

SENSResearch Foundation

has a unique mission: to ensure the development of cures which repair the underlying cellular and molecular damage of aging. This document, our **2015 Report**, demonstrates our commitment to **delivering on the promise** of that mission, and to **meeting the challenges** facing the rapidly emerging rejuvenation biotechnology field. Our  **research** program delivers key proof-of-concept results. Our  **education** program prepares the first generation of rejuvenation biotechnology professionals. Our  **outreach** program widens and connects our community. Our **Rejuvenation Biotechnology conferences** unite stakeholders from academic, industrial, political, regulatory and financial institutions. Together, we are **transforming the way the world researches and treats age-related disease.**

sens research foundation



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FOUNDATION LEADERSHIP

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Chief Executive Officer

Dr. Aubrey de Grey
Chief Science Officer

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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. We are committed to playing a pivotal role within the industry that will cure the diseases of aging, an industry based around what is called “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 KIDNEY FAILURE
CANCER MACULAR DEGENERATION
HORMONAL IMBALANCE STROKE
OSTEOPOROSIS INCONTINENCE
ALZHEIMER’S HEART DISEASE
SARCOPENIA PNEUMONIA DIABETES
EMPHYSEMA OSTEOARTHRITIS

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, preventing age-related disease.

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, returning aging tissues to health.



Mike Kope Chief Executive Officer

As I write, my grandmother is being kept alive by medical intervention. She is ninety-seven, and very sick. A pacemaker forces her ailing heart to beat. Her muscles are withered from sarcopenia, her bones are brittle from osteoporosis. She can scarcely leave her bed. Alzheimer's has been devastating: she cannot remember the family and friends who visit her every day, and so she lives in loneliness, even though surrounded by those who love her. Medical costs mount, savings are quickly being exhausted, and there is little more that can be done.

Her suffering is far from unique. It is a depressing reality of the world in which we live.

Every year sees the announcement of new and ever-more sophisticated ways to treat disease. But when it comes to the diseases of aging, the world needs equally sophisticated ways to preserve health, to prevent these diseases from ever taking hold. We *can* reimagine how we treat age-related disease. As a society, we *must*.

So now, imagine a world free from sarcopenia, osteoporosis, heart disease and Alzheimer's.

SENS Research Foundation is working to create that world.

**"We can reimagine how we treat age-related disease.
As a society, we must."**

In the following pages you will find much discussion of the scientific, political, regulatory, and financial challenges we face. The rejuvenation biotechnology community is increasingly well-placed to overcome these challenges. In return, rejuvenation biotechnologies offer the chance of a new global industry and a desperately-needed reduction in healthcare costs for both governments and individuals.

This year, however, my greatest source of encouragement and determination is far more personal. Against my grandmother's inexorable decline I set the knowledge that we are on a journey to end the suffering of age-related disease for countless others.

A handwritten signature in black ink, appearing to read 'Mike Kope', written in a cursive style.

Mike Kope
Chief Executive Officer

community

creating partnerships and collaborations to accelerate research progress and deliver translational pathways

SENS Research Foundation's proof-of-concept research has delivered real opportunities for technology transfer and our first steps towards a direct contribution to the building of an industry. At the same time, the wider community has reached a point where commonality of intent has been joined by a shared specialist language for rejuvenation biotechnology. The resources and environment are in place for real progress in the construction of bench-to-patient pathways.

We are already putting in place mechanisms for external oversight of our research program [see "2015 Research Symposium" in the Research: Maturity & Engagement section of this report]. Over the coming year we will match this commitment by seeking new opportunities for dialogues in the shared community challenges of investment, development and regulation.

As the landscape of rejuvenation biotechnology broadens, we are seeing increasing opportunities for technology transfer and infrastructure-building efforts, across several categories of transaction.

seed funding

We provide small seed funds—alone or with other funding sources—to companies able to perform mission-related research and development, saving costs against expanding our internal programs. Our research program on Advanced Macular Generation has been transferred using this approach, allowing further investigation whilst freeing up our own resources to focus on our next priority.

financial bridges for critical infrastructure

We have supplied small amounts of loan funding to private companies that are developing infrastructure for the rejuvenation biotechnology industry. This includes a loan to assist in the establishment of a tissue cryopreservation company that is working towards the creation of a supply chain for artificial organs.

technology transfer

We transfer appropriately mature research to well funded start-up companies pursuing specific disease fields, in return for a stake in those companies.

collaborative development of research tools

We have, for some time, been developing knowledge resources—databases and related tools—based on our analysis of the state of the industry. We are collaborating with private partners to disseminate this knowledge to a wider audience within the community.

inter-institutional collaborations

We are creating more collaborations—both among external institutions and with our internal programs—including a new international collaboration to develop assay technologies that could open up the investigation of several poorly-understood cancers.

strategic alliances to overcome shared challenges

We will be forming new alliances over the coming year, allowing us to share human resources and expertise with other organizations, address our shared challenges, and develop knowledge capital in the investment, development and implementation aspects of rejuvenation biotechnology and associated fields.



“ a community confronting the divide between bench and patient ”

CASE STUDY: technology transfer Human Rejuvenation Technologies, Inc.

SENS Research Foundation's LysoSENS program had been investigating methods of removal of unwanted intracellular aggregates since 2009. One project focused on aggregates that are the key drivers of the damage underlying plaque formation in atherosclerosis. Removing these aggregates from the immune cells that they disable would reduce plaque formation and dramatically lower the prevalence of heart disease. The project had successfully identified a non-human enzyme that was effective at eliminating some of these aggregates. It became clear that the research was at a stage where significant further investment could greatly accelerate progress, and that such investment could be achieved by transferring the research into a private company. This was done in 2014, when Jason Hope—himself a long-term supporter of the Foundation—formed Human Rejuvenation Technologies, Inc. (HRT). The technologies developed by the Foundation were transferred to HRT in return for a 10% stake in the company.

CASE STUDY: seed funding Oisin Biotech

SENS Research Foundation was considering the creation of an internal project to investigate novel rejuvenation biotechnology solutions to the ablation of senescent cells. (For an introduction to the importance of senescent cells see “Death-Resistant Cells: From Inhibiting SASP to Geroprotector” in the Research: Project by Project section of this report.) Instead we helped in the creation of Oisin Biotech, providing seed funding along with the Methuselah Foundation. Oisin is using licensed liposome technology matched with their own patent-pending DNA construct to perform apoptosis-induced eradication of senescent cells. They have demonstrated that their construct can selectively target senescent cells *in vitro*.

CASMI Translational Stem Cell Consortium (CTSCC)

CTSCC is an initiative led by the Centre for the Advancement of Sustainable Medical Innovations (CASMI), a partnership between Oxford University and University College London.

CTSCC and its members are working together in the ‘precompetitive’ spaces where standards, basic processes, shared tools and resources, and fundamental research needed to benefit the entire industry can be developed without giving any one actor a competitive advantage. The consortium is focused on addressing challenges to the emerging regenerative medicine industry in the methods, standardization, and regulation of cell-based manufacturing; in the establishment of strategic partnerships; and in the interface of manufactured cells and tissues with surgical delivery. They are also working to develop new models for the awarding, use, and enforcement of patents and similar intellectual property, which have sometimes acted as barriers to the regenerative medicine industry's freedom to operate, conduct research, and innovate.

“SENS Research Foundation is delighted to have helped in the formation of the CTSCC”

As the initial funding partner that created the opportunity for this program, SENS Research Foundation is delighted to have helped in the formation of the CTSCC. We have now been joined in our membership by key players in the development of translational pathways in regenerative medicine, including Lonza, Sartorius Stedim, Thermo Fisher, Celgene, Eisai, Roche, Oxford Biomedica, GE Healthcare, NIH, the New York Stem Cell Foundation, MediPost (Korea and US), Thomson Reuters, Aegate, and the Centre for the Commercialization of Regenerative Medicine.

outreach

building a widening community of informed and enthusiastic stakeholders

As the core concepts of rejuvenation biotechnology are accepted by a growing professional audience, SENS Research Foundation continues to build a network of informed and enthusiastic stakeholders. We also reach out to organizations and individuals who have yet to form valuable links with our community.

From its inception, SENS Research Foundation's outreach has been critical to the success of our mission. We inform the general public, policymakers, industry players and academia about the promise and challenges of the damage-repair approach to age-related disease.

newsletters documentaries interviews social media conferences

fundraising



HIGHLIGHTS

SENS Research Foundation's activities have been covered by a large number of media outlets, including *The Financial Times*, *The Guardian*, *The Washington Post*, *The Irish Examiner*, *The Australian*, *The Huffington Post*, *Forbes*, *CBS News*, and *NBC News*. Our research was featured in documentaries in the *BBC's Horizons* and *Al Jazeera America's Fault Lines* series and on *Dutch Public Television*.

Amongst our many articles in peer-reviewed publications, Dr. Haroldo Silva and David Halvorsen, together with Dr. Jeremy Henson, produced a review of their work on a damage-repair approach to cancer prevention in the April issue of *The Scientist*, "Control ALT, Delete Cancer".

CCTV, a Chinese network which also broadcasts on the *Dish Cable Network* in the U.S., sent correspondent Mark Niu to cover the Foundation's work on mitochondrial damage repair. The broadcast also featured CEO Mike Kope, who discussed the regulatory and investment challenges around our work.



Plenary Panel, RB2014 Conference: Stephen Minger, Jeff Karp, Richard Barker, Aubrey de Grey, Caleb Finch

Over the past year representatives of SENS Research Foundation have addressed audiences in **48** towns and cities, in **12** states in the U.S.A., and in **14** other countries.

Our regular newsletters are delivered to over **8,000** people, with subscribers growing at a rate of **25%** per year.

RB2015 Rejuvenation Biotechnology

a SENS Research Foundation Conference

The Rejuvenation Biotechnology conferences are part of SENS Research Foundation's commitment to an industry which builds on the strengths of regenerative medicine and delivers real-world solutions, based on damage-repair approaches to prevention and cure.

"Last year's conference represented a step-change in the coordination of our efforts, bringing together stakeholders from across the spectrum of academic, industrial, political, regulatory and financial institutions. This year we are building on that foundation, widening spheres of influence and strengthening networks within our community."

Mike Kope, CEO, SENS Research Foundation

Our 2015 conference runs from August 19th to 21st in Burlingame, CA, bringing together these stakeholders to deepen their mutual understanding of the field, further the adoption of the damage-repair approach to the diseases of aging, and spur collaborations which will accelerate industry growth.

Our keynote speakers are Frances Colon (Acting Science and Technology Adviser to the Secretary of State at the U.S. Department of State) and Chas Bountra (SGC Oxford Chief Scientist, Professor of Translational Medicine, Nuffield Department of Clinical Medicine; Associate Member, Department of Pharmacology, University of Oxford).

Find conference videos at www.sens.org/outreach.

presentations advocacy newsletters documentaries interviews

fundraising



FEEDBACK from Rejuvenation Biotechnology 2014:

extremely well organized

great speakers a forum for open collaboration

community, camaraderie, and honesty

networks of ideas, innovators and industry accelerators

tremendous amount of information new friends

a common mission to engineer an industry

a great experience

a diverse group of attendees

provoked conversations across disciplines

a passion for innovative discussion



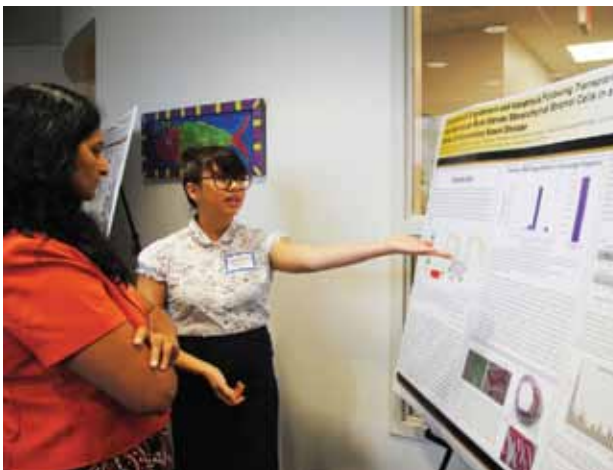
education

building the next generation 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.



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 interpersonal, communication, presentation and other associated 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.



Clockwise from top left: Senior Research Scientist Dr. Amutha Boominathan works with her intern Summer Wang at the SRF Research Center. Summer Scholar Shruti Singh presents her work from Professor John Jackson's lab. Professor Graça Almeida-Porada's Summer Scholar Abigail Hawkins at a poster session.

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



SRF Summer Scholars and student researchers at the 2014 Rejuvenation Biotechnology Conference



PARTNERSHIPS

SENS Research Foundation continues to build a strong network of partnerships through its educational efforts. Our partners give students the opportunity to conduct cutting-edge biomedical research to combat diseases of aging, such as cancer, Alzheimer's, and Parkinson's Disease.

Joining the SRF Summer Scholars Program in 2015:

Sanford Burnham Prebys Medical Discovery Institute

Scripps Research Institute

Stanford University

We are proud that some of the finest minds in the field of rejuvenation biotechnology serve as mentors in the Summer Scholars program. And, we are proud that our support allows promising young scientists to contribute to the groundbreaking research of our partner institutions.

“ Not only are the students a delight to have in the laboratory, they are also extremely bright and accomplished. They are as sharp as the most talented undergraduates I have encountered since moving to San Diego. ”

Dr. Evan Snyder, Professor
Stem Cell Research Director
Sanford Burnham Prebys Medical
Research Institute

STUDENT PROFILE: James Smith



“Participation in the SRF Summer Scholars Program was pivotal in helping me to decide to pursue postgraduate study and, ultimately, in securing a full scholarship for a DPhil at the University of Oxford. The work I undertook at the Harvard Stem Cell Institute (HSCI) was directly relevant to the DPhil project for which I applied. In fact, I presented my HSCI work during my Oxford interview.

The Summer Scholars Program has directly facilitated long-term collaborations for me. Of my two DPhil supervisors, Dr. David Brindley was one of the mentors who supervised my SRF research project, and I first met Prof. Andrew Carr when he gave a talk in Boston during my internship at HSCI.

In addition, I continue to work with HSCI Executive Director Brock Reeve, who was one of my Summer Scholar mentors and with whom I have published several book chapters.”

James Smith
University of Oxford Doctoral Candidate
Former HSCI SRF Summer Scholar

research: maturity & engagement

delivering a research program which meets the needs of a wider community

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 / Babraham Institute / Buck Institute for Research on Aging / Harvard University / Rice University / SENS Research Foundation Research Center / University of California, Berkeley / University of Oxford / University of Texas-Houston Medical School / Wake Forest Institute for Regenerative Medicine / Yale University

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.



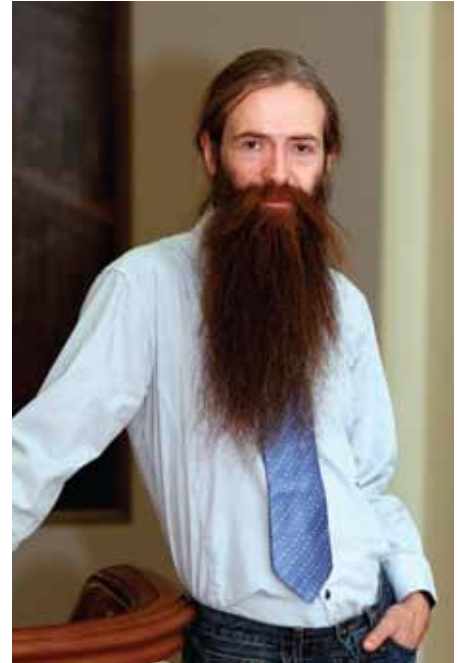
Foundation-funded research includes teams which are:

- > developing a regenerative medicine approach to treating inflammatory bowel disease, creating underlying technologies vital for future approaches to cancer
- > creating therapeutic approaches to intracellular aggregates which build up over time and compromise the functioning of cells in the brain, heart, and muscles
- > engineering healthy new tissue for the thymus, helping to restore the vigorous immune response of youth
- > engineering new mitochondrial genes to restore function to damaged mitochondria—a source of age-related disease and currently-incurable inherited disorders
- > exploring non-invasive approaches to the diagnosis and monitoring of certain underdiagnosed forms of heart disease—avoiding the need for cardiac biopsy—and identifying ways to remove aggregates which lead to impaired heart function
- > understanding the genetic basis of certain cancers which rely on a mechanism called ALT (alternative lengthening of telomeres), to pave the way for new cancer treatments
- > developing the tools needed to create therapies which reduce hypertension, stroke and kidney disease by breaking molecular cross-links which cause arteries to stiffen with age

“Vision” is a word which is often used when talking about big ideas. At SENS Research Foundation our vision is a world free from age-related disease, which is most certainly a big idea. It is not, however, the whole story, for we would never reach that goal if we did not have a clear view of the way ahead, and of our companions on the journey.

Announcing the Foundation, back in 2009, Mike Kope wrote: “Our own research will be governed by a strategic agenda to demonstrate the feasibility of SENS and regenerative medicine approaches, and therefore drive broader involvement.” Today, as that broader involvement grows at an ever-increasing rate, we find ourselves within a burgeoning rejuvenation biotechnology community. Where once our agenda sought to demonstrate our value to others, now it is predicated on our place at the heart of a global network.

Within that network, several of our connections arise from Foundation-funded collaborations, or are the result of tech-transfer from our facilities. But more and more, we are seeing independent research efforts based on the rejuvenation biotechnology approach, and independent publications which concern the underlying principles of that approach. Sometimes the terminology used differs from our own. Sometimes only certain precepts of damage-repair are adopted, or positions are taken with which we are not in complete agreement. Yet this is the nature of scientific progress, and in all these cases we are presented with, and take, opportunities to enlarge and strengthen our community.



Dr. Aubrey de Grey Chief Science Officer

“ a Foundation research program which engages with the community ”

This is what we mean when we talk about research engagement: a Foundation research program which engages with the community, through sharing of knowledge, expertise and best practice; through community influence on our trajectory and priorities; through transparency, and on-going community oversight of our work.

As for maturity, ours is a research program which now reflects the wider context of our Rejuvenation Biotechnology conferences, and which exists in a developing environment designed to ensure a pathway from bench to patient. It is a research program of which I am proud, and which I shall enjoy sharing with many of you, at Rejuvenation Biotechnology 2015 and throughout the coming year.

A handwritten signature in black ink that reads "Aubrey". The signature is written in a cursive, slightly stylized font.

Dr. Aubrey de Grey
Chief Science Officer

A wide-angle photograph of the Golden Gate Bridge in San Francisco, viewed from a low angle looking across the water. The bridge's towers and suspension cables are prominent against a hazy sky.

2015 Research Symposium

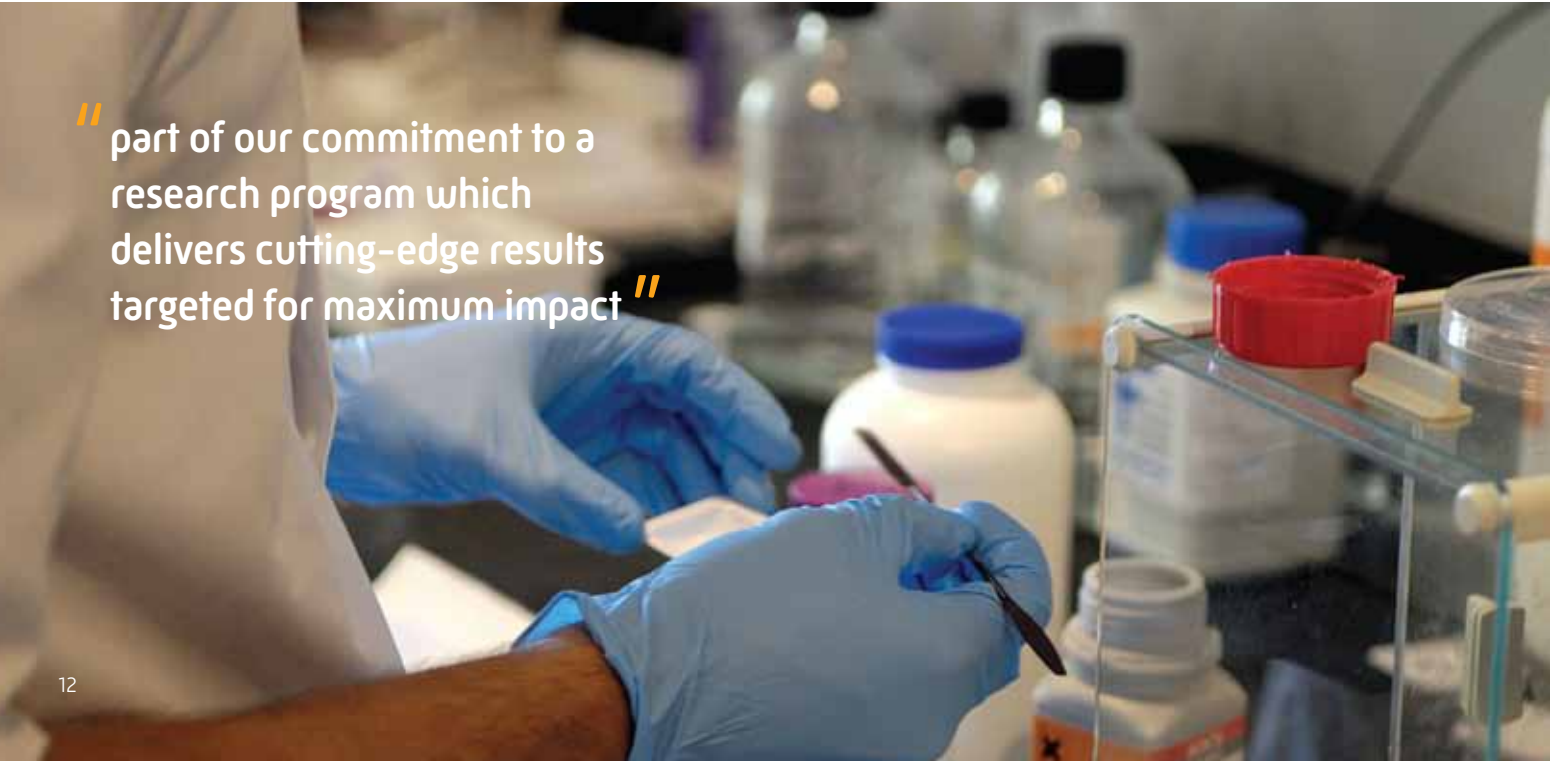
This year, for the first time, SENS Research Foundation is holding a one-day Research Symposium. The symposium brings together Foundation-funded researchers and gives them access to the wide-ranging expertise of our Research Advisory Board (RAB) and other external specialists in the field. The members of the RAB are afforded an opportunity to evaluate our research progress and focus, and ensure that our researchers are working as effectively as possible within the wider community of rejuvenation biotechnology professionals.

Each Principal Investigator will present his or her team's latest findings and proposed directions for future research. After a short Q&A session, there will be a private project meeting with selected RAB members, chaired by the Foundation's Chief Science Officer. Project reviewers will give their opinion on the project's progress, suggestions on how to overcome any obstacles to further progress, and thoughts on future research efforts.

The Foundation is also using this opportunity to involve external specialists in the evaluation of

potential new research projects and the development of the Foundation's global research strategy.

The Research Symposium is part of our commitment to a research program which delivers cutting-edge results targeted for maximum impact on the progress of rejuvenation biotechnology. It will be held just prior to our Rejuvenation Biotechnology 2015 conference, and we expect conversations which begin at the symposium to continue amongst a wider audience over the course of the conference.

A close-up photograph of a person wearing blue nitrile gloves working in a laboratory. They are using a pipette to transfer liquid into a multi-well plate. In the background, there are various laboratory supplies like bottles and containers.

" part of our commitment to a research program which delivers cutting-edge results targeted for maximum impact "

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, PhD
Research Director, Fondation Voir et Entendre, Institut de la Vision, Université Pierre et Marie Curie

Gabor Forgacs, PhD
Professor, Biophysics Laboratory, University of Missouri-Columbia; Founder, Organovo, Modern Meadow

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

Jay Jerome, PhD
Director, Graduate Program in Cellular and Molecular Pathology, Vanderbilt University Medical Center

Daniel Kraft, MD
Executive Director, FutureMed, Singularity University

Jeanne Loring, PhD
Director of the Center for Regenerative Medicine, The Scripps Research Institute

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

Stephen Minger, PhD
Director, SLM Blue Skies Innovations Ltd.

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
Scientific Director, The Jackson Laboratory

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, Mass General 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.

RESEARCH ADVISORY BOARD

Our Research Advisory Board is made up of 28 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.



finances

committed to the highest standards of transparency and accountability

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 have been prepared by Robert Lee and Associates, LLP and MKR Accounting, 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.

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 2014 we used \$1,913,488 of the grant in the furtherance of our mission.

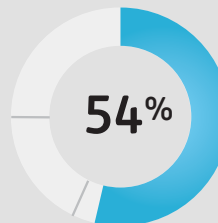
The generosity of our many supporters generated additional revenue of \$1,831,830 in 2014.

2014 REVENUE

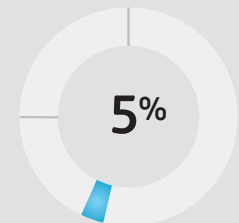
Individual	\$	572,619	31%
Corporate	\$	88,941	5%
Grants	\$	876,826	48%
Conference	\$	175,893	10%
Other	\$	117,551	6%

TOTAL REVENUE	\$	1,831,830	100%
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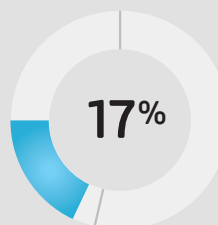
Research



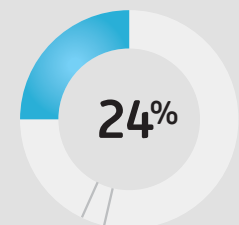
Education



Outreach



Administration



2014 EXPENSES

Research	\$	2,797,124	54%
Education	\$	236,754	5%
Outreach	\$	887,351	17%
Administration	\$	1,236,222	24%

TOTAL EXPENSES	\$	5,157,451	100%
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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. Further details and updates are always available at sens.org/research.

Cell Therapy for the Intestinal Tract

Wake Forest Institute for Regenerative Medicine (WFIRM)

Principal Investigator: Graça Almeida-Porada

Research Team: Joana Boura, Christopher Porada

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. IBD incidence does rise with age, but SRF's main reason for supporting this research is because therapies that repopulate the cells of the gut will be critical to the development of a new generation of cancer therapies that are likely to depopulate the stem cell reserves of several tissues and replace the missing cells with fresh, cancer-protected stem cells. Furthermore, regenerative therapies for the gut would be of enormous value to people receiving many existing cancer therapies that ravage intestinal tissue, such as radiation therapy during treatment for pelvic or abdominal cancer.

The WFIRM researchers are developing a combination 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. The researchers used a model of IBD in which naïve CD4+ T-cells from healthy, normal mice are repeatedly infused into mice with mutations that prevent them from producing their own immune cells. In such mice, inflammation develops throughout the length of the large intestine and produces symptoms reminiscent of human IBD.

The WFIRM researchers then took the IBD-model mice and divided them into four groups: one receiving unmodified human MSC, another receiving hMSC modified to increase their anti-inflammatory potential, and a third group receiving hMSC modified to have both anti-inflammatory potential and to migrate specifically to the deep pockets ("crypts") of the gut lining where stem

cells normally reside. The final group was kept as controls. This research is ongoing, but results so far indicate that mice that received hMSC modified to increase their anti-inflammatory potential suffered significantly less weight drop than all of the other groups — including the mice whose transferred cells were further modified to enhance homing to the crypt.

The WFIRM team determined that the inclusion of the crypt-homing transgene was blocking the anti-inflammatory transgene in the same construct. The cells in this case homed into their target, but were unable to exert a robust therapeutic effect. The team will now develop and test a new construct including both transgenes and thereby evaluate the true potential of combining these two features in the therapeutic cells. Further analysis is 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 Therapeutics Against Lipofuscin

Rice University

Principal Investigator: Pedro Alvarez

Research Team: Jason Gaspar, Jacques Mathieu

Many diseases of aging are driven in part by the accumulation of intracellular aggregates particular to specific cell types. For example, atherosclerotic lesions form when disabled, immobilized immune cells (macrophages) called *foam cells* adhere in the arterial wall after taking in *7-ketocholesterol* (7-KC) and other damaged cholesterol byproducts in an effort to protect the arterial wall from their toxicity. Alzheimer's and Parkinson's are also, in part, lysosomal diseases. Additionally, many types of cells that rarely or never divide throughout adult life accumulate a more generic form of lysosomal waste known as *lipofuscin*, which impacts such critical cell types as neural, cardiac muscle, and skeletal muscle cells. Lipofuscin is hypothesized to derive largely from inadequate degradation of aged or dysfunctional mitochondria.

This year the Rice University intracellular aggregate team developed a refined version of a previously-

developed method that allows researchers to generate abundant lipofuscin in cells much more simply and in significantly less time (~5-10 days) than the earlier iteration. This method will enable researchers to understand lipofuscin metabolism and the ways that it deranges cells much more conveniently, and also test interventions designed to clear it out of cells.

One of the ways that some lipids disable the lysosome in model foam cells is by lysosomal membrane permeabilization (LMP) — a process that keeps lysosomes from maintaining the necessary acidity to properly degrade wastes, and that leads to the leakage of acids, enzymes, and toxic wastes into the cell. Looking into previous research, the Rice team noted a small molecule that has benefits in a rodent model of a human genetic lysosomal disease. In their own studies, the team found that this molecule is capable of rescuing LMP induced by exposure to certain damaged lipids. This year, they found this same molecule is capable of reducing lipofuscin content their model of aged fibroblasts by roughly 30%, although it is not yet clear whether this is a true reduction in mature lipofuscin or is the result of more efficiently degrading its precursors.

This latter result was unexpected, as lipofuscin is not predicted to be solubilized by the small molecule utilized. Nor is it likely that the small molecule is simply interfering with the Rice team's system for generating lipofuscin in the cells. This opens up the possibility that the candidate drug is not merely helping the cell to export lipofuscin by making it more soluble, but is somehow contributing to the degradation of lipofuscin or to the rejuvenation of lysosomal function. The team is now testing several hypotheses for the mechanism, and is focused on how both aging and the small molecule may be affecting lysosome membrane content and function. After further exploration of the mechanism in their fibroblast model, the investigators would like to test drug efficacy in lipofuscin-laden heart cells (which are a more physiological model, albeit an expensive and difficult one with which to work) and eventually in aged mice.

Rebalancing Risk:Benefit Appraisal in Clinical Trials

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

*Principal Investigators: Sir John Bell, Andrew Carr
Research Team: David Brindley*

Since the days of the “blockbuster drugs” of the 1990s, there has been a worrying trend of declining productivity in biomedical research. Pharmaceutical companies are

spending more and more money on research to bring new therapies to market, and yet fewer drugs are being approved. This is despite major achievements and opportunities in novel technological platforms. Most of this increased failure rate appears to occur at the clinical trial phase; one key contributor to this is an inherently and perhaps increasingly risk-averse regulatory system. In this environment, rejuvenation biotechnologies may suffer an exceptionally high burden. Nearly all drugs today can be tested with fairly clear near-term outcomes, because they are designed to alleviate symptoms or reduce the rate of catastrophic outcomes in people with existing disease. Rejuvenation biotechnologies, by contrast, are designed to prevent people from developing age-related disease in the first place, or greatly delay its onset. This implies that rejuvenation biotechnologies are best tested in people who are aging, but still basically healthy — which tends to break the conventional model of weighing risks against benefits. If we are to continue to make medical progress, particularly against the diseases and disabilities of aging, regulators will need to adopt new ways of balancing the risks and benefits of clinical trials.

This investigation aims to assess risk-to-benefit appraisal methodologies used in the analysis of randomized controlled trials for innovative medicines, medical devices, and surgical procedures prior to regulatory approval. A panel of 16 quality factors for such methodologies was gathered from published literature and from practitioners from life sciences and non-life-science industries. These quality factors were prioritized through a consultation with external experts, weighed for utility, and used to produce a scorecard to assess the quality and effectiveness of the risk-to-benefit appraisal techniques surveyed in a systematic review of published methodologies. Ultimately, 6 records of the original 272 exceeded the predefined minimum quality threshold, and met the minimum stakeholder needs as determined by multi-stakeholder expert elicitation. In response to feedback, an additional international survey was distributed to nearly 4000 European pharmacists, which indicated a very strong desire by pharmacists (92.6%) to participate in risk-to-benefit appraisal.

In order to evaluate the impact of system risks in risk-to-benefit appraisal, an investigation into barriers to the translation of regenerative medicines was conducted concurrently. The key finding was that regenerative therapies (as compared with ‘conventional’ biomedical innovations) are subject to a number of unique systems risks, pertaining to intellectual property, biomanufacturing, the formation of strategic partnerships, and ensuring that licensed therapies are actually adopted in the clinic. Clearly, more work must be done to ensure that rejuvenation

research is translated into working regenerative medicine.

Death-Resistant Cells: From Inhibiting SASP to Geroprotector

Buck Institute for Research on Aging

Principal Investigator: Judith Campisi

Research Team: Kevin Perrott

Non-dividing “senescent” cells in our bodies resist signals for *apoptosis* (programmed cell death) and secrete numerous inflammatory signaling molecules and protein-degrading enzymes into their local environment. The latter phenomenon is called the *senescence-associated secretory phenotype*, or SASP, and is thought to play a role in the chronic disease-promoting inflammation widespread in aging tissues. Additionally, although activation of the senescence program can pre-empt the *initiation* of cancer, the long-term effects of the SASP may make the local tissue environment more vulnerable to the *spread* of cancer.

With SENS Research Foundation funding, the Buck Institute senescent cell project has been screening small molecules for their effects on fibroblasts (a type of skin cell) rendered senescent by ionizing radiation and other causes of DNA damage, including replicative stress. Their goal is to identify agents that can selectively kill senescent cells or interrupt the SASP. Earlier work by the Buck team revealed that a compound called *apigenin* suppresses the secretion of a representative constituent of the SASP. As part of the research completed this last year, the team traced *apigenin*'s ability to shut down the vicious cycle that enforces ongoing SASP back to its root: *IRAK4*, a key part of the signaling cascade that is activated inside cells when the SASP component IL-1 α engages its receptor. To keep the IL-1 α signal propagating, two separate IRAK4 structures must unite to engage a kinase domain, transferring a high-energy phosphate group from one part of the united structure to another. It is this higher-order active structure that then relays the inflammatory signal onward to NF κ B. The team have now shown that *apigenin* acts by blocking IRAK4 from transferring that critical energy group, interrupting the signal and shutting the vicious cycle down.

Looking at existing published research, the Buck senescent cell team noted that — at least in cell culture — *apigenin* inhibits signaling through the “pro-growth” pathway regulated by the *mammalian target of rapamycin* (mTOR) protein. Inhibiting mTOR reduces protein synthesis and facilitates the breakdown of used or damaged proteins, and the mTOR-inhibiting compound *rapamycin* is the only drug yet shown to clearly slow down the degenerative aging process in mammals.

Unfortunately, *rapamycin*'s potential to adversely affect immune function and increase diabetes risk seriously limits its clinical utility. Scientists are therefore looking for alternative drugs (“rapalogs”) that might have the beneficial effects of *rapamycin* without the side effects.

Following up on this new lead, the Buck team confirmed and expanded the previous findings on *apigenin*'s effects on mTOR. Because earlier experiments in the Campisi Lab showed that *rapamycin* could decrease the SASP in senescent cells, the team was intrigued to note that *apigenin* exhibited a similar effect and displayed signs of a similar mechanism of action. Unlike *rapamycin*, however, they now found that *apigenin* does not work by directly blocking the activation of mTOR itself, but by inhibiting other steps along the pathway it regulates, and *apigenin*'s inhibitory effect on the proliferation of *non-senescent* cells is much less severe. If studies in living organisms pan out similarly to these cell culture findings, *apigenin* (or drugs based on parts of its structure) could yield some of the benefits of *rapamycin* as well as dampen the SASP in senescent cells, making it an attractive prototype for a dual-action age-inhibiting drug. Of course, we don't yet know whether these effects will be seen in living, breathing organisms. Human *apigenin* studies suggest that the concentrations required for possible therapeutic benefit cannot be obtained from dietary supplements. The known side-effects of inhibiting mTOR with *rapamycin* may also emerge with *apigenin* analogs. To determine what actual potential exists in this area, this year, the senescent cell team at the Buck will test *apigenin* out for the first time in living organisms — the roundworm *C. elegans*. This study won't necessarily tell us much about the effects in mammals, but the team is also going to propose *apigenin* for testing in gold-standard mouse lifespan studies under the NIA's Intervention Testing Program — the same program that generated the earlier breakthrough with *rapamycin*.

Target Prioritization of Adventitious Tissue Crosslinking

The Babraham Institute

Principal Investigator: Jonathan Clark

As discussed in the project summary for “Glucosepane Crosslinks and Routes to Cleavage”, our arteries slowly stiffen with age, in substantial part because of adventitious crosslinking of the structural proteins collagen and elastin. Some of these crosslinks are the result of purely stochastic chemical reactions, including those with blood sugar and other fuels in the circulation. Other crosslinks arise from enzymatic processes that modify collagen — either as “collateral damage,” or for purposes

that help with short-term survival but whose cumulative burden over time eventually compromises function.

Developing rejuvenation biotechnologies to break these crosslinks is key to restoring youthful arterial function. It is vital, therefore, that we understand which crosslinks are the highest priorities for new crosslink-breakers. Much of what we think we know about the relative importance of different sources of crosslinking relies on work carried out some 40-50 years ago, using old methods that are known to create significant artifacts. Additionally, evaluations undertaken at SRF's Cambridge center have shown existing commercial antibodies against specific crosslinks to be highly nonspecific or impractical.

These and related issues make it critical to get more reliable data on the sources and relative impact of different kinds of crosslinks in aging tissues. SENS Research Foundation is funding groundbreaking work to deliver this data, at the Babraham Institute in Cambridge. Dr. Jonathan Clark and coworkers will be administering heavy isotopes of oxygen and the amino acid lysine (both important building blocks of proteins) to mice. By labeling newly-synthesized collagen and elastin strands with these heavy building blocks, mass spectrometry will allow him to track the laying-down, crosslinking, and breakdown of these key structural proteins during the aging process, without prejudice to the particular proteins or crosslinks involved. They expect to benefit greatly from newly-available samples of pure glucosepane supplied by Dr. David Spiegel, thanks to his SRF-funded research at Yale.

Rejuvenation of the Systemic Environment

University of California, Berkeley

Principal Investigator: Irina Conboy

Research Team: Keith Causey, Justin Rebo

Cells exist within in a complex network of communication, mediated by signaling molecules. The core of the degenerative aging process is the accumulation of damage to cells and biomolecules, which triggers them to change their signaling patterns accordingly. The full network of such signals is powerfully demonstrated by experiments in *heterochronic parabiosis*, in which the circulation of an aged animal is joined to that of a young one, exposing 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 an aged organism's cell and tissue function, including the regenerative capacity of tissue-specific stem cells. 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 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, safely, and non-surgically extract blood or plasma from laboratory animals, process that blood in any of several ways, and ultimately return it to the original animal, exchange it with that of an oppositely-aged animal, or extract or concentrate specific factors present in those biological fluids before returning it into the living environment or testing its effects in *in vitro* systems. The system also offers a way for scientists to disentangle the effects of the soluble factors in the shared systemic environment from the effects of an old animal having access to the young animal's blood cells and organs (and vice-versa). This feature will be important for any potential to translate the effects of heterochronic parabiosis to humans.

The UC Berkeley team has now successfully used the system to perform the first set of exchanges, comparing animals subjected to full heterochronic blood exchanges with old animals that have undergone one-way transfer of young blood; young animals that have received one-way transfer of old blood; and young and old same-aged animals that have undergone full blood exchange. They have furthermore tested the effects of these transferred systemic environments on the ability of the mice's muscles to mount a regenerative response after injury, with the analysis of the regenerating muscle cells still pending. The team has also isolated the brains, livers and hearts of these animals postmortem, and will soon assess the effects of the transferred systemic environments on the proliferation of stem and progenitor cells in these tissues under baseline conditions.

Tissue-Engineered Thymus

Wake Forest Institute for Regenerative Medicine (WFIRM)

Principal Investigator: John Jackson

Research Team: Silvia Gutierrez, Shruti Singh, Shay Soker, James Yoo

The *thymus* gland is responsible for the development of a class of immune cells called *T-cells*. As part of the degenerative aging process, the thymus shrinks in size, and the structure and function of the remaining tissue decays, with the critical *thymic epithelial* tissues responsible for maturing T-cells giving way to fat cells and collagen. This process of "thymic atrophy" prevents the body from maturing new T-cells, progressively weakening the body's ability to fight off never-before-encountered infections. Engineering new, healthy thymic tissue would help to restore the vigorous immune response of youth.

SENS Research Foundation is therefore funding this WFIRM group to apply tissue engineering techniques to

the creation of functional thymic tissue to fortify or replace the aging thymus. Engineering new tissues requires a “scaffold” in which to embed cells to give them structure and functional cues, and the WFIRM group is testing two different scaffolding systems: *decellularized donor scaffolds and hydrogels*.

In the decellularized scaffold paradigm, an organ of the type that is needed is taken from a donor, but is then stripped of its original cells and DNA, leaving behind a protein structure that can be repopulated with cells taken from the new organ recipient. This results in a new organ with the native structure and growth factors already present in the transplanted original organ, but with all the cells and most of the DNA and proteins of the recipient, eliminating the potential for immune rejection. The WFIRM group have been testing out different protocols for stripping donor material from scaffolds, and have so far determined that different methods yield different effects on the growth and the specialization of the cells that are seeded into them. They have also found that an intermediate concentration of epithelial cells gives the best growth and attachment, yielding cells with cell-surface markers specific to both important types of thymic epithelial cells. Upcoming studies will evaluate whether these elementary organs can support the development of bone marrow progenitor cells into early-stage T-cells.

In the hydrogel approach, cell aggregates are cultured in a 3D collagen-based hydrogel system. Hydrogel scaffolds resemble soft tissues more closely than any other purely human-made structure, and are highly biocompatible, making them unlikely to trigger an immune or rejection response. To generate the cells to seed into the hydrogel scaffold, the WFIRM group cultured thymus epithelial cells and bone marrow progenitor cells in microscopic wells that encouraged them to cluster together into spherical structures. These spheroids were then placed in a basic hydrogel scaffold, where they have so far remained viable for several weeks at a time. During the first three weeks, small numbers of mature T-cells begin to develop from the bone marrow stem cells. These early organ-like systems are now being observed to see how well the hydrogels support the development of new thymic epithelial cells.

Engineering New Mitochondrial Genes to Restore Mitochondrial Function

SENS Research Foundation Research Center

Principal Investigator: Matthew O'Connor

Research Team: Amutha Boominathan, Kathleen Powers, Shon Vanhoozer

Free radicals derived from our cells' energy-producing

mitochondria can mutate the organelle's DNA, leading to *deletions* of large stretches of the mitochondrial genome. These deletion mutations prevent the mitochondria from building various pieces of the electron transport chain (ETC), by which mitochondria generate most cellular energy. The accumulation of deletion-mutation-containing cells is a significant consequence of aging, and is implicated in age-related disease as well as in several currently incurable inherited mitochondrial disorders.

The SRF-RC mitochondrial mutations team is moving forward on a method for targeting engineered nuclear-encoded genes (that could function as “backup copies” for cells with deletion mutations) to the mitochondria, and for furthermore optimizing the precision of this targeting. The “working copy” of the relocated mitochondrial gene in this method is equipped with two special sequences. One “untranslated” sequence is not turned into a protein itself, but helps protect the engineered protein during the import process. The other, called the *mitochondrial targeting sequence*, is a tag appended to the final protein following expression that allows it to be imported once expressed. Combining the two sequences allows the “backup copies” of genes to be turned into working copies in the cell nucleus; to have the “working copies” targeted to the surface of the mitochondria to be decoded and turned into protein. Even as it is still in the process of being decoded, the emerging protein is quickly directed to the surface of the mitochondria for import and incorporation into the ETC, restoring mitochondrial function.

In 2013, the SRF-RC mitochondrial mutations group created two new cell lines which are 100% null for two mitochondrially-encoded genes: ATP8 and CYB. Using these two new cell lines, this year the SRF-RC mitochondrial mutations team was finally able to unleash their engineered ATP8 gene in cells whose mitochondria completely lack the ability to generate the corresponding proteins on their own. The team expects to be able to announce a dramatic rescue of such “ATP8 null” cells using their protein targeting strategy very soon. They anticipate that these results will deliver the proof-of-concept for the overall approach, which should then be applicable as a rescue platform for all thirteen mitochondrially-encoded proteins.

Further work by the team aims to enable delivery of working instructions for building proteins that can keep the ETC intact and functioning in the event of age-related mutations of the original mitochondrial genes for these proteins. This method utilizes a “borrowed” structure already employed by mitochondria to take in RNA from the main body of the cell. The team

has now achieved the critical first benchmark — i.e. delivering *any* RNA into the mitochondria — in this pioneering work using a convenient (but not naturally mitochondrially-expressed) RNA.

Novel Diagnostics for Transthyretin Amyloid **Harvard University and Brigham & Women's Hospital**

Principal Investigator: Brian O'Nuallain
Research Team: Adam Cantlon

This project has developed candidate antibodies for the noninvasive diagnosis and monitoring of amyloid disease caused by aggregates of wild-type *transthyretin* (TTR), a protein involved in the transport of thyroid hormone and vitamin A in the body. (See background information in the section for the complementary project in Dr. Sudhir Paul's laboratory at the University of Texas-Houston Medical School.)

The current standard diagnostic test for TTR amyloid requires a cardiac biopsy, which is invasive and dangerous in the people most likely to be suffering from TTR aggregate disease, i.e. those who have sustained significant aging damage. Recent studies have stimulated more interest in using nuclear imaging techniques to label cardiac amyloid, but they too have their limitations. The main radiotracers being studied tend to pick up prior heart attack damage, calcification, and other forms of amyloid in addition to TTR aggregates. It is also not clear whether these radiotracers can pick up TTR amyloid at subclinical levels, the presence of which would make a person the ideal recipient of future rejuvenation therapies.

Improved diagnostics for TTR amyloid will allow clinicians to identify the best candidates for clinical trials for rejuvenation biotechnologies targeting TTR amyloid, and to monitor those therapies' ability to clear TTR aggregates from aging tissues. This scenario would enable researchers to evaluate candidate therapies' efficacy and safety in real time instead of relying on biopsies, autopsies, or waiting until the end of a trial to see if treatment improved survival. Also, because TTR amyloidosis is difficult to diagnose with existing methods, it is greatly under-diagnosed and often confused with congestive heart failure from other causes.

The development of a convenient, noninvasive means of identifying harmful levels of accumulated TTR is thus a high priority for the Foundation. Such a test would ensure that people who could benefit from TTR-targeting therapies could get rapid and safe access to such therapies once they become available, saving the most lives and improving cardiac function as early as possible.

Using strategies previously employed to develop diagnostic antibodies against other forms of amyloid disease, the Harvard TTR aggregate diagnostic team generated more than 20 distinct monoclonal antibodies specific to TTR aggregates. Five proved themselves to be especially promising as candidate diagnostics, as they are highly selective for TTR aggregates, and retain their useful properties in human blood as well as in isolated systems. Furthermore, one candidate diagnostic antibody could have some *therapeutic* potential as well. The Harvard group has shown for the first time that soluble TTR aggregates derived directly from an actual patient heart are toxic to heart cells — and, importantly, that their lead antibody partially protects heart cells against this toxicity.

Catalytic Antibodies Targeting Transthyretin Amyloid

University of Texas-Houston Medical School (UTHMS)

Principal Investigator: Sudhir Paul
Research Team: Yasuhiro Nishiyama, Stephanie A. Planque

As part of the degenerative aging process, proteins that normally remain dissolved in bodily fluids become damaged, and adopt a misfolded form called *amyloid*. One form of amyloid that is composed of the transporter protein *transthyretin* (TTR) deposits in the heart and other organs with age, beginning to impair heart function in 20-25% of individuals over the age of 80, with increasing prevalence and severity at later ages. No other organization is funding research targeting aggregates composed of wild-type TTR. This makes wild-type TTR a critical-path target for the Foundation.

In loose collaboration with Foundation-funded research on diagnostic and potentially sequestering antibodies at Brigham & Women's Hospital (see the corresponding section in this report), the UTHMS extracellular aggregate team is working to develop novel catalytic antibodies ("catabodies") that would recognize and cleave TTR amyloid deposits deposited in the heart and other tissues. They have developed a system to identify native catabodies and engineered catabody fragments with more powerful amyloid-cleaving capacity, which can be used to augment the body's natural catabody defense system and prevent or reverse diseases of aging driven by extracellular aggregates. With Foundation funding, the UTHSC group have been able to identify native TTR aggregate-targeting catabodies and catabody fragments present in serum samples from young volunteers that were sufficient to account for nearly all of this cleaving activity. The effect was specific to misfolded TTR, leaving TTR in its native conformation untouched.

To mass-produce these native catabodies, the UTHMS team identified subsets of antibody-producing B-cells from patient blood that selectively recognized aggregated TTR, and then applied gene therapy to those B-cells in culture to allow them to proliferate indefinitely and continue generating the needed antibodies. The team's three lead catabody candidates appear to be highly selective amyloid-mincers that leave normal proteins alone, target aggregated TTR, powerfully hydrolyze its molecular bonds, quickly release amyloid fragments, and turn immediately to the next molecule of aggregate for destruction. An important next step will be to develop better ways to purify the candidate catabodies from the B-cell culture fluid. They are now working on a new method using gel filtration combined with ion-exchange chromatography, which should allow for catabodies to be purified while fully preserving hydrolytic activity. The researchers are also investigating whether they can sustain the catabodies' activity (potentially yielding a more effective rejuvenation therapy) if they are separated into a monomer form.

With continued progress, the team is looking to perform more robust proof-of-concept tests in two lines of mice engineered to express wild-type human TTR and common disease-associated mutations, using infused catabodies and possibly transfer of genes into cells in affected tissue for local secretion. Catabodies against beta-amyloid generated separately have already reached this stage and are performing very well.

Identification of the Genetic Basis of ALT

SENS Research Foundation, Research Center

Principal Investigator: Haroldo Silva

Research Team: David Halvorsen, Christine Wu, Manali Aggrawal

The most common way for cancer cells to re-lengthen their telomeres is to hijack the enzyme *telomerase*. However, other cancers — some of which are notoriously difficult to treat — rely on another, less commonly-exploited (and less well understood) mechanism to extend their telomeres: a system known as *alternative lengthening of telomeres* (ALT). The SENS Research Foundation Research Center (SRF-RC) ALT team is making progress along a number of paths toward demystifying ALT and enabling progress toward potentially revolutionary cancer treatments. They are rapidly developing faster, simpler, and less expensive assays to measure hallmarks of ALT activity such as APB (ALT-associated Promyelocytic-leukemia nuclear Bodies) and the linear and circular repeats of telomeric DNA called “C-circles”. The SRF-RC ALT team has, for instance, developed a fast (8 hour versus 2-4 days), high-throughput version of the assay that will enable

researchers to quantitatively measure C-circles in human ALT cells.

The team also submitted a patent application on their C-circle assay technology, which has recently been upgraded into a full patent application. They have received very favorable feedback for their presentations at the EMBO conference on “Telomeres, Telomerase, and Disease” and the Cold Spring Harbor Laboratories Telomeres & Telomerase conference. A collaboration with the inventor of the original C-Circle assay, Dr. Jeremy Henson of the University of New South Wales's Cancer Cell Immortality Group is ongoing: this collaboration has been awarded a \$200,000 grant for ALT research by Tour de Cure, an Australian cancer research charity. A separate collaboration with Dr. Denis Mottet of the Université de Liège in Belgium has also been initiated to study the possible involvement of a protein called HDAC5 in ALT. This year, the team was also awarded a \$25,000 grant from the Life Extension Foundation to advance the development of the APB assay; this work is now being extended with testing of a synthetic polymer drug whose structure is similar to peptides that was sent to the team by Dr. Robert Shmookler-Reis at the University of Arkansas.

As part of validating their assays, the SRF-RC ALT team has replicated the effects of “silencing” (negating the expression of) specific proteins on APB levels in ALT-exploiting cancer lines as reported using the earlier and more cumbersome assay, and also of two chemicals (telomestatin and hydroxyurea).

In collaboration with Capital Biosciences, the SRF-RC ALT team is now initiating the testing of more than 70 reference cell lines from the private, nonprofit biological resource center ATCC for the presence of ALT activity. This important line of investigation may identify new ALT-dependent cell lines in the collection which can be put to use as reference standards.

Glucosepane Crosslinks and Routes to Cleavage

Yale University

Principal Investigator: David Spiegel

Research Team: Cristian Draghici, Sarah Malkowski, Matthew Streeter, Tina Wang

Our arteries slowly stiffen with age. One of the key drivers of this stiffening process is the accumulation of molecular *crosslinks* that are formed between adjacent strands of structural proteins of the large arteries. One major cause of crosslink accumulation in aging is *Advanced Glycation Endproducts* (AGE), and one AGE in particular, called *glucosepane*, is currently thought to be the single largest contributor to tissue AGE crosslinking.

The Yale AGE team is working on new tools for the detection of AGEs and their precursors. This work has already achieved start-to-finish, high-yield synthesis of *glucosepane* from common laboratory reagents in only a few steps. Also being investigated are glucosepane's peptide adducts, its precursor MGH (methylglyoxal-derived hydroimidazolone modifications of arginine), and the understudied crosslink *pentosinane*. The team is now using these compounds to develop new antibodies and reagents to enable rejuvenation research. One of these is small peptides containing glucosepane structures, an early step toward enabling high-throughput screening of potential glucosepane-breaking drugs.

In earlier Foundation-funded research, a group at Cambridge University found that all of the commercially-available antibodies for the major AGE-related molecules are actually highly unreliable. This is a serious impediment to detecting such molecules in tissue samples and in evaluating the effects of interventions targeting them, whether in high-throughput screening or in later studies *in vivo*. The Yale glucosepane team is now tackling this problem. They recently published a scientific paper describing their use of the same underlying chemistry to generate antibodies targeting the three key precursors to *methylglyoxal*, a toxic AGE precursor molecule implicated in the cellular dysfunction underlying diabetic neuropathy and retinopathy. These antibodies are capable of detecting the methylglyoxal precursors inside cells, enabling more powerful research on the cellular targets of these molecules and the mechanisms of their toxicity to cells.

The team is now working to do the same thing for glucosepane, using the novel chemistry they have developed. They are working to synthesize a vaccine consisting of glucosepane peptide antigens, which will be administered to rouse antibodies targeting glucosepane-containing peptides *in vivo*. By isolating and modifying the immune cells that generate the antibodies, the team expects to be able to produce glucosepane-targeting antibodies on an industrial scale.

Epimutations: Targets or Bystanders for Rejuvenation Biotechnology?

Albert Einstein College of Medicine

Principal Investigator: Jan Vijg

Research Team: Xiao Dong, Sylvia Gravina

Just as our genes can suffer *mutations* that damage the instructions cells use to make their encoded proteins, so too our epigenetic structures can suffer *epimutations* that cause cells to aberrantly turn the expression of particular genes on or off. Some epimutations that

occur with age cause harm to us by leading to forms of aging damage (cancer, senescence, or apoptosis) for which rejuvenation biotechnologies are already under development. If those are the only ways that epimutations can harm us, then those rejuvenation biotechnologies will be enough to eliminate their impact on our health. The Albert Einstein College of Medicine (AECOM) epimutations team is investigating the possibility that separately from these harms, epimutations could also 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 cell 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. This means that each particular epimutation will be individually rare, even if large numbers of cells within a tissue suffer some epimutations. In short, only by looking at each cell's individual epimutation burden 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. In 2014, they validated their new assay in mouse tissues, confirming its ability to detect methylation patterns in single fibroblasts (a kind of skin cell), liver cells, and neurons. They were also able to show that the assay can detect epimutations induced in fibroblasts using *azacitidine*, a drug that strips methyl groups off of DNA in isolated cells. They demonstrated that it could also detect and assay the frequency of epimutations as deviations from the reference pattern across an intact tissue (the liver). These results were recently published in the journal *Nucleic Acids Research*.

With the new, validated tool in hand, the AECOM epimutations team are now able to get the first reliable answers to the key question of the rate of epimutation (other than those causing cancer, senescence, or apoptosis) in the cells of aging tissues, starting with a comparison of the epimutation loads in the livers and brains of normally-aging mice. As an indirect measure of the possible harmful effects of non-cancer epimutations, they will also be looking at ways to make cautious use of animal models with an increased rate of epimutation.



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