org). After completing his medical studies at Shandong Medical College in Jinan (China) and the China Medical University in Shenyang (China), he engaged in a PhD and postdoctoral training with Lenhard Rudolph at Hannover Medical School (Germany). He started his own research group in Beijing (China) in 2007 in continuous collaboration with Lenhard Rudolph.

Z.J.'s research focuses on the molecular mechanisms underlying the aging process of stem cells. He has carried out projects on the functional consequences of telomere shortening in vivo. His main contributions include the demonstration that (1) telomere dysfunction can induce cell intrinsic checkpoints limiting stem cell maintenance and function, (2) deletion of specific DNA damage checkpoints can improve stem cell function, organ maintenance, and the lifespan of telomere dysfunctional mice without increasing cancer formation, and (3) telomere dysfunction can limit hematopoietic stem cell function through age-dependent environmental alterations.

Sean J. Morrison, PhD

S.J.M. heads the University of Michigan Center for Stem Cell Biology (www.med.umich.edu/cdb). He is a Henry Sewall professor in medicine and an investigator at the Howard Hughes Medical Institute. He obtained his BSc in biology and chemistry from Dalhousie University, then completed a PhD in immunology at Stanford University and a postdoctoral fellowship in neurobiology at Caltech. Since 1999, S.J.M. has been at the University of Michigan, where his laboratory studies the mechanisms that regulate stem cell self-renewal and stem cell aging, as well as the role these mechanisms play in cancer. S.J.M. was a Searle Scholar (2000–2003), was named to Technology Review Magazine's list of 100 young innovators (2002), received the Presidential Early Career Award for Scientists and Engineers (2003), the International Society for Hematology and Stem Cell's McCulloch and Till Award (2007) and the American Association of Anatomists Harland Mossman Award (2008).

The Morrison laboratory studies the cellular and molecular mechanisms that regulate stem cell function in the nervous and hematopoietic systems and the role that these mechanisms play in cancer. In particular, they study the mechanisms that regulate stem cell self-renewal, and how changes in self-renewal pathways can contribute to cancer and stem cell aging. The Morrison laboratory has shown that networks of proto-oncogenes and tumor suppressors, originally discovered for their role in cancer, also regulate stem cell self-renewal. Indeed, proto-oncogenes and tumor suppressors probably evolved to regulate normal stem/progenitor cell function, and their role in cancer reflects the ability of cancer cells to hijack these mechanisms. These mechanisms also change with age, allowing stem cell function to be regulated in a manner that reflects the changing growth and regenerative demands of tissues, while also guarding against the increased risk of cancer during aging.

Hiromitsu Nakauchi, MD, PhD

H.N. is the director of the Division of Stem Cell Therapy and the Center for Stem Cell and Regenerative Medicine at the Institute of Medical Science at the University of Tokyo (www.ims.u-tokyo.ac.jp/imsut/en). He obtained his MD degree from the Yokohama City University School of Medicine and his PhD in immunology from the University of Tokyo Graduate School of Medicine. From 1983 to 1985, he was a postdoctoral fellow in immunogenetics and molecular biology