2021

ANNUAL REPORT

sens research foundation
reimagine aging

SENS RESEARCH FOUNDATION

110 Pioneer Way, Suite J
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www.sens.org

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FROM THE CEO

The global pandemic that destroyed more than three million innocent lives also exposed some important truths. Great effort can produce effective responses to a public health crisis more rapidly than experts thought possible. Poorly conceived regulation can cost lives by delaying effective solutions.

Both of these truths also apply to the public health crisis of aging. When our society puts the same resources, energy, and urgency into reversing aging damage that we devoted to preventing and treating SARS-CoV-2 infections, we'll extend millions of healthy lives by decades.

We're pushing for that moment to arrive soon, developing rejuvenation biotechnologies that will remove the cellular and molecular damage of aging from our tissues and restore youthful vigor. We made significant progress in 2020 toward rejuvenating the immune system, eliminating senescent cells, rejuvenating the neocortex, obviating mitochondrial mutations, understanding the range and impact of tissue crosslinks, and on various other fronts, all of which you can read about in these pages.

We also partnered with Dr. Evan Snyder at the Sanford Consortium for Regenerative Medicine to learn more about the role of aging in making us vulnerable to COVID-19. Under the expert mentorship of the Snyder lab, six of our Summer Scholars successfully established innovative lung and brain organoid models as well as a lung epithelium model. They demonstrated that these systems could be infected with the virus and that they could use them to test drugs that might thwart that infection and to profile aspects of COVID-19 that might make the elderly so vulnerable. The model systems they established may accelerate progress toward novel therapies against COVID-19 and against lung and brain aging.

At the end of 2020, we started building a vivarium in our Mountain View Research Center, which increased our capabilities by allowing us to do mouse work in-house.

Our education program put creative young scientists to work in our Research Center and other top research institutes across America. This year, 579 students from across the nation applied for our 14 Summer Scholar positions—more than 40 applicants per slot—while 112 recent graduates sought one of our 7 Postbaccalaureate Fellowship positions offered this year. We've entered a partnership with Dominican University of California to host students in their Master of Biological Sciences Program. With significant support from Dalio Philanthropies, we integrated experimental design and data interpretation into an online high school biology curriculum. Our first modules explore different clinical manifestations of COVID-19 and cellular senescence in aging.

Our outreach program won more converts to the feasibility and the benefits of rejuvenation biotechnology to extend healthy longevity, and taught them to understand the cascade that leads us from metabolism --> damage --> pathologies, and reversal rather than mitigation as the optimal strategy for medical intervention.

Our progress depends entirely on our donors, including Vitalik Buterin, the Forever Healthy Foundation, Michael Antonov, Harry McPike, Lei Ding, Karl Pfleger, Jim Foster, Ronny Hatteland, Brendan Iribe, Daniel Isaacson, and many others listed in these pages.

Our safety protocols ensured that not a single member of our team caught COVID-19, and allowed our lab workers to continue their research safely while the rest of us worked from home. I conducted many a video meeting just a few feet from a large old redwood, a model for healthy life that spans centuries.

We are ready to unlock longevity; we just need a few more keys.

INVESTING IN LONGEVITY

In addition to conducting research, SENS Research Foundation invests in the future of regenerative medicine by providing funding and support to promising biotechnology startups,

Underdog Pharmaceuticals develops simple and direct interventions targeting toxic forms of cholesterol, using rationally designed molecules to provide **the first true disease-modifying treatments for age-related diseases such as atherosclerosis, hypercholesterolemia, heart failure, and macular degeneration.** Underdog's research has combined computational and synthetic chemistry programs to create custom-engineered cyclodextrins (polysaccharides with known industrial and pharmaceutical excipient uses) to capture, and remove from cells, oxidized cholesterol derivatives such as 7-ketocholesterol, which are broadly toxic molecules with no known biological function.

Revel Pharmaceuticals is commercializing therapeutic designer enzymes to degrade the molecular damage that accumulates with aging. Much like the caramelization and browning of a steak on the grill, collagen and other important proteins in our bodies slowly brown with aging—damaging the integrity and function of organs. Revel has discovered enzymes which can reverse the cooking process that occurs during aging—**returning aged collagen to a youthful state** at the molecular level. Revel is developing therapies to reverse the molecular damage of aging with many clinical applications in sight.

Covalent Bioscience is developing the first-in-class **catalytic antibody (catabody) and e-vaccine technologies, paving the way for multiple new preventative and treatment measures for life-threatening disease.** Covalent's lead catabodies focus on healthy aging and age-associated diseases. Their lead E-vaccine has promise for effective prophylaxis and therapy of HIV infection worldwide.

Ichor Therapeutics has established a portfolio of highly focused companies, each of which targets a specific type of age-associated molecular damage. Ichor develops **drugs to target classes of molecular damage believed to drive the onset and progression of aging and age-associated diseases.** Each research program by is designed to treat a specific age-associated disease (such as macular degeneration), while at the same time, offering potential for synergistic effects on other aging conditions.

Senescent cells secrete molecules that cause inflammation in an effort to attract immune cells that would usually clear them. But for reasons that are not fully known, as we age, persistently senescent cells accumulate, leading to a vast number of age-related diseases. Oisín is developing a **highly precise, patent-pending, DNA-targeted intervention** to clear these cells. As a recent study has shown, clearing senescent cells both reduces negative effects of aging pathologies and also extends median lifespan and survival.

OncoSenx is a subsidiary of Oisín. OncoSenx targets solid tumors based on transcriptional activity using a unique Proteo-Lipid Vehicle and plasmid DNA. OncoSenx's treatment delivers a simple program that **induces apoptosis in cancerous cells.** This approach is a less invasive, more precise intervention against cancer.

Repair Biotechnologies is a preclinical biotechnology company focused on developing drugs for cholesterol and aging-related diseases. Their first-in-class **Cholesterol Degrading Platform (CDP) technology** is aimed at reversing atherosclerosis, familial hypercholesterolemias, and other conditions in which excess or modified cholesterol drives pathology.

2020 END OF YEAR CAMPAIGN

The global pandemic challenged every endeavor in 2020, but we pushed forward and found **safe and effective ways to continue our life-saving research**.

Our safety protocols protected our researchers in the lab.

Our education program expanded to include virtual internships and developed the RISE curriculum.

We postponed our Undoing Aging conference.

And while many nonprofits struggled to raise funds, our community rallied to unlock longevity with an unusually successful end-of-year campaign, led by Oculus co-founder Michael Antonov.

"I've followed and supported SENS research over the last few years and am excited to up my commitment this year because their organized, practical approach to combating aspects of aging, such as breaking down of crosslinks, rejuvenating mitochondria, and clearance of senescent cells has the potential to help human lives and achieve age reversal in the near future."

-Michael Antonov

SRF raised a total of $2,335,443 during our 2020 End of Year Campaign. A large part of that was due to the generosity and passion for the cause of one of our greatest supporters, Michael Antonov of the Michael Antonov Foundation.

Michael donated $1,000,000 to our campaign, while encouraging others to participate by matching their donations.

The Michael Antonov Foundation was founded with a vision of extending average human lifespan to over 120 and enabling people to better understand the world and become masters of their own destiny. The foundation makes grants and gifts to 501(c)(3) organizations that perform human longevity-centered research and collaborates with industry players in order to maximize the impact of longevity-centered projects.

Michael Antonov is a serial entrepreneur and philanthropist passionate about taking on a challenge to extend human lifespan.

THANK YOU TO OUR DONORS

Together, we can unlock longevity

Special thanks to our TOP DONORS (over $100,000 in 2020)

Vitalik Buterin, Lei Ding, The Michael Antonov Foundation, Forever Healthy Foundation, Foster Foundation, Karl R. Pfleger Foundation, The McPike Zima Foundation, Silicon Valley Community Fund, and Daniel Isaacson.
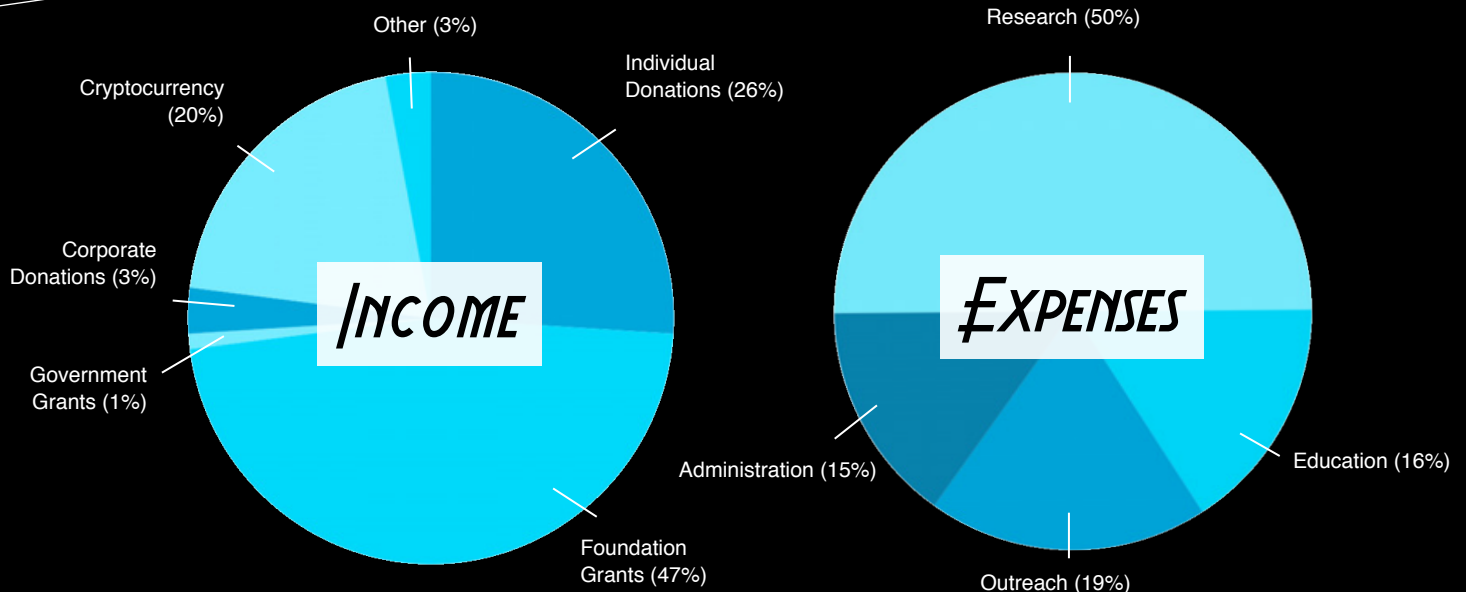
And to the rest of our donors!

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2020 Finances

Income
- Other (3%)
- Individual Donations (26%)
- Cryptocurrency (20%)
- Corporate Donations (3%)
- Government Grants (1%)
- Foundation Grants (47%)

Expenses
- Research (50%)
- Education (16%)
- Administration (15%)
- Outreach (19%)

SRF IS COMMITTED TO THE HIGHEST STANDARDS OF TRANSPARENCY AND ACCOUNTABILITY.

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Each year SRF sponsors a variety of longevity-based conferences and campaigns. Despite the switch to all virtual conferences early in 2020, SRF continued our tradition of supporting allies in the rejuvenation biotechnology space.

RAADfest 2020
(Coalition for Radical Life Extension)

Ending Age-Related Diseases 2020
(Lifespan.io)

The 2020 International Conference on Future Africa (Transdisciplinary Agora for Future Discussions)

The 2020 Longevity Activism Competition
(International Longevity Alliance)

Undoing Aging will return in 2022, again bringing together scientists and startups from around the globe in Berlin for a vibrant in-person experience. The Undoing Aging 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. Visit undoing-aging. org for updates!

EDUCATION

While our internal labs operated throughout the pandemic with safety measures, some of our external partner labs paused operations.

SRF Education adapted, and continued to provide our students with learning experiences and opportunities.

Dr. Gregory Chin
SRF Director of Education

Summer Scholars
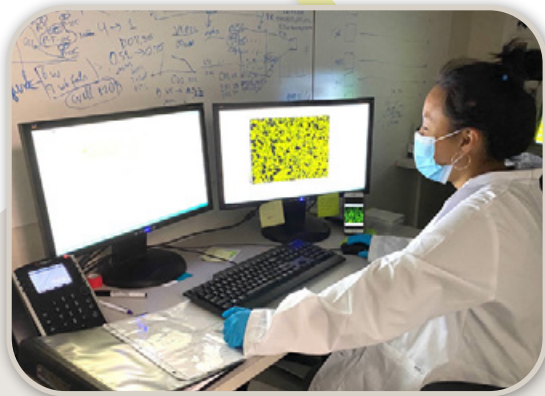
Summer Scholar Aly Ung

Students selected for the Summer Scholars Program were offered the choice of a virtual or in-person internship. SRF was one of the few summer internship programs in the country to offer onsite research experiences, enabling student participants to continue to learn and grow as scientists.

In total, eight students traveled to the SRF Research Center (SRF-RC) or the Sanford Consortium, while six students participated as virtual Summer Scholars with the Buck Institute for Research on Aging, Harvard Medical School, Stanford University, Turn Biotechnologies, and Underdog Pharmaceuticals. One student also opted to start graduate school early.

Postbaccalaureate Fellows

Students selected for Postbaccalaureate Fellowships worked with research leads at the SRF-RC, the Buck Institute for Research on Aging, the Sanford Consortium for Regenerative Medicine, and Stanford University. As with the Summer Scholars, internships were a mixture of in-person and virtual/remote experiences.

Postbacc Fellow Gina Zhou

Postbacc Fellow Lauren Kirk

Postbacc Fellow Kristie Kim

2020 Project Topics

2020 SRF Education program participants' research topics included:

- The impact of senescence on-neuronal nervous system cells
- Neuropeptide processing during biogenesis
- Lung organoid modeling
- The epigenetic effects of aging on a variety of diseases
- The impact of COVID-19 infection on brain protein secretion
- The impact of aging and cellular senescence on the immune system
- The recovery of particular gene functions in mitochondrial disorders
- Biotechnology VC firms and investment strategy
- Stem cell-derived models for COPD

Postbacc Fellow Carly Truong

Dominican University Master of Science Partnership

Dominican University of California's Master of Science (MS) in Biological Sciences is an advanced, research-intensive program designed to train students primarily for successful scientific careers focused on biomedicine. As of 2020, MS students at Dominican can complete their thesis with scientists at SENS Research Foundation. For more details, visit dominican.edu/gradbio

Spotlight: The Snyder Lab

Last summer, SENS Research Foundation partnered with Dr. Evan Snyder at the Sanford Consortium for Regenerative Medicine to learn more about COVID-19 and lung and brain aging. Under the expert mentorship of the Snyder lab, six SRF Summer Scholars successfully established innovative lung and brain organoid models (shown in the image at right; organoids are tagged with a red dye) as well as a lung epithelium model to uncover how SARS-CoV-2 infects these organs, investigate drugs that might treat or ameliorate the disease, and look for clues about what makes aging people more vulnerable.

These models contain blood vessels (shown in green), since abnormal clotting and damage to blood vessels are critical vulnerabilities in COVID-19. The lung epithelial model also offers the potential to identify age-related or virus-induced damage to specialized lung cells' ability to produce the critical surfactant needed to keep lung air sacs functional. Our Summer Scholars demonstrated that these systems could be infected with the virus and that they could use them to test drugs that might thwart that infection and to profile aspects of COVID-19 that might make the elderly so vulnerable (including increased inflammation, compromised vasculature, loss of critical lung proteins, and aging brain cells).
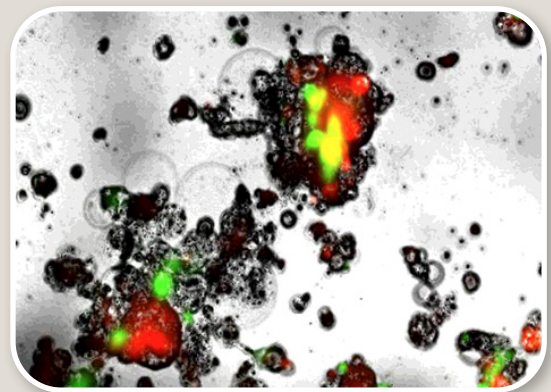

Image Credit: Summer Scholar Matangi Kumar

The progress achieved by our Summer Scholars over such a short time prompted SRF to extend one Summer Scholar for an extra quarter of research to do a deep dive into perfecting the model system to show that blood vessels that compose the lung may be particularly vulnerable to aging-related changes, especially those mediated by inflammation, but may be amenable to increasing surfactant production. Taken together, these studies established model systems that may accelerate progress toward novel therapies against COVID-19 and against lung and brain aging.

EDUCATION

While SRF Education has worked for years to support college students and recent graduates, RISE represents our first venture into the high school realm. With high school teachers forced to teach remotely, and students locked out of the laboratory classroom, keeping meaningful science education alive during the pandemic posed particular challenges.


The goal of RISE was to create a rejuvenation biotechnology curriculum introducing students to ideas, techniques, instruments and problem-solving approaches that they otherwise might not encounter until college (or an in-person lab internship). We designed RISE content to consistently engage students as active participants, and to give teachers readily accessible, user-friendly media for their lessons.

RISE provides distance-friendly lessons supported by high quality video explanations, interactive student activities, and discussion-based slides.

Our first two RISE modules (described below) are available online at:
https://www.sens.org/rise
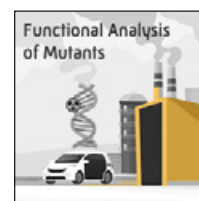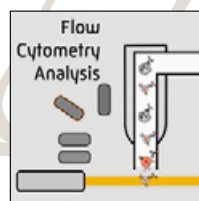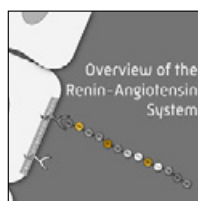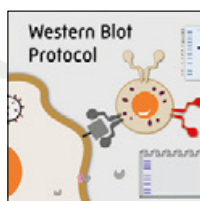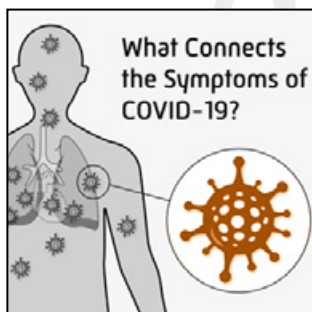
The first module introduces students to COVID-19 and explores how seemingly disparate clinical manifestations of the disease can be explained by a single molecular mechanism. It also introduces relevant methods and instruments, such as flow cytometry and Western blotting.
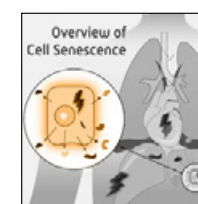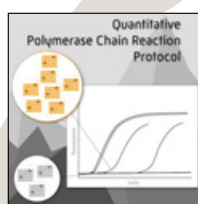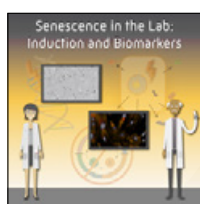
The second module explores the phenomenon of cellular senescence and its proposed role in aging and disease. Additionally, it introduces methods (such as PCR and immunofluorescence staining) used in the detection of senescence markers and evaluation of the impact of possible interventions.

EDUCATION

Virtual exercises coming soon

In 2021, SRF's RISE program will add virtual exercises that allow students to stretch and apply their scientific reasoning and analysis skills to challenges just like the ones our rejuvenation biotechnology researchers face in the lab.

The first of these exercises will explore senescence in the context of Alzheimer's disease. Students will analyze images of a mixed population of neurons and astrocytes, including amyloid beta (AB) oligomer-treated and untreated groups. The students' task will be to determine if this AB treatment caused the cells to display senescence markers.

The exercises are created by Elena Fulton, Ellen Wang, Dr. Chaska Walton, and Dr. Julie Andersen.
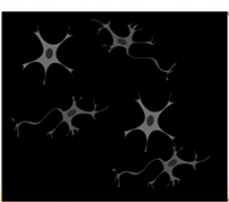

RISE Instructor: Elena Fulton

Elena Fulton
2019 Summer Scholar
2019 Postbacc Fellow
RISE Instructor/Narrator

Former Summer Scholar and Postbaccalaureate Fellow Elena Fulton was chosen to develop the inaugural RISE curriculum. Her SRF and Expeditionary Learning (EL) experiences helped her weave SENS themes into curriculum that can be taught in either a traditional or EL style.

"I was drawn to the RISE program because of the mission to bring engaging, purpose-driven curricula into high school classrooms. I grew up in an Expeditionary Learning school that gave me a sense of empowerment in my learning, and I wanted to offer that same experience to other students.

"This project challenged me to think creatively about how to explain scientific concepts in accessible ways, and I hope that our program continues to spread and impact the next generation of scientists."

SRF connects scientists, entrepreneurs, investors, and policymakers.

Deputy Secretary Eric Hargan (HHS)

SRF hosted two events in January 2020 before pandemic concerns compelled a move to virtual meetings.

On January 14th, we hosted **Rejuvenation Science 2020** at the Ritz-Carlton in San Francisco, with Deputy Secretary of Health and Human Services, Eric Hargan.

The following day we hosted our **Rejuvenation Pitch Day** at Local Kitchen. Aubrey served as master of ceremonies as 17 longevity entrepreneurs pitched their companies to nearly 100 investors.

Jim O'Neill (SRF)
Eric Verdin (Buck Institute)

Anja Krammer (Turn Bio),
Matthew Scholz (Oisin Bio),
Alexandra Stolzing (SRF)

Tom Lee, (One Medical, Galileo)

OUTREACH

Karl Pfleger (Agingbiotech.info)

Austin Diamond (Longevity Fund)
Sergey Young (Longevity Vision Fund)
Dr. Chee Yang Chen (Crossbow Capital,
Carta Genomics)

Michelle Guo (Helios Capital)
Sonia Arrison (100 Plus Capital)

Aubrey's Virtual Speaking Engagements (2020)

World Stem Cell Summit
January 23

Longevity Therapeutics
January 28

Commonwealth Club
January 30

Foresight Institute
March 5

Transdisciplinary Agora for
Future Discussions (TAFFDS)
April 21

Longevity2020
April 27 - May 1

Longevity Series by
R42 Institute
May 5

Metchnikoff's Day
Online Conference
May 18

Longevity Leaders Virtual
May 19 - 22

Global Health Summit
May 28

Being 100 Years Young
(Slovenia)
June 11-12

Koc University
July 28

Institute and Faculty of Actuaries
August 19

Ending Age-Related Diseases
August 20-21

Institute of Objective Studies
August 22

Great Contemporary Innovators
September 2

Aging Research and
Drug Discovery
September 2-4

Next Generation Nations
Corporate Connections
September 26

Eurosymposium on
Healthy Ageing
October 1

Longevity Investors Conference
October 1

Targeting Metabesity 2020
October 12-15

Business Insider Trends Festival
October 22

International Longevity Policy
and Governance Summit
November 11

The Longevity Week
November 12

Oxford Longevity Society
November 23

Rukami Fest
November 28-29

Healthy Masters Forum
November 29

GIANT 2020
December 1-2

University of Sheffield
December 11

Futures Literacy Summit
December 11

Freethought Arizona /
Secular AZ
Secular Speaker Series
December 13

TC Sessions: Space 2020
December 16

Futurist Foundation
Longevity Q&A
December 19

Dr. DeGrey's international messaging efforts continued during 2020 through online presentations, Q&A sessions, and conferences.

Laboratory work everywhere faced pandemic-induced disruption and delays last year, and SRF was no exception. We could not be prouder of all our scientists and support personnel who faced 2020's challenges head on, enabling our critical work toward ending age-related disease to progress.

Target Prioritization of Tissue Crosslinking
The Babraham Institute
Principal Investigator: Dr. Jonathan Clark
Research Team: Dr. Melanie Stammers

The extracellular matrix (ECM) is a network that holds our cells, tissues, and organs together and guides their function. The ECM's efficacy depends on its intricate structure, which falls into disrepair and dysfunction with age. Increased stiffness of ECM structures contributes to this dysfunction, and one cause of this stiffening is the **formation of crosslinks**, chemical bonds that tie together neighboring fibrils in the matrix and prevent them from moving independently. **Breaking these crosslinks could increase ECM flexibility** and improve its function.

For many years, geroscience has focused on one kind of crosslink: advanced glycation end products (AGEs), produced when reactive molecules derived from sugars and fats bind to the ECM protein collagen. The biotech startup Revel Pharmaceuticals, founded on SRF-sponsored technology, is focused on developing therapies to break glucosepane, the most common AGE crosslink we know of. But as we progress toward eliminating AGEs, there remains the question of **what other crosslinks impair function in aging tissues** — and some may prove even more important than glucosepane.

With SRF funding, Jonathan Clark's lab at the Cambridge-affiliated Babraham Institute is investigating just such questions. In previous years, Dr. Clark's work led to a number of important findings, including the surprising phenomenon of routine mechanical destruction and re-formation of tissue crosslinks as the tendon stretches and contracts.

Despite limited lab access due to the pandemic, Dr. Clark's group made progress in investigating inconsistencies between different evaluation methods for various aging ECM proteins, and are seeking to reconcile these findings. Further, they are exploring the hypothesis that some AGE formation involves abnormal rearrangements of the normal carbohydrate-based functional groups that attach to proteins.

They have also begun studies of crosslinking in tissues from an animal model with high arterial stiffness, but may not have enough data to draw reliable conclusions due to inadequate tissue supply. They may need to raise another batch of these animals and harvest additional tissue samples once increased stiffness is evident. Clark's lab has also **tested the mechanical properties of tissue from the aorta**, to evaluate how the positioning of crosslinks and glycation contribute to tissue stiffening.

The project's next steps will be laborious: measurement of underexamined crosslink types will require different tissue samples for analyses, different sample preparation methods, and development of new testing protocols. Elastin — the protein that gives ECM its stretch — is particularly challenging, because its lack of previous study means fewer established protocols exist. The team has already found **evidence of reactions never previously described** in the tissues.

In parallel, the Clark lab has acquired the equipment and the necessary institutional approvals to **begin processing aged human tissue**, and are looking for sources of such tissue for analysis once the lab is open and running again.

Engineering Mitochondrial Genes to Restore Mitochondrial Function
SENS Research Foundation Research Center
Principal Investigator: Dr. Amutha Boominathan
Research Team: Bhavna Dixit, Caitlin Lewis, Lauren Kirk, Carly Truong, Aly Ung, David Begelman

Mitochondria are the power plants in our cells, and dysfunctional mitochondria carrying large deletion mutations overwhelm a rising number of our cells as we age, contributing to Parkinson's disease, muscle dysfunction, and other age-related health problems. The SRF Research Center's MitoSENS program aims to solve this grand engineering challenge via allotopic expression (AE): placing unaltered 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 unaltered copies can then direct the cell's machinery to **produce engineered versions of the missing mitochondrial proteins** and deliver them to the mitochondria, restoring youthful mitochondrial function.

Following their demonstration of efficient rescue of one mitochondrial gene (ATP8) using this AE process, and partial simultaneous rescue of a second (ATP6), the team continues to work on improving the technology to cover all 13 mitochondrially encoded proteins in cell models. They have begun **moving these candidates into animal studies**, and are also exploring alternative strategies to revive mitochondrial function, such as whole organelle replacement.

This last year, the MitoSENS team **published a general strategy** to improve the expression of all 13 protein-coding genes of the human mtDNA in the nucleus. While a few groups have previously created constructs using the most common sequences seen in mitochondrial genes now moved by evolution to the nucleus, the **MitoSENS group was first to optimize such constructs** by applying algorithms incorporating the full range of what we know about the conditions under which organisms choose one codon spelling over another.

In fact, the MitoSENS team's previous groundbreaking success with ATP8 was achieved through constructs designed with this codon optimization process. The team has now shown that codon optimization in the allotopic expression of the remaining 12 mitochondrial genes, using transient constructs that are eventually degraded by normal cellular activities, causes cells to **more consistently produce their encoded protein**

— and to produce far more protein — than cells modified with constructs using the old default coding system.

They next developed constructs that would permanently integrate an allotopic copy of the mitochondrial protein into the nucleus. A codon-optimized allotopic ND1 gene, integrated into a cell line derived from a patient with an ND1 mutation, was not as successful as ATP8 had been — but it still **significantly improved mitochondrial function** in this mutant cell line, resulting in partial restoration of normal cellular energy production.

At this point, it was still unclear whether the proteins produced from five codon-optimized allotopic genes engineered permanently into the cell's nuclear genome could actually reach their targets in the mitochondria's energy-generating system. Thus, the team spent much of 2020 working to further refine their constructs.

The MitoSENS team was particularly focused on **improving the allotopic expression of ATP6**, congenital mutations of which cause NARP, a mitochondrial disease featuring progressive vision loss. After several trials, the team finally made an important breakthrough in the expression of this gene in the nucleus, and at least one attempt to improve the delivery system was effective in a common non-mutant human cell line.

The team is now working to definitively demonstrate that the protein successfully **integrates into the biological turbine that produces ATP**. Additionally, they have acquired a new cell line, derived from a NARP patient and carrying an ATP6 gene, with clear defects in its energy-production system. After more complete characterization of these defects, they will use the most promising ATP6 constructs to **repair the defective cells**.

SRF-funded work in Dr. Marisol Corral-Debrinski's lab a decade ago culminated in a gene therapy for the inherited mitochondrial mutation disease Leber's Hereditary Optic Neuropathy (LHON), which is caused by a mutation in the mitochondrial gene ND4 and ultimately leads to blindness. Building on this research, the French company GenSight has developed and licensed a therapeutic product under the brand name Lumevoq® that is currently in clinical trials for treating patients with LHON.

Lumevoq's design differs significantly from the MitoSENS team's more biologically informed codon optimization algorithm, and this presented MitoSENS with an opportunity to test the efficacy of their codon-optimized construct against not only Lumevoq but also the most minimally recoded ND4 construct. The team tested allotopic expression of their optimized ND4 (oND4), the minimally recoded control (rND4), and a construct with the same sequence as GenSight's Lumevoq (gND4) to compare each therapy's ability to return cell lines with a defective ND4 gene to proper functioning.

Somewhat surprisingly, but consistent with results of preliminary testing, both gND4 and even rDN4 seem to surpass oND4 in functional recovery, despite the fact that cells expressing oND4 produce a greater amount of functional ND4 protein. Determining the cause of this difference will be an important line of research in 2021.

After their breakthrough with ATP8, the team has begun to **test allotopic ATP8 in a living mammal**. There are very few mammalian models of mitochondrial mutations available, but fortunately, the FVB mouse strain harbors a mutation in the ATP8 gene with a moderately diseased phenotype. Unfortunately, the FVB mouse has additional mutations in its nuclear genome that could confound the influence of the ATP8 mutation -- which means even installing a copy of the ATP8 gene in the nucleus, bypassing the defective mitochondrial gene, might not produce a healthy mouse. To avoid confounding the experiment, these animals have been cross-bred with wild-type lab mice to produce animals with the mutant ATP8 gene in their mitochondria, but a normal nuclear genome.

After surmounting a series of challenges, the team **successfully derived two key lines of mice in the last year**, in collaboration with the Brand lab at the Buck Institute: one with the ATP8-mutant FVB mitochondrial genome in a mouse line with a healthy nuclear background, and another with the same overall genetics but with the gene for the allotopic ATP8 gene already engineered into its nuclear genome. The integration of the gene into the nuclear DNA has been confirmed in both mouse lines.

The MitoSENS team has thus begun preliminary characterization of the metabolism, physiology, and behavioral features of these mice as compared with genetically matched wild-type mice, looking for key differences that will, if the experiment works, be resolved in the allotopic ATP8 mice. By the end of 2021 the data will be published.

Targeting Secondary Senescence
SENS Research Foundation Research Center
Principal Investigator: Dr. Tesfahun Dessale

As humans age, senescent cells, via the Senescence-Associated Secretory Phenotype (SASP), disrupt metabolism and damage the body in several ways, driving chronic inflammation and permitting the spread of cancer. Most of these detrimental effects involve senescent cells wreaking havoc on their non-senescent neighbors, and one of their most compromising effects was only discovered recently. Senescent cells can, it seems, turn normal cells senescent, spreading senescence to healthy cells both nearby and in remote tissues.

At the SRF Research Center, Dr. Dessale is working to **characterize these secondary senescent cells and identify better ways to destroy them**. Senescent cells behave differently according to the cell types, tissues, and senescence-triggering stimuli they emerge from -- and, importantly, they vary in their susceptibility to various senolytic drugs. Dr. Dessale is pursuing the idea that secondary senescent cells might also differ from primary senescent cells in important ways, and therefore might require different senolytics.

Dr. Dessale is initially focusing on endothelial cells, which line our blood vessels. Unlike nearly all other cell types, endothelial cells are in constant, direct contact with the circulation. This proximity makes them most likely to encounter factors from elsewhere in the body that might turn them senescent -- and further, if they do turn senescent, their direct access to the circulating stream of chemical signals allows them to spread SASP signaling throughout the body, **turning yet more cells senescent**.

Rather than following the usual practice of relying on cell lines maintained for many years in culture, Dr. Dessale is working with **endothelial cells taken directly from volunteers**. Cultured cell lines have adapted to living for generations in the artificial conditions of cell culture, whereas cells from volunteers may better represent the way such cells behave *in vivo*.

After turning some cells senescent with genetic damage inflicted by the chemotherapy drug doxorubicin, Dr. Dessale will **trigger normal endothelial cells to enter secondary senescence** by exposing them to the primary senescent cells' SASP.

This could potentially identify targets to interrupt, or swiftly reverse the senescence switch, preventing the spread of secondary senescence. He has also compared the gene expression profiles of primary and secondary senescent endothelial cells to **identify differences in the SASP factors** secreted by each subtype and the pathways on which each type depends for survival. This latter study could identify new targets for senolytic drugs, specific to secondary senescent cells. These targets can then be tested against both existing and newly identified senolytics for selective efficacy.

Dr. Dessale also seeks to identify a **novel senescent cell surface marker**, which could be used to better isolate, study, and potentially target senescent cells for destruction. He has already made use of existing surface markers, but these are inappropriate for clinical use in destroying senescent cells, and development of senolytic antibodies and other immune therapies will require new targets.

Finally, Dr. Dessale is testing **another possible difference between primary and secondary senescence**: whether the SASP from secondary senescent cells in turn spreads senescence to yet more normal cells, carrying the pathology forward into tertiary senescent cells. Such a domino effect would clearly make senescent cells more dangerous, whereas the absence of such an effect would explain why we have not observed catastrophic chain reactions of senescent cell proliferation.

Rejuvenating Immune Surveillance of Senescent Cells
SENS Research Foundation Research Center
Principal Investigator: Dr. Amit Sharma
Research Team: Elena Fulton, Kristie Kim, Mikayla Stabile, Gina Zhu

Powerful evidence gathered in the last decade **identifies senescent cells as critical drivers of age-related disease, frailty, and death**. The body's immune system can, to some extent, detect and destroy senescent cells: when cells become abnormal in any of several ways — senescent, cancerous, or infected by viruses — an immune cell called the NK (Natural Killer) cell detects and eliminates them. In fact, a key reason why senescent cells exhibit the otherwise-destructive senescence-associated secretory phenotype (SASP) is to attract immune cells to ensure senescent cell removal once their core function has run its course.

Despite this innate immune surveillance, **senescent cells accumulate with age**. This happens in part because senescent cells, like cancer cells, use a variety of mechanisms to hide from NK cells and inhibit NK cells' ability to destroy them. Additionally, scientists hypothesize that — like other aspects of immunity — NK cells' ability to detect or destroy senescent cells may wane with age, for as-yet unknown reasons.

Dr. Amit Sharma's team at the SRF Research Center is investigating several potential ways to **rejuvenate, enhance, or supplement NK cells' immunological elimination of senescent cells**. One such approach clears away possible decoy receptors that senescent cells use to evade NK cells. Abnormal cells are programmed to "show their colors" to the NK cell authorities by raising flags (ligands) on their surface. When an NK cell's receptor locks on to a senescent cell's corresponding ligand, the NK cell is activated and destroys its senescent target. But eventually the SASP's protein-degrading enzymes cleave such ligands from the surface of senescent cells, reducing NK cells' ability to bind and destroy them. **NK cells may then mistakenly bind to shed ligands**, instead of seeking out and destroying the senescent cell that shed them.

This observation suggests that clearing shed ligands from the senescent cell environment could make NK cells more effective at eliminating senescent cells: without the distraction of shed ligands, they might more easily home in on and bind to their targets.

In 2020, Dr. Sharma's team performed experiments using two different kinds of lab-scale technology to deplete shed ligands from senescent cells in culture with NK cells, as an initial model of how such a therapy would work. Unfortunately, neither method improved senescent cell killing, perhaps because the senescent cells had lost too many ligands to enable the NK cells to target them no matter how few decoy receptors were present.

The SRF team is now negotiating for access to a more sophisticated technology currently in development as a **potential medical therapy** for depleting soluble factors implicated in aging and disease. If this approach more effectively clears soluble ligands away from senescent cells and enables greater NK cell killing activity in cell culture, it can quickly be tested in animal models and developed as a rejuvenation technology in humans.

Dr. Sharma also plans to, 2021 funding allowing, test whether clearance of other soluble factors associated with senescent cells might improve NK cell cytotoxicity against senescent cells. If any of these approaches look promising, the more advanced technology currently planned for use in ligand depletion could be quickly adapted to target these other soluble molecules instead.

Dr. Sharma and his team discovered that **senescent cells may release another factor to evade NK cells**, in addition to the aforementioned ligands. This mechanism looked especially promising because it was already known to modify the immune response to other kinds of damaged cells, and to increase in the circulation and many human tissues with age.

Unfortunately, depletion of this factor from the local environment of senescent cells again did not improve NK cells' ability to eliminate senescent cells, nor did treating the senescent cells with a drug (currently in human clinical trials for other purposes) that inhibits production of this factor. Dr. Sharma and the team will attempt this approach again in 2021, limiting production of the substance directly using silencing RNA, to see if this makes NK cells rally to the fight.

The Sharma lab 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.

Going forward, they will carry on recruiting donors and continue evaluating samples for a more robust data set characterizing agre-related changes in lethality of NK cells against senescent cells in mice and in humans.

Finally, Dr. Sharma and his team are investigating the possibility of **reinforcing aging people's native NK cells** with engineered alternatives aggressively targeting senescent cells, in mice and eventually in humans. The alternatives, called CAR-NK cells, are a biotechnological riff on CAR-T technology, which has proven revolutionary against a subset of human cancers for which it is now in clinical trials. CAR-NK cells will possess receptors engineered to enhance their senescent cell killing ability. The team has already identified several targets necessary to create these cells, and are testing them rigorously.

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

Throughout our lives, we can lose neurons to concussion and other trauma, strokes of varying clinical significance, and the eventual consequences of accumulated molecular damage (such as aberrant tau species and beta-amyloid in our brains). And while two regions of the brain continue to produce new neurons, most of them are temporary, leaving most of the brain to suffer slow neuron loss.

Whole-organ transplantation can quickly remedy cell loss in the aging heart, lung, and kidney, but this is clearly not an attractive option for the brain, the seat of our memory and identity. Instead, meaningful success in neural rejuvenation will require a strategy for **continuing replacement of neurons** that allows the new cells to disperse throughout the brain, survive, and fortify newly forming and existing neuronal circuitry.

With SRF sponsorship, Dr. Jean Hébert is advancing such a strategy. Using cellular reprogramming technology, his team's work takes advantage of both the brain's ability to readily accommodate externally introduced neuronal support cells called microglia, and the highly mobile nature of these cells. His strategy involves ablating a subset of the patient's own microglia (some of which are senescent or suffering from other age-related dysfunction) to make room for **new replacement microglia**, which they then introduce into the brain.

These therapeutic microglia have **two engineered properties**: they are resistant to the microglia-destroying drug used to clear out the senescent microglia they replace, and they contain a genetic circuit allowing a specific drug to reprogram them into neurons. After the new microglia disperse across the brain, the drug is administered, and the microglia transform into neurons, resulting in **fresh, youthful cells throughout the brain** that will join and maintain existing synaptic networks.

So far, the Hébert team has identified a way to engineer microglial resistance to a microglia-destroying drug, and demonstrated that their transplantation-and-dispersion protocol **effectively delivers engineered human neurons into the mouse brain** and causes these neurons to disperse widely. They have also confirmed that transplanted engineered human microglia can survive in the mouse brain probably long enough to reprogram them into neurons. Further, the group has successfully triggered such microglia to reprogram upon exposure to their gene-construct-inducing drug in vitro.

The Hébert team's protocol will be useful in the short term for **delivering therapeutic proteins and gene products** that can't readily cross the blood-brain barrier. They have filed a patent application and are preparing a scientific publication. To demonstrate the potential of this approach, they are advancing a study to show that such dispersed microglia can deliver the neuronal growth-and-survival factor BDNF widely across the brains of old mice.

Meanwhile, critical work continues toward the **bona fide rejuvenation strategy** of inducing such microglia to reprogram in the mouse brain after transplantation and dispersal. The team is reserving aging mice, developing mouse models of neurodegenerative aging, and working on protocols for evaluating the identity, local function, and ability to sustain and restore cognitive function in mice—all of which ensure that later stages in the project can pick up speed immediately once the key milestone of in vivo differentiation has been achieved.

Lipofuscin Degradation by Bacterial Hydrolases
German Institute of Human Nutrition
Project Director: Dr. Tilman Grune
Research Team: Annett Braune, Annika Höhn, Tim Baldesperger

Lipofuscin is an intracellular aggregate composed of debris from damaged organelles and other molecules inside the cell. Mammalian cells lack the ability to degrade lipofuscin, and while dividing cells (e.g., skin and lung surface cells) can prevent lipofuscin from accumulating by diluting it between daughter cells each time they divide, certain critical cell types such as neurons and heart and skeletal muscle cells do not have this option.

Lipofuscin thus accumulates in these cells as we age, leading to dysfunction. In experimental systems, lipofuscin causes cell death and impairs heart muscle cell contraction; autopsy studies suggest that its accumulation limits lifespan.

Dr. Tilman Grune's laboratory is taking the classic LysoSENS approach to this problem. Since our cells are unable to degrade lipofuscin, his team is **evaluating soil bacteria and other microorganisms for enzymes** capable of doing the job. If identified, such enzymes could serve as the basis for a rejuvenation biotechnology that cleans lipofuscin from our cells, restoring healthy, youthful function.

Critically, the Grune lab will **test candidate enzymes against real lipofuscin** derived from human and horse heart tissue. Before now, the extremely small levels of the substance present in aging tissue, combined with the difficulty in accessing aged tissue from longer-lived animals, led researchers to rely on a variety of crude procedures to produce artificial lipofuscin preparations. There has also been no guarantee that potential therapies showing efficacy against these artificial lipofuscin preparations would translate to the real material in our cells.

The Grune team's preliminary results show that artificial lipofuscin is only minimally susceptible to multiple powerful protein-degrading enzymes commonly used in the biotechnology industry to degrade tough substrates, leaving behind a tough residual core with few molecular "handles" for enzmes to bind onto. This finding emphasizes the challenge and importance of **finding highly effective and specific enzymes** to buzzsaw through the key molecular bonds holding this toxic cellular waste together.

In the next critical step toward identifying candidate lipofuscin-degrading enzymes, the Grune lab is growing a variety of types of environmental bacteria on artificial lipofuscin as the only nutrient source. These conditions harness the power of evolution in the identification of lipofuscin-degrading enzymes, as only **microbes with enzymes capable of degrading lipofuscin** will have the ability to derive energy and survive.

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Once such microbes are identified, the Grune team will use recombinant versions of enzymes encoded by their genomes to test each enzyme individually. This will allow them to zero in on the key enzyme or small number of enzymes that give them this ability. Such enzymes can then become **candidates for development into future lipofuscin-hydrolyzing rejuvenation biotechnologies**.

In the next critical step toward identifying candidate lipofuscin-degrading Going forward, the team plans to expand and repeat these preliminary experiments using **real heart-derived lipofuscin**, once supplies of the paradoxically precious toxic cellular waste allow.

Meanwhile, the Grune lab has **developed a new protocol** to isolate adult and old mouse heart muscle cells and keep them in culture for testing — a difficult task, for which heart-like cells or cells from newborn mice are more typically employed.

They will then use confocal laser scanning microscopy to see how exactly adding exogenous lipofuscin (or partially degraded lipofuscin) impairs the function of neonatal heart cells, and also whether the dysfunction of real adult and old heart muscle cells is related to their age-related accumulation of lipofuscin — and, critically, **whether candidate enzymes can alleviate either one**.

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PUBLICATIONS

Mkrtchyan GV, Abdelmohsen K, Andreux P, Bagdonaite I, Barzilai N, Brunak S, Cabreiro F, de Cabo R, Campisi J, Cuervo AM, Demaria M, Ewald CY, Fang EF, Faragher R, Ferrucci L, Freund A, Silva-García CG, Georgievskaya A, Gladyshev VN, Glass DJ, Gorbunova V, de Grey A, He WW, Hoeijmakers J, Hoffmann E, Horvath S, Houtkooper RH, Jensen MK, Jensen MB, Kane A, Kassem M, de Keizer P, Kennedy B, Karsenty G, Lamming DW, Lee KF, MacAulay N, Mamoshina P, Mellon J, Molenaars M, Moskalev A, Mund A, Niedernhofer L, Osborne B, Pak HH, Parkhitko A, Raimundo N, Rando TA, Rasmussen LJ, Reis C, Riedel CG, Franco-Romero A, Schumacher B, Sinclair DA, Suh Y, Taub PR, Toiber D, Treebak JT, Valenzano DR, Verdin E, Vijg J, Young S, Zhang L, Bakula D, Zhavoronkov A, Scheibye-Knudsen M. *ARDD 2020: from aging mechanisms to interventions*. Aging (Albany NY). 2020 Dec 30;12(24):24484-24503. PubMed: 33378272.

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