
sens research foundation
reimagine aging
Annual Report
2020

The seeds of a concept.
The roots of an idea.
The potential of a world
free of age-related disease.

Photo: Sherry Loeser Photography

Sherry Loeser Photography

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# Contents



# The SRF Team

Front row: Anne Corwin (Engineer/Editor), Amutha Boominathan (MitoSENS Group Lead), Alexandra Stolzing (VP of Research), Aubrey de Grey (Chief Science Officer), Jim O'Neill (CEO), Bhavna Dixit (Research Associate). Center row: Caitlin Lewis (Research Associate), Lisa Fabiny-Kiser (VP of Operations), Gary Abramson (Graphics), Maria Entraigues-Abramson (Global Outreach Coordinator), Jessica Lubke (Administrative Assistant). Back row: Tesfahun Dessale Admasu (Research Fellow), Amit Sharma (ImmunoSENS Group Lead), Michael Rae (Science Writer), Kelly Protzman (Executive Assistant). Not Pictured: Greg Chin (Director, SRF Education), Ben Zealley (Website/Research Assistant/ Deputy Editor)

Photo: Sherry Loeser Photography, 2019

# From the CEO

At our 2013 conference at Queens College, Cambridge, I closed my talk by saying, "We should not rest until we make aging an absurdity."

We are now in a very different place. After a lot of patient explanation, publication of scientific results, conferences, and time, our community persuaded enough scientists of the feasibility of the damage repair approach to move SENS and SENS Research Foundation from the fringes of scientific respectability to the vanguard of a mainstream community of scientists developing medical therapies to tackle human aging. Then we made the same case to investors and entrepreneurs; now, rejuvenation companies built on or inspired by our research are part of a robust ecosystem of basic science and biotech venture capitalists advancing the mission.

After serving on the board for ten years, it was great to join the team full time last fall.

While resources affect the pace of our progress, so do regulations and other government policies. So we began a lively dialogue with policymakers by inviting discussions of regulatory reform at our conferences and by hosting the Deputy Secretary of Health and Human Services, Eric Hargan, at our January health care event in San Francisco.

More and more influential people consider aging an absurdity. Now we need to make it one.

At SENS Research Foundation, we develop rejuvenation biotechnologies that will repair the accumulated cellular and molecular damage in our tissues and restore youthful vigor. As you'll see in these pages, we made significant progress in 2019 toward strengthening immune systems, eliminating senescent cells, rejuvenating the neocortex, eliminating cells with rogue remains of ancient viruses, building backup copies to fill in for mutations in our mitochondrial DNA, and other fronts. And we launched some of our previous work into new pharma companies.

We responded to the SARS-CoV-2 pandemic in typical SRF fashion: we led the way with an early work-from-home policy and rigorous safety practices in our lab. As scientists around the world scrambled to understand what risk factors predict disease progression and death from the disease, we contributed what we had learned about the way the damage of aging — from immunosenescence to senescent cells and mitochondrial depletion — underlies the so-called comorbidities. Then we showed how rejuvenation biotechnologies could eliminate this damage by providing case studies of such interventions preventing and reversing similar pathology in experimental animals, as they potentially will for aging humans. As I write,six SRF Summer Scholars at the Sanford Consortium for Regenerative Medicine are generating brain and lung organoids to establish models to study SARS-CoV-2 infection and the resulting pathologies in those organs as well as investigate drugs to prevent or reverse the damage.

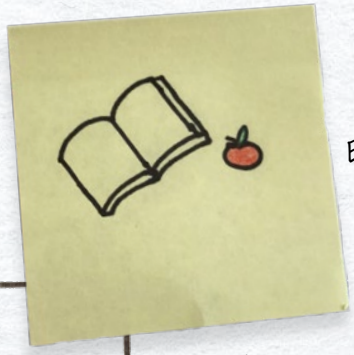
Our education program put creative young scientists to work in our Research Center and in top labs across America and Britain; and our outreach program taught thousands how metabolism leads to aging damage, which drives the pathologies of old age — and how reversal of that damage rather than mitigation of its consequences is the most practical and the most complete response.

Of course our progress depends entirely on the donors listed on the next page, especially the Forever Healthy Foundation, the Antonov Foundation, Vitalik Buterin, the Foster Foundation, James Mellon, Karl Pfleger, and the Dalio Family Fund.

Together, we are building the tools and knowledge to turn back the clock, rejuvenate humanity, and restore health.

CEO

# 2019 Finances



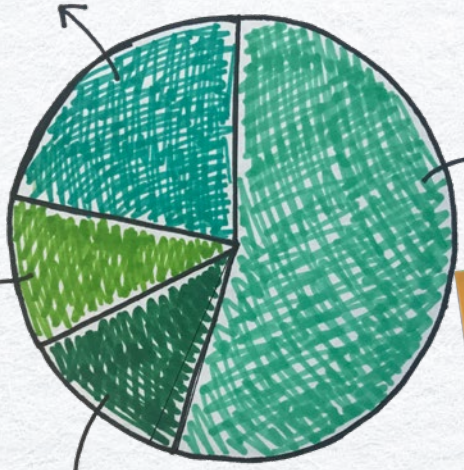
20%
Education

## 2019 Expenses:

- Research – $2,331,364
- Education – $859,222
- Outreach – $642,056
- Administration – $582,616

TOTAL: $4,361,258

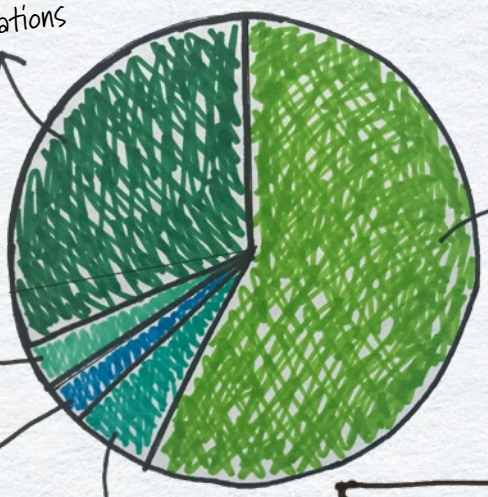
12%
Administration



53%
Research

Outreach
15%

30%
Individual Donations

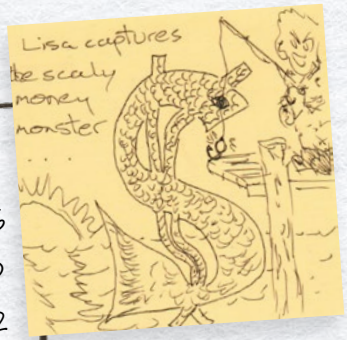


58%
Foundation Grants

4%
Other

cryptocurrency Donations
4%

Corporate Donations
5%




## 2019 Revenue:

- Foundation Grants – $1,562,226
- Individual Donations – $805,140
- Corporate Donations – $126,092
- cryptocurrency – $95,879
- Other – $94,275

TOTAL: $2,683,611

SRF is committed to the highest standards of transparency and accountability. All accounts are prepared by CCA, LLP accountants and independently audited annually by Wheeler Accountants, LLP.

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# 2019 Donor Appreciation Event

## Las Vegas, Nevada

Each year, SENS Research Foundation holds a Donor Appreciation Event to celebrate the roots of our foundation - our donors! In 2019, the event was held in Las Vegas during RAADfest. Our staff members love getting to meet the people who enable our foundation to continue fighting for a world without age-related disease.

SENS Research Foundation staff, including Aubrey de Grey, meeting with some of our donors at the Las Vegas event

# Crypto Meets Longevity

## New York City


During New York City's 2019 Blockchain Week, SRF's Global Outreach Coordinator, Maria Entraigues-Abramson, organized a special Cyrpto Meets Longevity event. The event, sponsored by SRF, Lifespan.io, Life Extension Advocacy Foundation, OpenCures, Repair Biotechnologies, Blockcon, ChainFund, and Blockchain Week, brought together experts in the fields of Rejuvenation Biotechnology and cryptocurrency for a night of networking.

Want to donate cryptocurrency to SRF?

# Undoing Aging 2019

Berlin, Germany

Undoing Aging 2019 had more than 500 participants from 30 countries!

The Undoing Aging Conference is an academic conference series that we introduced in 2018 with the sponsorship and guidance of the Forever Healthy Foundation in Berlin. The conference is focused on the cellular and molecular repair of age-related damage as the basis of therapies to bring aging under full medical control.


The SENS Research Foundation staff at Undoing Aging 2019 with Frank Schüler (far left), COO of Forever Healthy Foundation.

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# Where in the World is Aubrey de Grey?

## 2019 Events and Speaking Engagements

21st Future of Health Technology Summit
Cambridge, MA, USA

4Gamechangers
Vienna, Austria

Asian Actuarial Conference
Resorts World Sentosa, Singapore

Basel Life:
Aging Research for Drug Discovery
Basel, Switzerland

Bay Area Aging Meeting
Stanford, CA, USA

Biohack The Planet
Las Vegas, NV, USA

CPK SRF Fundraiser
Palo Alto, CA, USA

Digital Health Nordic
Helsinki, Finland

Effective Altruism Global
San Francisco, CA, USA

EmTech Asia
Singapore

Ending Aging-Related Diseases Conference
New York, NY, USA

Envision: The Future of Us
Princeton, NJ, USA

Fiduciary Investors Symposium
Cambridge, MA, USA

Foresight Institute Vision Weekend
San Francisco, CA, USA

Founders Forum Healthtech
London, England

Geek Picnic
Moscow, Russia

Health Optimisation Summit
London, England

Heart Summit
Little Rock, AR, USA

In4Med
Coimbra, Portugal


IXPO Tech and Innovation Playground
Bratislava, Slovakia

KES (Knowledge Exchange Sessions)
Sao Paolo, Brazil

Liberty Risk Writers Conference
Cape Town, South Africa

Longevity Leaders Congress
London, England

Master Investor:
Investing in the Age of Longevity
London, England

me Convention
Frankfurt, Germany

Mercer Global Investment Forum
Sydney, Australia

New Tomorrow Together Summit
Whistler, British Columbia, Canada

RAADfest 2019
Las Vegas, NV, USA

Re.comm
Kitzbühel, Austria

Singularity University: Rigmora
Nevis

Singularity University: Temasek
Suntec City, Singapore

Social Innovations
Moscow, Russia

Undoing Aging 2019
Berlin, Germany

University of Oslo (talks)
Oslo, Norway

Vaduz Roundtable
Liechtenstein

Visioneering Summit 2019
Los Angeles, CA, USA

World Healthspan Summit, Redux
Tel Aviv, Israel

World Law Congress
Madrid, Spain

World Stem Cell Summit 2019
Miami, Florida, USA

XPOMET
Berlin, Germany

# SRF's Global Outreach


## 2019 Longevity World Forum:

SENS Research Foundation was one of many sponsors of the 2019 Longevity World Forum in Valencia, Spain. The Longevity World Forum aims to bring together world leaders in the scientific community to discuss ways to improve the quality of life and prevent age-related disease. longevityworldforum.com

Maria Entraigues-Abramson, SRF's Global Outreach Coordinator, presenting at the Longevity World Forum in November, 2019. Maria's presentation, titled "Why We Must End Aging," focused on the burden aging puts on society and our healthcare system.

## RAADfest 2019:

Over the last two years, SENS Research Foundation has sponsored RAADfest. RAADfest combines the energy and fun of a festival, the empowerment and interaction of personal development, with cutting edge science presented for a lay audience to create the most holistic radical life extension event ever. raadfest.com

RAADfest panel featuring (from left to right) Natasha Vita-Moore, SRF's Maria Entraigues-Abramson, Gregory Fahy, and Jim Strole.

## Other SRF-Sponsored Events in 2019:

In 2019, SENS Research Foundation also sponsored Ending Age Related Disease, a Lifespan.io conference in New York City; the International Symposium Biology of Aging in Canada; the Impact Roadmap Lab with XPRIZE; and the Aoki Games by the Aoki Foundation in Las Vegas.

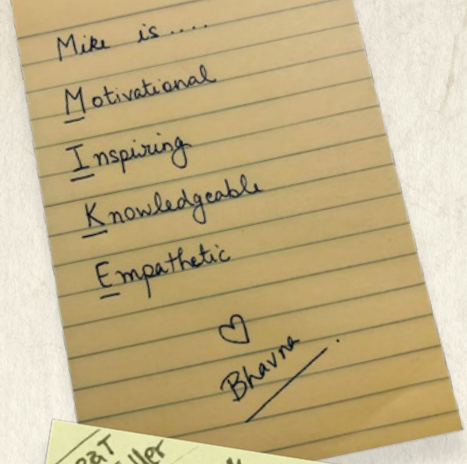

## Leaders in Longevity

Erin Ashford Photography

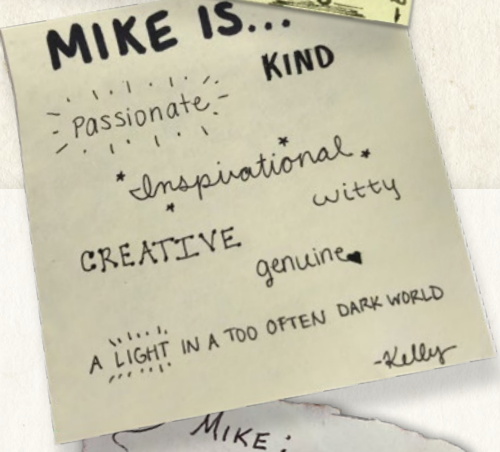
In 2019, SRF's Vice President of Operations, Lisa Fabiny-Kiser (top right), and Global Outreach Coordinator, Maria Entraigues-Abramson (bottom left), were recognized as two of the Top 50 Women Longevity Leaders; Lisa, in the category of Entrepreurs, and Maria, in the category of Media and Publicity Influencers.

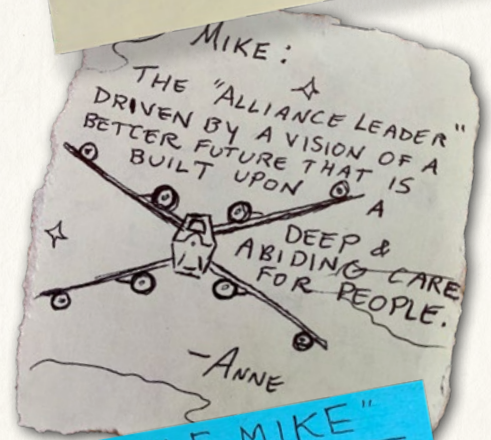
Erin Ashford Photography

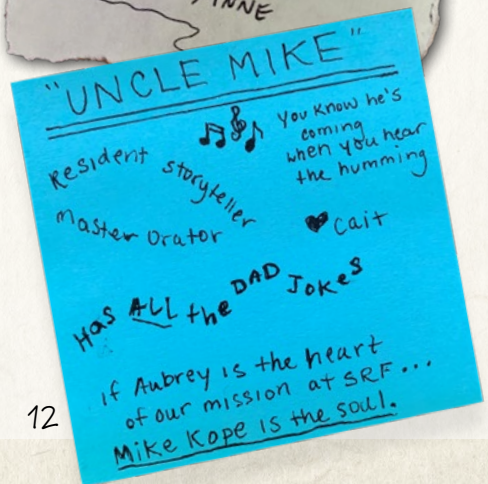
To read more about the Top 50 Women Longevity Leaders of 2019, visit: analytics.dkv.global








# A Decade of Dedication

Before founding SENS Research Foundation with Dr. Aubrey de Grey in 2009, Mike Kope worked in biotech and licensing for universities and private companies, while dreaming of ways to change medicine for the better. Upon joining SRF as CEO, Mike asked, "What would the world look like if we addressed Aubrey's theory of the underlying causes of aging?" The answer to this question became the sketch from which Mike methodically guided SRF for the past decade.


Erin Ashford Photography

Michael Kope, CEO, 2009–2019

SRF's evolving suite of research projects began as a handful of small partnerships with faculty in relevant fields at revered institutions. Ten years later, Mike's leadership has helped ensure a steady stream of research project proposals flooding in through SRF's online grant application portal, and multiple investment partners looking for translational outlets. Mike also built a role for SRF in encouraging big funders, like the NIH, to realize the promise and necessity of a new approach to address the healthcare needs of an aging population, and worked hard to get private industry on board with investing in treatments for age-related pathologies that focused on underlying causes, not just symptoms.

Now, Mike begins a new chapter with Underdog Pharmaceuticals.

# A Noble Pursuit

On November 14, 2019, SENS Research Foundation announced the launch of Underdog Pharmaceuticals, Inc. (Underdog), a pharmaceutical company focused on the development of disease-modifying treatments for atherosclerosis and other age-related diseases.

Underdog was built from an SRF flagship program that has driven two years of applied development designed to explore and repair the underlying causes of cardiovascular disease. Its co-founders are Matthew O'Connor, Ph.D., and Michael Kope, formerly the Vice President of Research and the founding Chief Executive Officer, respectively, of SRF.

Mike and Oki have worked incredibly hard to transition a piece of SRF's basic research to the next level, stepping into the private sector and creating a treatment for age-related disease based on one of SRF's successful proof-of-concept programs. Ten or twenty years ago, cardiovascular disease research meant developing better stents or bypass techniques; Underdog aims to ensure that atherosclerosis won't even exist in the future. All of us at SRF wish Mike and Oki success in this endeavor.

To learn more about Underdog, visit www.underdogpharma.com.

UNDERDOG PHARMACEUTICALS

Mike's leadership at SRF will be missed, but his vision continues to motivate us all.
GC

Mike is
Incredible Storyteller
Warm,
Charming if he wants
Amit

All of us
the larger prolongevist world
owe you an enormous debt
of gratitude. Your leadership
was central to keeping us
moving forward, and to the
recent gelling of a true
rejuvenation biotech industry.
We swear to build on that
work to progressively put
an end to the plague of
biological aging. You have
big boots to fill. -MP

Mike is a great inspirational leader, awesome storyteller, and I admire how he is able to forge a personal connection with each and every one of us at SENS.

-Amutha

Need the Bridge again
speech
ToDo:
- Contract terms
- Outreach Strategy
- Biomarker Research

Don't forget ELKO

Mike is a
visionary
comedian
philosopher
scholar
dreamer
storyteller
friend
JL

MIKE....
- can run an org with me in it
- without losing his mind
- for TEN YEARS
THAT'S NOT EASY
Thank you my friend!


"Underdog may well become one of the most significant endeavors in the rejuvenation biotechnology industry, and Mike and Oki are the perfect team to make it a success."

– Aubrey de Grey, CSO, SRF

Photos: Erin Ashford Photography

Oki and Mike with a model of the molecule whose toxicity Underdog hopes to defeat: 7-ketocholesterol.

# We Invest in Tomorrow

SENS Research Foundation invests in the future of regenerative medicine by providing funding and support to promising biotechnology startups. SRF invested in the following companies during 2019:

COVALENT BIOSCIENCE
Nature-Made Catabodies, Engineered Vaccines

ICHOR

ARIGOS BIOMEDICAL

OISÍN BIOTECHNOLOGIES

## One of SRF's Greatest Investments

Matthew [Oki] O'Connor, PhD, worked with SRF for nearly a decade, from 2009 until the end of 2019. He started off as the Head of Research and later became Vice President of Research. It was Oki's leadership and expansive knowledge of biotechnological research that led many of SRF's projects into startup companies.

Matthew [Oki] O'Connor, PhD

Erin Ashford Photography

Revel

Revel Pharmaceuticals is a biotechnology company located in San Francisco, California with a technology platform based on the SRF-sponsored work of Yale professors David Spiegel and Jason Crawford. Revel is commercializing therapeutic designer enzymes to degrade molecular damage that accumulates with aging. By addressing one of the hallmarks of aging, Revel is strategically positioned to develop therapeutics for multiple diseases of aging including osteoarthritis, kidney disease, cardiovascular disease, skin aging, and complications of diabetes.

UNDERDOG PHARMACEUTICALS

Underdog's research has combined computational and synthetic chemistry programs to create custom-engineered cyclodextrins to capture and remove from cells oxidized cholesterol derivatives such as 7-ketocholesterol, which are broadly toxic molecules with no known biological function. Underdog hopes to provide the first true diseasemodifying treatments for age-related diseases such as atherosclerosis, hypercholesterolemia, heart failure, and macular degeneration.

# Meet the New Faces at SRF

We welcomed three outstanding scientists to our team in 2019.

## Dr. Alexandra Stolzing
### Vice President of Research

I studied basic biology to explore the marvels and mysteries of life. I learned about biochemistry, human genetics, plant growth and the croaking of frogs. One thing intrigued and annoyed me: all these wonders should deteriorate and diminish in time? So I resolved to investigate aging and what could be done about it. I have not looked back. I researched neurodegeneration and the aging brain at Charite Berlin Germany, regeneration at a tissue engineering hub in Sheffield, UK. Seeking to not just observe but to develop findings into practical tools and cures, I led a group on stem cell biology at the Fraunhofer Institutes, worked with various regenerative medicine ventures in translational R&D, and became the first Professor of Biogerontologial Engineering in the UK.

Meanwhile, SRF was applying just such an engineering mindset to the challenges of aging. I joined the scientific advisory board early on, delighted to observe SRF starting to make a real impact in rejuvenation research - changing themindsets of scientific colleagues and wider society. When approached in 2019 about helping to lead the scientific programme, I did not need much convincing. Few other organisations combine the mindsets of scientific curiosity and pragmatic engineering in such a bold vision to **understand, preserve and celebrate life.**

## Dr. Amit Sharma
### Group Lead, Senescence Immunology Research

'Do not go gentle into that good night.' Dylan Thomas wrote these words for his dying father. These words have always resonated with me, as I saw my grandfather - this self-made proud man who once escaped violence and loss during the partition of India and Pakistan and dedicated his life to helping refugees - deteriorate in his advanced years.

The inevitability of aging and death is accepted and even celebrated as part of life in all human societies. However, I often imagine how much better our world could be if we increased the productive years of people like my grandfather, with their years of experience and wisdom. I joined SRF recently with this the mission of my life. The focus of my lab is to understand the mechanisms by which the innate immune system is influenced by aging and the ability to selectively eliminate senescent cells. Our long-term goal is to develop therapeutic interventions by harnessing the immune system in various age-related diseases and disorders.

## Dr. Tesfahun Admasu
### Forever Healthy Foundation Research Fellow

I joined SRF as a Research Fellow through FHF. It is my privilege to work with this smart team. At SRF I am leading the secondary senescence project. This project seeks to test the hypothesis that secondary senescent cells are different from primary senescent cells and would therefore need a different set of senolytics to eradicate. In addition, the project will study the role of the different SASP components involved in the spreading of senescence, and test the hypothesis that intervening in SASP signalling could be therapeutically viable.

To learn more about everyone at SRF, visit:
www.sens.org/about-us/staff

Photos by Sherry Loeser

# SRF Education

SRF Education strives to create a well-trained generation of regenerative medicine scientists, doctors, and policymakers. Our Summer Scholar and Postbaccalaureate Fellowship programs provide students and recent graduates with a unique opportunity to learn while making concrete contributions to high-stakes, cutting-edge research.

## SRF Summer Scholars Program

In 2019, fourteen SRF Summer Scholars joined labs at Harvard Medical School, the Buck Institute for Research on Aging, the Sanford Consortium for Regenerative Medicine, the SRF Research Center, and Stanford University.

Project topics ranged from identification of age-related changes in gene expression across multiple human tissues, engineered cell therapies for glioblastomas, and research on such age-related diseases as Huntington's, Alzheimer's, and atherosclerosis.

SRF Summer Scholars – 2019
(l-r, back) Daron Yim, Eric Sun, Emily Yang, Danielle Hoffman, Elena Fulton. (l-r, front) Tori Lazerson, Helen Heo, Sanjana Saravanan.

Stanford University

sens research foundation
reimagine aging

Sanford Consortium
FOR REGENERATIVE MEDICINE

Buck
Live better longer.

HARVARD
MEDICAL SCHOOL

Dr. Gregory Chin
SRF Director of Education


Dr. Gordon Lithgow, Buck Institute VP of Academic Affairs, leading a facility tour for SRF Education trainees and mentors at the Summer Scholars Symposium.

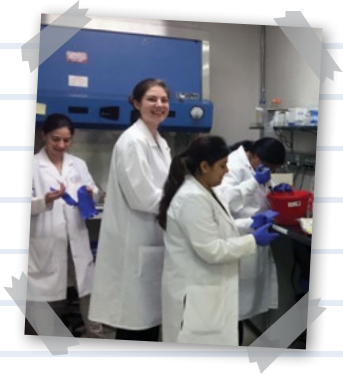
## Summer Scholars Symposium

The Summer Scholars presented the results of their work at the 2019 Summer Scholars Symposium, hosted by the Buck Institute for Research on Aging in Novato, CA, on September 27, 2019.

Dr. Evan Snyder, the Director of the Sanford Center for Stem Cells and Regenerative Medicine, highlighted the work of several SRF trainees (2017 Summer Scholar Aashka Patel, 2017 Summer Scholar Alefia Kothambawala, 2018 Summer Scholar Joshua Sampson, 2018 Postbaccalaureate Fellow Heather Tolcher, and 2019 Summer Scholar Kristin Barbour) in his keynote presentation on the molecular pathophysiology underlying complex neurological disorders.

## SRF Postbaccalaureate Fellowship Program

SRF's newest education program gives recent graduates a chance to spend 10 months engaged in an intensive research experience. This competitive Fellowship, whether as a prelude to graduate school, medical school, or industry work, enables participants to build valuable bench, data analysis, and presentation skills.



Heading into its second year, the Postbaccalaureate Fellowship program expanded from six to seven research projects in 2019. Amit Sharma (SRF RC) and Lisa Ellerby (Buck Institute) joined Amutha Boominathan (SRF RC), Jeanne Loring (Aspen Neuroscience), Julie Andersen (Buck Institute), and Evan Snyder (Sanford Consortium) as mentors.

SRF Postbacc Fellows – 2019
(l–r) Angielyn Campo, Carter Hall, Matthew Stocker, David Begelman, Heather Tolcher.


July 2019 – the first SRF Postbaccalaureate class, representing the Sanford Consortium, the Buck Institute, and the SRF Research Center, presented the results of their projects at the SRF-RC.


## Industry Training

SRF is working with a growing number of industry partners to offer interested students a full range of experiences across the research and development spectrum. Both SRF Education programs now offer opportunities at companies in the regenerative medicine space in addition to academic research labs.

Dr. Jeanne Loring's new company, Aspen Neuroscience, was the first to host SRF Education program participants in 2018-2019; these students participated in a genomics project to help develop an autologous induced pluripotent stem cell (iPSC)-derived neuron replacement therapy for Parkinson's disease.

Dr. Jeanne Loring
Aspen Neuroscience

# 2019 Publications

## by SRF staff, students, partner labs, & other associates

**One-Step Synthesis of 2,5-Diaminoimidazoles and Total Synthesis of Methylglyoxal-Derived Imidazolium Crosslink (MODIC).**
Sabbasani VR, Wang KP, Streeter MD, Spiegel DA.
Angew Chem Int Ed Engl. 2019 Dec 19;58(52):18913-18917. doi: 10.1002/anie.201911156. Epub 2019 Nov 12. PMID: 31713976

**Chronic inflammation in the etiology of disease across the life span.**
Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N, Slavich GM.
Nat Med. 2019 Dec;25(12):1822-1832. doi: 10.1038/s41591-019-0675-0. Epub 2019 Dec 5. Review. PMID: 31806905

**Biocatalytic Reversal of Advanced Glycation End Product Modification.**
Kim NY, Goddard TN, Sohn S, Spiegel DA, Crawford JM.
Chembiochem. 2019 Sep 16;20(18):2402-2410. doi: 10.1002/cbic.201900158. Epub 2019 Aug 9. PMID: 31013547

**Toward a unified theory of aging and regeneration.**
West MD, Sternberg H, Labat I, Janus J, Chapman KB, Malik NN, de Grey AD, Larocca D.
Regen Med. 2019 Sep;14(9):867-886. doi: 10.2217/rme-2019-0062. Epub 2019 Aug 28. PMID: 31455183

**Potential lifetime quality of life benefits of choroideremia gene therapy: projections from a clinically informed decision model.**
Halioua-Haubold CL, Jolly JK, Smith JA, Pinedo-Villanueva R, Brindley DA, MacLaren RE.
Eye (Lond). 2019 Aug;33(8):1215-1223. doi: 10.1038/s41433-019-0492-1. Epub 2019 Jul 17. PMID: 31312000

**Targetable mechanisms driving immunoevasion of persistent senescent cells link chemotherapy-resistant cancer to aging.**
Muñoz DP, Yannone SM, Daemen A, Sun Y, Vakar-Lopez F, Kawahara M, Freund AM, Rodier F, Wu JD, Desprez PY, Raulet DH, Nelson PS, van 't Veer LJ, Campisi J, Coppé JP.
JCI Insight. 2019 Jun 11;5. pii: 124716. doi: 10.1172/jci.insight.124716. PMID: 31184599

**Bioprocess decision support tool for scalable manufacture of extracellular vesicles.**
Ng KS, Smith JA, McAteer MP, Mead BE, Ware J, Jackson FO, Carter A, Ferreira L, Bure K, Rowley JA, Reeve B, Brindley DA, Karp JM.
Biotechnol Bioeng. 2019 Feb;116(2):307-319. doi: 10.1002/bit.26809. Epub 2018 Nov 8. PMID: 30063243

**Clonal derivation of white and brown adipocyte progenitor cell lines from human pluripotent stem cells.**
West MD, Chang CF, Larocca D, Li J, Jiang J, Sim P, Labat I, Chapman KB, Wong KE, Nicoll J, Van Kanegan MJ, de Grey ADNJ, Nasonkin IO, Stahl A, Sternberg H.
Stem Cell Res Ther. 2019 Jan 8;10(1):7. doi: 10.1186/s13287-018-1087-7. PMID: 30616682

**Transient Redirection of SVZ Stem Cells to Oligodendrogenesis by FGFR3 Activation Promotes Remyelination**
Wenfei Kang, Ken C.Q. Nguyen, and Jean M. Hébert
Stem Cell Reports. 2019 Jun 11; 12(6): 1223–1231. Epub 2019 Jun 11. doi: 10.1016/j.stemcr.2019.05.006. PMID: 31189094

**Dysregulated iron metabolism in C. elegans catp-6/ATP13A2 mutant impairs mitochondrial function**
Anand N, Holcom A, Broussalian M, Schmidt M, Chinta SJ, Lithgow GJ, Andersen JK, Chamoli M.
Neurobiology of Disease, 2020 Feb 4:104786. doi: 10.1016/j.nbd.2020.104786. [Epub ahead of print]. PMID: 32032734

**Deficiency in the DNA repair protein ERCC1 triggers a link between senescence and apoptosis in human fibroblasts and mouse skin.**
Kim DE, Dollé MET, Vermeij WP, Gyenis A, Vogel K, Hoeijmakers JHJ, Wiley CD, Davalos AR, Hasty P, Desprez PY, Campisi J.
Aging Cell. 2020 Mar;19(3):e13072. doi: 10.1111/acel.13072. Epub 2019 Nov 18. PMID: 31737985

**Using TARGATT™ Technology to Generate Site-Specific Transgenic Mice.**
Chen-Tsai RY.
Methods Mol Biol. 2019;1874:71-86. doi: 10.1007/978-1-4939-8831-0_4. PMID: 30353508

# Research Advisory Board

These distinguished specialists help guide our research, ensuring SRF's focus on scientific projects with the best potential to lead to a comprehensive panel of age-reversing biomedicine.

Pedro Alvarez, PhD
Rice University

Julie K. Andersen, PhD
Buck Institute for Research on Aging

Anthony Atala, MD
Wake Forest Institute for Regenerative Medicine

Maria A Blasco, PhD
Spanish National Cancer Research Centre

Judith Campisi, PhD
Buck Institute for Research on Aging

George Church, PhD
Harvard University and MIT

Irina Conboy, PhD
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Harvard University

Fyodor Urnov, PhD
UC Berkeley and Altius Institute for Biomedical Sciences

Jan Vijg, PhD
Albert Einstein College of Medicine

Michael West, PhD
AgeX Therapeutics

# Research – 2019 Project Summaries

## Descriptions and updates for work conducted, funded, and supported by SRF

***Stepwise Visualization of Autophagy for Screening Remediation of Intraneuronal Aggregates***
**Buck Institute for Research on Aging**
**Project Director:** Dr. Julie Andersen
**Research Team:** Anand Rane, Manish Chamoli, and Cyrene Arputhasamy

Aging cells accumulate specific types of intracellular protein and lipid aggregates according to cell-type-specific metabolic processes. Brain neurons, for instance, accumulate intracellular aggregates composed of beta-amyloid (which also forms the plaques that appear outside of cells in Alzheimer's disease (AD) and brain aging), alpha-synuclein (which forms the Lewy bodies and Lewy neurites that play a central role in Parkinson's disease), and aberrant forms of the protein tau (which is involved in AD and many other neurological aging diseases).

The lysosome is the cell's recycling center for such damaged proteins, but before damaged proteins even reach the lysosome, they must first be captured and delivered there by a process called autophagy. When things are going well, the cell initially forms vesicles called autophagosomes (APGs) around targets for the lysosome. APGs are dragged to a functional lysosome and fuse with it, forming an autophagolysosome (APL) and depositing their cargo for degradation.

People often assume that an increase in autophagy automatically results in an increase in the ultimate degradation of those substrates, but in fact the word only refers to the delivery process: it's possible to have an increase in autophagy (or in markers of autophagy) that is ultimately futile, failing to clear out the damaged proteins it bears. This can happen as the lysosome takes in aggregated material that it can't successfully clear, which is why simply stimulating more autophagy (via fasting or autophagy-stimulating drugs) slows down but doesn't ultimately resolve related cellular dysfunction. Therefore, equipping the lysosome with new hydrolytic enzymes to degrade such aggregates remains the key to eventually clearing them from aging cells and restoring those cells to health.

Such futile autophagy is thought to be responsible for a common abnormality in the brains of Alzheimer's patients. The branching axons and dendrites that extend from AD-affected neurons accumulate long lineups of APGs. This APG traffic jam is thought to result from a failure of lysosomal function, as the already-overburdened organelle refuses to take up any more cargo, so APGs just continue to build up without doing anything to improve the health of the cell.

In such cases, typical methods of testing autophagy activity can fool investigators into thinking that the affected cells are engaged in robust and successful autophagy, when instead they are signs of futile autophagy and associated with cellular dysfunction.

To sort out this confusion, determine what's really being delivered to the lysosome, and pinpoint disruptions in the autophagy process, Dr. Andersen's team has been developing a system to visualize each of the key steps along the way. They have developed and performed preliminary tests of human and rat neuronal cell lines that produce APGs with a molecular tag that changes color as it moves through the autophagy process. The tag, initially fluorescent green, is taken up by APGs, which release it into APLs when the two organelles fuse; it then loses the green color as the enzymes in the APLs break the tag protein down. Meanwhile, the same cells also produce a second tracker protein that fluoresces red in the background, creating a control for the overall level of protein substrate in the cell. Scientists can combine readouts from the two tags to track the production of APGs in neurons (or, in the future, other cell types), their fusion with APLs, and the functionality of the APLs that ensue.

Looking ahead, these engineered neurons could be used to screen for compounds that increase the successful trafficking of APGs and their cargo to the lysosome as well as the subsequent recycling. Compounds that pass this preliminary test could then be evaluated in neurons expressing (or treated with) intracellular aggregates that drive diseases of aging, such as small soluble beta-amyloid aggregates, to see if these compounds will prevent or reverse the formation of insoluble aggregates. The most intriguing possibility is that they could test whether the autophagic traffic jam in the neuronal cytoplasm in AD and neurodegenerative diseases of aging is actually a primary effect of beta-amyloid, and whether the stable inclusions of aberrant tau that subsequently appear are secondary to this primary, beta-amyloid-driven lysosomal-autophagic dysfunction.

***Retrolytic Therapy to Destroy Cells with Reactivated "Jumping Genes"***
**Roswell Park Comprehensive Cancer Center**
**Project Director:** Dr. Andrei Gudkov
**Research Team:** Marina Antoch, Aimee Stablewski, Nickolay Neznanov, Olga Leontieva, Liliya Novototskaya, Prof. Albert Pinhasov (Department of Molecular Biology at Ariel University, Ariel, Israel)

Nearly half of the mammalian genome is composed of "invasive" genetic material left behind by viruses, including millions of retrotranspons. Retrotransposons are "dead" DNA, but their long- and short- interspersed virus-like repetitive elements (LINEs and SINEs) encode machinery that —under certain circumstances — allows them to reactivate, replicate, and spread through the genome. Degenerative aging causes the intracellular machinery that suppresses LINE reactivation to fail over time, resulting in more and more cells falling prey to retrotransposon reactivation with age.

These reactivation events can cause mutations in our functional genes and even disrupt the normal expression of non-mutated genes, leading to cancer, cellular self-destruction (apoptosis), and cellular senescence. In fact, cellular senescence and reactivation of retrotransposons such as LINE1 are tied intimately together. On the one hand, entry into senescence is one cause of retrotransposon reactivation — yet conversely, retroviral reactivation is a pathway for initiating the senescence-associated secretory phenotype (SASP), which is secreted by senescent cells and is responsible for much of their systemic harm. Targeting the reactivation state in cells with reactivated retrotransposons is thus another approach to tackling senescence-related inflammation.

As a last resort, cells with reactivated retrotransposons can signal the immune system to destroy them. To do this, the cells initiate a pathway leading to the production of the inflammatory signaling molecule *interferon gamma* to recruit the immune system to lyse the affected cell. However, this immunological clearance mechanism is limited, leading to accumulation of damaged interferon-signaling cells (another source of chronic inflammation beyond their role in the SASP). Accordingly, active LINE1 has been tied to tissue inflammation in aging, and suppressing retrotransposon activity with drugs has been shown to inhibit tissue inflammation in aging mice.

With SRF sponsorship, Dr. Gudkov's lab is developing a proof of concept for future rejuvenation biotechnologies that will ablate cells with active retrotransposon activity. For this initial demonstration, Gudkov will use a transgenic "suicide gene" system similar to the INK-ATTAC system that first demonstrated the rejuvenating effects of destroying senescent cells in aging mammals. In this case, the suicide gene system will be triggered by the activation of the interferon response to retroviral reactivation instead of a senescence-associated gene. Just as INK-ATTAC paved the way to the development of today's senolytic therapies (drugs and other approaches that destroy senescent cells), this suicide gene system for the elimination of cells harboring reactivated retrotransposons holds the promise of paving the way for similarly-powerful future "retrolytic" therapies.

Work on this suicide gene system for reactivated retrotransposons is already underway, with Dr. Gudkov's lab constructing the system and inserting it into cells. The next step is to breed mice that will harbor this inducible time bomb in all of their cells. These mice should be able to destroy cells with reactivated retrotransposons whenever they are administered an activating drug.


Sherry Loeser Photography 2019

*Functional Neuron Replacement to Rejuvenate the Neocortex*
**Albert Einstein College of Medicine (AECOM)**
**Project Director:** Dr. Jean Hébert
**Research Team:** Hiroko Nobuta, Joanna Krzyspiak, Alexander Quesada, Marta Gronska-Peski, Jayleecia Smith

When livers, lungs, or kidneys fail, they can be replaced with transplants or supplemented with machines like dialysis. Rejuvenation biotechnology aims to engineer replacements for these organs. But the brain —especially the neocortex — as the seat of our memories, personalities, and emotions is irreplaceable, and so must be rejuvenated.

The maintenance of the brain against degenerative aging processes, however, poses extreme challenges. Only recently have researchers succeeded in integrating new neurons into areas of the brain involved in cognitive functions. Moreover, the vast majority of transplanted cells in these cases have failed to survive, and it is difficult to determine whether those that do survive actually succeed at integrating into synaptic circuits and improving local function.

Surgically transplanting a small number of neuronal progenitors into a local brain structure has been done to date but cannot realistically scale to the sheer size of the brain, or keep up with the rate of age-related neuronal loss. Even trying to do so across the entire brain at the necessary pace would be completely impractical, and would also inevitably do more harm than good, as repeatedly inserting needles deep into the brain would injure the very tissues we're trying to maintain. Therefore, maintenance of the aging brain requires a system for ongoing dispersal of neuronal precursor cells across the brain.

To accomplish this goal, SENS Research Foundation is supporting Dr. Jean Hébert's innovative strategies to overcome each of these critical challenges.

To enhance the survival and integration of transplanted neuronal precursor cells, Hébert's team has co-transplanted them with blood-vessel-forming cells. This ensures that the new neuronal precursor cells have the blood supply necessary to deliver nutrients and oxygen and remove wastes. In young mice, Hébert's group has found that while the co-transplanted vascular precursor cells do contribute to this goal, they provide little additional benefit to the neuronal precursor cells, as the young brain readily supplies its own vascular precursors. By contrast, when the same cells are co-transplanted into stroke model animals, they provide fully 80% of the required vasculature. A much greater number of both neurons and vascular cells is needed to repair a large stroke lesion, and the inflammatory signaling milieu encourages the repairing action of both types of cell. Importantly, grafted neuronal precursors extend projections beyond the lesioned area, forming connections to distant target neurons in the host brain.

The patterns hold true, albeit to a less dramatic extent, when vascular and neuronal precursor cells are transplanted into the aging but otherwise undamaged mouse brain. The next step is transplanting human cells.

To enable the dispersal of replacement neurons noninvasively and throughout the brain, Dr. Hébert's team will next take advantage of the unique properties of microglia, the specialized macrophage immune cells of the brain. Unlike neurons and their precursors, microglia are highly motile cells, able to disperse widely throughout the brain. Hébert's strategy is to transplant microglia into the brains of mice that have already been engineered with the genes needed to initiate this transformation in response to an activating drug, and then reprogram the new microglia into cortical projection neurons after they disperse throughout the brain.

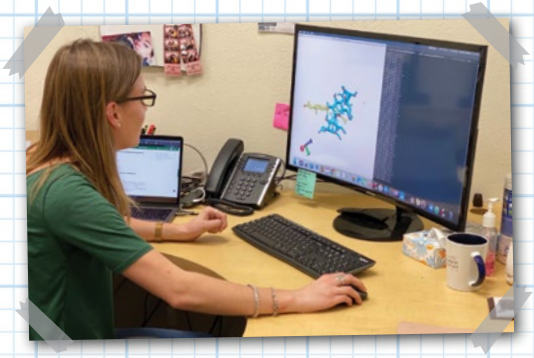
As an important initial proof of concept, Dr. Hébert's group has demonstrated that transplanted mouse microglia will spread across broad areas of the mouse cortex after it is transiently depleted of its own microglia. Demonstrating the same thing using human-derived microglia is going to take a bit longer, as the mouse brain cannot produce an important growth factor the human cells need to survive. The team are overcoming this problem by using a line of transgenic mice that express this human factor; later, the factor could be engineered into the microglia themselves.

From there, the team will characterize the integration of the transplanted microglia-cum-neurons into host circuits and determine whether depleting host microglia enhances these processes in aging mice and in different models of neurodegenerative aging. To demonstrate that the grafted transformed neurons are truly functional, the team will train grafted mice in a learned behavior and then reversibly deactivate the transplant-neurons: if the mice suddenly lose the memory of the learned behavior and associated electrophysiological activity, it will prove that the grafted neurons were responsible for the learning.

*Engineering cyclodextrins for the Removal of Toxic Oxysterols as a Treatment For Atherosclerosis and other diseases of aging*
**SENS Research Foundation Research Center**
**Principal Investigator:** Dr. Matthew O'Connor
**Research Team:** Amelia Anderson, Tamari Kirtadze, Daniel Clemens, Angielyn Campo, Elena Fulton, Anne Corwin

Many diseases of aging are driven in part by the accumulation of waste products derived from their normal metabolic processes. The accumulation of these waste products can inhibit cellular processes and even kill the cells in question. After decades of silent accrual, a critical number of these cells become dysfunctional, causing tissue-specific diseases of aging to erupt. For example, atherosclerotic lesions form when immune cells called macrophages take in 7-ketocholesterol (7-KC) and other damaged cholesterol byproducts in an effort to protect the arterial wall from these byproducts' toxicity — only to ultimately fall prey to that same toxicity themselves. This toxicity causes macrophages to become dysfunctional "foam cells," immobilized in the arterial wall and releasing inflammatory molecules that in turn promote advanced atherosclerosis, heart attack, and stroke. In other organs, the accumulation of damaged molecules inside vulnerable cells drives Alzheimer's disease, as well as age-related macular degeneration.

If such damaged molecules could be removed from cells, then the associated cellular dysfunction and age-related diseases could be prevented — and potentially even reversed, especially if combined with other rejuvenation biotechnologies targeting other cellular and molecular damage involved in the disease process.



Dr. O'Connor's team has created a family of novel cyclodextrins that are able to selectively remove toxic forms of cholesterol from early foam cells and other cells in the blood. Cyclodextrins are polysaccharides (complex sugar molecules) composed of glucose molecules arranged in a truncated conical shape. Cyclodextrins are known to bind hydrophobic (water-repelling) molecules such as cholesterol and many of its byproducts, thereby conferring solubility to otherwise insoluble molecules. Cyclodextrins are in wide use for industrial and drug delivery applications, and have an excellent safety profile. Clinical studies are underway using one form of generic cyclodextrin as a potential way to remove normal cholesterol from children with Niemann-Pick type C disease, a genetic disorder in which patients cannot export excessive cholesterol from their cells.

Dr. O'Connor's team has designed their new cyclodextrins using computer modeling to predict the likely behavior of rationally-designed molecules. Preliminary testing of the new cyclodextrins suggests enhanced activity against 7-KC relative to the existing family of cyclodextrins in conjunction with lower affinity for normal cholesterol. Specificity for 7-KC is important both from a therapeutic standpoint, and for the sake of reducing the potential for side effects such as hearing loss (which can occur when the ear's outer hair cells are deprived of normal cholesterol, an essential biomolecule for those cells). Patents have been filed to protect this valuable intellectual property and a new spinoff company, Underdog Pharmaceuticals, has been launched in order to bring in the private venture capital needed to turn this basic research into a working rejuvenation biotechnology available for medical use. Underdog successfully attracted their seed round of funding, with Kizoo Ventures taking the lead. If effective, these small molecules could serve as the basis for a groundbreaking therapy that would prevent and potentially reverse atherosclerosis and, possibly, heart failure.

The Underdog team has developed an ex vivo foam cell assay in which to test the novel molecules. This assay aims to recapitulate what happens when 7-KC prevents macrophages from metabolizing both normal and damaged cholesterol products. If the drugs manage to remove 7-KC from foam cells in this model, leading to successful rehabilitation of foam cells into functioning macrophages, it will be a strong signal that Underdog's candidate drugs will help ameliorate, and potentially even reverse, cardiovascular disease in human patients.

### *Targeting Secondary Senescence*

**SENS Research Foundation Research Center**
**Principal Investigator:** Dr. Tesfahun Dessale Admasu

In addition to the classical causes of cellular senescence (see "Rejuvenating Immune Surveillance of Senescent Cells"), scientists have relatively recently discovered the phenomenon of secondary senescence. For reasons which we are only beginning to understand, existing senescent cells can cause other cells in the body to become senescent. Some of this effect is mediated by the SASP, which has been termed "paracrine senescence;" additionally, one group has reported a form of secondary senescence imposed independently of SASP, which is instead mediated through direct contacts between the primary and secondary senescent cells in what they term "juxtacrine" secondary senescence. Secondary senescence is emerging as one of the reasons why senescent cells are so dangerous: they can in a sense "replicate" themselves, seemingly even to anatomically remote sites in the body, ratcheting up their own baleful influence in a kind of senescent metastasis.

Although this research is still in an early stage, it is beginning to appear that secondary senescent cells behave differently from primary senescent cells: they produce less SASP, but more fibrillar collagens — something that is normally suppressed in primary senescent cells. Granted their differences in origin and function, might secondary senescent cells also be differentially susceptible to senolytic therapies? For instance, might they be resistant to senolytic drugs that are effective against primary senescent cells, requiring a new generation of targeted "secondary senolytics" to eliminate — or might they be exceptionally susceptible to particular such treatments?

SENS Research Foundation Forever Healthy Postdoctoral Fellow Tesfahun Admasu's work seeks to find answers to these questions. Dr. Admasu aims first to characterize secondary senescence in endothelial cells (which comprise the linings of organs like the GI tract, the blood vessels, and the lungs. Until now, the great majority of senescent cell research has been performed in fibroblasts (cells from the deeper layers of the skin and various organs' extracellular matrixes). In another distinction from much of the work in the field, these cells will be taken directly from donors, rather than from cell lines that have long been maintained in culture. Senescence will be induced in endothelial cells using several of the standard lab methods, and these primary senescent cells will then be used to generate secondary senescent endothelial cells by bathing normal endothelial cells in the SASP-rich medium suctioned off of the primary senescent cells. Later, when budgeting allows, Dr. Admasu plans to also induce secondary "juxtacrine" senescence in these cells by culturing senescent and normal endothelial cells together, allowing for direct cell-to-cell contact.

He is furthermore experimenting with the use of the cell-surface marker DPP4 as a potential marker of senescent cells (which has been reported but is understudied). If confirmed, DPP4 would allow for much more convenient sorting of samples of cells into senescent and non-senescent populations; this would be especially valuable for the study of paracrine senescence, where only a minority of exposed cells enter senescence (whereas typical senescence-inducers may push 90-95% of cells over the edge).

Once the above goals are met, Dr. Admasu plans to investigate just how secondary senescent cells differ from primary senescent cells. He will begin by evaluating differences in gene expression, looking in particular at the known molecular targets of existing senolytic drugs. He will then test several of the standard senolytic drugs for their effects in primary vs. secondary senescent cells, to see if secondary senescent cells are differentially vulnerable to particular senolytics with particular mechanisms of action. These two sets of experiments should help reveal good targets for new drugs geared toward the specific elimination of primary or secondary senescent cells, and may also allow future clinicians to tailor existing senolytics for people with secondary-senescence-associated disorders.

Ultimately, this work should greatly enhance our understanding the full spectrum of senescent cell types and the spread of senescent cells through the body in aging, enabling us to take the battle to the enemy on all fronts and in all of its guises.

### *Target Prioritization of Tissue Crosslinking*

**The Babraham Institute**
**Principal Investigator:** Dr. Jonathan Clark
**Research Team:** Dr. Melanie Stammers

Structural proteins in our bodies play many important roles. The gradual loss of elasticity in the tissues composed of these long-lived proteins is a significant feature of aging damage. Age-related stiffening of the arteries hinders their ability to cushion the surge of blood on its way from the heart to end-target organs. The result is that the same heartbeat's worth of blood hits these organs all at once and at full intensity, leading to progressive kidney damage, lesions in the brain called white-matter hyperintensities, strokes, and other chronic and acute end-organ damage.

Sherry Loeser Photography 2019

One cause of stiffening in long-lived tissues is crosslinking, where one strand of structural protein becomes chemically bound to an adjacent strand, limiting the range of motion of both strands. Loss of elasticity increases as more and more such crosslinks accumulate in our tissues with age. Continuous exposure to blood sugar and other highly reactive molecules that are necessary for life can mature into a kind of crosslink termed Advanced Glycation Endproducts (AGE). It is currently thought that the single most common AGE crosslink in collagen – a key structural protein — is a molecule called glucosepane.

Prior SRF-funded work in Dr. David Spiegel's lab at Yale paved the way to the discovery of the therapeutic glucosepane-cleaving enzyme candidates that our startup company Revel Pharmaceuticals is now working to advance into functional rejuvenation biotechnologies. However, AGEs are not the only cause of crosslinking in aging tissues. The sheer number of a given type of crosslink is moreover not necessarily a good parameter for determining how we should prioritize that crosslink type as a rejuvenation target. Different crosslinks have different effects on the mechanical properties of a given kind of protein, and on how much they interfere with the body's ability to repair damaged tissue.

Recognizing the importance of prioritizing our targets, SRF is funding a systematic study in "normally"-aging, nondiabetic mice by Dr. Jonathan Clark at the Babraham Institute in Cambridge. These mice are fed diets containing labeled amino acids, which are then incorporated into extracellular matrix proteins during synthesis. This allows Dr. Clark's group to track the rate at which proteins are synthesized, crosslinked, and replaced over time.

An early and surprising finding was that crosslinks that one might think permanent in tissue are actually continuously breaking apart and re-forming under the stress and strain of normal activity. In fact, Clark's group has shown a decline in the steady-state level of reversible crosslinks with age that actually exceeds the total increase in irreversible crosslinks. Some of the crosslinks that others have reported as accumulating in aging tissues were not detected in these tissues — though importantly, the age-related rise in glucosepane previously reported primarily in a few human tissues was also seen in the tendons and (of special significance) aorta of aging mice. This rise in glucosepane level appears to correlate well between tissues: if verified, it could serve as a useful research and clinical metric. For instance, doctors and scientists could use a simple skin biopsy as a proxy for the level of glucosepane in a mouse or human patient's other tissues, such as the aorta.

Another important finding was that after elastin is produced and incorporated into an overall extracellular matrix structure, it is then actively crosslinked via biological processes that were hitherto unknown outside the cell. If these regulated, "intentional" crosslinking processes decline with age, the ensuing elastin would be friable and easily broken.

Drs. Clark and Stammers have additionally been conducting extensive *in vitro* and *in vivo* mechanical testing of tissues in an effort to gauge the functional impact of the changes detected in chemical analysis on tissues. They have confirmed previous researchers' finding that the stiffness of the artery (as measured by pulse-wave velocity, the clinical gold standard) rises with age in mice as it does in humans. Finding ways to tie these rises in stiffness to each other and to specific crosslinks will be key to developing future rejuvenation biotechnologies to keep our tissues supple and youthfully functional, even as glucosepane crosslink-breakers enter into animal testing.

### *Engineering New Mitochondrial Genes to Restore Mitochondrial Function*

**SENS Research Foundation Research Center**
**Principal Investigator:** Dr. Amutha Boominathan
**Research Team:** Bhavna Dixit, Caitlin Lewis, Sanjana Saravanan, Carter Hall, Nana Abena Anti, David Begelman

Mitochondria are the power plants in our cells, and like other power plants, they generate waste as they work — free radicals, which over time damage mitochondrial DNA. A small but rising number of our cells get taken over by such dysfunctional mitochondria as we age. These damaged cells in turn export toxic molecules to far-flung tissues, contributing to Parkinson's disease, age-related muscle dysfunction, and other conditions.

The MitoSENS program at the SRF Research Center is dedicated to solving this grand engineering challenge, via the central strategy of allotopic expression (AE) of functional mitochondrial genes. AE involves placing backup copies of the mitochondria's protein-coding genes in the cell's nucleus with the rest of our genetic material. From this safe harbor, the backup genes can then direct the cell's machinery to produce engineered versions of the missing mitochondrial proteins and deliver them to the mitochondria.

Sherry Loeser Photography 2019

In 2016, the MitoSENS team demonstrated efficient, functional allotopic replacement of the missing mitochondrial ATP8 gene in cells from a human patient with an ATP8 mutation. In the process, they observed and then verified that a change in the way AE genes are encoded can greatly increase the production of actual AE proteins and their ultimate ability to restore mitochondrial function. Mitochondria specify amino acids for protein synthesis differently from nuclear genes, meaning that even if we knew the exact sequence of a mitochondrial gene, the mammalian cell's protein synthesizing machinery would misinterpret the unfamiliar mitochondrial language and produce defective proteins.

To overcome this problem, AE researchers have hitherto chosen which of several alternative nuclear spellings for a given amino acid to substitute for the mitochondrial choice of encoding based primarily on how frequently that spelling is used overall in the nuclear genome. In other fields of biotechnology, such tally-based minimally-recoded methods have long been known to work poorly for synthesizing human proteins in bacteria, as is done to produce therapeutic biological products like insulin and growth hormone. Scientists have learned that the particular choice of alternative coding for a given amino acid indirectly affects a number of characteristics of the resulting mRNA — the working copy of the gene that is actually used directly as a blueprint for protein production. Biotech has thus developed codon optimization algorithms to guide the engineering of recombinant genes according to these secondary effects of alternative codings for translating between human and bacterial cells.

The MitoSENS team realized that the insights of codon optimization from other fields of biotechnology could greatly improve the process of producing mitochondrial genes from the mammalian cellular machinery. They have since successfully created optimized versions of AE genes previously generated through the simple, frequency-based minimal recoding method. When the optimized genes were engineered into human cells, eight of the thirteen proteins achieved sustained protein production, versus only a fraction of the conventionally-engineered genes— and the optimized proteins actually reached their mitochondrial targets. The MitoSENS team are now using codon-optimization technology to advance work on the mitochondrial subunit genes ND4 and ND1. Importantly, this will allow them to compare the minimally-recoded versions of these genes used in prior work (including one that has advanced into clinical trials) to the codon-optimized versions with no other changes, as well as to versions that are further improved in other respects. The MitoSENS team also continues to fine-tune their process for engineering the allotopic ATP6 previously used to push the ATP8 mutation patient cells over the hump into functionality.

Going forward, the ability of the SRF MitoSENS team and AE researchers around the world to optimize the sequence of their AE proteins should now accelerate progress toward success with all 13 mitochondrially-encoded genes. The next necessary step in applying AE genes as a human rejuvenation biotechnology is to move beyond cell models and demonstrate effective rescue of mitochondrial defects in living, breathing mammals. Thanks to the generous support of our donors through our partners at geroscience crowdfunding platform Lifespan.io, research is now underway to do just that. This will be the first time that any AE gene will be tested in mice with a mutation in their mitochondrial DNA.

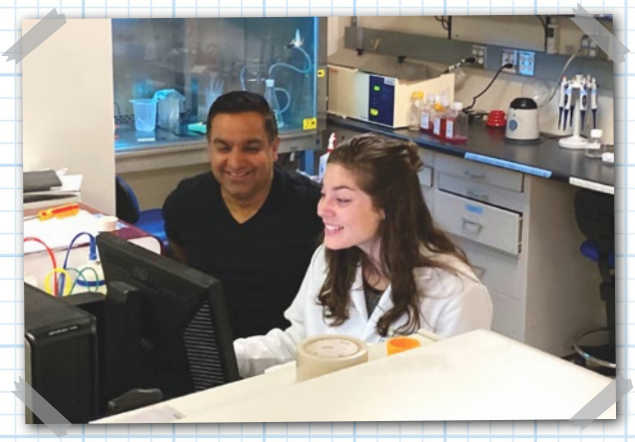
This work will employ the Maximally Modifiable Mouse (MMM), created by SRF-funded research over the last several years. Using these mice, the allotopic version of the mitochondrial subunit ATP8 was engineered into a safe "landing pad" in the nuclear genome — the same optimized AE ATP8 gene that the MitoSENS team previously proved effective in human cells. Then, these mice will be crossed with female C57BL/6J FVB mice, which have a mild but specific mutation in the ATP8 gene. The result will be a new MMM-derived mouse model with the defective FVB mouse ATP8 gene still in their mitochondria, but with the allotopic ATP8 construct engineered into their nuclear genomes and available to supplement the mutated mouse gene.

In previous work, the SRF MitoSENS team showed that cells from FVB mice that are engineered with our codon-optimized AE ATP8 produce significantly more actual ATP8 protein than those engineered with a minimally-recoded version of the same gene. Moreover, the optimized AE protein works as intended. By now engineering the AE ATP8 gene into living MMM-FVB mice, we will be able to demonstrate that AE ATP8 can rescue their defective mitochondrial function *in vivo*, giving them energy-production capacity and metabolisms similar to healthy, normal mice.

### *Rejuvenating Immune Surveillance of Senescent Cells*

**SENS Research Foundation Research Center**
**Principal Investigator:** Dr. Amit Sharma
**Research Team:** Elena Fulton

Senescence is a state of cellular growth arrest, activated when cells are subjected to potentially cancer-promoting stresses. This helps protect the rest of the body from danger, but with a cost as senescent cells accumulate in our tissues with age. Rising numbers of senescent cells reduce our regenerative potential; moreover, they spew out a mixture of inflammatory signaling molecules, growth factors, and tissue-degrading enzymes called SASP. Senescent cells contribute to age-related disease, frailty, and death, and are specifically implicated in osteoarthritis, age-related diabetes, age-related lung dysfunction, cancer, certain side-effects of conventional chemotherapy drugs, and neurodegenerative diseases of aging like Parkinson's and Alzheimer's.



Powerful evidence for the role of senescent cells in aging has emerged from studies using senolytic drugs: small molecules that selectively destroy senescent cells. Both in mice undergoing physiological aging, and in animal models of age-related disease, administration of senolytic drugs has led to sweeping rejuvenating effects and the prevention, arrest, or even reversal of some diseases of aging. Clinical trials of senolytic drugs in humans are still very preliminary, but may end up being the first steps toward making the earliest rejuvenation biotechnologies available for widespread clinical use.

Still, as powerful as senolytic drugs are, they are not a perfect solution. Toxicity remains a risk, due to the incomplete specificity of these drugs for senescent cells. Fortunately, there is an alternative way to eliminate senescent cells — and it's already built into us.

Scientists have known for over a decade that the body's immune system can destroy senescent cells. This ability is centered on a type of immune cell called the Natural Killer or NK cell. Whereas T-cells and B-cells are specialists, focused on eliminating specifically-identified threats (such as cells infected with specific viruses), NK cells are more like sentinels patrolling the perimeter of a military camp, on the lookout for anything that looks like an intruder, rather than hunting for a specific enemy.

Fortunately, when cells go rogue — senescent, cancerous, or infected by viruses — they are programmed to show their colors to the NK cell authorities by raising flags (ligands) on their surface that interact with receptors on the NK cell surface. When an NK cell's receptor locks on to a senescent cell's corresponding ligand, the NK cell destroys the senescent target. Still, it is clear that senescent cells accumulate with age, despite the body's reasonably effective system for detecting and eliminating them. Part of the explanation for this lies in the inherent imperfection of all of our inbuilt damage-repair mechanisms. Inevitably, there are tradeoffs involved in making these mechanisms more aggressive, numerous, or precise; small traces of damage are thus always left unaddressed, and accumulate over time.

We also now know that both senescent and cancer cells use a variety of mechanisms to hide from NK cells, or inhibit NK cells' ability to destroy them. Several such mechanisms have been uncovered by scientists, including our partners at the Buck Institute for Research on Aging, who are performing SRF-funded work to advance the target-discovery process.

In 2019, Dr. Sharma's team at the SRF Research Center (RC) discovered preliminary evidence of another such mechanism of NK evasion. This mechanism was already known to modify the immune response to other kinds of damaged cells, and to be elevated in the circulation and many human tissues with age. The Sharma team's preliminary evidence suggests that senescent cells also exploit the mechanism. In 2020, Dr. Sharma and his team will begin testing drugs and other molecules that block this mechanism from interfering with NK cell killing, to see if this enhances the NK cells' senescent cell elimination ability.

Additionally, the Sharma team collected preliminary data in 2019 showing a significant decline in the proportion of NK cells exhibiting markers of strong cell-killing ability in older volunteers. In 2020, they will investigate whether this holds up in a larger sample. If so, they will also evaluate whether this decline translates into reduced ability to kill senescent cells, by comparing the performance of freshly isolated NK cells from younger humans, and running similar tests on NK cells from the spleens of young (6 months) and old (24 months) mice.

If these more rigorous studies validate the RC team's preliminary finding, it will make the case that aging peoples' NK cells have less capacity to eliminate senescent cells, independently of evasive maneuvers on the part of their senescent targets. The next step will therefore entail developing strategies to rejuvenate the NK cells themselves. Animal experiments are planned as a preliminary test of such rejuvenated NK cells' potential.

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