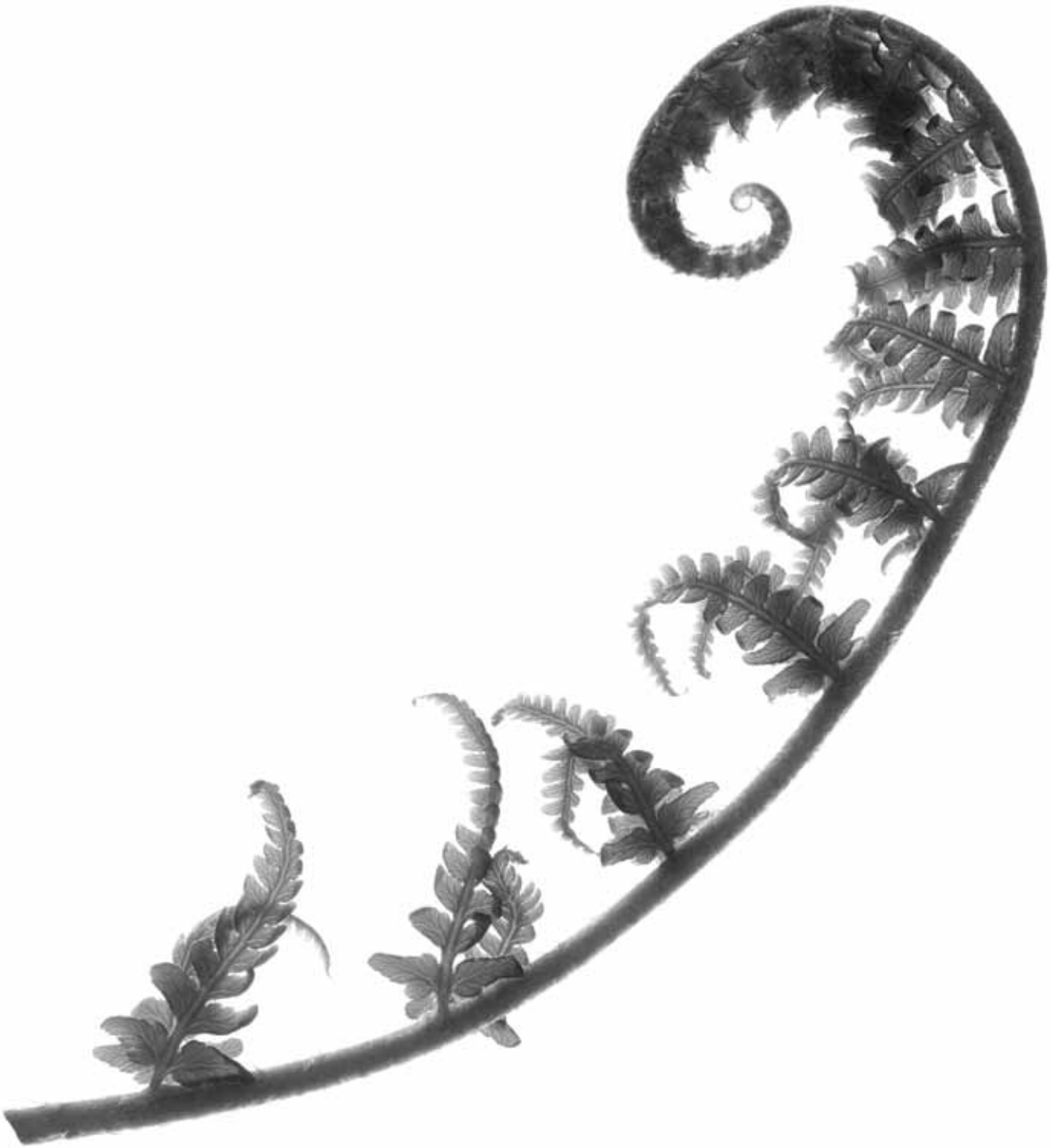


sens research foundation

foundation report
august 2014

a: 110 Pioneer Way, Suite J / Mountain View, CA 94041 / USA p: 650.336.1780 f: 650.336.1781 www.sens.org

transforming the way the world researches and treats age-related disease

sens research foundation

reimagine aging

We fund research at institutions around the world, and at our own Mountain View facility. Our research is integrated with wide-ranging outreach and education programs. Our goal is to see the emergence of an industry that will cure the diseases of aging, an industry based around what we call rejuvenation biotechnology.

Many things go wrong with aging bodies, but at the root of them all is the burden of decades of unrepaired damage to the cellular and molecular structures that make up the functional units of our tissues. Faced with the diseases and disabilities caused by this damage, today's medicine is too often reduced to crisis management in the emergency room, painfully harsh treatments for diseases such as cancer, or best efforts at palliative care.

PARKINSON'S CANCER SARCOPENIA
DIABETES MACULAR DEGENERATION
HORMONAL IMBALANCE PNEUMONIA
REDUCED SEX DRIVE OSTEOPOROSIS
ALZHEIMER'S STROKE EMPHYSEMA
INCONTINENCE OSTEOARTHRITIS
KIDNEY FAILURE HEART DISEASE

SENS Research Foundation is transforming the way the world researches and treats age-related disease.

In contrast, rejuvenation biotechnologies are targeted therapies that apply the principles of regenerative medicine to the entire scope of the damage of aging. These therapies will restore the normal functioning of our bodies' cells and essential biomolecules, returning aging tissues to health.

In other words, instead of merely slowing down the accumulation of aging damage in our tissues, rejuvenation biotechnologies will remove, repair, replace or render harmless our damaged cellular and molecular machinery, bringing back our bodies' youthful vigor.

Mike Kope Chief Executive Officer

In the 1950s the surfaces used for high-jump landings began to change from hard sawdust to soft foam rubber. On October 20th, 1968, a twenty-one year old from Portland, Oregon astonished the world by jumping head-first over the bar and landing safely on his back. 80,000 people in Mexico City watched Dick Fosbury set a new Olympic record and win high-jump gold that day. Within a few years Fosbury's style became by far the most popular technique in the sport.

There are times when the confluence of circumstance, ideas and people combine to create a moment of real change.

Over the past five years we at SENS Research Foundation have placed ourselves squarely at the forefront of research into rejuvenation biotechnologies with the potential to deliver real cures for age-related disease. We operate in an environment shaped by two decades of rapid progress in regenerative medicine, brought about by a huge investment in bench and translational research, and supported by political and regulatory changes.

It is against this background that we are now seeing the birth of a rejuvenation biotechnology industry. As I write, the Foundation is making final preparations for its first Rejuvenation Biotechnology conference. It will bring together representatives of academic, industrial, political, regulatory and financial institutions to explore how we can work together as a community, building a successful and durable industry.

Dick Fosbury must have known that his competitive advantage would be reduced as soon as others adopted his technique. At SENS Research Foundation, however, we have always recognized that the success of our mission is dependent on the success of others. We are a non-profit precisely because it allows us to work with multiple stakeholders, avoiding any agenda of self-protectionism. In many areas we are deeply involved with the key players, but in others we are beginning to see “organic growth” where shared ideas define a widening community, without any specific action on our part. It is hard, for example, to look at recent candidate therapies for Alzheimer’s Disease and not conceptualize them as damage-repair mechanisms, addressing multiple types of damage, and supported by early-stage testing and surrogate-outcome endpoints for clinical trials.

> “we are beginning to see ‘organic growth’ where shared ideas define a widening community”

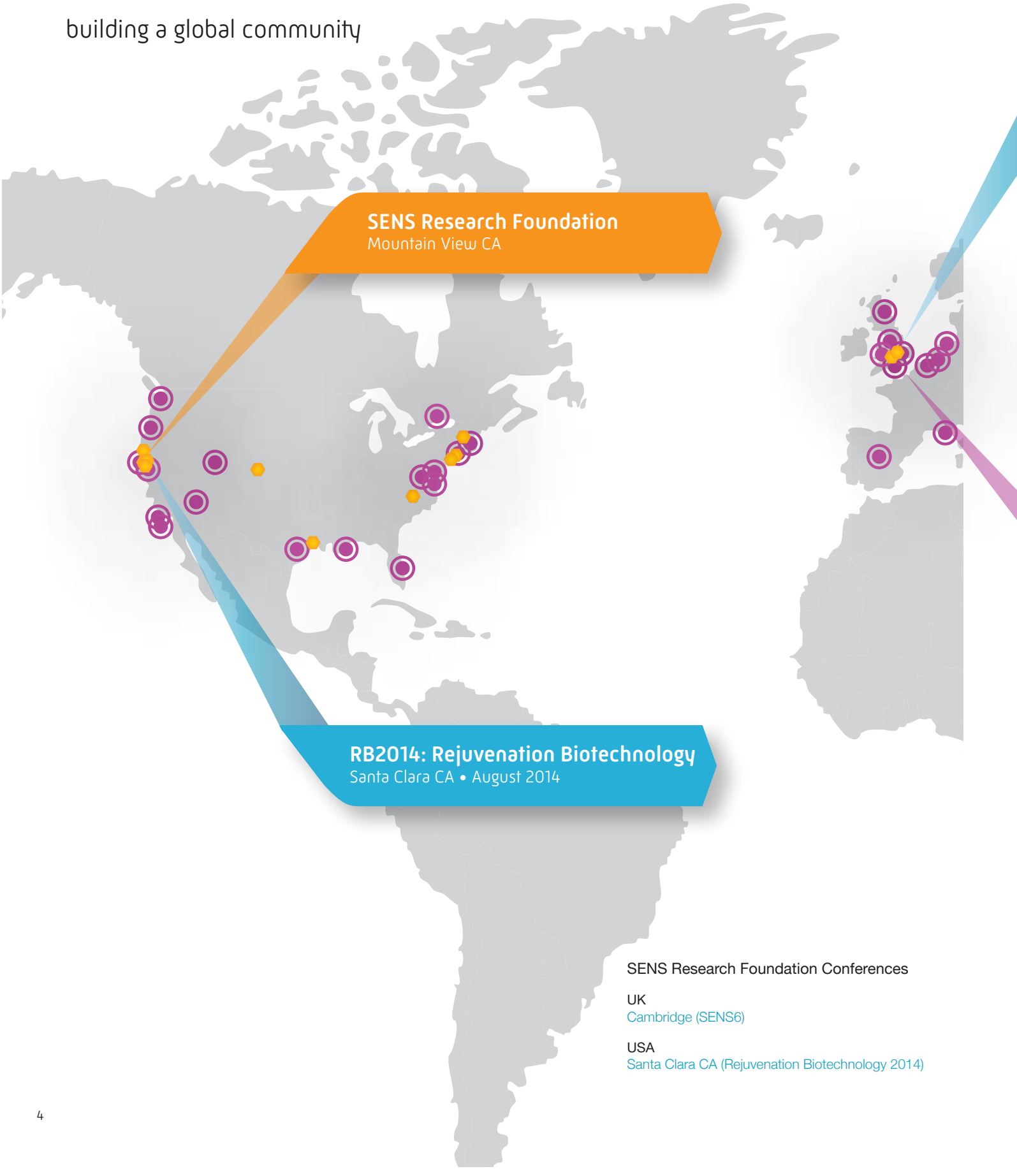
The pieces are in place for a moment of real change, but we must seize this opportunity. If we do not attract seed funding for new ventures, investment trends will move on to other technology sectors. If we fail to influence political and regulatory decisions, we will face insurmountable hurdles in translating research to real cures.

Our worst mistake would be to operate within narrowly-defined ‘silos’. We would lose the influence and analytical power of a close-knit community, born of a commonality of approach but seeking to cure a multiplicity of age-related diseases. That community, and the industry it will create, is far too important to let slip through our fingers.

Mike Kope
Chief Executive Officer

outreach

building a global community



SENS Research Foundation Conferences

UK
Cambridge (SENS6)

USA
Santa Clara CA (Rejuvenation Biotechnology 2014)

SENS6: Reimagine Aging
Queens' College, Cambridge • September 2013

G8 summit on dementia
London • December 2013
attended by Mike Kope, CEO

Research Locations

UK
Cambridge (University of Cambridge)
Oxford (University of Oxford, Centre for the Advancement of Sustainable Medical Innovation)

USA
Berkeley CA (University of California, Berkeley)
Boston MA (Brigham and Women's Hospital, Harvard University)
Bronx NY (Albert Einstein College of Medicine)
Denver CO (University of Denver, Frederick S. Pardee Center for International Futures)
Denver CO (University of Denver, Josef Korbel School of International Studies)
Houston TX (Rice University)
Houston TX (University of Texas-Houston Medical School)
Menlo Park CA (Applied StemCell, Inc.)
Mountain View CA (SENS Research Foundation Research Center)
New Haven CT (Yale University)
Novato CA (Buck Institute for Research on Aging)
Winston-Salem NC (Wake Forest Institute for Regenerative Medicine)

Speaking Engagements / Conference Attendence

Austria
Vienna (TEDxVienna)

Belgium
Brussels

Canada
Niagara Falls

France
Montpellier

Germany
Cologne
Eisenach
Rostock
Tübingen (Hilgendorf Lecture)

Hungary
Budapest (TEDxDanubia)

Israel
Beersheba (European Congress on Biogerontology)
Tel Aviv (Israel's National Science Day)

Netherlands
Amsterdam (TEDxAmsterdam)

Spain
Madrid

Switzerland
Zurich (St. Gallen Symposium)

UK
Cambridge (Cambridge Science Festival)
Edinburgh (Edinburgh International Science Festival)
Hereford
London (G8 Summit on dementia)
London (Royal Society of Medicine)
Manchester
Newcastle (British Science Festival)
Oxford
Salford (TEDxSalford)

USA
Baltimore MD
Bethesda MD (GSIG)
Boston MA
Fort Lauderdale FL
Laughlin NV
Long Beach CA (TED)
Los Angeles CA (TEDxLAMiracleMile)
Miami FL
New Orleans LA (Gerontological Society of America)
New York City NY (GF2045)
New York City NY (FasterCures)
Novato CA
Orlando FL (TEDxOrlando)
Portland OR
Salt Lake City UT
San Antonio TX (American Aging Association)
San Diego CA (World Stem Cell Summit)
San Francisco CA (Regenerative Medicine Foundation Conference)
Washington DC

outreach

social media
conferences
advocacy
presentations
speeches
newsletters
fundraising
documentaries
interviews

"building a wider community of informed and enthusiastic stakeholders"

Actor and comedian Billy Connolly visits SENS Research Foundation.

As the number of rejuvenation biotechnology professionals grows, it becomes increasingly important that we build a wider community of informed and enthusiastic stakeholders.

From its inception, SENS Research Foundation's outreach has been critical to the success of its mission. We focus on informing the general public, policy-makers, industry players and academia about the promise and challenges of the damage-repair approach to age-related disease. We not only provide information about the work of the Foundation itself, but also seek to coordinate the exchange of knowledge and experience amongst a larger community of interest.

STAFF FOCUS: Jerri Barrett

Jerri Barrett
Vice President of Outreach

Jerri earned her Bachelor of Arts in Biology from Mount Holyoke College and her MBA in Marketing from the William E. Simon School of Business at the University of Rochester. She was previously Chief Marketing Officer of Global Tech Women and Vice President of Marketing for the Anita Borg Institute for Women and Technology. Prior to entering the nonprofit world Jerri led marketing, business development and customer service for telecommunications startups. She joined SENS Research Foundation in 2013 with responsibility for fundraising, business development and marketing.

"I joined SENS Research Foundation because I recognized the incredible importance of the work we are doing. We have a strong, dedicated community of people who support us, and I'm excited to take the lead in building that support as the Foundation continues to grow."

OUTREACH HIGHLIGHTS

SENS6, the sixth of SENS Research Foundation's *SENS* conferences, was held in September 2013. World-renowned Harvard geneticist George Church delivered the keynote address. Presentations were given by James Appleby (Gerontological Society of America), Jan van Deursen (Mayo Clinic), Eric Lagasse (McGowan Institute), Todd Rider (MIT), Alan Russell (Carnegie Mellon), Robin Franklin (University of Cambridge), and many others. Over 262 attendees came from around the world.

The research activities of the SENS Research Foundation were highlighted by a wide range of leading media outlets including the BBC, Japanese Public Television, *The Huffington Post, Reddit,* the *Financial Times, BioWatch News, Paris Match, Wired* magazine, and Fox Business.

Time magazine sought out our Chief Science Officer, Dr. Aubrey de Grey, in September 2013 to write a piece for its website: *Google's Calico: the War on Aging has Truly Begun.*

Dr. de Grey delivered over 50 speaking engagements globally in 2013. These included an address as part of Israel's National Science Day, the plenary at the St. Gallen Symposium, a keynote address at the Regenerative Medicine Foundation Conference, and several TEDx talks.

RB2014 Rejuvenation Biotechnology

a SENS Research Foundation Conference

The continuing growth of research into the underlying causes of the diseases of aging brings with it the opportunity to build a rejuvenation biotechnology industry, an industry which builds on the strengths of regenerative medicine.

"As the key players in this new industry are realizing, the translation of this research into real products promises great rewards but comes with unique challenges. Overcoming these challenges will require the coordinated efforts of multiple stakeholders, including academic, industrial, political, regulatory and financial institutions."

Mike Kope, CEO, SENS Research Foundation

The Rejuvenation Biotechnology 2014 conference, which ran August 21st to 23rd in Santa Clara, CA, brought together these stakeholders to deepen their mutual understanding of the field, build communities of interest, and spur collaborations which will accelerate progress towards a mature industry.

Presentations and panel discussions included leaders in Alzheimer's, cardiovascular, and cancer research, together with key players in business and venture capital. These conference sessions combined scientific discussion with the wider considerations necessary for a successful pipeline from research to product.

"a successful pipeline from research to product"

George Church (Harvard and MIT), Peter Diamandis (XPRIZE and Human Longevity Inc.) and Jim O'Neill (Mithril Capital Management) gave keynote speeches.

research

Our Research Advisory Board is made up of 25 field-leading scientists who help guide our research strategy, assisting us in our mission to transform the way the world researches and treats the diseases of aging.

Pedro Alvarez, PhD
Chair, Department of Civil and Environmental Engineering, Rice University

Anthony Atala, MD
Director, Wake Forest Institute for Regenerative Medicine

Maria A. Blasco, PhD
Director, Molecular Oncology Programme, Spanish National Cancer Research Centre (CNIO)

Judith Campisi, PhD
Professor, Buck Institute for Research on Aging; Senior Scientist, Lawrence Berkeley National Laboratory

George Church, PhD
Professor, Department of Genetics, Harvard Medical School

Irina Conboy, PhD
Assistant Professor, Department of Bioengineering, UC Berkeley, and Berkeley Stem Cell Center

Marisol Corral-Debrinski
Research Director, Fondation Voir et Entendre, Institut de la Vision, Universite Pierre et Marie Curie

Leonid Gavrilov, PhD
Senior Research Scientist, Center on the Demography and Economics of Aging, NORC and the University of Chicago

S. Mitchell Harman, PhD
Director and President, Kronos Longevity Research Institute

William Haseltine, PhD
Chair, Haseltine Global Health

Daniel Kraft, MD
Executive Director, FutureMed, Singularity University

Chris Mason, PhD
Chair of Regenerative Medicine Bioprocessing, University College London

Stephen Minger, PhD
Global Director of R&D, Cell Technologies, GE Healthcare

Janko Nikolich-Žugich, MD, PhD
Chair, Department of Immunobiology and Co-Director, Center on Aging, University of Arizona

Graham Pawelec, PhD
Professor of Experimental Immunology, Tübingen University

Bruce Rittmann, PhD
Director, Swette Center for Environmental Biotechnology, Biodesign Institute, Arizona State University

Nadia Rosenthal, PhD
Director, Australian Regenerative Medicine Institute

Jerry Shay, PhD
Chair in Geriatrics, Department of Cell Biology, University of Texas Southwestern Medical Center

Vladimir Skulachev, ScD
Director, A.N. Belozersky Research Institute of Physico-Chemical Biology, Moscow State University

David Spiegel, PhD
Associate Professor of Chemistry, Yale University

Alexandra Stolzing, PhD
Group Leader, Stem Cell Biology and Regeneration, Fraunhofer Institute

Rudolph Tanzi, PhD
Director, Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease, Harvard University

Fyodor Urnov, PhD
Head, Advanced Genomics Technologies, Sangamo Biosciences; Associate Adjunct Professor, UC Berkeley

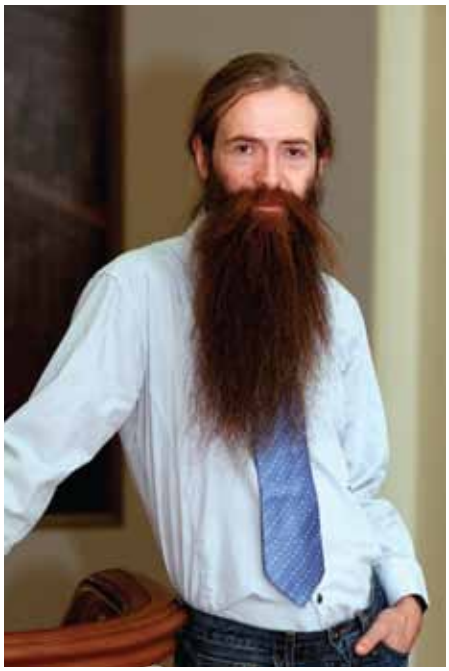
Jan Vijg, PhD
Chair, Department of Genetics, Albert Einstein College of Medicine

Michael West, PhD
CEO, Biotime Inc.

Looking back over what I have written in Foundation reports from the past years, I cannot but feel huge pride at the progress we have made.

In 2009 I wrote of my excitement at the challenges ahead and of my confidence in the then-new team with which I would face those challenges. By 2010 we had built on our initial portfolio of intra- and extramural research, and my contribution to that year's report focused on key research results, and the expansion of our scientific staff and Research Advisory Board. Over the next two years the Foundation continued to mature and I reflected on the changes I saw in my dealings with the media and in my other outreach activities. We had moved well beyond the point of needing to defend the intrinsic value of our work. Instead we were discussing how SENS Research Foundation could best go about its task of building a rejuvenation biotechnology industry.

Today, the Foundation continues to target its support at research projects which offer a balance of cost-effectiveness and the potential to deliver key proof-of-concept results, but which would otherwise suffer from a lack of funding. All our potential projects go through a rigorous selection process that includes reviews by our Research Development Committee, whose decisions are ratified by our Board of Directors. The result is a range of Foundation-funded projects at our own research facility and at world-renowned institutions, which place us in the heart of a growing rejuvenation biotechnology community.



Aubrey de Grey Chief Science Officer

> "This year is about an industry which is beginning to form, and the Foundation's long-held strategy to act as a catalyst for its formation."

This year is about that community. It is about an industry which is beginning to form, and the Foundation's long-held strategy to act as a catalyst for its formation. It is about an industry founded on scientific research, and capable of translating that research into real interventions against the diseases of aging.

As SENS Research Foundation's Chief Science Officer I find it extremely heartening that the excitement I felt in 2009 is as strong as ever.

Aubrey de Grey
Chief Science Officer

research

SENS Research Foundation supports a global research effort. Our own scientists are based in our Mountain View, California facility and we fund researchers at field-leading institutions around the world.

Albert Einstein College of Medicine / Applied StemCell, Inc. / Buck Institute for Research on Aging / Harvard University / Rice University / SENS Research Foundation Research Center / University of California, Berkeley / University of Cambridge / University of Denver / University of Oxford / University of Texas-Houston Medical School / Wake Forest Institute for Regenerative Medicine / Yale University

How do we fix an aging immune system?

As we age, our immune system becomes less effective at fighting off infections, making us increasingly vulnerable to disease. Our loss of immunity is caused by more than one type of underlying damage. SENS Research Foundation is funding research into two of these damage types.

The Shrinking Thymus

T cells, a critical component of our immune system, develop and mature in the thymus, a small organ just below the breastbone, level with the heart. The thymus grows during childhood but begins to shrink at the onset of puberty. This shrinkage continues throughout adult life, resulting in decreased T cell production, and a weakened immune system.

We are funding studies at Wake Forest Institute for Regenerative Medicine that are using tissue engineering techniques to regenerate the thymus. These are the first steps towards restoring the thymus to its optimal state, replenishing our bodies' supply of the T cells which are critical to a healthy immune system.

Cells Which Do Not Die

The cells of our body contain a genetic program that stops them from dividing when they sense certain abnormal conditions.This is a process called senescence. It protects us from the unlimited cell growth that could lead to cancer, or to an excess of fibrous tissue as our bodies heal wounds.

Unfortunately, once cells become senescent they do not die, but linger, ignoring signals for the programmed cell death that would normally remove them from the body. They continue to grow and often secrete molecules that lead to unwanted immune responses and changes in the behavior of surrounding cells. A key example is the secretion of inflammatory molecules that attract immune cells and cause them to go needlessly on the attack, disrupting our immune system in ways that make us vulnerable to frailty and disease.

We are funding a team at the Buck Institute for Research on Aging with the aim of identifying agents that could either selectively kill senescent cells, or interrupt the secretion of harmful molecules.

Our research is carefully targeted to deliver proof-of-concept results for rejuvenation biotechnologies. It underpins our outreach and education programs, and provides the preparatory steps for the translation of laboratory work into real cures for the diseases of aging.

The last section of this report gives technical details of our research portfolio and, of course, you can always find further information at sens.org.

As we age, we accumulate decades of unrepaired damage to the cellular and molecular structures of our bodies. The types of damage are few in number – we count seven, currently – but cause a great many diseases of aging, including cancer, Alzheimer's and atherosclerosis.

Rejuvenation biotechnologies target this underlying damage, restoring the normal functioning of our bodies' cells and essential biomolecules. As preventative interventions they halt the harmful accumulation of damage, stopping disease before it ever starts.

Damage and disease have a many-to-many relationship. That simply means that sometimes one type of damage can cause multiple diseases, and sometimes one disease is caused by multiple types of damage.

What links failing eyesight and failing hearts?

As our cells carry out their normal functions their contents become damaged or simply outlive their usefulness. One part of the cell, called the lysosome, acts like a cellular 'incinerator'. It uses enzymes to break down unwanted materials into manageable pieces. Sometimes, however, the cell's garbage is too tough to be broken down. When this happens the garbage builds up in the lysosome, eventually impairing the function of the cell itself. This one type of damage – the build-up of waste within the lysosome – is a key factor in several diseases of aging, including Alzheimer's and, as we discuss here, macular degeneration and heart disease.

The most direct solution is to supply the lysosome with new enzymes that can degrade the unmanageable waste.

The Leading Cause of Blindness Over the Age of 65

Age-related macular degeneration is the leading cause of blindness in people over the age of 65. It is caused or exacerbated by the presence of chemicals called bisretinoids in the cells in the retina of our eyes. The lysosomes of these cells cannot break down these chemicals fast enough to prevent their accumulation. Eventually, this leads to impaired vision.

Scientists at the SENS Research Foundation Research Center are testing enzymes for their ability to restore the health of cells loaded with toxic bisretinoids.

The Leading Cause of Heart Attacks and Stroke

Our immune system includes cells called macrophages, which protect our arteries by surrounding and 'swallowing' toxic materials. The lysosomes of these cells break down most of these toxins but some are beyond their ability. These include a particular toxin called 7KC, which is related to cholesterol. The accumulated 7KC in the macrophages causes them to sicken and die, and they build up in the artery walls. This is the basis of atherosclerosis, the plaques in our arteries that cause most age-related heart attacks and strokes.

We are funding a team at Rice University to investigate the identification and introduction of enzymes capable of breaking down this toxic 7KC. New plaques would be prevented from happening, and existing ones would be reduced, allowing the diseased artery to heal.

Hello.

You've probably noticed that these two pages look different from all the others. We realized that sometimes the best thing for a simple message is simplicity.

And the message on these pages is as simple as it is important.

Support us, please.

Your support will help SENS Research Foundation to do all it can do, every day, to ensure that rejuvenation biotechnologies end the inevitability of age-related disease.

We all know that million-dollar donations can fund entire projects, and greatly expand research facilities and education programs. Needless to say, we encourage and welcome that level of philanthropy. Flip ahead and you'll see some of our larger donations discussed on the finances page.

But turn to the last page and you can see our thank-you to over four hundred and fifty donors. Every single donation helps us, and we are grateful for every one. Every donation we receive, from a few dollars to a few million dollars, takes us a step closer to a key research result, a new SRF Scholar, a … Well, the report in your hands shows you what we do.

Matching grants often help to double or triple your donation. A regular, monthly donation gives us a solid baseline income for costs such as laboratory consumables and outreach materials. And it's not just that many small donations quickly start to add up. Putting them to use raises our profile and attracts even more funding.

Now is the time to seize our opportunity, an opportunity given to us by the coming together of opinion, the will to act, and the dedication of individuals working toward real cures. At the same time, we recognize that no other field of medicine faces the particular challenges that lie before us. SENS Research Foundation is unique in building its entire mission to overcome these challenges and create a thriving rejuvenation biotechnology industry.

We believe that our mission must succeed.

We know that our success requires your donation.

The message on these pages is simple but important.

Support SENS Research Foundation, please.

Because sometimes these things just need to be said. No elaborate design cues. No gentle hints. Just a polite, genuine and justified ‘ask’.

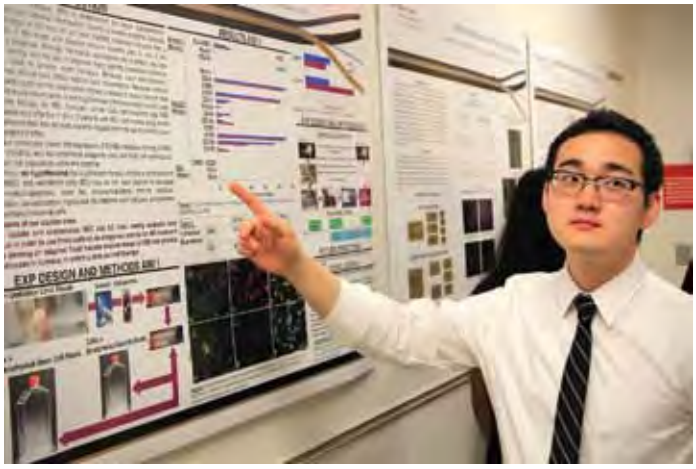
Find out more at sens.org/donate.

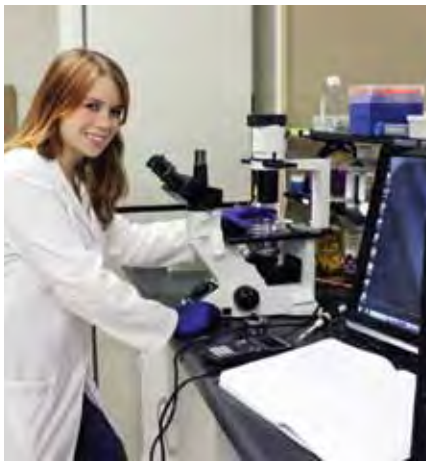
Thank you, on behalf of everyone at SENS Research Foundation.

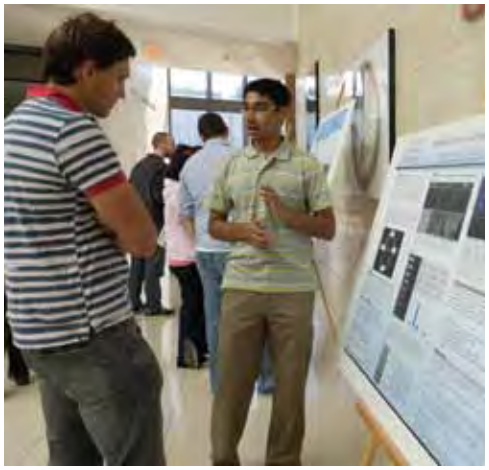
education

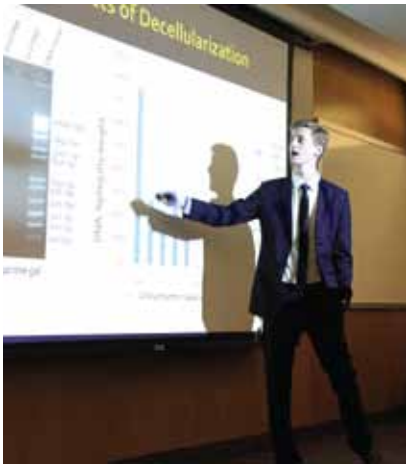
"a next-generation community of rejuvenation biotechnology professionals"

SENS Research Foundation is committed to building a next-generation community of rejuvenation biotechnology professionals. We believe that this community is critical to the successful development of damage-repair solutions to the diseases of aging and the translation of those solutions into effective medical interventions.









Clockwise from top left, SRF Scholars John Moon (Wake Forest Institute for Regenerative Medicine), Meredith Giblin (Buck Institute for Research on Aging), Daniel Bullock (Wake Forest Institute for Regenerative Medicine), Navneet Ramesh (SRF Research Center) and Jennie Sims (SRF Research Center).

Through our expanding education programs we provide an environment for students to learn from and contribute to a wide range of our research interests. Our financial support and learning resources enable students from a range of backgrounds to immerse themselves amongst leaders in the field, both at our own facilities and in other institutions around the world.

In addition to hands-on research experience, we aim to give our students ample opportunity to develop the interpersonal, communication, presentation and other skills that are critical components of being an effective scientific professional.

It is important to us that our students give back something to their host institutions. We work closely with our partners to develop projects that deliver meaningful contributions to their overall research goals.

Learn more about the SRF Education programs, at: **sens.org/education**

EDUCATION PROGRAMS

During the summer of 2013, our Summer Scholars Program placed sponsored students at our own research center and other institutions, including the Buck Institute for Research on Aging, SUNY Upstate Medical Center, the University of Cambridge, the Wake Forest Institute for Regenerative Medicine, and the Weizmann Institute. Many of these students presented their findings at the *SENS6: Reimagine Aging* conference, held at the University of Cambridge in August of that year.

SRF Summer Scholar Ethan Sarnosky presents at the SENS6 conference at the University of Cambridge.

We are delighted that we have recently expanded the Summer Scholars Program to include new host partners at the Harvard Stem Cell Institute and the Center for the Advancement of Sustainable Medical Innovation at University College London and the University of Oxford. All of the 2014 Summer Scholars were invited to present their findings at August's *Rejuvenation Biotechnology* conference.

Our new Undergraduate Research Scholars Program has been designed to deliver the educational benefits of our Summer Scholars Program extended across the entire academic year of select institutions.

We will continue to build on the success of our Scholars Programs, widening our reach to graduate students and postdoctoral fellows and increasing our contribution to the ever-growing community of professionals working in the field.

STUDENT PROFILE: Ethan Sarnosky

"I found my calling"

The time I spent as a SRF Summer Scholar was a defining period in my life. I learned a great deal and made great friends. Most importantly, I found my calling: the pursuit of research on aging. My immersion into the literature and research of aging, shared with other enthusiastic individuals, nurtured an interest that I have harbored for many years.

Thanks to the SRF Summer Scholars Program, I have focused my Ph.D. research on replicative aging in the budding yeast Saccharomyces cerevisiae. Ultimately, I hope to translate my findings into treatments for age-related degeneration. The excellent mentorship I received as a SRF Summer Scholar enhanced my ability to think and work as an independent researcher and will certainly help me to achieve this goal.

Ethan Sarnosky, Graduate Student
Yale University
former SRF Summer Scholar

"the SRF Summer Scholars Program is unique and outstanding"

The SRF Summer Scholars Program is unique and outstanding in several regards. SRF attracts and screens applicants for high excellence, motivation and long-term potential to contribute to the field. They have been enormously successful in selecting scholars that exceed the standards and success of other programs in which my laboratory has participated. The SRF scholars my laboratory has had the pleasure of hosting have been superb: very bright, eager, curious and hard-working. More strikingly, they have made material and substantial contributions to the success of very important projects.

Dr. Judith Campisi, Professor,
Buck Institute for Research on Aging
Principal Investigator,
SRF Summer Scholars Program

finances

SENS Research Foundation is committed to the highest standards of transparency and accountability in its management of the generous donations and grants received from its supporters. Our accounts for 2012 and 2013 have been prepared by Robert Lee and Associates, LLP. and independently audited by LMGW Certified Public Accountants, LLP.

It is a core value of the Foundation to ensure that the funds entrusted to us are expended in a manner which maximizes their contribution to our mission. We would like to thank all of the individuals and foundations without whom we would be unable to pursue that mission.

Without the support of the Thiel Foundation we could not have moved to a larger research center, with more of our own scientists performing key research, and more SENS Research Foundation Scholars joining us in Mountain View.

Without Jason Hope's donations we could not fund our partners at Yale University, and others, as they research ways to undo the stiffening and damage which protein cross-links do to our bodies as we age.

Without the grants we receive from SENS Foundation EU we could not fund core activities including our conferences, which are critical to building a wider community of interest.

Without the support of the Rose Winslow Foster Family Foundation we could not have expanded our education programs, allowing more students, in more institutions, to begin their own journeys as rejuvenation biotechnology experts.

FUNDING SOURCES

In 2012 SENS Research Foundation received a restricted grant from SENS Foundation EU, resulting from the settlement of the de Grey family trust. The total value of this grant, $13.1 million, was recorded as revenue in 2012 and added to our current assets as a pledge receivable.

The terms of the grant allow SENS Research Foundation to use a specified amount of the total grant each year on research, education and outreach. In 2013 we used $2,381,952 of the grant in the furtherance of our mission.

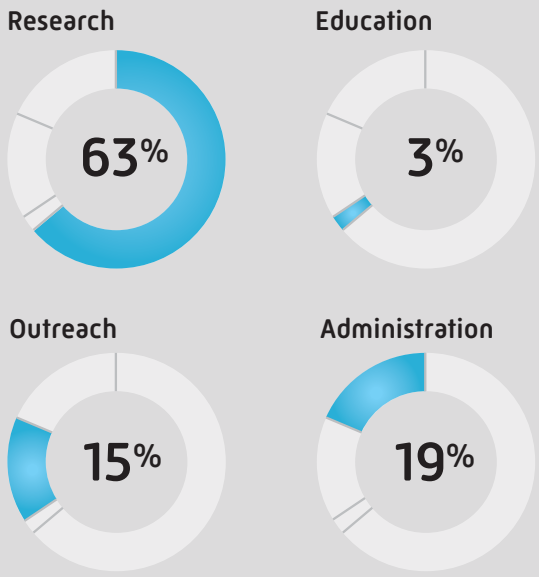
The generosity of our many supporters generated additional revenue of $1,721,904 in 2013.

2013 Revenue

Individual	$	787,785	46%
Corporate	$	72,500	4%
Grants	$	755,722	44%
Other	$	105,897	6%
TOTAL REVENUE	$	1,721,904	100%

2013 EXPENSES

Research	$	2,882,298	63%
Education	$	124,667	3%
Outreach	$	701,888	15%
Administration	$	842,867	19%
TOTAL EXPENSES	$	4,551,720	100%



"We cannot take for granted that the future will be better, and that means we need to work to create it today."

Peter Thiel and Blake Masters
Zero to One, September 2014

Research: Project by Project

SENS Research Foundation performs intramural research at our own facility in Mountain View, CA, and funds extramural work at top universities and institutes around the world. The following pages are designed for those who wish to read a more in-depth, technical summary of our current research projects. Projects are listed in alphabetical order of Principal Investigator (PI). Further details and updates are always available at sens.org/research.

Cell Therapy for the Intestinal Tract

Wake Forest Institute for Regenerative Medicine (WFIRM)

Graça Almeida-Porada (PI), Joana Boura, Connor Crowley[S], Abigail Hawkins[S], Saloomeh Mokhtari, John Moon[S], Christopher Porada (PI), Chris Rodman, Sarah Rudasill[V], Melisa Soland, Weihong Yin

At WFIRM, SENS Research Foundation is funding Dr. Graça Almeida-Porada's group in a project to restore intestinal structure and function. Dr. Almeida-Porada's central goal in this project is the development of a regenerative medicine approach to treating inflammatory bowel disease (IBD), an autoimmune disorder that devastates the cells lining the intestine.

Though IBD is not a disease of old age, therapies that repopulate the cells of the gut are critical to the development of a new generation of cancer therapies, as these therapies are likely to depopulate the stem cell reserves of several tissues (and replace the missing cells with fresh, cancer-protected stem cells). As a side-benefit to this research, regenerative therapies for the gut would benefit people receiving many existing cancer therapies that ravage intestinal tissue, such as radiation therapy during treatment for pelvic or abdominal cancer.

The WFIRM intestinal cell therapy researchers are developing a cell therapy based on the transplantation of modified *human mesenchymal stem cells* (hMSC), which have potent anti-inflammatory/ immunomodulatory effects to protect them from attack by the body's immune system. They used a model of IBD in which naïve CD4+ T-cells (a kind of immune cell) from healthy, normal mice are repeatedly transferred into mice with mutations preventing them from producing their own immune cells, resulting in inflammation and symptoms analogous to those observed in human IBD.

The WFIRM researchers then took the mice that developed IBD and divided them into four groups, three of which received experimental treatments while one group was kept as untreated controls. The research is still not complete, but so far it is apparent that mice in the treatment group that received hMSC modified to increase their anti-inflammatory potential suffered significantly less weight drop than any of the other groups. There is still significant room for improvement, however: another group of animals received cells with a combination of two therapeutic transgenes, and unfortunately one of those transgenes blocked the expression of the anti-inflammatory transgene, making the combination far less effective than cells with the anti-inflammatory transgene alone. The WFIRM group will now develop and test a new combination transgene to see if it works better still. Further analysis is also being performed to fully characterize and quantify the benefit of the different cell therapies on intestinal inflammation at the immunological and microscopic tissue level.

Clearance of Macrophage Oxysterols Driving Atherosclerosis

Rice University

Pedro Alvarez (PI), Jason Gaspar, Jacques Mathieu

The SENS Research Foundation-funded team at Rice University is working to tackle two intracellular aggregates driving age-related disease and dysfunction: *macrophage oxysterols* (the core lesion underlying heart disease, via *foam cell* formation) and *lipofuscin* (a potential factor in multiple degenerative aging processes).

Recognizing that existing methods of generating foam cells may be generating misleading results, the macrophage oxysterol team at Rice has developed a new approach in which macrophages are exposed to low-density lipoprotein ("bad") cholesterol loaded with the macrophage oxysterol 7KC. One harmful effect of 7KC exposure is *lysosomal membrane permeabilization* (LMP). The Rice team's work has included testing of compounds relevant to the removal of lipofuscin from cells, and early data suggest some reversal of overall LMP, raising the potential for the development of therapeutic candidates.The group is also refining and expanding the testing of microbial enzymes that degrade macrophage oxysterols, and testing ways to enhance their efflux.

In 2013, the Rice University research group also developed significant and reliable methods of producing,

s: indicates a SENS Research Foundation Scholar
v: indicates a volunteer researcher

quantifying, and imaging lipofuscin. Their protocol combines the free radical precursor H_2O_2 with a form of iron that catalyzes its breakdown into more reactive radicals, along with *leupeptin*, a bacterial enzyme that inhibits a wide range of protein-degrading enzymes. The team can now use these lipofuscin-laden cells to investigate ways to eliminate it.

Future work will focus on understanding how accumulated lipofuscin affects cells' expression of a number of genes involved in autophagy, mitochondrial uncoupling, and how treatments with selected compounds may ameliorate any observed abnormalities. As well, enzymes derived from different microorganisms will be cloned and targeted to the lysosomal membrane to look for candidates for lipofuscin-degrading rejuvenation biotechnology.

Chemistry Toward Cleavage of Advanced Glycation Crosslinks

University of Cambridge, Yale University

William Bains (PI), Sven Bulterijs, Cristian Draghici, Rhian Grainger, Chris Lowe (PI), Ariana Mirzarafie-Ahi[S], David Spiegel (PI), Ishik Ustok, Tina Wang

Advanced glycation end-products (AGEs) are a class of compounds that accumulate in our tissues as part of the degenerative aging process, and at even faster rates in conditions such as diabetes and cardiovascular disease. AGEs have been shown to induce inflammation, oxidative stress, and other pathological effects. Of particular concern are *crosslinks* that some AGEs form between adjacent structural proteins, reducing their ability to move freely and impairing tissue function. This is an especially great problem in arterial collagen, where AGE crosslinking contributes to the age-related rise in arterial stiffness and systolic hypertension, and thereby to the rising risk of stroke and kidney disease with age.

The Yale AGE team is working on new tools for the detection of AGEs and their precursors. The program will synthesize *glucosepane*, currently thought to be the single largest contributor to tissue AGE crosslinking, as well as its peptide adducts, its precursor MGH (methylglyoxal-derived hydroimidazolone modifications of arginine), and the understudied crosslink *pentosinane.* The team will then to use these compounds to develop new antibodies and reagents to enable rejuvenation research.

The Yale AGE team have recently developed the first-ever protocol for the synthesis of glucosepane. This route should also enable synthesis of all other isomers of glucosepane found *in vivo* — work that is currently ongoing, and that will give rise to a comprehensive set of reagents for the interrogation of the chemistry and biology of crosslinks, and for the development of crosslink-breaking rejuvenation biotechnology.

The Yale group is also making headway on the development and testing of reagents for detecting precursors to glucosepane and pentosinane. They have now produced the first antibodies that can detect specific AGEs when bound to proteins. Ongoing experiments in collaboration with SENS Research Foundation's Cambridge research center are focused on developing antibodies against CML (a common reactive glycation product) and MGH. These efforts will be expanded once glucosepane constructs are prepared. Piece by piece, the Yale AGE team is developing the tools we need to unravel the true extent of AGE-related pathology in our tissues, and to enable the development of highly effective AGE-breaking therapies.

Investigating the Nature of Academia-Industry Interaction in the Translation of Gene Therapies

University of Oxford, Centre for the Advancement of Sustainable Medical Innovation (CASMI)

Richard Barker (PI), Natasha Davie

SENS Research Foundation is committed to the rapid, global deployment of rejuvenation biotechnologies. This project supports that commitment by examining the relationship between academia and industry in early stage preclinical development. The first stage of the project analyzes the features of researchers and research at the University of Oxford which have led to support from industry. Surveys of industry partners aim to identify how these features are perceived, and why they influence the allocation of industry funds. This project also examines the mechanisms by which collaborations form in preclinical research.

The recent clinical success of gene therapy has increased the visibility of the field, attracting interest from industry. It faces commercialization challenges which differ from conventional therapeutics due to complex manufacturing procedures, record-breaking price tags, and the potential for truly personalized approaches. The second stage of the project considers the critical role of academia-industry collaboration in the translation of these novel high-risk, high-cost technologies. This collaboration is critical in bringing these therapies to patients. The project is surveying and interviewing members of both industry and academia who are engaged with gene therapy, as a case study for advanced medical research and development. The aim of this research is to identify how the barriers, motivations,

and outcomes of collaboration in gene therapy differ from those in more conventional pharmaceutical development.

Optimising the Quality and Effectiveness of Risk

University of Oxford, Centre for the Advancement of Sustainable Medical Innovations (CASMI)

Sir John Bell (PI), David Brindley, Andrew Carr (PI)

There is declining productivity in biomedical research and development in terms of new product approvals, in part due to an inherently risk averse regulatory pathway for novel healthcare innovations. This is despite major achievements and opportunities in novel technological platforms. The portfolio of risk:benefit methodologies have been applied inconsistently and often conflated with cost-effectiveness analyse. This yields results that do not effectively inform clinical practice or strategies for biomedical innovation.

This investigation aims to assess risk:benefit appraisal methodologies in the analysis of published randomised controlled trials for pre-licensure biomedical. *Internally* generated factors were gathered from published literature and practitioners in life-sciences and non life-science focused industries. These factors were prioritised through an *external* assessment with a multi-stakeholder group of life-sciences leaders. Utility weightings derived for externally verified factors were then used to assess the risk:benefit appraisal techniques surveyed.

The project has generated papers in a range of high impact, multi-disciplinary publications including *Nature Biotechnology* and *BMJ.*

Subsequently, an expanded expert-elicitation will be conducted, with simultaneous paralinguistic analyse to assess non-cognitive indicators of respondent uncertainty.

It is hoped that a robust and externally validated scorecard can be produced to assist stakeholders in selecting the appropriate risk:benefit methodology for their technologies.

Targeting the Senescence-Associated Secretory Phenotype

Buck Institute for Research on Aging

Judith Campisi (PI), Kevin Perrott

Our cells are equipped with machinery to detect signs of cancer or other forms of excessive cell growth, and to respond to the threat by shutting down cell division. These "senescent" cells also develop resistance to signals for *apoptosis* (cellular suicide) and secrete inflammatory signaling molecules and protein-degrading enzymes into their local environment. This last phenomenon is called the *senescence-associated secretory phenotype* (SASP). SASP is thought to play a role in the chronic inflammation that is widespread in aging tissues, which in turn promotes the progression and propagation of age-related frailty and the many diseases of aging. Additionally, SASP is believed to make the local tissue environment more vulnerable to the spread of cancer into and out of the surrounding tissues.

With SENS Research Foundation funding, the Buck Institute SASP project has been screening small molecules for their effects on fibroblasts (a kind of skin cell) that have been rendered senescent by ionizing radiation, with the aim of identifying agents that could either selectively kill senescent cells, or interrupt the SASP and prevent its harmful effects. Such agents could potentially ameliorate diseases and disabilities of aging that are driven by the SASP.

Previously, the team showed that treatment with the naturally-occurring compound *apigenin* decreased the production of the representative SASP component *interleukin-6* (IL-6) by such senesced fibroblasts. Some of this effect could be explained via a 50% reduction in the activity of *nuclear factor-κB* (NFκB), a transcription factor that helps to regulate the expression of IL-6 by but not all. The SASP group is testing the potential involvement of CEBP and AP1, transcription factors involved in many inflammatory pathways. Additionally, they have developed evidence that apigenin interrupts a self-perpetuating feedback loop that enforces SASP, possibly by acting on IRAK1 and IKBA. More definitive tests are now underway.

Maximally-Modifiable Mouse

Applied StemCell, Inc., Menlo Park, CA

Ruby Yanru Chen-Tsai (PI), Jiabin Qiu, Ivy Zhang, Qi Zheng

The goal of the Maximally Modifiable Mouse (MMM) project is to generate mouse models allowing easy genetic modification at any time point during the mouse's lifespan, thus hastening the process of testing potential interventions against age-related disease. The MMM project aims to generate a new line of transgenic mice with "docking sites" for a high-precision targeting system for gene insertion that are not typically found in

mammals engineered into their genomes. The docking site will then be ready for the insertion of new therapeutic transgenes at any time during the mice's lifespan, allowing for the testing of candidate therapies. SENS Research Foundation is funding the team of experienced mouse genome engineers at Applied StemCell to generate two mouse models, each containing the docking site in a different site in the mouse genome: H11 (on mouse chromosome 11) or Rosa26 (on mouse chromosome 6).

The MMM team have successfully generated a strain with the docking site positioned at H11, using a standard method used to engineer genes into embryonic stem (ES) cells. ES clones that screened positive for the engineered docking sites were microinjected into early mouse embryos to generate mice that were then further bred to establish the docking site into the germline. PCR technology was then used to identify embryos with twinned copies of the allele on the gene.

To make the Rosa26-MMM, the team took a new approach, using the powerful new CRISPR/Cas9 gene editing technology (to whose development SENS Research Foundation Research Advisory Board member George Church has made key contributions). This technology advantageously enables gene modification without requiring the ES cell step, allowing the MMM scientists to make the Rosa26 MMM faster and in a more desirable mouse strain. The MMM team have obtained 33 pups via this method, and one of them appears to be positive for the Bxb1 docking site. They are currently confirming that the insertion is at the Rosa26 locus, and performing additional microinjections to create more Rosa26-MMM.

Rejuvenation of the Systemic Environment

University of California, Berkeley

Irina Conboy (PI), Michael Conboy (PI), Keith Causey, Justin Rebo

The experimental technique of *heterochronic parabiosis*, in which the circulation of an aged animal is joined to that of a young one, exposes the aged organism's tissues to a youthful systemic environment (and vice-versa). Many studies have confirmed that parabiosis with a young animal partially rejuvenates many aspects of cell and tissue function in aged organisms, including the regenerative capacity of local specialized stem cells. As the body undergoes aging, this research provides a useful means of studying the systemic environment as the interface for the application of multiple potential rejuvenation interventions.

The UC Berkeley systemic environment team is exploring the influence of the systemic environment on aging processes using a novel computer-controlled technological platform and specialized hardware made from off-the-shelf and custom 3-D printed parts. This platform enables the group to easily and safely extract blood from small animals, process what they extract in any of several ways, and either return it to the original animal or exchange it with that of an oppositely-aged animal. The Berkeley group's parabiosis device will overcome the inefficiency and animal-stress hurdles typical of existing protocols by working primarily as a *"heterochronic plasmapheresis"* system. Plasma contains the soluble signaling molecules of interest in parabiosis experiments, and the use of plasma instead of whole blood enables scientists to disentangle the effects of an old animal having access to the young animal's blood cells and organs from the effects of the factors found circulating in the systemic environment.

The plasma-exchange module was successfully used for the first plasma separation in December 2013, and the team is currently running quality-control tests prior to further applications. Moving forward, the UC Berkeley systemic environment team is recapitulating serum experiments performed previously - by Dr. Conboy and other researchers - on muscle and brain cells, to determine the need for platelets in these effects and modify the device accordingly. Additionally, the team will perform *in vivo* imaging of aged mice exposed continuously to young plasma using one of two advanced new imaging platforms to ongoingly monitor the effects of interventions, giving scientists the first opportunity to witness tissues being *progressively* rejuvenated *in vivo*. And along with their mouse work, the Berkeley group will be performing a pilot experiment examining proteins present in plasma from young and old humans, to explore translatability and identify important components of the plasma that either help or impede rejuvenation of old organs and systems.

Clearance of RPE Aggregates Driving Macular Degeneration

SENS Research Foundation Research Center

Ghezal Beliakoff, Ehud Goldin (PI), Anuj Kudva[S], Hana Lejmi[V], Karina Liker[S]

Our cells contain vesicles called *lysosomes* that use enzymes to recycle cellular wastes. Some stubborn wastes, however, are beyond the lysosome's evolved capacity to break down. These products accumulate in the cell's main body or in the lysosome, and may even make their way outside the cell. In the eye, extracellular garbage called *drusen* gradually accumulates in a

portion of the retina called the *macula.* Drusen accumulation is an indicator for *age-related macular degeneration* (ARMD), the leading cause of blindness in persons over the age of 65. Although the causal relationships are not yet established, it seems clear that the accumulation of drusen, the death of macular photoreceptors, and the progression to ARMD and blindness are linked together by the gradual failure of the *Retinal Pigment Epithelial* (RPE) cells responsible for maintaining macular photoreceptors. In turn, the failure of RPE is driven by their inability to degrade their accumulated burden of cellular wastes.

The SRF-RC RPE aggregate team is working to identify enzymes capable of degrading recalcitrant wastes and restoring lysosomal activity in RPE cells, which could enable ongoing maintenance of macular photoreceptors and prevent the appearance of drusen and the development of ARMD. They have identified a human enzyme codenamed *SENS20* which has the capacity to break down the toxic vitamin A metabolite *A2E* (an important RPE waste product) *in vitro* and reduce the content of A2E in cultured RPE cells. The team has also developed a novel method for quantifying A2E using HPLC technology, as well as methods for quantifying the reduction in A2E in cells using flow cytometry (FACS) and automatic microscopy, and for assessing the toxicity of A2E and its breakdown products in cells. To ensure that the results of ongoing experiments have maximum biomedical significance, the RPE aggregate group is genetically manipulating cultured RPE cells to "age" them, thus providing a better model for the aged eye. This process will indicate whether the enzyme may benefit people who have already undergone significant aging. Positive results in this study will provide the basis for identifying endpoints for animal studies to correct retinal degeneration, and further into human studies.

Opportunities and Challenges of a World with Negligible Senescence

Frederick S. Pardee Center for International Futures, Josef Korbel School of International Studies, University of Denver

Barry B. Hughes (PI), Randall Kuhn (PI), Eli S. Margolese-Malin, Dale S. Rothman, José R. Solórzano

Along with our research into finding cures for diseases of aging, SENS Research Foundation is dedicated to investing in the creation of a robust rejuvenation biotechnology industry. Toward this end, we are funding a University of Denver project that utilizes the Pardee Center's International Futures (IFs) long-term, multi issue, global forecasting system as its central tool to explore the wider ramifications of our work.

The Denver group aims to analyze the implications of a rapid shift toward a much larger population of longer-living individuals who do not suffer the health decline and common maladies of aging. In particular, their analysis considers a scenario entailing rapid deployment and distribution of effective rejuvenation biotechnologies over a 20 year period. The International Futures (IFs) system facilitates such analysis by uniquely integrating demographic, economic, human development (education and health), physical (agriculture, energy, and infrastructure) and sociopolitical data into their models, representing 186 countries with annual forecasts from 2010 through 2100.

Tissue-Engineered Thymus

Wake Forest Institute for Regenerative Medicine (WFIRM)

Dan Bullock[S], Silvia Gutierrez, John Jackson (PI), Ashis Mondal, Julie Marco[S], Sook Won Ryu, Shruti Singh[S]

The *thymus gland* is an organ that produces *T-cells* and supports other kinds of immune cells, bolstering our immune systems against illness. Unfortunately, the thymus atrophies as part of degenerative aging, resulting in a loss of the ability to produce new T-cells, which in turn leads to increasing vulnerability to infectious disease as we age.

The thymus engineering group at WFIRM is working to produce new thymus tissue with a rejuvenated ability to produce T-cells, helping to restore the immune system's youthful strength. The scientists are using the powerful "decellularized scaffold" approach. Researchers begin with a donor organ and strip it of its original cells, leaving a "scaffold" of extracellular matrix (ECM) onto which cells derived from the transplant recipient can be seeded. Because the final organ is populated with the recipient's own cells, it is expected to be treated as "self" by the patient's immune system instead of being attacked as "foreign."

The WFIRM thymus engineers have successfully generated decellularized thymus scaffolds from rodents as well as from pigs. ECM structural proteins collagen and laminin of pig-derived thymus scaffolds are were fully preserved after decellularization, although its fibronectin content was reduced.

The scientists have also shown that these scaffolds retain signaling molecules capable of guiding and supporting the growth of incoming seeding cells, and that factors in these scaffolds improve the *in vitro* expansion and maturation of *thymic epithelial cells*, which are critical players in the "education" of T-cell

precursors in the thymus. In upcoming work, the WFIRM thymus engineering team will re-seed intact mouse thymus scaffolds with these thymic epithelial cells, along with bone marrow stem cells to supply the T-cell progenitors. These tissue-engineered constructs will be followed to characterize their ability to produce T-cells, and ultimately transplanted into mice lacking their own thymus glands to see if they can indeed take the place of the native organ and establish T-cell production *in vivo*.

Allotopic Expression of Mitochondrially-Encoded Proteins

SENS Research Foundation Research Center

Amutha Boominathan, Matthew O'Connor (PI), Alexandra Crampton[S], Anagha Kelkar-Sane[V], Kathleen Powers, Shon Vanhoozer, Jayanthi Vengalam, Summer Wang[S]

Free radicals derived from our cells' energy-producing mitochondria can mutate this organelle's DNA. This in turn can lead to disabling *deletions* of large stretches of the mitochondrial genome. These deletion mutations prevent the mitochondria from building various subunits of the *electron transport chain,* by which mitochondria generate most cellular energy. The accumulation of cells harboring deletion-mutation-containing mitochondria is a significant consequence of aging, and is implicated in age-related disease.

The SRF-RC mitochondrial mutations team is working to develop engineered mitochondrial genes that could be stored safely in the cell's nucleus and function as "backup copies" for cells whose mitochondria harbor deletion mutations. They are currently working to realize the potential of a new method for targeting these engineered nuclear-encoded genes to the mitochondria, and to optimize the precision of this targeting. Ultimately the mitochondrial mutations group aims to demonstrate functional rescue of these cells through this "allotopic expression" technique, both by restricting their fuel source to galactose (which kills cells lacking functional electron transport chains) and through direct measurement of the metabolism of cells that have been rescued from failure.

In principle, a gene therapy based on this technology could be used both to prevent and to correct the effects of mitochondrial mutations. A therapy of this nature would have the potential to prevent or cure various rare but serious inherited conditions and diseases of aging.

In 2013, the SRF-RC mitochondrial mutations group helped to create two new experimentally-important cell lines which are 100% null for two mitochondrially-encoded genes: ATP8 and CYB. These new tools mean that the team can now test their engineered genes in mitochondria that cannot generate the corresponding proteins on their own. They have also successfully targeted CYB mRNA to the surface of mitochondria. The mitochondrial mutations team is continuing to test other means of localizing mRNA and improving mitochondrial import, as well as improving their existing system to optimize delivery of protein to the electron transport chain complexes.

Diagnostic and Therapeutic Antibodies against Transthyretin Amyloids

University of Texas-Houston Medical School (UTHMS); Harvard University

Brian O'Nuallain (PI), Sudhir Paul (PI), Stephanie A. Planque

A key driver of age-associated ill health is a form of molecular damage in which certain proteins in the body lose their native structure and bind together with one another, forming harmful aggregates. The most well-known example is beta-amyloid (Aβ), the major driver of Alzheimer's disease (AD), but there are at least 27 other disorders driven by amyloids. One less-known amyloid disease is *senile systemic amyloidosis* (SSA), a disorder caused by aggregation of a hormone-transporter protein called *transthyretin* (TTR). These TTR aggregates accumulate primarily in the heart, where they disrupt the organ's structure and impair its function. SSA first becomes prevalent in people in their fifties, and rises rapidly as they reach their eighties and beyond.

With SENS Research Foundation support, the UTHMS TTR amyloid team is working to develop engineered catalytic antibodies ("catabodies") targeting misfolded TTR as a rejuvenation biotechnology for prevention and treatment of TTR amyloidosis. These "catabodies" combine the specificity of conventional antibodies with the catalytic power of enzymes, giving a single catabody molecule the ability to permanently degrade large amounts of target amyloid.

The UTHMS TTR amyloid team has already gone a substantial distance toward proof-of-concept of this approach in animal models of Alzheimer's disease. The team is applying the same methods to identify and improve the native catabodies targeting transthyretin (TTR) amyloid to develop therapies to rejuvenate the amyloid-impaired SSA heart. In collaboration with Drs. Robert Kyle and Angela Dispenzieri of the Mayo Clinic, the UTHMS TTR amyloid team is studying the hypothesis that a failure of innate and adaptive catabody production may accelerate or signal the onset of SSA, whereas maintenance of this innate immunity may hold off the disease.

In parallel to the UTMS TTR team, the TTR amyloid

team at Harvard, led by Dr. Brian O'Nuallain, has developed monoclonal IgG-class antibodies that bind TTR amyloid by immunizing mice with misfolded TTR for early detection of amyloidosis.

Identification of the Genetic Basis of ALT

SENS Research Foundation Research Center

Manali Aggrawal[V], David Halvorsen, Thomas Hunt (Thiel Fellow), Navneet Ramesh[S], Haroldo Silva (PI), Avni Singhal[V], Christine Wu[S]

As cancer cells replicate, they quickly wear down their *telomeres* — short "caps" of protective non-protein-making DNA that shield their genes and allow them to keep reproducing themselves. To survive, all cancers must develop a mechanism to re-lengthen their telomeres. Many cancers do this by hijacking the genes involved in regulation of the enzyme *telomerase,* which are only supposed to be expressed by certain specific cell types under very tight control. 10-15% of cancers, meanwhile, employ a telomerase-independent mechanism known as *alternative lengthening of telomeres* (ALT). One hallmark of ALT activity is *APB* (ALT-associated Promyelocytic leukemia (PML) nuclear Bodies). The established automated APB assay requires complex three-dimensional confocal image acquisition followed by supercomputer analysis. The SRF-RC ALT team has developed an improved, high-speed version of this assay that uses a much less expensive microscope to take multiple two-dimensional "image slices" of the sample and then process the slices into a composite 2-D image projection using software that can run on a typical desktop computer. Early testing has successfully reproduced key published data at a speed 5-6 times faster than original assays were capable of. The SRF-RC ALT team is currently validating their platform by screening thousands of cells for the effects of chemicals previously reported to modulate APB levels.

A second cellular hallmark of ALT cells is that they generate extra-chromosomal telomeric repeats, including partially double-stranded C-rich (CCCTAA)n circles of DNA, or *C-circles* for short. The SRF-RC ALT team has developed a fast (8 hour), high-throughput version of the established C-circle assay that adapts established fluorescence-based approaches previously validated for detection of telomerase activity, to quantitatively measure C-circles in human ALT cells from multi-well plates. The new assay also works across a wider range of C-circle values than the older methods, without loss of sensitivity. The team is currently validating their assay using small molecules and other treatments previously established to modulate ALT activity. In 2014, the SRF-RC ALT group will use the new, faster ALT assays to hunt for genes that might be involved in the ALT machinery, and screen libraries of drugs to identify new candidate treatments that would shut down ALT cancer cells.

Epimutations: Targets or Bystanders for Rejuvenation Biotechnology?

Albert Einstein College of Medicine

Kemal Akman, Silvia Gravina, Achim Tresch, Jan Vijg (PI)

Just as our genes can suffer *mutations* that damage the instructions cells use to make their encoded proteins, so too our cells can suffer damage to the *"epigenetic"* structures that help to regulate whether a particular gene is turned on or off in a particular kind of cell at a particular time. These *epimutations* therefore cause cells to turn the expression of particular genes on or off aberrantly. The Albert Einstein College of Medicine (AECOM) epimutations team is investigating the possibility that epimutations could be contributing to age-related disease. Numerous cells in a tissue could, in this scenario, be engaging in aberrant gene expression, leading over time to tissue dysfunction and eventual pathology.

A major focus of the AECOM epimutations group has been the development, application, and optimization of single-cell epimutation quantification assays. Unlike adaptive changes in epigenetic states, which often happen systematically across a tissue, each true epimutation occurs at a different, random location in each individual cell that suffers one, meaning that each particular epimutation will be individually rare, even if large numbers of individual cells within a tissue each suffers such epimutations. In short, only by looking at each cell's epimutation burden individually can we get a clear picture of the real load of cells damaged by epimutations in a tissue with age.

With SENS Research Foundation funding, the epimutations team at AECOM have adapted an established method for evaluating one epigenetic control structure (DNA methylation) at the level of the base pair for use in single-cell analysis. The team has improved their single-cell DNA methylation state detection procedure and performed testing, validation, and optimization. Working in collaboration with Dr. Achim Tresh and Mr. Kemal Akman at the University of Munich, the group developed bioinformatics methods to analyze the enormous volumes of data generated by their new experimental tools, and have begun to use their single-cell assay to compare epimutation loads in the livers and brains of aging mice. As an indirect measure of the possible harmful effects of non-cancer epimutations, the team have started to look at ways to incorporate animal models exhibiting accelerated epimutation formation into their research.

Jean-Pierre Abello Daniel Abraham Michael Achey Georgios Adamopoulos Jonathan Adams Wayne Addison Anchit Agarwal Arif Al Abdulsalam Fabio Albertario Heinz-Jürgen Albrecht Keith Allison Orr Alroy Jerome Altmetz Maria Vera Altschuler American Endowment Program Matthias Andre Cláudio Angelo Michael Angelo Alan Antholz Tom Appleqvist Reeve Armstrong Stefan Asbeck Samantha Atkins James Atkinson Jan Babiuch-Hall Mikael Baez Patryk Bajer Galt Barber Nadia Barbu Bats & Bytes Michael Beasley Perry Beeson Ingo Beineke Jeff Bencin Elliot Bergman Ryan Berkani Joao Tristan Bettencourt Abhishek Bharadwaj David Biasi Parsel Bilir Biodiversity Biogerontology Research Foundation Mike Blakeslee Thomas Blakeslee Rolf Böhme Jeff Bollen Izabelle BorgNilsson Carl Borrowman Claudio

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