sens research foundation

reimagine aging

2023 | ANNUAL REPORT

A **UNIQUE** APPROACH TO CURING AGING FOR **EVERYONE**

sens research foundation

reimagine aging

Driven to create an equitable impact on aging through scientific rigor, ignited by our passion and guided by our respect for the global community.

PASSION for our mission to cure age-related disease

RESPECT for our staff, donors, and the global community

IMPACT DRIVEN to create real-world outcomes

SCIENTIFIC RIGOR for robust and unbiased quality research

EQUITY to ensure accessible therapies for all people

We aim to **PRISE** life from death.

Message from the CEO

LISA FABINY-KISER

CEO

Growth is a continuous journey. It requires consistent care, patience, and a guiding hand to cultivate a seed into fully prosperous maturity. We have spent the last year at SRF growing internally and within our community. Our growth is not just about the size of our Research Center – it is a magnification of our collective capabilities, an amplification of our voice, and a broader horizon of opportunities.

Let us grow this new world together, one seed at a time.

In 2021, we focused on rebuilding, encouraging community, and making new connections externally - emphasizing the collaborations which are necessary to propel our field forward. This led us to review our own internal growth, to look at how we operate, where our priorities lie, and how those priorities serve us, and our community.

While we have always innovated in research, our values were never fully defined, leading us at best on a haphazard growth trajectory. After much discussion and debate, we have finally created a structure for our growth, as defined in our company values – Passion, Respect, Impact, Scientific Rigor, and Equity. With this framework imbedded in our minds, hearts, and on

the walls of our Research Center, we move forward as a stronger, more confident, organization.

Our goals for the upcoming year will build upon those roots. SRF is not just an organization, but an ecosystem, thriving from the shared vision and enthusiasm for a world free of age-related disease. Our community is the force propelling our progress and we are profoundly grateful for the unwavering trust and belief in our mission and the support we have seen from so many individuals and organizations. In the coming year we will continue to build impactful partnerships, expand our advocacy efforts, and launch new initiatives and engagements.

The journey to cure age-related disease is full of obstacles and rife with setbacks. The fundraising world is seeing a decline, both in charitable giving and in investment, largely due to the economic downturn. This lack of rain will not stop our progress, will not force us to wither and retreat, and will not defeat this community which has grown into beautiful abundance in the last five years. Our communal work is a testament to the resilience of the human spirit, and our passion for this mission will sustain our growth.

We stand on fertile ground, and we are eager to grow further and reach higher. SRF remains unwavering in our mission, inspired by our vision, and guided by our values. Our ambition is our defining priority.

Let us grow this new world together, one seed at a time.

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The Team | 2023

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Senior Investigator I, MitoSENS

DR. AMIT SHARMA
Senior Investigator I, ApoptoSENS

DR. ABDELHADI REBBAA
Senior Investigator I, RepleniSENS

SRF's team consists of dedicated individuals who are driven by a common mission to eliminate age-related diseases. They work tirelessly towards achieving this goal and are integral to our future success.

DR. TESFAHUN ADMASU
Staff Scientist I

KATRINA ANDERSON
Accounts Payable Clerk

DR. MARCELA ATZORI
Staff Scientist I

ANNA BARKOVSKAYA
Staff Scientist I

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Development Associate

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Research Technician

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Science Writer

DR. MANIKANDAN SAMIDURAI
Staff Scientist I

SAMUEL WEISIGER
IT Technician

GARY ABRAMSON
Creative & Web Lead

Meet the Team Videos

The SRF team shares personal stories and the driving force behind their unwavering commitment to combating aging. Discover the individuals behind the SRF mission as they share their work, passion, and what motivates them in the fight against aging.

Watch at **youtube.com/SENSFVideo**
See *Meet the Team* & *Meet the Students* playlists

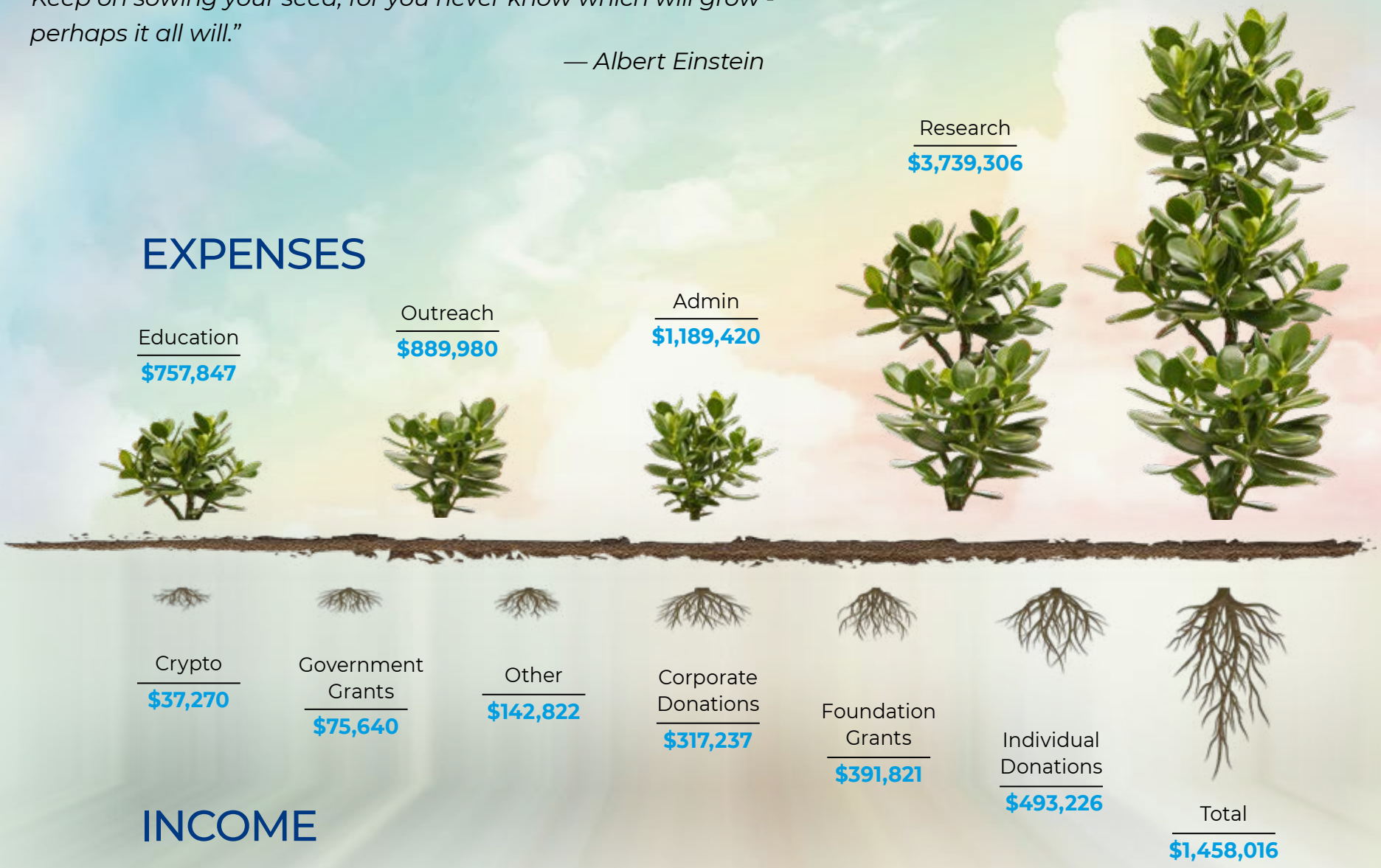
Meet the Students Videos

SRF's brilliant students share why they got involved, what drew them to SRF's education programs, the impact these programs have on their lives, and what it's like to be a part of SRF.

Financials SRF 2022

"Keep on sowing your seed, for you never know which will grow - perhaps it all will."

— Albert Einstein



Investments

In addition to SRF's research efforts, funding and support are provided to promising biotechnology startups, investing in the future of regenerative medicine.

CYCLARITY THERAPEUTICS

A promising small-molecule approach to removing 7-ketocholesterol from foam cells, the drivers of atherosclerosis, to prevent and reverse humanity's number one killer.

LysoSENS

COVALENT BIOSCIENCE

Nature-Made Catabodies, Engineered Vaccines

SRF funded successful research to engineer candidate AmyloSENS therapies to precisely bind and cleave wild-type transthyretin amyloidosis, a major driver of heart failure in people at the extremes of current lifespans.

AmyloSENS

ICHOR LYSOCLEAR

Ichor is a diversified longevity therapeutics company founded by SRF alumnus Kelsey Moody. Their lead LYSOCLEAR is a LysoSENS therapy for age-related macular degeneration, founded on technology transfers from SRF.

LysoSENS

ANTOXERENE

An Ichor Portfolio Company

Antoxerene's proprietary RecombiPure expression technology allows them to manufacture full- length, properly-folded, biologically active human p53 and other hard-to-synthesize proteins at scale in E. coli, enabling high-throughput screening of drugs to target them.

ApoptoSENS

OISÍN BIOTECHNOLOGIES

Seed funding from SRF and the Methuselah Foundation launched Oisín Biotech, a longevity therapeutics startup that uses licensed liposome technology and a patent-pending DNA construct to deliver "suicide genes" that trigger the self-destruction of senescent cells.

ApoptoSENS

Repair Biotechnologies

By safely breaking down excess cholesterol, Repair Biotechnologies believes that CDP can repair the failure of reverse cholesterol transport that is at the heart of atherogenesis. Rather than accumulating to make macrophages dysfunctional, excess cholesterol will instead be catabolized.

LysoSENS

Revel

Spun out from Yale to turn SRF-funded fundamental research on the AGE crosslink glucosepane into working GlycoSENS rejuvenation biotechnology to reverse the stiffening of the arteries by aging.

GlycoSENS

New Partnerships

angel protocol

A Web3 crowdfunding organization empowering changemakers. Their longevity initiative allowed donors to contribute cryptocurrency that supported vital anti-aging research and advocacy. Through the Angel Alliance, the first $10,000 in donations were matched.

VitaDAO

VitaDAO is a community-owned collective dedicated to funding and advancing longevity science that can improve people's lives. They supported SRF's ApoptoSENS's research with $253,000 in an IP-NFT Transfer to help develop CAR-NK cells to target senescent cells in vivo.

THE ALLIANCE FOR LONGEVITY INITIATIVES

SRF joined A4LI's Longevity Science Caucus, to unite experts, policymakers, and community leaders to advocate for research, develop solutions, and accelerate progress to extend healthy lifespan. This will engage the public to enhance global quality of life.

Rosalind Franklin Society

SRF became a member of the Council of Academic Institutions of the Society. Named in honor of the x-ray crystallographer whose work was crucial in the discovery of the double-helix structure of DNA, the Society advances the contributions of women in life sciences and affiliated disciplines.

Lifespan.io
CROWDSOURCING THE CURE FOR AGING

Lifespan.io is the strongest advocacy organization in the longevity field. They became integral media partners for significant events such as SRF's Ending Aging Forum, Donors Appreciation Event, and the End of Year Campaign. They additionally partnered with SRF and Life Noggin to create a video series on the SENS approach to aging that featured a fun and accessible pop-science style and was hosted on Life Noggin's 3.26+ million subscriber YouTube channel.

Methuselah Foundation

As part of the Angel Protocol campaign, the Methuselah Foundation was the original backbone organization for the Strategies for Engineered Negligible Senescence (SENS) that SRF spun out from in 2009.

Fable of the Dragon Tyrant

Emerging charity token, Tyrant, donated $25,000 to SRF to fund the "Dragon Tyrant scholar," providing in-lab experience to an exceptional student as part of the MitoSENS program. The funds were raised through an exclusive collection of 750 NFTs that sold out in 30 minutes.

SOLIMANLOPEZ

A Bio-Art NFT collection was created in collaboration with Spanish digital artist Soliman Lopez. This collection took the unprecedented step of connecting live entities to blockchain technology. Through this novel approach, a new NFT was dynamically generated, fed by in vivo cultures at our Research Center.

New Content

Life Noggin Videos

SRF, Noggin, and Lifespan.io produced a series of seven fun and educational videos called “Fighting Aging with SENS”. Each explained one of the seven types of damage that cause aging and the damage-repair approaches to tackle them. The series aimed to educate the public, inspire new scientists, and raise awareness of regenerative medicine’s potential.

Ask Me Anything

The End of Year Campaign produced video interviews with Michael Rae, Science Writer and co-author of “Ending Aging”, and the SRF senior scientists and extramural scientists whose work SRF supports. The interviews expanded on both internal research programs at the SRF Research Center and sponsored extramural research.

Watch at sens.org/eoy2022-videos

2022 End of Year Campaign

Week ONE
Challenging Alzheimer's

ApoptoSENS
Removing Dysfunctional Cells

Week TWO
Challenging Sarcopenia

MitoSENS
Preventing Damage from Mitochondrial Mutations

Week THREE
Challenging Atherosclerosis

LysoSENS
Clearing Waste Accumulations Out of Cells

Week FOUR
Challenging Stroke

GlycoSENS
Repairing the Extracellular Matrix

Week FIVE
Challenging Parkinson's

RepleniSENS
Replacing Lost Cells

Week SIX
Challenging Cancer

OncoSENS
Making Cancerous Mutations Harmless

Week SEVEN
Challenging Heart Disease

AmyloSENS
Removing Junk from Between Cells

Since its founding, SRF has continually operated at the forefront of innovation in medical research. In the same spirit, we embraced exciting and innovative ways to fund our vital work.

This campaign highlighted each of the 7 Strands of research to challenge the seven types of damage that cause the diseases of aging.

Each week one of the 7 Strands was featured, along with two new ways to support our work.

In collaboration with digital artist Soliman Lopez, a historic NFT/digital bio-art collection was created called VI7A. The project minted unique NFT works of art that could be purchased. Each NFT was based on one of the SENS 7 Strands, and was connected to live data streams from cell cultures in the Research Center by means of electrodes and an oscilloscope. NFTs were fed information about the cells creating a unique work every minute.

Donations made between November 6 and December 31 earned voting tokens which were used to vote for one of the 7 strand projects to receive a "Request For Proposals" for 2023 as part of the Web3-style gamification of the fundraising effort. NFT owners also earned tokens to vote.

With weekly videos by Life Noggin, AMAs with SRF researchers, scientific animations and other materials, we created an informative campaign so that together we can Leave No Damage Unchallenged!

Explore the full campaign at **sens.org/eoy2022**

NFTs by SOLIMANLOPEZ

Each unique NFT was tied to one of our 7 Strands and included data from live cellular cultures. The tradable NFTs marked purchasers' contributions to ending the diseases of aging. Proceeds funded SRF research and earned tokens for deciding which program received a new RFP for 2023.

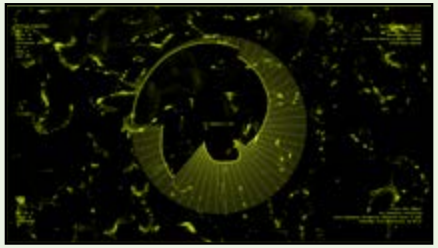
NFTs are available at **vi7a.sens.org**

Photo: Courtesy of Domestika

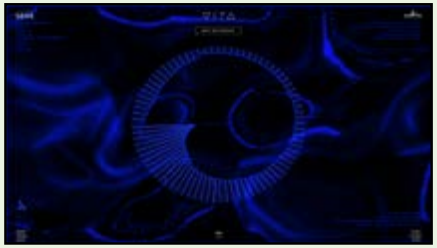
MitoSENS NFT

LysoSENS NFT

GlycoSENS NFT

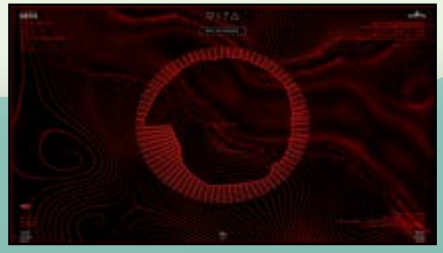


ApoptoSENS NFT



AmyloSENS NFT

RepleniSENS NFT



OncoSENS NFT

SENS Tokens

During our End of Year Campaign, donors earned tokens to vote for the SENS program they wanted to receive a new Request for Proposals in 2023.

At the end of the voting period. The winning program was **GlycoSENS** and the RFP is out!

View at **sens.org/glycosens-rfp**

GlycoSENS

Repairing the Extracellular Matrix: Request for Proposals

Have an innovative approach to repair age-related extracellular damage?

Apply for funding!

Thank You to Our Generous Donors!

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SENSible Question

Each month, Science Writer Michael Rae delves into the fascinating world of rejuvenation biotechnology through SRF's SENSible Questions initiative. People like you send in their inquiries via email, and Michael carefully selects one question to address in a dedicated blog post on our **SENSible Blog** at **sens.org/blog**

SENSible Question: *How would the SENS strategy of placing backup copies of mitochondrial genes in the nucleus be delivered to the roughly 37 trillion cells in the human body?*

SENSible Question: *Cellular reprogramming turns an old person's cells young again. Can't we fix aging by reprogramming a person's old cells with reprogramming factors?*

SENSible Question: *Is there any established correlation between SASP or senescent cell burden and measured hsCRP level or any inflammatory marker on the other side?*

PubMed Publication Search

The PubMed search uses an advanced search algorithm to scan 5,000 scientific publications per day. Relevant studies are shared with staff and collaborators, helping SRF to stay up-to-date on the latest aging-related research. Explore the repository at **sens.org/pubmed**

The SENSible Blog

The SENSible Blog discusses the development of rejuvenation biotechnology around the world: progress being made in the field of longevity, the design of medical therapies to cure, reverse and prevent the diseases and disabilities of aging, and much more.

Our content is a blend of popular interest articles – labelled "Easy Reads", and designed to require no specific background knowledge – as well as more detailed scientific commentaries, labelled as "In-Depth" and aimed towards readers with some grounding in the biological/ medical sciences.

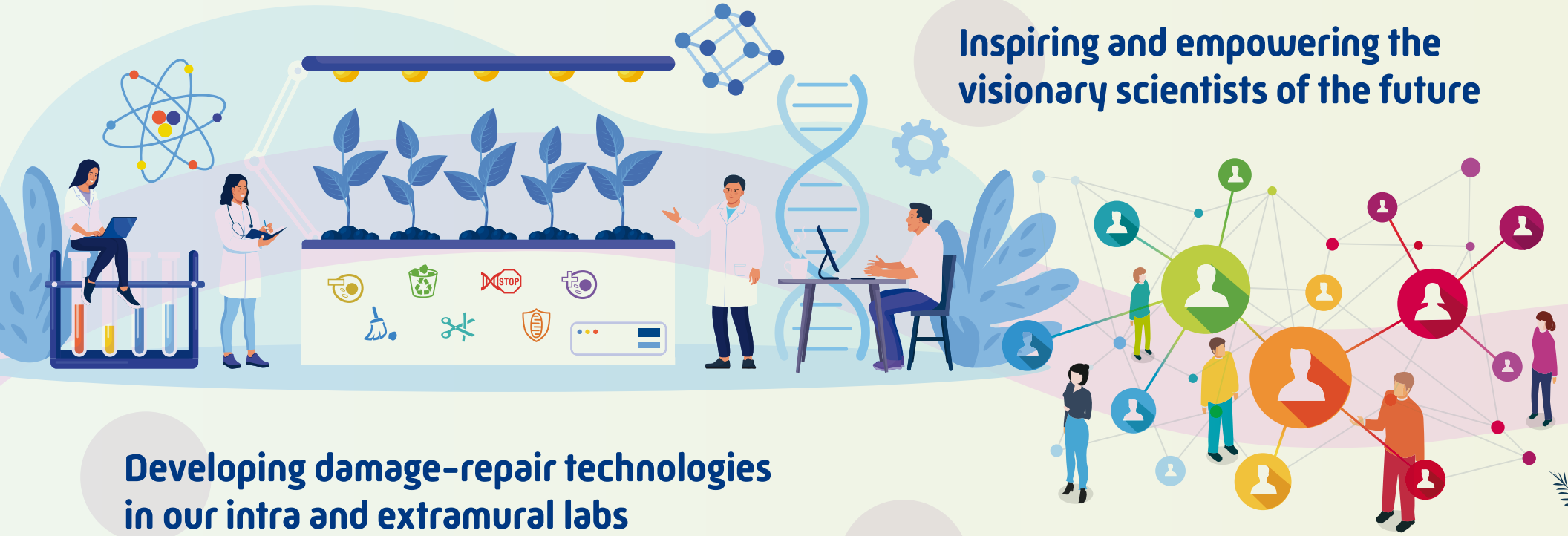
Visit: www.sens.org to stay up to date on all things SENS.

Learn about the latest in SENS Research Foundation's developments and opportunities in:

Research Education Outreach

The SENS Vision: Repairing the Damage of Aging for All

Strategies for Engineered Negligible Senescence: SENS Research Foundation's strategy to prevent and reverse the damage of aging is to apply the principles of regenerative medicine to repair this damage as it occurs.



Inspiring and empowering the visionary scientists of the future

Developing damage-repair technologies in our intra and extramural labs

Spinout companies further develop promising technologies

SENS is a new kind of medicine: regenerative therapies that remove, repair, replace, or render harmless the cellular and molecular damage that has accumulated in our bodies with time. By reconstructing the structured order of the living machinery of our tissues, these rejuvenation biotechnologies will restore the normal functioning of the body's cells and essential biomolecules, returning aging tissues to health and bringing back the body's youthful vigor.

Working to reverse the seven types of damage that occur in the body:

AmyloSENS
Removing Junk from Between Cells

ApoptoSENS
Removing Dysfunctional Cells

GlycoSENS
Repairing the Extracellular Matrix

LysoSENS
Clearing Waste Accumulations

MitoSENS
Preventing Damage from Mitochondrial Mutations

OncoSENS
Making Cancerous Mutations Harmless

RepleniSENS
Replacing Lost Cells

Clinical trials to translate into effective therapies

Regenerative medicine available to all

Happy and HEALTHY people (including YOU!)

SRF Events

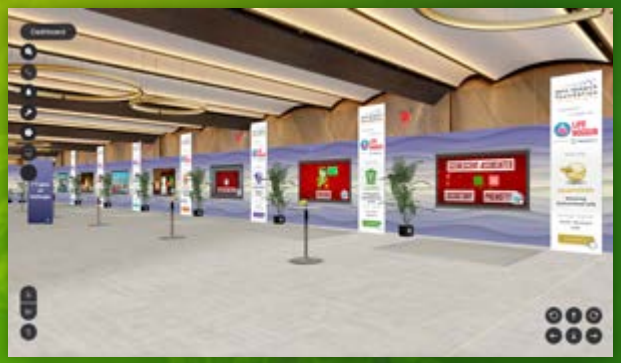
There has been a remarkable shift in public mindset since the founding days of SRF. This transformation is significantly attributed to dedicated outreach efforts. SRF acknowledges the pivotal role of outreach in driving positive change and fostering greater understanding in our mission to combat age-related diseases.

2022 SRF Donors Appreciation Event

This year's event was held in January of 2023 on the EXVO VR platform.

Every year, this gathering serves as a special occasion to celebrate and extend SRF's sincere appreciation to those who have made the mission possible.

Clickable research banners in VR EXVO Expo room.



Clickable Life Noggin banners in VR EXVO Expo room.

INTERNATIONAL LONGEVITY

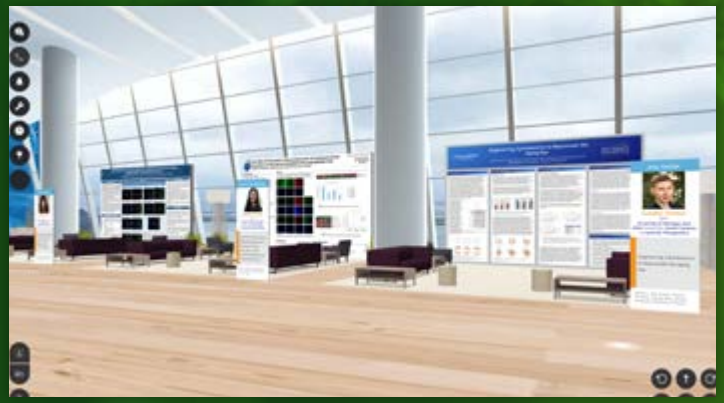
International Longevity Month/Day

SRF celebrated Longevity Day 2022 in partnership with the International Longevity Alliance, commemorating 10 years of the Longevity Day/Month Campaign. Members of the ILA met in SRF's Virtual Reality Room.

Following the tradition, events focused on supporting longevity research take place internationally throughout the entire month of October.

Ending Aging Forum

This virtual event allowed us to share SRF's in-house researchers' latest advances toward new rejuvenation biotechnologies, as well as highlight the work of some of our education program participants and outside SRF-funded researchers. In addition to the formal presentations, one-on-one discussions were facilitated with the scientists and other members of the team, as well as with citizens, donors, and activists who dream of and work for a future free of degenerative aging.



Student poster booths in VR EXVO Conference room.

Research booths in VR EXVO Conference room.

Main presentation stage in VR EXVO Conference room.

Airdrop Donors' open Forum (via Zoom)

SRF Senior Staff and members of the Outreach team held an open Zoom forum on December 16th, 2022 for PulseChain Airdrop donors to ask questions about SENS Research Foundation's recent expansion, research progress, future plans, or any other topic. Both a morning and evening forum were held for donors to participate from anywhere in the world.

Media Appearances

Science Writer Michael Rae's interview by Dr. Robert Rodgers to discuss Parkinson's and aging.

VitaDAO IP-NFT Transfer Ceremony with Molecule, funding ApoptoSENS research with $253,000.

An Ask Me Anything session at the Ending Age Related Disease (EARD) conference, with CEO, Lisa Fabiny, moderated by Lifespan.IO's Executive Director, Stephanie Dainow.

A very informative and engaging Longevity and Aging Series episode with Dr. Amit Sharma, ApoptoSENS Group Lead.

A Twitter Spaces event to launch the Angel Protocol Longevity Campaign in partnership with Methuselah Foundation and Lifespan.io.

Phil Newman interviewing CEO, Lisa Fabiny

An article by Longevity Technology about the Angel Protocol Longevity Campaign.

A video by Lifespan News at Lifespan.io about SRF's End of Year Campaign and innovative ways to fundraise.

Events Sponsored - 2022

ALCOR (presented by ALCOR Life Extension Foundation)
6/3 - 6/5/2022

Ending Age-Related Diseases (EARD)
8/11 - 8/14/2022

Longevity Investors Conference
9/28 - 9/30/2022

International Cell Senescence Association (ICSA)
9/29 - 10/1/2022

ILA's - Longevity Day 2022
10/1/2022

RAADfest (by Coalition for Radical Life Extension)
10/6 - 10/9/2022

New Media Room

As part of our facility expansion, SRF added a new Media Room to facilitate interviews, meetings, and promotion. The room both repurposes and stores our conference booth backdrop that features the SENS Approach to repair the damage of aging.

Conference Participation - 2022

Israel Aging & Epigenetics Meeting
4/1/2022
Dr. Alexandra Stolzing presented: *Senescence and Senolytics.*

Bay Area Aging Meeting (BAAM)
5/17/2022
Dr. Tesfahun Admasu, Ashley Brauning, Kristie Kim, and Jenny Ng all presented posters: *Identification of Novel Senescent Cell Surface Targetable Proteins.*

American Aging Association (AGE2022)
5/17 - 5/20/2022
Dr. Tesfahun Admasu presented: *Cellular Senescence in Aging and Disease.*

Longevity Tech Trees, Tools and Prizes (presented by Foresight Institute)
5/21 - 5/22/2022
Dr. Alexandra Stolzing presented: *Creating Good Pre-Clinical Lifespan Studies to Test Senolytics.*

ALCOR Conference
6/3 - 6/5/2022
Maria Entraigues Abramson attended.

UMFD Mitochondrial Medicine 2022 Symposium (presented by United Mitochondrial Disease Foundation)
6/8 - 6/11/2022
Dr. Amutha Boominathan and Carly Truong presented: *Safe-harbor Allotopic Expression of Mitochondrial ATP8 Gene from the Nucleus in Vivo.*

Ending Age-Related Diseases (EARD)
8/11 - 8/14/2022
Dr. Abdelhadi Rebbaa presented: *The Combination of Senolytics & Stem Cell Transplantation as a Potential Anti-Aging Therapy.*
Lisa Fabiny-Kiser participated: *AMA session*
Staff & students attended virtually.

People Unlimited - August Super Longevity Weekend
8/19 - 8/21/2022
Maria Entraigues Abramson presented.

The 9th Aging Research and Drug Discovery Meeting (ARDD)
8/29 - 9/2/2022
Dr. Ravi Jain attended.

Longevity Investors Conference
9/28 - 9/30/2022
Dr. Ravi Jain presented on the *Latest Scientific Discoveries* panel.
Lisa Fabiny attended.

Association of Independent Research Institutes
9/11 - 9/15/2022
Lisa Fabiny, Kelly Boemmel and Jessica Blair attended.

International Cell Senescence Association (ICSA)
9/29 - 10/1/2022
Dr. Amit Sharma presented: *Eliminating Senescence: More Ways to Kill Death-Resistant Cells from Novel Senolytics to Immune-Based Therapeutics.*

RAADfest (by Coalition for Radical Life Extension)
10/6 - 10/9/2022
Lisa Fabiny-Kiser presented.
Maria Entraigues Abramson presented and moderated.

Rejuvenation Startup Summit
10/14 - 10/15/2022
Lisa Fabiny, Kelly Boemmel, Dr. Ravi Jain, Dr. Emily Fishman, Bill Liao and Maria Entraigues Abramson attended.

American Academy of Stem Cell Physicians
10/28 - 1/30/2022
Dr. Abdelhadi Rebbaa Attended.

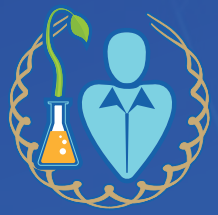
Healthy Masters Forum
11/5 - 11/6/2022
Maria Entraigues Abramson presented.

Cell Symposia-Multifaceted Mitochondria
11/6 - 11/8/2022
Dr. Amutha Boominathan presented.

Cell Symposia
12/8 - 12/10/2022
Dr. Abdelhadi Rebbaa Attended.

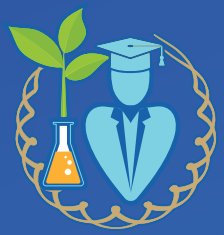
Maria Entraigues Abramson at RAADfest

SRF EDUCATION PROGRAMS



Summer Scholars

SRF's Summer Scholars Program offers undergraduate students the opportunity to conduct biomedical research to combat diseases of aging, such as cancer, Alzheimer's, and Parkinson's Disease. Under the guidance of a scientific mentor, each Summer Scholar is responsible for their own research project in such areas as genetic engineering and stem cell research.



Postbaccalaureate Fellowship Program

SRF's Postbaccalaureate Fellowship Program offers recent graduates a gap year option where they can strengthen their research and communication skills in preparation for such opportunities as graduate programs, medical programs, and biotech positions. The goal of the Postbaccalaureate Fellowship Program includes assignments and training that hones writing and presentation skills. These training exercises are completed within the framework of a research project that the Fellow will be tasked with completing under the guidance of a scientific mentor.

DOMINICAN UNIVERSITY of CALIFORNIA 1890

Dominican Master of Biological Sciences

SRF's partnership with Dominican University of California offers students the opportunity to receive a Master's degree while working at our Research Center in Mountain View, CA and at the same time pursue fast-paced research to advance their scientific career with a funded graduate degree.

PhD Students

Students have the opportunity to conduct research towards dissertation under the advisement of our scientists.

Learn more at **sens.org/education**

Aspen NEUROSCIENCE

Berkeley UNIVERSITY OF CALIFORNIA

Buck Live better longer.

CYCLARITY THERAPEUTICS

HSCI HARVARD STEM CELL INSTITUTE

SBP Medical Discovery Institute

sens research foundation reimagine aging

JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING HNRCA Tufts UNIVERSITY

2022 Education Program Scholars

PhD Students

Oliver Frost
SRF Rebbaa lab
Loughborough University

Dominican Masters

Ashley Brauning
SRF Sharma lab
Dominican University of California

Postbaccalaureate Fellows

2021-2022 Postbaccalaureate Fellows

Mohit Aspal
Snyder lab - Sanford Burnham Prebys

Annalise Bracher
Cyclarity Therapeutics

Madeline Howarth
Garrison lab - Buck Institute

Longsha Liu
Shah lab - Harvard University

Jenny Ng
Anderson lab - Buck Institute

2022-2023 Postbaccalaureate Fellows

Isaac Collibee
SRF Sharma lab

Nikita Sajeev
Snyder lab - Sanford Burnham Prebys

Nathan Schaumburger
SRF Boominathan lab

Summer Scholars

Alec Eames
Cyclarity Therapeutics
University of Michigan

Grace Goetz
Snyder lab - SBP
University of Connecticut

Keefer Li
SRF Boominathan lab
University of Massachusetts

Sheryl Lin
Aspen Neuroscience
Johns Hopkins University

Mustafa Mahmood
SRF Rebbaa lab
Sienna College

Bronwyn Mogck
Wiley lab - Jean Mayer USDA HNRCA at Tufts University
Villanova University

Chinkuli Munkombwe
Snyder lab - Sanford Burnham Prebys
Georgia State University

Marek Pinto*
SRF Boominathan lab
Boston University

Benjamin Ramsell
SRF Rebbaa lab
Oregon State University

Anastasiia Rudenko
Garrison lab - Buck Institute & Lishko lab - University of California, Berkeley
Pace University

Nikita Sajeev
Snyder lab - Sanford Burnham Prebys
Temple University

Rushmeen Tariq
Wiley lab - Jean Mayer USDA HNRCA at Tufts University
University of Utah

*Marek distinguished himself within the Boominathan lab, and was therefore hired as a part-time researcher at the conclusion of the program.

Programming

This year SRF hosted many career and student scientific development programs including: "How to Read a Paper" and "How to Get into Grad School" workshops. Presentations were by intramural senior investigators and student presenters; a literature review was also featured.

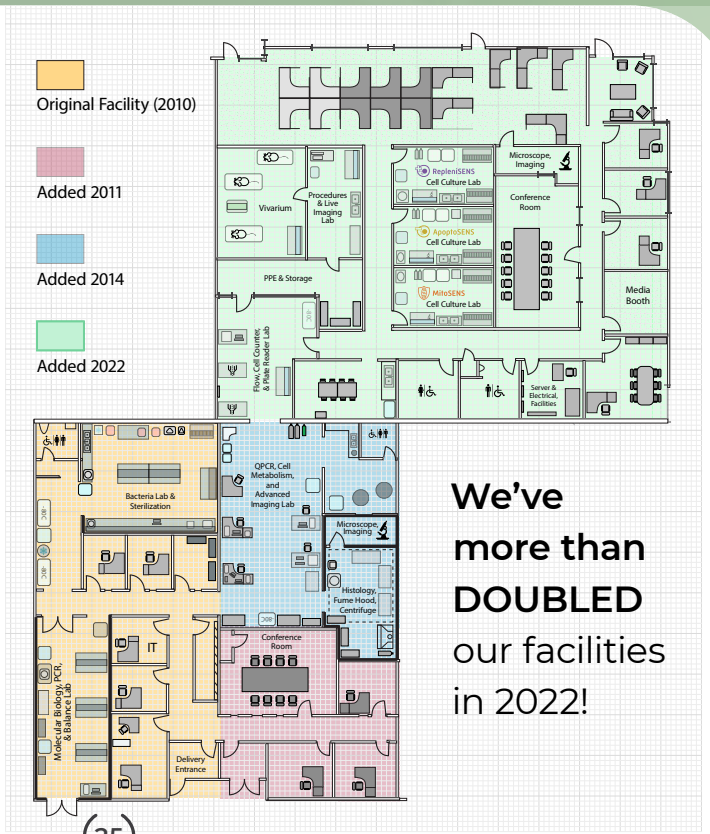
Recruiting

During the spring recruitment season, SRF participated in 14 career fairs - primarily through Handshake. These fairs included (among others) the Ivy+ just in time fair, Dallas College, Villanova, and the University of Wisconsin.

In the fall recruiting seasons, SRF participated in 40 fairs, including: University of Southern California, University of Michigan, Santa Clara State, University of San Francisco, University of Maryland, University of Massachusetts, Harvard University, Brown University, Michigan State, and many others. SRF met over 391 students and received over 180 applications combined for the Summer Scholars and Postbaccalaureate Fellowship programs, with Pomona College and Cornell University students leading the submissions.

A Bigger, Better, Research Center

With your generous support and the hard work of our scientists, SRF's rejuvenation research has once again outgrown the size of the Research Center! SRF has been busy knocking down barriers inside the building to build out the labs in order to keep knocking down the barriers to human health and longevity. Have a look around!



We've more than DOUBLED our facilities in 2022!

Still headquartered in the original Mountain View location, SRF opened up more space to match the growth of humanity's horizon. Between SRF's founding in 2009 and 2014, the Research Center's footprint doubled, which allowed SRF to make room for more researchers and equipment and to open incubating space for longevity therapeutics startups like Turn.bio and Cyclarity Therapeutics, who shared the equipment and cross-pollinated insights.

But as SRF kept adding research projects and sponsoring more Summer Scholars, interns, and staff, things began to get shoulder-to-shoulder in more ways than solidarity! So now SRF has doubled the campus size again, with more space to accommodate new longevity scientists and equipment that will reveal experimental results with greater speed and precision.

New Tools for Scientific Rigor

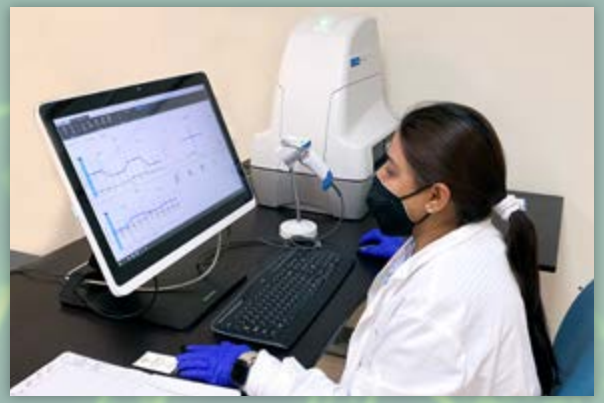
SRF has acquired vital new equipment that will empower SRF scientists to probe aging and rejuvenated cells and tissues with greater speed and finer granularity, multiplying their abilities and sharpening their insights to bring forward new therapies faster.

Spectral Instruments AMI imaging system - enables both luminescence and fluorescence imaging in both cells and live animals. It can be used to, for instance, show different relative levels of senescence markers in mice engineered to exhibit such markers.

Tyto Cell Sorter - enables SRF scientists to introduce a population of mixed cells into the instrument and receive the specific sub-population of cells they need as output.

Flow Cytometer - used by SRF researchers to rapidly identify, quantify, and evaluate cells according to size, type, intracellular proteins, and surface receptors.

Seahorse XF Pro Analyzer - enables SRF scientists to evaluate key cellular functions such as mitochondrial respiration and glycolysis by measuring rates of mitochondrial oxygen flux and extracellular acidification from live intact cells.



SRF Vivarium

With the expansion came the opportunity for SRF to establish in-house facilities for animal housing, care, and testing. While much of SRF's research is carried out in cells, studying the effects of aging and rejuvenation biotechnologies in living mammals is a key step in turning initial discoveries into working longevity therapeutics for humans.

Until now, SRF has performed such studies with help from outside academic partners or outsourced to contract research organizations. Now SRF scientists can conduct can conduct these studies on-site, which will save time and build skills that make them stronger investigators.

SRF RESEARCH

Learn more at **sens.org/research**

Our bodies are awesomely complex, magnificent biological machines. Like all machines, they are subject to wear and tear, damaging themselves at the cellular and molecular level as they carry out the dizzyingly intricate biochemistry that keeps us alive. When our cells and functional molecules are damaged, they can no longer carry out their duties in our tissues, and we slowly lose the life-giving function they provide. Lost neurons can no longer hold memories; mitochondria bearing mutations can no longer produce energy cleanly and efficiently; cellular recycling centers called lysosomes can no longer keep the cell free of debris and provide the scavenged building blocks needed to keep the cell running.

SENS Research Foundation is dedicated to repairing that damage, because restoring our tissues to their youthful structural integrity means restoring youthful health, function, and future life. Last year as every year we conducted cutting-edge rejuvenation research in our own Research Center in Mountain View and funded longevity science in world-class universities and qualified independent research centers around the world.

ApoptoSENS: Building Better Ways to Destroy Senescent Cells

The rejuvenating effects of senolytic drugs — drugs that selectively destroy senescent cells — are astonishing. But as we look ever more deeply into the effects of these drugs, the more problems we see. Subsets of renegade cells escape the drugs' effects. The drugs occasionally inflict collateral damage on healthy cells, and can interfere with wound resolution and regeneration. Dr. Amit Sharma and SRF's ApoptoSENS team are developing ways to target senescent cells that evade existing senolytic strategies while reducing damage to healthy cells.

Slaying Secondary Senescent Cells: One blind spot in the senolytic story has been the effects of these drugs on "secondary senescent cells." Secondary senescence is a more recently-discovered and understudied form of senescence that occurs when cells are driven into senescence by the signaling molecules released by other cells that had previously become senescent (the "primary" senescent cells).

SRF ApoptoSENS scientist Dr. Tesfahun Admasu's studies on secondary senescent cells made him wonder if they might elude many of our existing senolytic drugs, since all such drugs were developed by testing them against *primary* senescent cells. Scientists had already found that any given senolytic drug will be more or less effective against particular subsets of primary senescent cells, and secondary senescence is driven by a totally different process from any primary senescence induction method.

Sure enough, Dr. Admasu found that secondary senescent cells could shrug off several of the best-studied senolytic drugs. Fortunately, he found a novel route of senolytic attack that works well against both types of senescence. These cells intensively engage pathways involved in iron metabolism, and also seem to be primed for *ferroptosis*, a kind of programmed cell death that depends in part on iron as a trigger. And Dr. Admasu's own work also confirmed previous reports that both types of senescent cells greedily hoover up and retain iron.

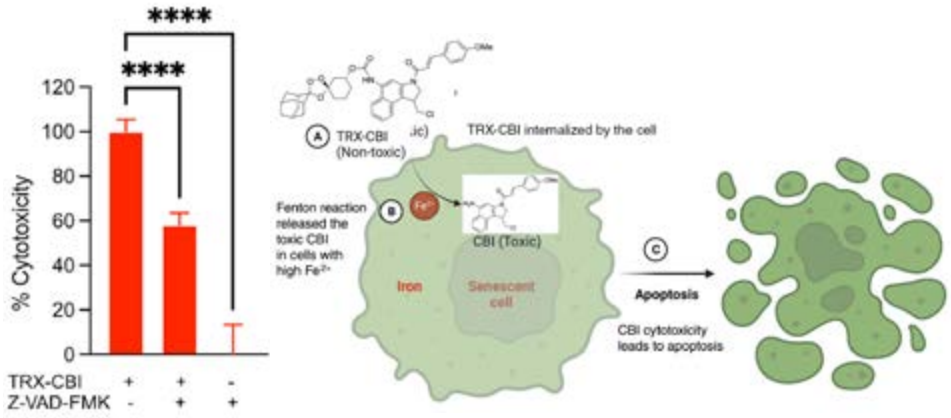
Probing this further, the ApoptoSENS team found that both primary and secondary senescent cells are susceptible to novel attack routes that exploit pain points along this pathway: either their knife's-edge teetering on the brink of ferroptosis or the high iron load itself. Notably, a "sleeper drug" that is activated by the kinds of iron found at high levels in senescent cells can destroy both primary and secondary senescent cells alike.

Judging a Cell by its Cover: The SRF ApoptoSENS group has also been working to confirm that several markers they found on the surface of senescent cells are sufficiently distinctive to differentiate them from normal cells. If they pan out, the team could use such markers to measure the burden of senescent cells in culture or tissues, or even as targets for new senolytic strategies. One approach they are working on entails testing a peptide that they found binds to one of the senescent cell-surface targets and promptly kills many of them while sparing nonsenescent cells.

In a second line of research, one such cell-surface marker gave Dr. Sharma and his team an insight into the abnormal metabolism of senescent cells that may lead to a completely different inroad to their destruction. The SRF ApoptoSENS lab is now testing existing drugs that were previously developed for a completely unrelated use but were discovered to inhibit this pathway. So far it seems to be working, and they are now testing a tweaked version of this drug in living, breathing mice to see if it safely eliminates senescent cells.

Waking the Guardians: Meanwhile, Dr. Amit Sharma is leading work to rejuvenate or reinforce our immune system's ability to destroy senescent cells. Our inborn senolytic warriors have two conceptual advantages over senolytic drugs: 450 million years of natural selection has sculpted them for this purpose, and they patrol tirelessly for abnormal cells throughout the lifespan rather than only removing senescent cells during periodic treatment cycles.

One of the ways the ApoptoSENS team is working to harness the immune system is by using the same core biotechnology behind the more famous "CAR-T cells" that have revolutionized the treatment of some cancers in the last decade — but in this case using a different immune cell type: natural killer cells (NK cells). Until recently, NK cells have been the most effective class of immune cells known to selectively destroy senescent cells. These engineered "CAR-NK cells" would use the ApoptoSENS team's senescent cell surface-binding peptides to lock onto senescent cells and destroy them.



Left: Iron-activated prodrug's senolytic mechanism involves "cellular suicide." Right: Illustrating the prodrug mechanism.

Better yet, Dr. Sharma's group has also discovered that a different cell type— one not previously known to target senescent cells — is even more effective against senescent cells than NK cells, opening up a greater potential for immune-based senolytic rejuvenation therapies.

Removal and Regeneration: Combining Longevity Therapeutics

Senolytics — senescent cell-destroying drugs — are now one of the most rapidly-advancing rejuvenation biotechnologies. Unfortunately, these drugs do inflict some collateral damage to nonsenescent cells. So how much better might senolytics work if SRF scientists coupled them with strategies to enhance the aging body's flagging regenerative response after treatment? The SenoStem group is preparing to test just such a combination.

To reduce damage to healthy bystander cells, the team initially planned to use a *prodrug* form of the widely-used senolytic drug navitoclax. The prodrug would build on navitoclax's inherent selective toxicity to senescent cells, but minimize the odds of mistakenly killing blood-clotting and immune cells by chemically altering it to only become active in cells that produce high levels of a senescence-indicating enzyme. But even with this "safety switch," navitoclax still proved too toxic to mice for the SenoStem project. Instead, the SenoStem team is turning to repurposed and newly-designed senolytic candidates that destroy senescent cells by exploiting their iron-hoarding behavior.

Dr. Rebbaa and his team will then seek to fortify the surviving nonsenescent cells with pro-regenerative signaling factors from mesenchymal stem cells (MSC). They will also test whether they can make MSC secretions more effective by boosting their production of factors that studies suggest are particularly important for the regenerative response.

The SenoStem team will soon test the effectiveness of their iron-based senolytics in mice. In parallel, they will assess the regenerative cocktails produced by MSC under different culture conditions on cells, both with and without senolytics, before returning to the mice to test the optimized combination.

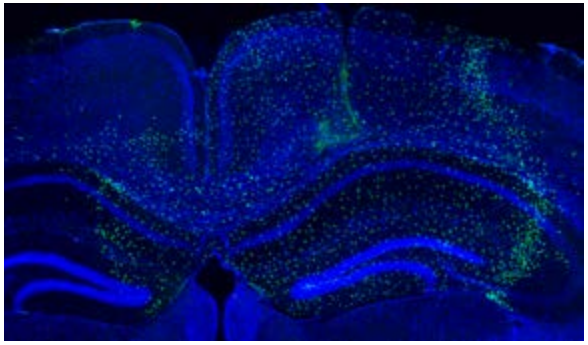
Rebuilding the Seat of Consciousness

We lose neurons throughout adult life: they are destroyed both by acute injuries (such as head trauma and stroke) and by chronic aging damage, including the molecular lesions driving diagnosed neurodegenerative aging diseases like Parkinson's and Alzheimer's. Losing neurons from our neocortex is especially terrifying, because this is the region of the brain that centers our memories, our sense of ourselves, and our histories. And while a small number of brain regions can generate new neurons, the neocortex is not one of them. Therefore, if we are to sustain our memories and identities throughout our currently-expected lifespans and over future extended lives, we need to maintain and restore the cells and circuits of this critical brain region.

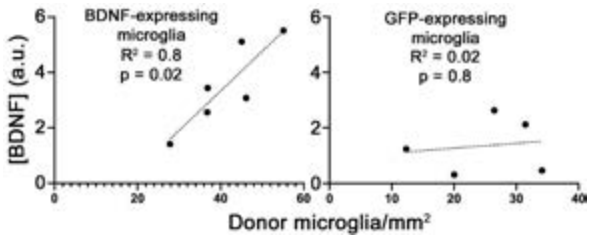
Dr. Jean Hébert, with SRF funding, has been pursuing a bold strategy to replace lost neocortical neurons and reinforce neuronal circuits. Brain neurons are accompanied by support cells called *microglia* that patrol the brain, destroying invading pathogens and supporting the remodeling of neuronal connections. When they are destroyed, other microglia quickly replicate themselves and move in to fill in for the missing cells. Dr. Hébert's plan is to harness this repopulating ability and the exciting biotechnology of cellular reprogramming to replace and reinforce neurons in the aging brain.

The first step in Hebert's plan is to use a selective drug to clear out some of the aging brain's damaged microglia. Then, he would repopulate the brain with engineered replacement microglia that can fan out throughout the organ. Finally, the reprogramming machinery engineered into those new microglia would be activated, turning them into robust neuronal precursors capable of integrating into the brain's local structures.

This year Dr. Hébert and his team have further optimized every prong of this strategy. They tested a range of concentrations of different drugs using a variety of delivery methods to destroy enough of the old microglia to make room for repopulation with a targeted number of engineered cells. The goal is to introduce enough of the engineered microglia to generate clinically significant numbers of replacement neurons all across the brain. They have also achieved larger harvests of donor microglia, developed a better genetic shielding system to protect transplanted microglia against lingering levels of microglia-destroying drug, developed a screening protocol to select microglia that have successfully integrated the shielding system, and improved their protocol for reprogramming microglia into neurons in cell culture.



Engineered microglia (green) disperse widely across the brain.



Microglia engineered to produce BDNF greatly increase the level of BDNF in the brain; control (GFP-producing) microglia have no significant effect.

Moving forward, this RepleniSENS group is also repurposing this basic approach as a platform to deliver large therapeutic molecules into the brain. You can't get such molecules into the brain by simply injecting them, because the brain's protective blood-brain barrier (BBB) shields it from all but a select few large molecules. Though it exists for our protection, the BBB is therefore also an obstacle to delivering LysoSENS therapies that break down the intracellular aggregates that drive neurodegeneration. It will do us no good to engineer enzymes to degrade tau oligomers and alpha-synuclein aggregates inside neurons if we couldn't get them into the brain in the first place! Removing old brain microglia and replacing them with microglia engineered to produce these therapeutic molecules offers a potential solution, as the repopulating-patrolling microglia could produce the therapeutic proteins inside the brain itself.

As a proof-of-principle, Dr. Hébert and his group have tested their approach using the neuronal survival factor brain-derived growth factor (BDNF) as a therapeutic payload. With a single minimally-invasive injection, they can replace the resident microglia with engineered replacement cells that produce high levels of BDNF, allowing them to crank the levels of BDNF up all across the brain to *triple* the amount present in a young mouse.

Engineering Mitochondrial Genes to Restore Mitochondrial Function

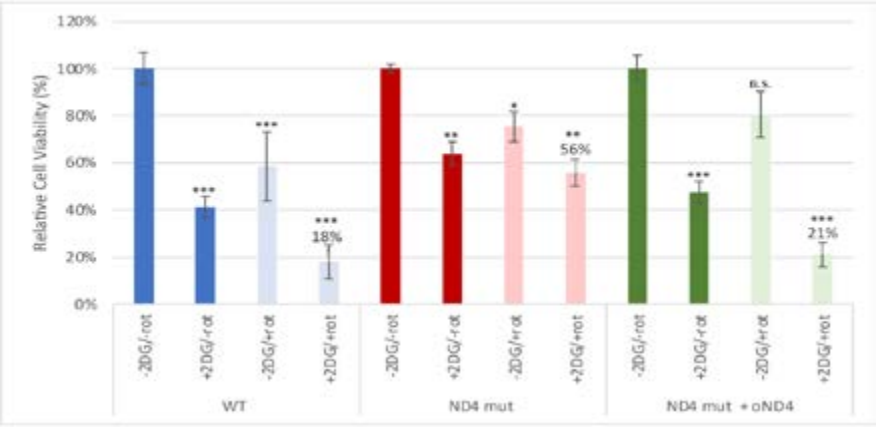
SRF's MitoSENS team is now working on three ways to deal with mitochondria that bear large deletion mutations. The first approach, which they've been working on since SRF's founding, entails creating "backup copies" of the mitochondrial genes in the nucleus. The team's standout success with the gene ATP8 enabled an engineered backup copy of this gene to express in living mice. The mice's cells reliably produce the modified ATP8 protein, which is then absorbed by the mitochondria and integrated into the energy-production system's proper Complex without harming the animal. The team's engineered version of a second mitochondrial gene (ND4) can similarly restore the function of its correct Complex in cells derived from a patient with an inherited mutated version of this gene.

Other genes are proving harder to engineer such that their proteins are reliably produced, delivered, and correctly placed in the energy-production machinery. The MitoSENS team is working to overcome the tendency that some mitochondrial proteins have to curl up

on themselves, which prevents mitochondrial uptake. Based on computer model predictions, the team is testing versions of such proteins (including COX2) with key amino acids exchanged for others that should preserve protein function while finessing this problem. They are also trying out different possible ways to "spell" a given amino acid to slow down protein production, thus giving the cell's machinery a better opportunity to mold these proteins into their functional shape.

The MitoSENS team is also in the early stages of working on two alternative strategies. One is a version of a "gene drive," using therapeutic mitochondria engineered with an enzyme that can destroy *all* the existing mitochondrial genomes in the cell. Once transplanted into an aging patient, these aggressive mitochondria would enter the patient's cells and replicate themselves while buzzsawing through the existing mitochondrial population, replenishing the cell with pristine, functional mitochondria.

The other strategy aims to overcome the culling-avoidance superpower of mitochondria that bear large deletions in their genome. The team is testing several different drugs that may be able to force deletion-bearing mitochondria to show their faces and be marked for destruction.



The usual way of "spelling" the ND4 gene for expression in the nucleus (red) did not restore normal mitochondrial function (blue), but the improved "spelling" (green) does.

Hitting Tau Aggregates Where It Counts

Small, soluble aggregates (*oligomers*) of the protein tau are one of the key drivers of neurodegenerative aging, including Alzheimer's disease. Many major drug companies are developing AmyloSENS-type antibody therapies to remove abnormal tau from *outside* the neurons. The problem is that they don't do anything to remove aggregated tau *inside* the neuron, where it is much more damaging. Dr. Amit Sharma is leading SRF's LysoSENS team to realize an ingenious strategy to clear aging neurons of tau oligomers.

Their strategy consists of two major components: a novel cell-penetrating platform to deliver their therapeutic antibody inside the neurons, and the use of *catabodies* instead of conventional binding antibodies to attack their target. Catabodies, unlike conventional antibodies, cleave their targets into harmless fragments, rather than dragging intact target aggregates one by one out of the brain (and in doing so, damaging the brain's blood vessel barrier). This means while one antibody can only remove a single tau aggregate before leaving the brain, a single catabody molecule can cleave one tau oligomer and then move on to the next and then the next, like an action hero dispatching one bad guy after another. And because this action is carried out on-site, the brain's blood vessels are left unharmed.

The LysoSENS team is developing both a suite of potential catabodies to test and synthetic tau oligomers against which to test them, to ensure that catabodies that successfully buzz their way through the artificial target will also obliterate the real enemy inside the neuron. When they are satisfied with the oligomers, they will begin testing catabody candidates, and after that move on to studies in cells and in mouse models of tau-driven neurodegenerative aging.

The Great White Whale of Intracellular Waste

Scientists have been pursuing a way to clear aging cells of lipofuscin for longer than any other LysoSENS target. Past efforts have failed in part because real lipofuscin is hard to isolate from cells, forcing scientists to resort to artificial mixtures of crosslinked materials or a lipofuscin-like material produced by cells under abnormal conditions. With SRF funding, Dr. Tilman Grune and his group are now attacking the problem using new techniques to isolate true lipofuscin derived from human donor and horse heart tissue.

Fortunately, Dr. Grune has confirmed that horse and human heart lipofuscin are very similar, allowing them to work with the larger available quantities of horse material with confidence that the results will also apply to human lipofuscin. This true lipofuscin's mixture of protein building blocks is different from that of the cell itself, and it is chock full of several trace metals, confirming and extending earlier findings of high iron levels in artificial lipofuscin mixtures. The horse lipofuscin inflicts many of the toxic effects on the cell predicted from previous studies, including locking away trace minerals, inhibiting enzymes, and disrupting heart muscle cell function.

Dr Grune's team is now attacking this isolated lipofuscin using the classic LysoSENS strategy of screening environmental bacteria for the ability to survive by breaking it down. Excitingly, their mixed soil bacterial population can degrade lipofuscin and release fluorescent breakdown products. They are now winnowing this population down to determine which species produce the enzyme(s) that do the critical work. Promisingly, they found that the bacteria *release the key enzymes into their environment* rather than having to take the lipofuscin inside themselves for the enzymes to digest. This may make it easier to identify the critical enzymes and modify them for use as human rejuvenation biotechnologies.

Prioritizing Targets for Extracellular Matrix Rejuvenation

When we think about the drivers of degenerative aging, our minds immediately jump to things that go wrong in our cells. But it is the feedback, physical support, and containment provided by the structural proteins that make up our various types of *extracellular matrix* (ECM) that enable our cells and our bodies as a whole to function. Our mobility and functioning suffers when aging damages the ECM because it compromises our bones, tendons, and the "nurseries" (niches) of our stem cells..

Nowhere is this more clear-cut than the large blood vessels, which stiffen with age due to a combination of changes in the ECM. As our major blood vessels stiffen, they lose the ability to cushion the organs at the end of the circulatory line, leaving these organs defenseless against the pummeling impact of the pulse. Over time, this leads to progressive kidney damage, strokes, lesions in the brain called white-matter hyperintensities, and other chronic and acute end-organ damage.

One key change in aging ECM is *crosslinking*, in which one strand of a structural protein becomes chemically bound to an adjacent strand, limiting both strands' range of motion. Continuous exposure to blood sugar and other essential but highly reactive molecules in the blood can lead to a kind of crosslink termed *Advanced Glycation Endproducts* (AGE). The evidence currently suggests that the single most common AGE crosslink in the key structural protein *collagen* is *glucosepane*.

SRF is funding Dr. Jonathan Clark at the Babraham Institute in Cambridge to drill down into the different crosslinks that form in our tissues with age and dissect their impact on the tissues' mechanical properties so that we can identify the best targets for

future rejuvenation biotechnologies. By feeding "normally"-aging mice special diets in which the building blocks of proteins have been labeled, Dr. Clark can track the rate at which new proteins are synthesized, crosslinked, and degraded.

The picture turns out to be bewilderingly complex. Each kind of tissue undergoes its own distinct crosslinking pattern, and the crosslinks that form don't simply accumulate over time as was previously believed. Instead, a subset of crosslinks easily breaks during regular tissue stretching, only for new crosslinks of the same type to form afterward. In fact, while Dr. Clark and coworkers have confirmed that *irreversible* crosslinks increase in aging tendons with age, this increase is more than counterbalanced by a net *loss* of the *reversible* crosslinks, which may contribute to putting us at greater risk of rupturing our tendons as we age.

Moreover, while the team has confirmed that the age-related rise in glucosepane seen in human tissues also occurs in mice, there's no sign of some of the other crosslinks previously reported in either species. Dr. Clark's careful work is showing that some of these are instead either methodological artifacts or cases of misidentification.

Another of Dr. Clark's significant findings is that a previously-unknown biological process actively crosslinks the ECM protein *elastin*. If the body's ability to form these regulated, "intentional" crosslinks decline with age, it could cause elastin to fragment ever more quickly over time under the cyclic stress of the pulse. Dr. Clark also found that the collagen in the arteries has a mixture of crosslinks distinct from other tissues, including a much higher level of glucosepane — and that the latter starts forming at a very young age in this tissue.

Drs. Clark and Mohanan have additionally used pulse-wave velocity, the gold standard test for human clinical use, to confirm earlier reports that arterial stiffness rises with age in mice just as it does in humans. Untangling how these functional abnormalities integrate to affect arterial function and linking them back to specific kinds of ECM damage will be foundational to developing future rejuvenation biotechnologies to keep our tissues supple and youthfully functional.

Recent Publications:

- Kim K, Admasu TD, Stolzing A, Sharma A. **Enhanced co-culture and enrichment of human natural killer cells for the selective clearance of senescent cells.** *Aging* (Albany NY). 2022 Mar 4;14(undefined). doi: 10.18632/aging.203931. Online ahead of print. PubMed: 35245208

- Saravanan S, Lewis CJ, Dixit B, O'Connor MS, Stolzing A, Boominathan A. **The Mitochondrial Genome in Aging and Disease and the Future of Mitochondrial Therapeutics.** *Biomedicines*. 2022 Feb 18;10(2):490. doi: 10.3390/biomedicines10020490. PubMed: 35203698

- Brauning A, Rae M, Zhu G, Fulton E, Admasu TD, Stolzing A, Sharma A. **Aging of the Immune System: Focus on Natural Killer Cells Phenotype and Functions.** *Cells*. 2022 Mar 17;11(6):1017. doi: 10.3390/cells11061017. PMID: 35326467; PMCID: PMC8947539

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