

The 2006 Harvard / Paul F. Glenn

Symposium on Aging

June 5, 2006



Paul F. Glenn Laboratories for the Biological Mechanisms of Aging

By 2029, more than 70 million Americans will be over the age of 65, placing a heavy burden on the health care system. Recent advances in aging research over the past few years have shown that it is possible to slow aging and extend the healthy lifespan of laboratory animals. Extending lifespan by 30-60% is no longer considered remarkable. Our challenge in the coming years is to translate these discoveries into medicines that postpone and treat diseases of aging, thereby extending our healthy years into the eighth, ninth and possibly tenth decades of life.

Many leaders in the aging field predict that significant strides will be made in understanding how human health and lifespan are regulated, leading to novel medicines to forestall and treat diseases of aging, such as diabetes, cancer, Alzheimer's and heart disease. A recent study¹ concluded that advances in medicine arising from aging research would be 10-100 times more cost-effective than any breakthroughs in other area of medical research.

Seeking to accelerate the pace of research into the molecular mechanisms that govern aging, Harvard Medical School and Paul F. Glenn (an alumnus of Harvard Law School and founder of the Glenn Foundation for Medical Research) launched the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging on Jan 1, 2005. Harvard Medical School aims to attract additional support for the potential creation of a larger Institute that would be the world's leading center for the study of aging.

The Glenn Laboratories are located on two floors of the New Research Building at Harvard Medical School, which opened in 2003. We are pleased to announce the recruitment of Professor Bruce Yankner to the Glenn labs this year. Dr Yankner is known for his seminal discovery of the role of the A β protein in causing Alzheimer's, and is now considered a leader in the aging field. The Glenn labs include seven adjunct faculty at the Medical School, each of whom is a leader in their respective fields related to aging research.

To promote aging research at Harvard and foster collaboration, the Glenn Labs Steering Committee awards two \$100K pilot research grants each year to Medical School investigators with innovative approaches to applying their expertise to addressing critical questions in the aging field. The Labs also seek new technologies to speed aging research and, to this end, a state-of-the-art mass spectrometer was purchased in 2005, which has greatly accelerated biochemical and proteomic studies.

On behalf of The Paul F. Glenn Laboratories and Harvard Medical School, we welcome you to the Harvard Symposium on Aging, 2006.

David Sinclair
Associate Professor of Pathology
& Co-Director, The Paul F. Glenn Laboratories

¹RAND Corp and Stanford University Study, Goldman et al. 2006.

Symposium on Aging Agenda

June 5, 2006

9:00 - 5:00

- 9:00 - 9:15 Introductions by:
Dr. Joseph B. Martin, Ph.D., MD, Dean, Harvard Medical School
Paul F. Glenn, Founder, Paul F. Glenn Laboratories
- 9:15 - 10:00 Leonard P. Guarente, Ph.D.- Keynote Speaker
SIR2 Genes, Calorie Restriction and Aging
- 10:00 - 10:40 Andrzej Bartke, Ph.D.
Why Dwarf Mice Live Longer
- 10:40 - 11:20 Frederick W. Alt, Ph.D.
Lessons from Mouse Knockouts
- 11:20 - 12:00 Makoto Kuro-o, M.D., Ph.D.
Boosting Klotho Gene Extends Life Span in Mice
- 12:00 - 1:00 Lunch Break
- 1:00 - 1:45 Cynthia Kenyon, Ph.D.- Keynote Speaker
Insulin/IGF-1 Longevity Pathways
- 1:45 - 2:25 Bruce A. Yankner, M.D., Ph.D.
Aging of the Human Brain
- 2:25 - 3:05 C. Ronald Kahn, M.D.
Links Between Aging and Metabolism
- 3:05 - 3:45 Stephen L. Helfand, Ph.D.
"I'm Not Dead Yet" and Other Genes that Modulate Lifespan
- 3:45 - 4:25 David A. Sinclair, Ph.D.
Small Molecules that Extend Lifespan & the Prospect of Novel Pharmaceuticals
- 4:30 - 5:00 Social - Cheese and Crackers

Leonard P. Guarente, Ph.D. - Keynote Speaker



Leonard P. Guarente from the Massachusetts Institute of Technology, Cambridge, MA received his B.S. from MIT and PhD from Harvard University in Molecular Genetics. In studying regulation in eukaryotes, his lab first purified the TATA-binding protein TBP and cloned the gene, discovered UASs, identified the first heteromeric transcription factor (HAP2/3/4/5), and provided the first evidence for coactivators. He then turned

his studies to the mechanism of aging and its regulation using yeast and subsequently higher organisms. His lab identified SIR2 as the key gene regulating life span in yeast and *C. elegans* – an extra copy of SIR2 significantly increases the life span of both organisms. Notably, his lab first discovered the novel biochemical activity of the SIR2 gene product – NAD-dependent deacetylase. This activity suggested that SIR2 might be involved in linking diet to the regulation of aging, addressing the longstanding question of how calorie restriction (CR) might slow aging. His lab established a system of studying CR in yeast and showed that CR extended the life span in yeast mother cells by activating SIR2. This activation requires up-regulation of electron transport, which increases the NAD/NADH ratio and activates Sir2p.

More recently, his lab has made several findings regarding the mammalian ortholog of SIR2, Sirt1. This protein is also an NAD-dependent deacetylase. Importantly, it controls several physiological processes impacted by CR. First, Sirt1 renders cells stress resistant by inhibiting pro-apoptotic transcription factors p53 and forkhead. Second, Sirt1 also promotes the mobilization of fat from white adipocytes upon food limitation. It does this by inhibiting the factor PPAR γ , which is important promoting fat storage in white adipocytes. Dr. Guarente's findings show that the life and health extension by CR are not passive events, but result from the activation of Sirt1, which then impacts on cellular and organismal processes to deliver the benefits.

Cynthia Kenyon, Ph.D. - Keynote Speaker

Cynthia Kenyon graduated valedictorian in Chemistry and Biochemistry from the University of Georgia in 1976. She received her PhD from MIT in 1981, where, in Graham Walker's laboratory, she was the first to use "enhancer trap" methods to look for genes solely on the basis of their regulatory properties, discovering that DNA damaging agents switch on a battery of DNA repair genes in *E. coli*. She then did postdoctoral studies with Nobel laureate Sydney Brenner at the MRC Laboratory of Molecular Biology in Cambridge, UK. Since 1986 she has been at the University of California, San Francisco, where she has been the Herbert Boyer Distinguished Professor of Biochemistry and Biophysics, and is now an American Cancer Society Professor. Kenyon's early studies contributed to the remarkable discovery that patterns of body structures are generated in a similar way in all animals, by an ancient and evolutionarily-conserved set of genes called Hox genes. In 1993, Dr. Kenyon's discovery that a single-gene mutation could double the lifespan of the small nematode worm *C. elegans* sparked an intensive study of the molecular biology of aging. The gene affected by this mutation encodes a hormone receptor similar to the human insulin and IGF-1 receptors; thus aging is regulated hormonally. Dr. Kenyon went on to show that hormones control aging in *C. elegans* by regulating the expression of antioxidant, metabolic, antimicrobial and other types of subordinate genes. By manipulating genes and cells, she has now been able to extend the lifespan and period of youthfulness by six times. Dr. Kenyon's findings have now led to the discovery that insulin/IGF-1 signaling controls aging in other organisms as well, including mammals. Kenyon has received many honors and awards for her findings, including the King Faisal Prize for Medicine, the American Association of American Medical Colleges Award for Distinguished Research in Biomedical Sciences, and the Ilse & Helmut Wachter Award for Exceptional Scientific Achievement in the Field of Medicine. She is director of the UCSF Hillblom Center for the Biology of Aging.



Andrzej Bartke, Ph.D.



Andrzej Bartke received his Master's degree in Biology in his native Poland in 1962 and his Ph.D. in Zoology from the University of Kansas in 1965. He held various positions at the Institute for Cancer Research in Philadelphia, PA, Jagiellonian University in Krakow, Poland, Worcester Foundation for Experimental Biology in Shrewsbury, MA, University of Texas Health Sciences Center in San Antonio, TX and Southern Illinois University in Carbondale, IL and Springfield, IL, including chairmanship of Physiology Department at SIU School of Medicine between 1984 and 2002. During most of his career, his research was in the area of endocrinology of reproduction with particular emphasis on the role of prolactin in the male, effects of hyperprolactinemia, role of prolactin in mediating the effects of photoperiod on reproduction in seasonal breeders and effects of altered growth hormone signaling on female and male reproductive functions. During the last 10 years, most of his work concerned the genetic and hormonal control of aging, use of long-lived mutants in aging research and interaction of caloric restriction with longevity genes. He published approximately 500 research papers and approximately 100 review articles and book chapters and served as President of the American Society of Andrology, Society for the Study of Reproduction and American Aging Association.

Dr. Frederick Alt received his Ph.D. from Stanford University in 1977 where he worked with Robert Schimke and discovered gene amplification in mammalian cells. He then moved to MIT for his postdoctoral work with David Baltimore, where he helped elucidate basic principles of recombination events in the immune system. In 1982, he moved to Columbia University and became Professor of Biochemistry and Molecular Biophysics in 1985 and a Howard Hughes Medical Institute Investigator in 1987. At Columbia, he continued his studies of the immune system and also discovered the N-myc oncogene based on its amplification in human neuroblastomas. In 1991, Dr. Alt moved to Harvard Medical School as an HHMI Investigator at Boston's Children's Hospital and a Senior Investigator at the CBR Institute for Biomedical Research (CBRI), as well as a Professor of Genetics and Pediatrics. He was appointed the Charles A. Janeway Professor of Pediatrics in 1993 and Scientific Director of the CBRI in 2005. His work continues to focus on lymphocyte development, genomic instability, and cancer. His group played a key role in elucidating the non-homologous DNA end-joining pathway of DNA double strand break repair in mammalian cells and more recently uncovered roles for DNA break response proteins in maintenance of genomic stability and suppression of cancer. In 2003 he was named an Ellison Medical Foundation Senior Scholar in Aging, allowing him to initiate new work on the mouse SIRT family. In 1994, Dr. Alt was elected to the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Academy of Microbiology and in 1999 was elected to European Molecular Biology Organization. In 2004, he received the Clowes Memorial Award from the American Association of Cancer Research and in 2005 he received the Rabbi Shai Shacknai Prize from The Hebrew University, the Pasarow Foundation Prize for Extraordinary Achievement in Cancer Research, the Leukemia & Lymphoma Society de Villiers International Achievement Award, and the Irvington Institute Immunology Award.



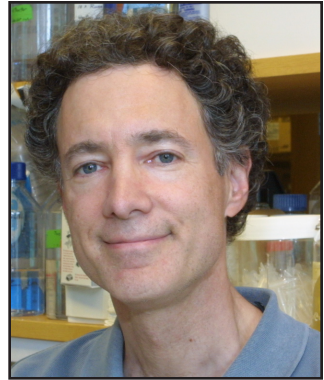
Makoto Kuro-o, M.D., Ph.D.



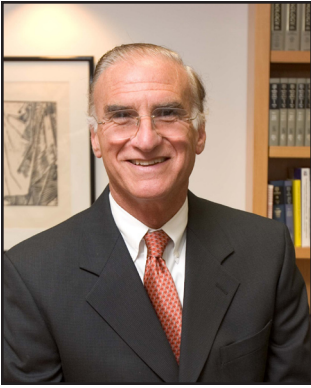
Makoto Kuro-o received an M.D. in 1985 from the University of Tokyo, Japan, where he spent the next two years completing his medical internship. From 1987 until 1988 he received his residency training at Tokyo Metropolitan Geriatric Hospital after which he returned to the University of Tokyo as a clinical fellow in cardiology until 1998. He received a Ph.D. in 1991 from the University of Tokyo. From then

until 1998 he pursued postdoctoral training at the National Institute of Neuroscience in Japan. During the seven years postdoctoral work he identified the *klotho* gene that seemed to be an aging suppressor gene in mammals. In 1998 he became an assistant professor of pathology at the University of Texas Southwestern Medical Center at Dallas. His laboratory focuses on understanding the molecular mechanism by which Klotho protein suppresses aging.

Bruce A. Yankner, M.D., Ph.D. is Professor of Pathology and Neurology at Harvard Medical School and Co-Director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging. Dr. Yankner graduated from Princeton University, received his M.D. and Ph.D. from Stanford, and did his residency at the Massachusetts General Hospital. His early work was seminal to the understanding of the pathology of Alzheimer's disease, and included the discovery of beta amyloid neurotoxicity, the elucidation of cell death mechanisms in Down's syndrome, and the biology of the presenilin genes. His more recent work has defined molecular features of the aging process in the brain, and has demonstrated a genetic signature of brain aging characterized by changes in genes that are critical for learning and memory. His laboratory has also demonstrated that gene damage may contribute to the aging of the brain, and may start in middle age. He has received many awards, including the Major Award for Medical Research from the Metropolitan Life Foundation, the Derek Denny-Brown Award from the American Neurological Association, the Zenith Award from the Alzheimer's Association, and the Ellison Medical Foundation Senior Scholar Award in Aging.



C. Ronald Kahn, M.D.



C. Ronald Kahn, B.A., M.D., M.S., D.Sc. is President and Director of the Joslin Diabetes Center in Boston. Dr. Kahn received his M.D. from The University of Louisville School of Medicine (with highest honors) and holds honorary doctorates from University of Louisville (Honoris Causa) (1984), Universite de Paris Pierre et Marie Curie (1994) and The University of Geneva (2000). He has received over 60 awards and honors and is

the author of over 170 publications. The Kahn lab seeks to understand the link between metabolism and aging. Recent studies from the lab showed that a reduction of fat mass without caloric restriction can be associated with increased longevity in mice, possibly through effects on insulin signaling. Work in the lab is also aimed at defining the roles of each of the IRS-proteins and isoforms of PI 3-kinase in insulin signaling and insulin resistance, the same pathway that regulates aging in *C. elegans* and *Drosophila*. The Kahn lab has also found interesting links between SIRT1-3 and the control of metabolism and longevity. Ronald Kahn has also been recognized for his pioneering work in the field of diabetes, including seminal discoveries that have defined the molecular and cellular mechanisms of insulin action and have yielded critical information about insulin resistance in obesity and diabetes. His recent work has made important contributions to the aging field by demonstrating that a mutation of the insulin receptor gene in adipocytes and that the hormone Klotho, which down-regulates insulin and IGF-1 signaling, extends mouse lifespan.

Dr. Helfand received his BS at Stanford University where he worked with Dr. Norman K. Wessells and discovered the neuronal growth factor later named Ciliary NeuroTrophic Factor. Dr. Helfand obtained his MD degree from Albert Einstein College of Medicine, completed his Medical Internship at Montefiore Medical Center and his Neurology Residency at the Massachusetts General Hospital. He is Board Certified in Neurology.



After Postdoctoral training with Drs. Corey Goodman and David Hogness at Stanford and Drs. John Carlson and Doug Kankel at Yale he took a position at the University of Connecticut Health Center where he worked from 1990 to 2005. In 2005 he moved to Brown University where he is Professor in the Department of Molecular Biology, Cell Biology and Biochemistry in the Division of Biology and Medicine.

Dr. Helfand's laboratory focuses on understanding the molecular genetic mechanisms underlying aging and longevity using the model system, *Drosophila melanogaster*. Dr. Helfand is an Ellison Medical Foundation Senior Scholar and a recent recipient of two RO1 awards and a MERIT award from the National Institute on Aging. His recent work on the molecular genetics of aging has appeared in journals including Science, Nature, Proceedings of the National Academy of Sciences, Cell Metabolism and Current Biology.

David A. Sinclair, Ph.D.



David A. Sinclair, Ph.D. is Co-director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging, an Associate Professor of Pathology at Harvard Medical School, Associate Member of the Broad Institute for Systems Biology, and co-founder of Sirtris Pharmaceuticals, Cambridge, MA. Dr. Sinclair's research aims to identify conserved longevity control pathways and devise small molecules that

activate them, with a view to preventing and treating diseases caused by aging.

His lab was the first to identify small molecules called STACs that can activate the SIRT pathway and extend lifespan of a diverse species. They also discovered key components of the aging regulatory pathway in yeast and is now focused on finding genes and STACs that extend the healthy lifespan of mice.

Dr. Sinclair obtained a BS with first-class honors at the University of New South Wales, Sydney. In 1995, he received a Ph.D. in Molecular Genetics. He worked as a postdoctoral researcher with Dr. Leonard Guarente at M.I.T. before being recruited to Harvard Medical School. Dr. Sinclair has received several additional awards including a Helen Hay Whitney Postdoctoral Award, a Special Fellowship from the Leukemia Society, a Ludwig Scholarship, a Harvard-Armenise Fellowship, an American Association for Aging Research Fellowship, and was a New Scholar of the Ellison Medical Foundation. He won the Genzyme Outstanding Achievement in Biomedical Science Award for 2004 and coordinated with Lenny Guarente the article, "Unlocking the Secrets of Longevity Genes" in *The Scientific American*, March 2006 issue.

The Paul F. Glenn Laboratories Faculty

Lewis C. Cantley, Ph.D.



Dr. Cantley joined the faculty of Harvard Medical School in 1992, when he was also appointed Chief of the Division of Signal Transduction in the Department of Medicine at Beth Israel Hospital. He graduated summa cum laude from Wesleyan College and earned his Ph.D. from Cornell University in 1975.

His postdoctoral research and first faculty appointment were in the Department of Biochemistry and Molecular Biology at Harvard University.

Although Dr. Cantley has made major contributions to numerous fields, he is best known for his discovery of the phosphoinositide 3-kinase (PI3K) pathway, which opened a window on the way biochemical signaling pathways control normal cell growth and how they can trigger the development of cancer when they are defective. Dr. Cantley's discoveries formed the foundation for the elucidation of longevity pathways in the worm *C. elegans*. His work has also enabled researchers to use the genetic blueprints of signaling proteins to predict their cellular targets, with a view to finding new cancer therapies.

Dr. Cantley has received numerous awards in recognition of these achievements. He received the Caledonian Prize of the Royal Society of Edinburgh in 2002. He has well over 300 publications to his name, including research papers, reviews, and book chapters. Cantley was elected to the National Academy of Sciences in 2001.

Stephen J. Elledge, Ph.D.

Stephen J. Elledge, Ph.D. is The Gregor Mendel Professor of Genetics and Professor of Medicine at Harvard Medical School and Senior Geneticist at Brigham and Women's Hospital. He is also an Investigator of the Howard Hughes Medical Institute, and is a Pew Scholar in the biomedical sciences. He is a recipient of the G.H.A.



Clowes Memorial Award, the Paul Marks Prize in cancer research, the Michael E. DeBakey Award for research excellence, and the 2002 National Academy of Sciences Award in molecular biology. Dr. Elledge was elected to the National Academy of Sciences in 2003.

The Elledge lab uses model organisms to characterize cell cycle control and the cellular response to DNA damage. They have identified and characterized a signal transduction pathway that senses and responds to DNA damage. The lab is interested in technology development to aid in gene and drug discovery, and most recently applied a screen to identify transcriptional regulators of telomerase, an important player in human cancer. Currently they are initiating genome wide siRNA screens for regulators in cell cycle, checkpoint signaling tumorigenesis and cell proliferation. Until recently large-scale genetic screens have not been possible in mammals. The Elledge Lab initiated a genetic screen to find transcriptional regulators of human telomerase, an important player in human cancer. Using a technique that places endogenous genes under the control of a regulated promoter, we uncovered multiple negative regulators of this pathway.

Judith A. Glaven, Ph.D.



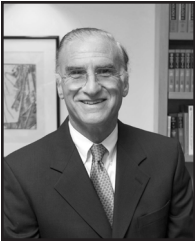
Judith A. Glaven, Ph.D. – Dr. Glaven is the Director of Basic Science Programs at Harvard Medical School. Dr. Glaven came to HMS with over four years of experience as a Senior Scientific Editor at the journal *Cell*, where she evaluated and recruited scientific papers and worked closely with the scientific

community in the areas of basic Cell Biology, Immunology, Cancer Biology and Aging. Previous to being at *Cell* her own research focused on basic molecular mechanisms of cell proliferation and migration. She brings a broad perspective of basic biomedical science to the steering committee and represents the involvement and commitment of the Medical School to this initiative.

Peter M. Howley, M.D., is the George Fabyan Professor of Comparative Pathology Head of the Department of Pathology at Harvard Medical School. Research in the Howley laboratory is focused on the molecular biology of cancer and the role of viruses in its formation. The lab studies “high risk” HPV types such as HPV16 and HPV18 encode two oncoproteins, E6 and E7, which target the important cellular growth regulatory proteins p53 and pRb, respectively. They have previously shown that E6 promotes the ubiquitination and degradation of p53, and are now interested in the general question of how proteins are recognized within cell by the ubiquitin proteolytic machinery. The E6 promoted ubiquitylation of p53 is mediated by a cellular protein, , called the E6 Associated Protein (E6AP), that binds to E6 and participates directly in its ubiquitination. We are interested in how E6AP is regulated and the identification of additional cellular proteins that E6AP targets in cells, either in the presence of or absence of the viral E6 protein.



C. Ronald Kahn, M.D.



C. Ronald Kahn, B.A., M.D., M.S., D.Sc. is President and Director of the Joslin Diabetes Center in Boston. Dr. Kahn received his M.D. from The University of Louisville School of Medicine (with highest honors) and holds honorary doctorates from University of Louisville (Honoris Causa) (1984), Universite de Paris Pierre et Marie Curie (1994) and The University of Geneva (2000). He has received over 60 awards and honors and is the author of over 170 publications. The Kahn lab seeks to understand the link between metabolism and aging. Recent studies from the lab showed that a reduction of fat mass without caloric restriction can be associated with increased longevity in mice, possibly through effects on insulin signaling. Work in the lab is also aimed at defining the roles of each of the IRS-proteins and isoforms of PI 3-kinase in insulin signaling and insulin resistance, the same pathway that regulates aging in *C. elegans* and *Drosophila*. The Kahn lab has also found interesting links between SIRT1-3 and the control of metabolism and longevity. Ronald Kahn has also been recognized for his pioneering work in the field of diabetes, including seminal discoveries that have defined the molecular and cellular mechanisms of insulin action and have yielded critical information about insulin resistance in obesity and diabetes. His recent work has made important contributions to the aging field by demonstrating that a mutation of the insulin receptor gene in adipocytes and that the hormone Klotho, which down-regulates insulin and IGF-1 signaling, extends mouse lifespan.

Gary B. Ruvkun, Ph.D., is a Professor in the Department of Genetics at Harvard Medical School. The Ruvkun lab identified some of the first ever longevity genes using the nematode *C. elegans* as a model and have been instrumental in deciphering the insulin/IGF-1 pathway of longevity regulation. The lab showed that longevity is regulated by insulin signaling within the nervous system, suggesting that it is the metabolism within particular neurons that are key to regulation of lifespan. They study how these neuroendocrine pathways are coupled to sensory inputs. For example, the insulin pathway is coupled to a thermosensory pathway, allowing metabolism to be coupled to temperature. We are now exploring the neural signaling pathways that couple these systems. They have used powerful genetic selections to identify signaling molecules downstream of insulin-like receptors, as well as a novel insulin reception pathway that may act more broadly in animals. Another Glenn Lab Associate, Dr Ron Kahn, showed that disruption of the same insulin-signaling pathway can extend the lifespan of mice.



Pamela A. Silver, Ph.D.



Pamela A. Silver, Ph.D. is a Professor in the Department of Systems Biology at Harvard Medical School and a member of the Department of Cancer Biology at the Dana Farber Cancer Institute. She studied translocation of proteins across membranes as a graduate student with Bill Wickner at the University of California and

nuclear transport as an ACS Postdoctoral Fellow with Mark Ptashne at Harvard University. First as a faculty member at Princeton University, and later at Harvard Medical School, she developed novel genetic and cell biological approaches to study movement of macromolecules in eukaryotic cells. Her current interests range from the systems biology of the nucleus to the use of genomics, chemical genetics, cell-based screening and proteomics in the study of diseases and the brain. She has been the recipient of an NSF Presidential Young Investigator Award, an Established Investigatorship from the American Heart Association, the BBS Mentoring Award from Harvard Medical School and an NIH MERIT award. The Silver group focuses on several major areas in biology from a systems-wide point of view. They model and design biological circuits and parts with well-defined properties for engineering biological systems with an emphasis on intracellular spatial programming. Their recent work has identified new aging regulatory genes in yeast and has led to “cellular oscillator” technology for analyzing cellular aging. The system allows researchers to determine the lifespan of individual yeast cells based on nuclear/cytoplasmic localization.

David A. Sinclair, Ph.D. is Co-director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging, an Associate Professor of Pathology at Harvard Medical School, Associate Member of the Broad Institute for Systems Biology, and co-founder of Sirtris Pharmaceuticals, Cambridge, MA. Dr. Sinclair's research aims to identify conserved longevity control pathways and devise small molecules that activate them, with a view to preventing and treating diseases caused by aging.



In 1997, Lenny Guarente and David Sinclair discovered the molecular cause of aging in yeast, a first for any species. Dr. Sinclair is also recognized for providing the first evidence that the health benefits provided by a very low calorie diet is the result of an active defense response to mild biological stress. Dr. Sinclair is also known for discovering that nicotinamide is a physiological regulator of Sir2 enzymes and for finding a conserved “master regulatory gene” for aging that governs the activity of the Sir2 family of enzymes. In 2003, with Konrad Howitz, he proposed the “Xenohormesis Hypothesis of Aging”, the idea that plant stress signaling compounds provide advance warning of environmental deterioration and trigger lifespan extending pathways in animals. His lab was the first to identify small molecules called STACs that can activate the SIRT pathway and extend lifespan of a diverse species. They also discovered key components of the aging regulatory pathway in yeast and is now focused on finding genes and STACs that extend the healthy lifespan of mice.

Dr. Sinclair obtained a BS with first-class honors at the University of New South Wales, Sydney, and received the Commonwealth Prize for his research. In 1995, he received a Ph.D. in Molecular Genetics and was awarded the Thompson Prize for best thesis work. He worked as a postdoctoral researcher with Dr. Leonard Guarente at M.I.T. before being recruited to Harvard Medical School. Dr. Sinclair has received several additional awards including a Helen Hay Whitney Postdoctoral Award, a Special Fellowship from the Leukemia Society, a Ludwig Scholarship, a Harvard-Armenise Fellowship, an American Association for Aging Research Fellowship, and was a New Scholar of the Ellison Medical Foundation. He won the Genzyme Outstanding Achievement in Biomedical Science Award for 2004.

Bruce Yankner, M.D., Ph.D.



Bruce A. Yankner, M.D., Ph.D is Professor of Pathology and Neurology at Harvard Medical School and Co-Director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging. Dr. Yankner graduated from Princeton University, received his M.D. and Ph.D. from Stanford, and did his residency at the Massachusetts General Hospital. His early work was

seminal to the understanding of the pathology of Alzheimer's disease, and included the discovery of beta amyloid neurotoxicity, the elucidation of cell death mechanisms in Down's syndrome, and the biology of the presenilin genes. His more recent work has defined molecular features of the aging process in the brain, and has demonstrated a genetic signature of brain aging characterized by changes in genes that are critical for learning and memory. His laboratory has also demonstrated that gene damage may contribute to the aging of the brain, and may start in middle age. He has received many awards, including the Major Award for Medical Research from the Metropolitan Life Foundation, the Derek Denny-Brown Award from the American Neurological Association, the Zenith Award from the Alzheimer's Association, and the Ellison Medical Foundation Senior Scholar Award in Aging.

Junying Yuan, Ph.D. is a Professor in the Department of Cell Biology at Harvard Medical School. Dr. Yuan received a Ph.D. in Neuroscience from Harvard University in 1989. Dr. Yuan carried out her postdoctoral research at the Massachusetts Institute of Technology where she made seminal discoveries about apoptosis



that formed the basis of a Nobel Prize for Medicine in that field. She was first appointed as Assistant Professor at Harvard Medical School in 1992, when she became a Principal Investigator of the Cardiovascular Research Center at Massachusetts General Hospital. She joined the Department of Cell Biology in 1996 and was appointed a Professor of Cell Biology at Harvard Medical School in 2000. The Yuan lab aims to understand the basic mechanisms of cell death as well as their implications in neurodegenerative diseases using cellular, genetic, molecular and chemical biological approaches. The lab has developed a high throughput assay for ER stress and identified a small molecule inhibitor of ER stress induced cell death, which they named salubrinal (sal). They have identified a new form of cell death called “necroptosis” and identified a small molecule inhibitor named necrostatin-1 (Nec-1). Nec-1 reduced ischemic brain injury with an extended time window for treatment and thus may be very important for mediating acute neurological injury.



Nearby locations for lunch:

- 1. Elements Café
located at Harvard Medical School, New Research Building
- 2. Bertucci's
(at Children's), 1 Blackfan Circle (Exit rear of Harvard Medical School)
- 3. Galleria Longwood Food Court
342 Longwood Avenue

