HARVARD MEDICAL SCHOOL

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RESEARCH MISSION

Our goal is to discover genes and pharmacological approaches to treating and delaying the onset of age-associated diseases – thereby extending healthy lifespan. The past 10 years has seen a paradigm shift in our understanding of aging. Until the 1990s, almost all researchers believed that the aging process was too complex to find drugs that could slow it. Then geneticists began to uncover single genes that could dramatically extend the lifespan of laboratory organisms such as yeast, worms, flies, and mice.

How could this be? We now know that the rate of aging is not pre-set – it is naturally regulated by a few critical genes. These genes underlie the remarkable effects of the diet known as calorie restriction (CR), which delays aging in every species tested, from yeast to primates. CR is currently the only treatment that can prevent all diseases of aging including cancer, heart disease, osteoporosis, diabetes and neurodegeneration.

Recent studies in our lab and others demonstrate that the ability of CR to extend lifespan in model organisms is governed by the Sirtuins. Animals lacking Sirtuin genes do not respond to CR, and additional gene copies extend lifespan. Based on these findings, we have engineered small molecules that can activate mammalian Sirtuins in vivo, with a view to developing drugs that can (i) treat the diseases of aging and (ii) promote cell survival and recovery following an injury. We utilize any approach we need to answer a specific question – including chemistry, biochemistry, genetics, and cell biology. Models systems include yeast, C. elegans, mammalian cell culture and rodents.

IMPORTANT FINDINGS

Aging is caused, in part, by the DNA-damage induced reorganization of chromatin, a phenomenon we have termed the "RCM response," for redistribution of chromatin modifiers.

Nicotinamide (viatmin B3 relative) regulates lifespan.

Engineering of SIRT1 activators, including the master regulator of sirtuins, “PNC1/Nampt”

KEY PAPERS

Baur, J, Pearson K, Puigserver P, de Cabo R, Sinclair DA, et al. Resveratrol increases health and survival of mice on a high calorie diet. **Nature**. 2006 Nov 16;444(7117): 337-342. PMID: 17086191

Pearson K, Elliott PJ, Ingram D, Sinclair DA, de Cabo RA, et al. Resveratrol delays age-related deterioration and mimics aspects of dietary restriction in mice on a standard diet. **Cell Metabolism**. 2008 Aug;8(2):157-68. PMID: 18599363

Oberdoerffer P, Michan S, Mostoslavsky R, Prolla TA, Sinclair DA, et al. SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. **Cell**. 2008 Nov 28;135(5):907-18. PMID: 19041753

Milne JC, Yang H, Sinclair DA, Elliott PJ, Westphal C, et al. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. **Nature**. 2007 450(7170):712-716. PMID: 18046409

Yang H, Lavu S, Sinclair DA., Nampt/PBEF/Visfatin: a regulator of mammalian health and longevity? **Experimental Gerontology**. 2006 Aug;41(8):718-26. Epub 2006 Jul 13. PMID: 16842957

Sinclair, DA, Guarente, LP. Unlocking the Secrets of Longevity Genes. **Scientific American**. 2006, **294**:48-51, 54-57.

BIO

Dr. Sinclair obtained a Bachelors of Science (Summa Cum Laude) at the University of New South Wales, Sydney, and was awarded the Australian Commonwealth Prize. In 1995, he received a Ph.D. in Molecular Genetics then worked as a postdoctoral researcher at M.I.T. with Leonard Guarente before being recruited in 1999 to Harvard Medical School.

Dr. Sinclair has received several additional awards, including a Helen Hay Whitney Postdoctoral Award, and a Special Fellowship from the Leukemia Society, a Ludwig Scholarship, a Harvard-Armenise Fellowship, an American Association for Aging Research Fellowship, and a Scholarship from the Ellison Medical Foundation. In 2003, one of his papers was considered a "Discovery of the Year" by Discover magazine. In 2004, he won the Genzyme Outstanding Achievement in Biomedical Science Award. In 2006 he was voted one of Australia's Top 10 scientists under 45, and co-authored the cover article of the March '06 issue of *Scientific American*. In 2004, Dr. Sinclair co-founded Sirtris Pharmaceuticals to develop drugs that harness the body's own defenses against diseases of aging. This was featured on the cover of Fortune magazine in Jan 2007.

One of Sinclair's most important discoveries was the elucidation of the key role of rDNA circles in determining the lifespan of yeast. At the time this received much media attention. As it turned out, this rDNA circle mechanism of aging is unique to a particular strain of yeast and is not observed either in other invertebrates or mammals. A more recent study by Sinclair, published in November 2006 by the journal *Nature,* indicated that resveratrol had life-extending activity in mice, fed an extremely high fat diet (60% fat). Preliminary results showed that these obese mice lived considerably shorter than normally fed mice and that obese mice treated with resveratrol lived an average of 15% longer than obese mice not provided the supplement. The question, however, of whether normally fed mice also show lifespan extension by resveratrol remained unanswered in that study.

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