Healthy Aging Initiative at The Scripps Research Institute
Toward Healthy Aging

Good health as we age remains the most critical aspect of maintaining quality of life—what some call our “healthspan.” Researchers at The Scripps Research Institute (TSRI) are working to find ways to make healthy aging a possibility within the grasp of us all.

“Old age ain't no place for sissies.”
—Bette Davis
Aging

My old eyes aren’t what they used to be - did you see where my ball went?

Yep... but I can’t remember!
An Urgent Challenge

- Aging results in impaired function of all organs and tissues.
- Currently, those over the age of 65 comprise the fastest growing segment of the world’s population:
  - By 2030, there will be about 72.1 million people 65 or older in the United States, more than twice their number in 2000.
  - 70% of these individuals will have at least two chronic diseases that rob them of quality of life.
- The annual cost of age-related diseases to the U.S. economy is $1.3 trillion, 75% of our country's health care costs.
- Discovering ways to prevent decline in physical and mental function during aging with a single type of treatment will help elderly individuals maintain independence.
- Targeting aging therapeutically will produce better health and economic returns than advances against specific diseases.
The Diseases of Aging

Aging is associated with a range of conditions, including:

- Coronary heart disease and stroke, which affects 18 million Americans.
- Cancer, which has a median age at diagnosis of 68 years.
- Neurodegeneration, including diseases such as Alzheimer’s and Parkinson’s and age-related cognitive decline.
- Vision and hearing loss.
- Osteoarthritis, which affects nearly half of all elderly people.
- Osteoporosis, which contributes to bone fractures with poor recovery leading to a loss of independence and increased risk of death.
- Frailty, which is caused by loss of muscle mass and strength contributing to increased incidence of falls.
- Altered metabolism and increased risk of type II diabetes.
Current Aging Research Efforts Are Inadequate

- Federal funding for basic biomedical research has declined by 30% in the last decade, which impedes innovative science.

- The National Institutes of Health (NIH), the primary source of basic biomedical research funding in the U.S., favors lower risk projects that impact medicine incrementally. Tackling aging is a high-risk, high-reward effort of imperative importance.

- Pharmaceutical companies rarely invest in the basic biomedical research necessary to search for novel diagnostic and therapeutic approaches.

- Unlike Europe and Australia, the U.S. FDA does not recognize aging as a disease, so federal research is not adequately directed to treatment of aging.
What We Know - As We Age

- Damage to cells, proteins and DNA accumulate.
- The damage elicits stress responses and chronic inflammation.
- Mitochondria, where energy is made in cells, become dysfunctional and produce oxygen radicals that elicit more damage.
- Stem cells become less able to repair tissues.
- Damaged cells change function (senescence) or die (apoptosis).
- Tissue homeostasis is lost, meaning balance cannot be restored once stressed.
- Hormone production and neuron signaling decline.
What We know - Improving Healthspan

Healthspan in model systems can be improved by:

- Eliminating damaged proteins.
- Eliminating senescent cells.
- Improving mitochondrial function.
- Replacing stem cells.
- Restoring hormone and neurotransmitter signaling.
- Improving insulin sensitivity.
The Healthy Aging Initiative at TSRI Offers a Solution

- Aging research demands a team approach since aging affects all organs and is the number one risk factor for numerous debilitating diseases.
- This interdisciplinary group of scientists will leverage the unique resources provided by TSRI, including cell-based screening, high-throughput drug screening facilities, medicinal chemistry and models of accelerated aging.
- Working together, the researchers will shed light on underlying causes of aging and novel therapeutic targets for extending healthspan.
- For optimal results, this initiative will bring together experts in numerous scientific disciplines (including neurodegeneration, ophthalmology, cancer biology and medicinal chemistry) and research areas (including proteins, DNA, signaling, mitochondria, stem cells, metabolism and drug screening).
Goals of the New Healthy Aging Initiative

The goals of the Healthy Aging Initiative are to:

- Discover novel therapeutic and preventative strategies to extend healthspan including:
  - Adult stem cells.
  - Biologics, e.g. positive factors secreted by the body's cells.
  - Small molecule drug candidates.
  - Nutraceuticals and natural products.
- Establish safety and efficacy of drug candidates using unique animal models and technologies.
- Develop early diagnostics (biomarkers) of unhealthy aging.
Why TSRI?

- TSRI has a track record of rapidly translating basic discoveries into new therapies, including treatments for arthritis, lupus, hemophilia and cancer.
- TSRI has a new department dedicated to basic research on aging—one of only a few in the nation focused on age-related metabolic changes.
- TSRI is unique in having top scientists in aging, metabolism, neuroscience, cancer and drug development who work together to develop novel approaches.
- TSRI is the leader at the intersection of biology and chemistry—ranked number one in the world in chemistry, number two in microbiology.
- More than 50 companies have been launched from TSRI discoveries.
- 30 pharmaceuticals are currently in clinical development.
Scientists at TSRI have made significant contributions to the field of aging, including, to name only a few:

- Identifying signaling pathways activated with aging that represent novel therapeutic targets.
- Defining pathways necessary for cognition that decline with aging.
- Identifying therapeutic targets to prevent onset of metabolic syndrome during aging.
- Developing models that age six times faster than normal to accelerate the pace of research.
- Developing model systems to test the effects of diet and drugs on aging.
- Pioneering mechanism-based approaches for treatment/prevention of osteoarthritis.
- Developing the use of adult stem cells for treating age-related diseases, including vision loss and muscle-wasting.
Key TSRI Scientists for Healthy Aging

- Hiroshi Asahara, MD, PhD
- Joel Buxbaum, MD
- Anutosh Chakraborty
- Bruno Conti, PhD
- Boaz Cook, PhD
- Sandra Encalada, PhD
- Eros Lazzerini Denchi, PhD
- Martin Friedlander, MD, PhD
- Larry Gerace, PhD
- Matt Gill, PhD
- John Griffin, PhD
- Patrick Griffin, PhD
- Wendy Havran, PhD
- William Ja, PhD
- Eric Johnson, PhD
- Shuji Kishi, MD, PhD
- Thomas Kodadek, PhD
- Anastasia Kralli, PhD
- Luke Leman, PhD
- Jeanne Loring, PhD
- Martin Lotz, MD
- Courtney Miller, PhD
- Richard Milner, PhD
- Ulrich Mueller, PhD
- Laura Niedernhofer, MD, PhD
- Takanori Otomo, PhD
- Michael Petrascheck
- Howard Petrie, PhD
- Steve Reed, PhD
- Paul Robbins, PhD
- Karsten Sauer, PhD
- Peter Schultz, PhD
- Roy Smith, PhD
- Supriya Srinivasan, PhD
- Andrew Su, PhD
- Peiqing Sun, PhD
- Mark Sundrud, PhD
- Seth Tomchik, PhD
- Eric Topol, MD
- Luke Wiseman, PhD
- Xiaohua Wu, PhD
- Xiang-Lei Yang, PhD

For faculty bios, see www.scripps.edu
Identifying the Most Innovative Research

Grants
- TSRI investigators submit requests for funding of innovative collaborative and multidisciplinary research focused on understanding the causes of aging and developing novel approaches for improving healthspan (see Appendix 1 for sample projects).
- Accepted projects receive funding for up to three years to generate sufficient traction to compete for federal funding or attract industry support.

Oversight
- A scientist-director, who is a leader in the field of aging and appointed by the president of TSRI, holds an endowed chair to provide scientific direction for the Healthy Aging Initiative.
- A grant review committee, including external experts in the field of aging, reviews proposals and provides funding recommendations.
- A Scientific Advisory Board, comprised of both internal and external experts in the field of aging, monitors progress and the clinical relevance of the research.

Yield
- The goal is to develop and initiate clinical testing of at least 10 new methods of treatment to improve healthspan and reduce polypharmacy in old age.
Funding

The Healthy Aging Initiative will be funded by contributions totaling $40 million:

- $3 million – Endows a chair for a scientific director, enabling him/her to devote significant effort and scientific creativity to the Healthy Aging Initiative.
- $7 million – Funds an endowment to ensure resources are available to pursue the most promising findings, with the goal of initiating multiple clinical trials within a decade.
- The remaining funds of $30 million will be drawn down by $3 million per year for 10 years:
  - $550,000 per year to support seven exceptional postdoctoral fellows conducting aging research; this will help recruit the most creative young scientists to the field of aging.
  - $2.45 million per year to fund the most meritorious collaborative projects; this will enable principal investigators and their labs to dedicate a considerable amount of their effort to aging research.
A Lasting Contribution

There are few questions more important than how and why we age, and how we can age more healthfully. Aging affects everyone. Your contributions will support world-class talent and fund innovative research projects devoted to finding new ways to ensure healthy aging. Add to that the federal and industry funding that will result from the discoveries from this Healthy Aging Initiative, and together we will have an enormous impact on our generation and generations to come.
Appendices
Appendix 1: Potential Healthy Aging Research Projects

- Developing drug candidates to protect the brain from age-related memory loss and dementia
- Finding therapeutic targets to prevent age-related changes in metabolism, fat distribution and muscle loss
- Identifying and characterizing novel hormones that prevent loss of brain function during aging
- Screening for and characterizing drug candidates to improve energy production by mitochondria, the powerhouses of the cell
- Exploring novel approaches to inhibiting the formation of protein aggregates in the brain to prevent age-related neurodegeneration, such as Alzheimer's and Parkinson's diseases
- Developing new approaches to treat common types of age-related vision loss using adult stem cells
- Screening for methods and drugs able to reverse aged stem cell dysfunction and improve tissue regeneration
- Analyzing the effect of telomere dysfunction on aging in different organs
Appendix 2: Drugs Developed from TSRI Discoveries

- **Humira®** for rheumatoid arthritis, plaque psoriasis, Crohn’s disease, ulcerative colitis and other inflammatory conditions
- **Benlysta®** for lupus, a debilitating autoimmune disease
- **Leustatin®** for hairy cell leukemia, an unusual cancer of the blood
- Purification of **Factor VIII** for the bleeding disorder hemophilia
- **Vyndaqel®** for transthyretin familial amyloid polyneuropathy (TTR-FAP), a rare, progressive and fatal neurodegenerative disease
- **Surfaxin®** for infant respiratory distress syndrome, a life-threatening condition affecting pre-term infants
- **Cyramza®** for gastric and non-small cell lung cancer
- **Unituxin™** for the childhood cancer neuroblastoma
Appendix 3: Companies from TSRI Technology or Faculty

2014
- Aldabra Biosciences
- Padlock Therapeutics
- Transplant Genomics, Inc.

2013
- Blackthorn Therapeutics Inc.
- iGenomiX
- Sirenas Marine Discovery
- Zebra Biologics

2012
- Abide Therapeutics
- Cypher Genomics
- Vesper Biologics

2011
- RQx Pharmaceuticals

2010
- Ember Therapeutics
- Epic Science

2009
- Receptos Pharma
- Protix, Inc.
- Zyngenia

2008
- aTyr Pharma
- Curna
- Eyecyte, Inc.

- Fate Therapeutics
- Proteostasis Therapeutics
- Sapphire Energy

2007
- Fabrus, Inc.
- Xcovery

2006
- Affinity Pharmaceuticals
- Calmune
- Viriome LLC
- Wittycell S.A.S.

2004
- Achaogen Inc.
- Motility, Inc.
- Prromosome
- Rincon Pharmaceuticals (acquired by Sapphire Energy)

2003
- Ambrx Inc.
- FoldRx Pharmaceuticals
- Prion Solutions (acquired by Chiron)

2002
- CovX Research (acquired by Pfizer)
- NanoRX (acquired by Adaptive Therapeutics)
- VAXDesign (acquired by Sanofi Pasteur)
Appendix 3 - continued

2001
- Kalypsys
- Phenomix
- Syrxx (acquired by Takeda)

2000
- ActivX Biosciences (acquired by Kyorin)
- Neurome

1999
- Geneformatics (merged with Structural Bioinformatics)
- Optimer Pharmaceuticals
- Prolifaron (acquired by Alexion Pharmaceuticals)

1997
- Epicyte (acquired by Biolex Therapeutics)

1996
- Digital Gene Technologies (purchased by Neurome)
- Discovery Labs (merged with Acute Therapeutics)
- Drug Abuse Sciences
- Sangamo Biosciences

1995
- PharMore
- Thrombosys

1994
- Apovia AG (formerly EVAX Technologies, originally Immune Complex Corp.)
- Applied Molecular Evolution (formerly Lxsys; acquired by Lilly, Inc.)
- CombiChem (acquired by Dupont-Merck Pharmaceutical and merged with Bristol-Myers Squibb)

1993
- Ciphergen Biosystems (acquired by Bio-Rad Laboratories)

1992
- Sequel Therapeutics (later acquired by Cytel, which was subsequently spun-out as Epimmune)

1989
- Avanir Pharmaceuticals (formerly Lidak)
- Corvas (acquired by Dendreon Corporation)
- UNASYN

1986
- MP Biomedicals (formerly Obiogene and Bio101)
- NeoMPS (formerly Multiple Peptide Systems)

1984
- Stratagene

1982
- Synbiotics

1981
- Quidel
## Appendix 3
### Therapeutic Pipeline

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