sens research foundation
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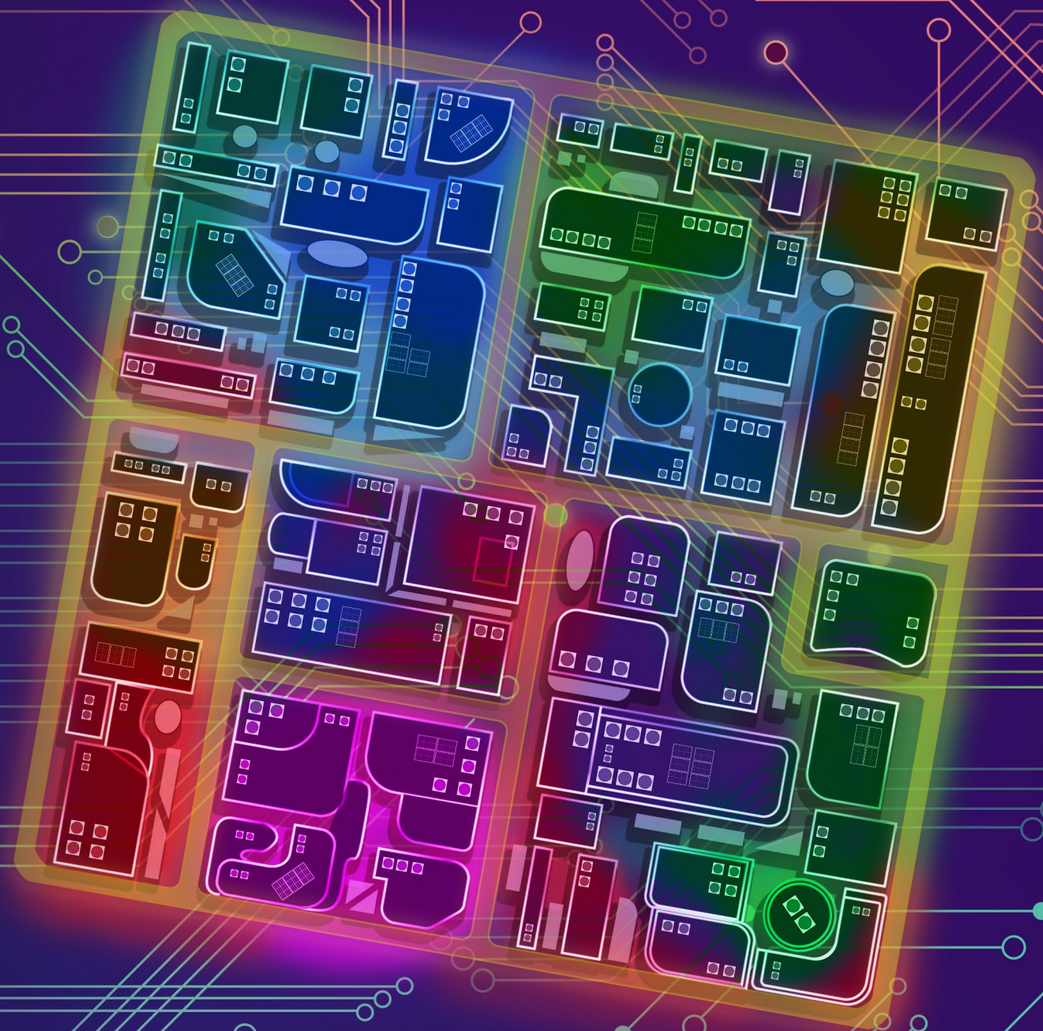

2024 | ANNUAL REPORT

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LISA FABINY-KISER | CEO

When you look at our industry, the longevity community and the global aging community, you see a multitude of connections, spanning the entire globe. Every country is dedicating resources to the fight against aging.

The downward spiral into ill health, and the desperate fight to maintain a longer healthspan, is inherent in the human condition. We all understand what it means to feel weaker, to lose physical and mental capabilities that we once had, due to aging. We all understand the devastation that comes from the irreparable loss of a loved one and watching with helplessness as others around us go down the same path.

Governments are starting to recognize the sheer economic toll that comes from a severely aging population. They are now investing heavily into technologies that will support us as we age and biotechnologies that will compress our morbidity and keep us healthier, longer.

Together we are making headway against the diseases of aging when not too long ago these steps seemed impossible. It is our collective knowledge, our collective technology, that is driving us forward. Building partnerships, strengthening our networks, increasing our capacity to move progress forward - it is these connections that SRF strives to create and reinforce in our industry. It is not enough for one of us to do well – we must all succeed to light the path forward and enact real change. We need researchers, yes, but we also need entrepreneurs, investors, policy makers, doctors, students, big pharma, programmers, operators, and world leaders. We need all their buy-in to make this work.

The aging and longevity communities are rising up against the onslaught of age-related disease, and together we are forming a strong circuit – one that has the potential to defeat the diseases of aging. By making connections instead of building barriers, we stand on the brink of transformative breakthroughs for a healthier, vibrant future.

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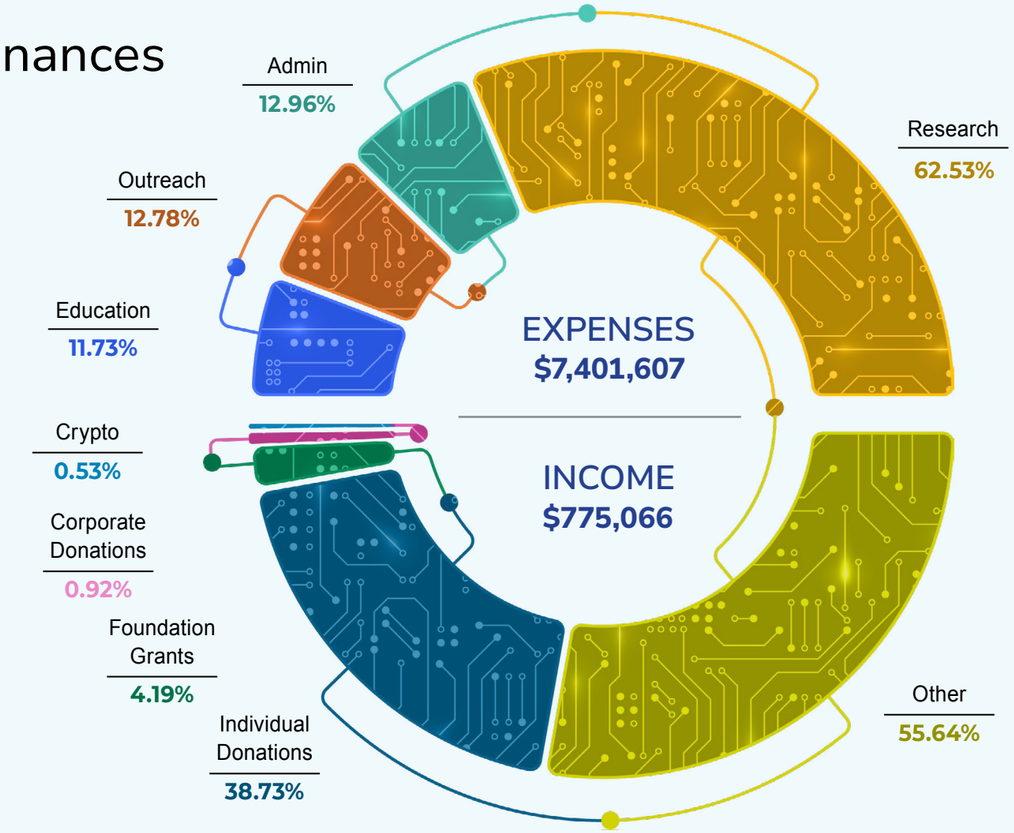

Investments

Funding and support 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

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

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

Summer Scholars
10-12 weeks for undergraduates

Post-Baccalaureate
10 months for Bachelor's degree graduates

Graduate Internship
9 month internship for Graduate students.

Master's Students
1.75yr program to earn a Master's based on SRF research with the Dominican University of California

PhD Students
5yr program to pursue a PhD at SRF with the University of Toledo

EDUCATION PROGRAMS

Education staff and students meet weekly in the summer and bi-weekly during the academic year to provide students with presentation and written training, and other support to complement their technical training in the labs.

Summer 2023

Suhanee Zaroo
San Jose State University
SRF

Sahiba Dogra
St. Mary's college of California
SRF

Danielle Vansover
New York University
SRF

Anagaa Nathan
University of Toledo
SRF

Nick Oh
John's Hopkins University
University of California, Davis

Nandini Seth
University of California, San Diego
Sanford Burnham Consortium

Temiloluwa Ogunyamoju
Caldwell University
Sanford Burnham Consortium

Sanjana Nistala
University of Connecticut
Albert Einstein College of Medicine

Eric Sha
Vanderbilt University
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

Emily Verran
University of Washington, Seattle
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

Amelia Lehmann
University of Wisconsin – Madison
Harvard University

Sukhneet Bhogal
Boston University
Washington University at St. Louis

Post-Baccalaureate 2023-24

Tam Do Gia Vo
Michigan State University
SRF

Kristen Abe
California State University, Fullerton
SRF

Simon Garey
University of Wisconsin, Eau Claire
SRF

Rameen Farrukh
Mount Holyoke College
Sanford Burnham Consortium

Bronwyn Mogck
Villanova University
Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University

Laura Lin
Cornell University
Harvard University

Luctamuelle Joseph
The College of New Jersey
Albert Einstein College of Medicine

Graduate Students

Gabriel Mecca-Laguna
Medical College of Vienna
SRF
Master's student

Oliver Frost
Loughborough University
SRF
PhD Student

Ashley Brauning
Dominican University of California
SRF
Master's student
Now at: University of Washington - PhD

Our new Graduate Internship program and our PhD program with the University of Toledo launched in 2023. As part of these programs, Drs. Lilli Fishman, Amutha Boominathan, and Amit Sharma were given Special Graduate Faculty Status at the University of Toledo.

Where Are They Now?

Nathan Schaumburger
University of Connecticut
SRF – Boominathan lab
Now at: Harvard University - PhD

Nikita Sajeev
Temple University
Sanford Burnham Consortium – Snyder lab
Now at: Washington University at St. Louis - MD

Isaac Collibee
University of Massachusetts Amherst
SRF – Sharma lab Lab
Now at: California State University, Monterey Bay - PhD

Student Awards

Anagaa Nathan
University of Toledo
Annual Biomedical Research Conference for Minoritized Scientists

Sumedha Bobba
University of Alabama, Birmingham
National Conference for Undergraduate Research

Anantha Korrapati
University of Alabama, Birmingham
National Conference for Undergraduate Research

Francesco Neri
Buck Institute for Research on Aging
Bay Area Aging Meeting

Sneha Rao
University of California, San Francisco
Bay Area Aging Meeting

Danielle Vansover
New York University
SRF Speed Presentations - Summer

Sahiba Dogra
St. Mary's College of California
SRF Speed Presentations - Summer

Babraham Institute

Center for life sciences research, specializing in epigenetics, immunology, and aging, driving scientific breakthroughs for healthier futures. SRF funds Dr. Jonathan Clark to study proteins supporting cells and tissues, exploring crosslinkers' impact on mechanical properties for rejuvenation targets.

Age Wave

A leading authority on the societal and economic impacts of our aging population. SRF is proud to work in concert with AgeWave to align on addressing the challenges of an aging society.

TAFFD's

A global hub for innovation, engaging people through education on the use of technology across high-impact industries and disciplines worldwide. SRF is a sponsor of TAFFD's AfroLongevity Conference, and will be collaborating on a new African Education initiative in the coming year.

Alliance for Longevity Initiatives

A4LI creates social and political action around the issues of combating age-related chronic conditions. SRF sponsors the work of A4LI in their work to change our systems in favor of aging research.

Stanford University

A premier institution fostering innovation, research, and academic excellence, shaping future leaders to drive global progress, including in aging and longevity. SRF funds Dr. Annelise E. Baron to develop small peptides combatting Abeta-amyloid aggregates in Alzheimer's patients' brains.

University of Toledo

The Department of Biological Sciences offers both undergraduate and graduate programs for students with a passion for the study of life and living organisms. SRF offers eligible students the opportunity to pursue their Doctoral degree (PhD) whilst conducting research in our Research Center.

Afrolongevity

A non-profit focused on educating Africans about ethical strategies for achieving a longer and healthier lifespan. SRF is starting an education program through Afrongevity to fund students at labs in African universities working on aging.

DIFE

Research institution investigating nutrition's impact on health and disease, and fostering scientific breakthroughs for improved well-being. SRF funds Dr. Tilman Grune to explore clearing aging cells of lipofuscin waste using bacterial enzymes for treating age-related degenerative diseases.

Dominician University of California

Dominican'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. SRF offers eligible students the opportunity to pursue their Master's degree whilst conducting industry research in our Research Center.

Albert Einstein College of Medicine

A university innovating medical education and research, advancing healthcare for humanity. SRF funds Dr. Jean Hebert's research on replacing neurons and reinforcing circuits for age-related neuronal diseases.

The Michael J. Fox Foundation

The MJFF, founded by Michael J. Fox, is a non-profit dedicated to curing Parkinson's disease. SRF partners with MJFF in their PD-AGE consortium to apply damage-repair solutions to Parkinson's and other neurological diseases.

Parkinson's Foundation

A national organization that funds research and provides educational resources to Parkinson's disease patients and caregivers. SRF is proud to showcase our work while Walking to End Parkinson's.

Women In Longevity Leadership

Women in Longevity Leadership aims to lift up and connect empowered women in the longevity space to create a stronger industry. Two members of SRF's Senior Staff co-founded the group in conjunction with Natasha Vita-Moore and guide its vision.

Lifespan.io

Lifespan.io promotes the advancement of medical technologies which will increase healthy human longevity. Lifespan and SRF sustain a media partnership that amplifies event visibility, crowdfunding to support our research, and content creation for science communication.

AFROLONGEVITY — SANUS LONGEVITAS (HEALTHY LONGEVITY)

Longevity+Desci SUMMIT NYC — Ending Age-Related Diseases 2023

HEALTHY MASTERS FORUM

Independent Ageing Convention — October 23-25, 2023 | Aichi, Japan

NEXT MD .HEALTH

Oxford Society of Ageing and Longevity

PHAEDON INSTITUTE

RAAD FESTIVAL™

Breaking New Ground in Destroying Senescent Cells

SENS Research Foundation Research Center

SENS category: ApoptoSENS

Principal Investigator: Amit Sharma

Research Team: Tesfahun Admasu, Anna Barkovaskaya, Ashley Brauning, Isaac Collibee, Yafei Hou, Gabriel Meca Laguna, Manikandan Samidurai

When cells suffer genetic damage or duplicate themselves so many times that they are in danger of becoming cancerous or driving fibrosis in our tissues, they pull a molecular "emergency brake" that stops them from dividing further and changes their behavior. These "senescent" cells accumulate in our tissues as we age due to rising numbers of cells undergoing such existential crises and because the immune system becomes progressively less effective at clearing them. Drugs or genetically-engineered "suicide genes" that cause such cells to self-destruct are called "senolytic" therapies, and using these therapies to remove senescent cells from the tissues of aging vanimals broadly rejuvenates aging mice and delays or reverses model diseases of aging.

Dr. Amit Sharma's ApoptoSENS team at SENS Research Foundation is working to develop better senolytic therapies to combat aging in humans. One arm of his lab's work is is their discovery of a key blind spot of the classical senolytic drugs: they fail to destroy ***secondary senescent cells***. Secondary senescence is an understudied form of senescence in which cells are driven into senescence by signals produced by cells that went senescent before them. Using an improved protocol to study secondary senescence, the SRF team revealed that both the original and the secondary senescent cells engage in abnormal iron metabolism, and that they can destroy both kinds of senescent cells at once by targeting either of two different aspects of this dysfunctional activity.

Additionally, the ApoptoSENS team has discovered an entirely new way that senescent cells inflict harm on surrounding tissues and propagate secondary senescence. Most of these data come from senescent cells in Petri dishes, but the ApoptoSENS team has also tested samples from older versus younger people, and the results support the idea that this mechanism is actually at work in aging humans. They have now partnered with scientists from an independent lab with specialized expertise to help narrow down the exact proteins responsible for this insidious process.

On top of that, the ApoptoSENS team has uncovered a kind of cell behavior that is on overdrive in senescent cells and on which senescent cells rely for survival. Tellingly, they have also found that senescent cells are vulnerable to a form of cell death closely linked to this activity. They identified an existing drug that was ineffective for the unrelated purpose for which it was originally intended, but that inhibits this key activity. And as their findings would suggest, this drug selectively destroys senescent cells in lab culture experiments. The team is now preparing to test this drug's senolytic effects, as well as its ability to make old mice behave more youthfully and head off frailty.

Closing in on Biotech Enzymes to Clear Cells of Lipofuscin

DIfE (Deutsches Institut für Ernährungsforschung Potsdam-Rehbrücke)

SENS category: LysoSENS

Principal Investigator: Tilman Grune

Research Team: Tim Baldensperger, Annett Braune, Annika Höhn, Julia Jelleschitz, Tobias Jung, Patricia Owesny, Vanessa Schnell, Sophia Walter

Critical cells that last a lifetime (like heart muscle and brain cells) accumulate stubborn waste products that damage them and render them dysfunctional as we age. Lipofuscin is the best-known of these wastes, and yet in many ways it is the least understood. It is only present in miniscule amounts in a limited number of cells, and the methods typically used by scientists to extract such materials can only isolate a small fraction of the small amount that is there in the first place. Until now, these limits have made it impossible to get enough lipofuscin to properly study it. On top of that, while most intracellular aggregates are mutilated versions of a single, defined protein, lipofuscin is a complex hodgepodge of proteins, fats, metals, and whole organelles. Until now, this inability to isolate lipofuscin has stymied researchers from developing rejuvenation biotechnologies to clear it from our cells.

With SRF funding, Dr. Tilman Grune at the German research institute DIfE has finally overcome these problems. He has solved the lipofuscin supply bottleneck by developing a novel way to isolate a high fraction of this toxic yet precious waste product directly from aging cells without altering its chemical makeup, and has also secured a reliable source for enough aging human and horse heart tissue from which to isolate it.

Now, Dr. Grune is using multiple analytical techniques to characterize lipofuscin. While earlier research with synthetic lipofuscin material had suggested that lipofuscin was full of iron, genuine lipofuscin turns out to be jam-packed with much more toxic metals than mere iron. On top of that, he has isolated the major fluorescent component in the material.

Now that he has enough genuine lipofuscin to work with, Dr. Grune is attacking it with the classic LysoSENS strategy of identifying microbes in the environment that can survive solely on lipofuscin as an energy source. By definition, such microbes must posess enzymes that can break lipofuscin down into digestible bits. Identifying and re-engineering these enzymes for delivery to our cells to digest lipofuscin inside them could potentially restore our aging cells to health.

When Dr. Grune's team treats human deep skin cells with extracted lipofuscin, the cells readily take it up and are soon overcome: their cellular "recycling centers" (lysosomes) seize up, leading to oxidative stress and a distinct form of cell death.

Excitingly, Dr. Grune has already found bacteria from a mixed soil sample that degrade lipofuscin, leaving behind fluorescent breakdown products. His group has narrowed down the microbes responsible for lipofuscin cleavage to a single genus of bacteria. Only a limited number of strains are players in the process, and he is working to narrow them down further using novel methods.

Crosslinks Lost, Crosslinks Imposed: Target Selection in Aging Structural Tissue

Babraham Institute

SENS category: GlycoSENS

Principal Investigator: Jonathan Clark

Research Team: Archana Geetha Mohanan

Our arteries, joints, and muscles all become stiffer with age, and damage to the structural proteins of the ***extracellular matrix*** (ECM) (such as ***elastin*** and ***collagen***) is central to this process. Stiffening joints and muscles rob us of our strength and mobility and increase our risk of injury, while the stiffening of our major arteries leaves our brains and kidneys vulnerable to stroke and kidney diseases. So identifying and removing or repairing the aging damage responsible for age-related stiffening is key to our health, survival, and independence.

Chemical "handcuffs" that accidentally form between adjacent strands of collagen during the aging process are a key player in this stiffening, with ***glucosepane*** as the dominant form of this handcuffing in humans. Breaking these aging-imposed crosslinks is therefore likely to be one element of rejuvenating aging tissues. Previously, SRF funded research that produced tools to empower scientists to target glucosepane, and backed a startup company out of Yale founded to do just that. But we knew that there was more to the stiffening of aging ECM than glucosepane alone.

With SRF funding, Dr. Jonathan Clark's GlycoSENS lab at the Babraham Institute has revealed how much more complex the changes in aging ECM are, which gives us lead for new targets to bring aging tissues back to youthful function. While the GlycoSENS team confirmed that aging collagen accumulates abnormal new kinds of crosslinks like glucosepane, it simultaneously loses other kinds of normal, physiological crosslinks. Additionally, some crosslinks that scientists had thought to be irreversible turn out to be routinely torn apart as tendons stretch during muscle contraction, only to form again once the muscle is relaxed. This even appears to happen to glucosepane, although Dr. Clark thinks this finding may be an artifact created by stretched tendons changing their structure or composition in ways that mislead the assay. And surprisingly, non-crosslinking glycation (chemical reactions with sugar molecules that are not guided by the body's enzymes) also seems to impact the aging tendon's mechanical properties.

Putting this all together suggests that fully rejuvenating aging ECM may require a rejuvenation biotechnology that replaces some of the lost crosslinks, even as we remove others that shackle our tissues as we age. Dr. Clark has performed some painstaking preliminary experiments that

seem to support this therapeutic concept and is now puzzling out a more realistic way to test it.

The GlycoSENS team has also now analyzed aged mice's aortas (the main large blood vessel). The mouse aorta stiffens with age as expected, and as Dr. Clark saw in the tendons, the aorta suffers the loss of many kinds of crosslinks even as it accumulates other kinds. But the total number of different crosslinks in both categories is larger in the aorta than in the tendon, and there is no single predominant driver of the overall changes. There is also a hint that different kinds of proteins may get crosslinked together in aging, which is quite unexpected if true. The team will next perform mechanical tests on young and old tissues to get a better handle on how these crosslinks and non-crosslink glycation affect the aging tissue's functional changes.

Dr. Clark's group has also begun looking at the signatures of crosslinks in human skin and bicep tendon samples. In the tendon, they have detected precursors to glucosepane and enzymatic (non-pathological) pyridinoline crosslinks, as well as previously-unseen alternative glycation structures. The crosslink profile they have uncovered in human bicep tendons appears to be different from the one they saw in mice, but they need to do more work to determine if these are intrinsic mouse-versus-human aging differences or if they result from the different stresses experienced by human bicep tendons versus the tendons of four-paw-walking mice.

Hitting Tau Aggregates Where It Counts

SENS Research Foundation Research Center
SENS category: LysoSENS
Principal Investigator: Amit Sharma
Research Team: Manikandan Samidurai

Beta-amyloid is a key driver of neurodegenerative aging of the Alzheimer's type (AD), but it inflicts much of its harm indirectly, through its effects on aggregates formed of the protein tau. Pharmaceutical companies have developed many would-be AmyloSENS therapies consisting of antibodies designed to bind to and remove tau aggregates, but several of these have failed in clinical trials, and more failures are likely to follow. That's because these antibodies can only reach tau aggregates located outside the neurons, and they mostly target the larger, more readily-visualized tau aggregates. By contrast, the tau aggregates that most impair brain function are small clusters of tau (***oligomers***) that can remain soluble in solution and that primarily impact the brain from *within* our neurons.

So why aren't well-capitalized pharma giants with wide scientific expertise targeting the most important species of tau? It's because antibodies are our best tool for targeting many aggregates, and antibodies normally don't penetrate into cells — or if they do, they don't get into the body of the cell to do their job.

Another limitation to attacking tau aggregates with conventional antibodies is that in order to lower the tau aggregate burden, such antibodies must first latch onto their targets and then somehow pull them out of the brain, which requires dragging them through the barrier that shields the brain from foreign substances. It's this process that most likely injures the blood vessels in the brain and leads to the ARIA side-effects that are common with the current generation of AmyloSENS antibodies against beta-amyloid.

Dr. Amit Sharma and his LysoSENS team at SENS Research Foundation are working on a new tau oligomer targeting strategy that would overcome these limitations by taking advantage of two novel biotechnologies: a new way to smuggle therapeutic antibodies into the neurons themselves, and the use of ***catabodies*** instead of conventional binding antibodies to chop up tau oligomers on the spot instead of trying to haul them out of the brain. In contrast to conventional antibodies, catabodies bind to their targets and then cleave them into pieces, eliminating the need to make the perilous journey out of the brain. And because catabodies don't have to hold onto their targets once they've reduced them to mincemeat, they can remain on site and proceed to cleave another target molecule, and then another — and then another. This means that a small number of catalytically-active catabodies can do the job of many conventional binding antibodies, which can each only bind and pull away a single target molecule.

The LysoSENS team's method of developing catabodies is to first identify antibodies that will bind to tau oligomers and then re-engineer them into catabodies proper. After receiving a disappointing set of candidate antibodies from an outside contractor, the LysoSENS team is now working up an in-house screening system that will identify suitable candidate antibodies for them. They will engineer the best of them into catabodies and test them against synthetic tau oligomers and then in neurons that express abnormal forms of tau, and then move on to animal testing and (if all signs are "go") human clinical trials.

Keeping the Cellular Lights On, Come Hell or Mitochondrial Deletion Mutations

SENS Research Foundation Research Center
SENS category: MitoSENS
Principal Investigator: Amutha Boominathan
Research Team: Jonathan Ayache, Bhavna Dixit, Sahiba Dogra, Simon Garey, Kathlene Joyce, Anagaa Nathan, Marek Pinto, Nathan Schaumburger

People do confounding and sometimes dangerous things to cope when there's a power outage – and so do our cells when their power plants (the mitochondria) suffer large deletion mutations. As we age, such mitochondria completely overtake a small percentage of our cells, deranging those cells' function and likely leading to them poison cells elsewhere in the body. There are no foreseeable biotechnologies to completely prevent or directly repair the deletions themselves, so SENS Research Foundation's MitoSENS team, led by Dr. Amutha Boominathan, is working on ways to circumvent the problem so that our cells can keep operating normally even in the face of such deletions.

Their flagship program is ***allotopic expression*** (AE): engineering "backup copies" of the genes encoded in the mitochondria. With these backup copies, our cells would be able to produce replacement parts for the components that the mitochondria need to sustain energy production when the original mitochondrial genes are mutated away. After a breakthrough success with the mitochondrial gene ATP8 in cells, the MitoSENS team has now developed transgenic mice in which the AE gene competes with a mutated ATP8 gene that the mice inherit, leading to better mitochondrial function in every tissue tested.

They are now working to develop AE versions of the remaining 12 genes. It has proven much more challenging to get these 12 to work: the level of the proteins trails off over time, and different AE proteins are tough to get into the mitochondria, and/or for the mitochondria to "unpackage" them upon delivery, and/or for the mitochondria to properly slot them into the energy-generating machinery and ignite power production.

One reason for some of these problems is the tendency of some of these proteins to ball up on themselves when produced in the watery main body of the cell. The team has tested several strategies to keep the proteins in their proper shape. One is to intentionally switch out the amino acid "links" in their protein chains that are more prone to kink, informed by computer modeling of the structure of different potential variants. Others include experimenting with different combinations of "start buttons" that allow the cell to turn on the expression of the genes, biochemical "zip codes" and other temporary sequences that deliver the AE proteins to the mitochondria, and other elements.

The MitoSENS team is also working to develop a tool to make it easier to detect the AE proteins in the mitochondria without interfering with their "unpacking" or their integration into the energy-producing machinery. One two-part system the team tried was too faint to reliably detect, and "turning up" the signal interfered with the "working copies" that the cell uses to produce the protein. To address this issue, they are placing tags at different locations on the protein where the tags are less prone to obscure the protein or interfere with its essential functions.

The SRF MitoSENS team is also working on two alternative ways to overcome the deletion mutation problem. One is a "***gene drive***" approach: transplanting engineered mitochondria into the cells. These engineered mitochondria would be able to destroy the native mitochondria and take over the cell, replacing whatever came before them with fully-functional cellular power plants. These aggressive mitochondria would be engineered with an enzyme that can slice up the native mitochondria's genomes, whereas the souped-up mitochondria themselves would be fabricated to lack the site that is vulnerable to the enzyme. This "slash and burn" strategy would purge the cell of existing mitochondria — mutant or not — and leave only intact engineered mitochondria behind.

The team's first milestone along this path has been a protocol to ensure that their transplanted mitochondria stay where they're put. Until now, mitochondria transplanted by the SRF MitoSENS team or by other scientists have never hung around in their recipient cells for more than a few days to a couple of weeks, which would make them useless as a solution for mitochondrial deletion mutations. The MitoSENS team's new protocol only results in a very small number of transplanted mitochondria persisting — but if they can be engineered according to plan, a handful of them would suffice.

Their second alternative or complementary strategy to combat mitochondrial deletion mutations is to pierce the "cloaking field" that allows deletion-bearing mutations to escape the cell's mitochondrial quality-control system (mitophagy). The team is testing several variants of one drug (and potentially others) that may force deletion-bearing mitochondria to show their faces, which would allow the mitophagy machinery to tag them for destruction. The best drug they've tested so far can expand the fraction of intact mitochondria in a cell containing a mixture of healthy and deletion-bearing organelles. By contrast, the drug seems to have little or no effect in cells with mitochondria bearing mutations in just one gene from patients with an inherited mitochondrial disease. This finding potentially points to a mechanism specific to the kinds of mutations that dominate in the cells of aging people.

Rebuilding the Seat of Consciousness

Albert Einstein College of Medicine
SENS category: RepleniSENS
Principal Investigator: Jean Hébert
Research Team: Rohan Hofland, Felipe Vilicich

We lose neurons to acute injuries throughout adult life, and even more of them to aging damage in the last decades of current lifespans. Neuronal loss, in turn, drives neurodegenerative aging diseases like Parkinson's and Alzheimer's. And while we can replace our livers and hearts when they fail, replacing our brains "would rather defeat the purpose," even if it were feasible. Instead, we need a way to maintain and restore the neuronal circuitry patterns unique to each of us — especially those of the ***neocortex***, which houses critical human faculties such as our sense of ourselves as unique persons in space and time and the powers to plan and reason. This is an intimidating challenge: there are vast numbers of neurons in the neocortex over a huge surface area, and it would be prohibitively complex and dangerous to surgically implant neuronal precursor cells all across its folded surface once every few years.

Happily, Dr. Jean Hébert has devised an ingenious strategy to deliver young neuronal precursor cells all across the neocortex. While neuronal precursor cells set down roots wherever you happen to implant them, brain immune cells called ***microglia*** routinely patrol throughout the neocortex. When the microglia find an area unguarded by any of their compatriots, they lay down stakes to defend it.

Dr. Hébert realized that if he were to clear out a fraction of a person's existing microglia to make room for replacement cells, he could send in microglia engineered with cellular reprogramming cassettes that would transform them into neuronal precursor cells when the patient took a drug to turn the cassette on. This would allow future doctors to distribute engineered microglia all across the neocortex and then transform them into neurons on site, allowing for widespread neuronal replacement.

With SRF funding, Dr. Hébert and his team have demonstrated several of the main steps in this plan in mice. They are now working to bring the model closer to human use by delivering engineered human microglia and human blood precursor cells into the brains of mice whose immune systems won't reject them. Meanwhile, the team has shown in cell culture that they can convert a fraction of engineered microglia into neurons, and is now working to improve the efficiency of this process.Scientists could also use the core of this approach to deliver large therapeutic molecules into the brain, such as LysoSENS enzymes that degrade intracellular aggregates that drive neurodegeneration. Drug developers can't just put such molecules in pills or even injections because of the elaborate way the brain is shielded from foreign molecules. Microglia engineered to produce such therapeutic molecules (rather than to transform into neuronal precursors) could deliver them widely across the brain and continue producing them for extended time periods. Dr. Hébert and his group have already used a version of this approach to deliver the neuronal survival factors BDNF and GDNF into the brains of mice. With a single minimally-invasive injection, they can replace the old mice's aged microglia with microglia engineered to deliver BDNF, thereby boosting BDNF levels all across the brain to triple the amount in a young mouse.

One Molecule Tackles Two Drivers of Alzheimer's Neurodegenerative Aging

Stanford University
SENS category: AmyloSENS, "PathoSENS"
Principal Investigator: Annelise Barron
Research Team: John Fortkort, Jennifer Lin, Josefine Nielsen, Kristian Sorensen, Claudi Zielke

Infectious diseases are driven by pathogens that invade our bodies from without. By contrast, diseases of aging are driven by the damage inflicted on our bodies from within — by the normal operation of the biochemical processes that keep us alive. But there's now a lot of evidence that neurodegenerative aging of the Alzheimer's type (AD) is accelerated by microbes like the oral herpes virus and P. gingivalis (the bacteria most responsible for gum disease) infiltrating our brains. It appears that these pathogens trigger our neurons to release beta-amyloid (the malformed protein that drives AD), which acts as a kind of ***antimicrobial peptide*** (AMP) to neutralize the pathogen.

When things are working properly, amyloid-entrapped microbes trigger brain immune cells called ***microglia*** to activate, become inflammatory, and swallow and digest the beta-amyloid/microbe complex, after which the microglia return to standby mode. Eventually, however, the burden of beta-amyloid and microbial marauders locks the microglia into a continuous state of activation, engulfing the brain in chronic inflammation and abnormally pruning the connections between our neurons, hastening the downward slide into AD.

With SRF funding and co-conception, Dr. Annelise Barron is working to develop a rejuvenation biotechnology that would simultaneously destroy many microbial culprits in AD while also partly defanging beta-amyloid in the brain. She got her initial data using ***Peptoid-1***, a derivative of the natural AMP ***LL-37*** with chemical tweaks that make it hang around longer in the body and modify its biological properties. In cell culture experiments, Peptoid-1 can destroy many of the microbes most suspected of accelerating AD. On top of that, LL-37 (and Peptoid-1) have a surprising complementary relationship with beta-amyloid: they strongly bind to it in a sequence-specific way that appears to hold both LL-37 and beta-amyloid in check, blocking the toxic assembly of beta-amyloid and preventing LL-37 from inducing inflammation. These powers of LL-37 prompt the question: could the declining levels of LL-37 in the brain as we age be part of the reason why beta-amyloid plaque burden rises over much of the same time period?

Peptoid-1 turned out to have some toxicity to cells, so Dr. Barron has since synthesized 11 derivative peptoids that seem to preserve its ability to kill a range of bacteria. Her lab is now testing these derivatives to see which are the best at killing other important brain pathogens and at bearhugging beta-amyloid without Peptoid-1's accompanying toxicity.

Based on her original data and the therapeutic potential of this peptoid-based approach to AD, Dr. Barron filed a patent application on it (PCT Application No. PCT/US2022/070465) to ensure that she, Stanford, and SENS Research Foundation's research budget will benefit if she is successful in developing it into a working rejuvenation biotechnology.

By destroying the microbes that trigger some of the aging brain's beta-amyloid synthesis and taming some of the beta-amyloid produced for other reasons, one of these peptoids could be a powerful tool to protect our brains against AD. And other research suggests that Peptoid-1 or LL-37 may similarly interrupt the pathological aggregation of IAPP amyloid (implicated in diabetes and heart failure) and alpha-synuclein aggregates (implicated in neurodegenerative aging of the Parkinson's type), hinting at even broader benefits.

Squeezing the Iron Fist

SENS Research Foundation Research Center
SENS category: ApoptoSENS
Principal Investigator: Abdelhadi Rebbaa
Research Team: Marcela Atzori, Apoorva Shankar, Tam Vo Do Gia, Kristen Abe, Oliver Frost, Danielle Vansover, Nahom Zewde

Scientists have been reporting for the last ten years that senescent cells accumulate remarkably high levels of iron and that they process it abnormally. (See the earlier section on Dr. Sharma's ApoptoSENS lab for a brief refresher on senescent cells and senolytics). Three years ago, Dr. Rebbaa and scientists at Ichor Life Sciences showed that they could distinguish senescent cells from normal ones using a compound that fluoresces in the presence of high levels of iron. And last year, the Sharma lab at SRF found a way to exploit this defective biology in senescent cells to destroy them.

Last year, Dr. Rebbaa's lab at SRF focused on another possible way to use senescent cells' high iron burden against them. The team initially identified senolytic effects from a drug widely used for unrelated purposes. Digging through the literature, they found that previous scientists had already found evidence that a different form of iron plays a role in the mechanism of that drug's original use. Based on this information, they began developing a new assay to track the level of this form of iron to enable their further studies.

Dr. Rebbaa's team then sought to make the original drug and some of its derivatives even more effective as senolytics by forcing senescent cells to double down on their iron-hoarding behavior. In the process, they found that albumin — a major protein used to shuttle hormones and other factors in the serum — protects cells against the theoretical possibility that normal iron metabolism might be enough to drive cells into senescence. Still, the damage that unregulated iron inflicts on albumin in the process is consistent with many previous reports of the harmful effects of damaged albumin on aging humans and mice and the pro-youth effects of replacing it with the undamaged protein.

Recent Publications:

Admasu TD, Kim K, Rae M, Avelar R, Gonciarz RL, Rebbaa A, Pedro de Magalhães J, Renslo AR, Stolzing A, Sharma A. **Selective ablation of primary and paracrine senescent cells by targeting iron dyshomeostasis.** *Cell Rep.* 2023 Feb 28;42(2):112058. doi: 10.1016/j.celrep.2023.112058. PMID: 36753419

Quezada A, Ward C, Bader E, Zolotavin P, Altun E, Hong S, Killian N, Xie C, Batista-Brito R, Hébert JM. (2023). **An in vivo platform for rebuilding functional neocortical tissue**. *Bioengineering* 10, 2:263. PMID: 36829757, PMCID: PMC9952056