By 2030, annual direct medical costs associated with cardiovascular diseases in the United States are expected to rise to more than $818 billion.\(^1\)

62% of Americans over age 65 have more than one chronic condition.\(^1\)

THE CLOCK IS TICKING.

By 2050, the American 85 years and older population will triple.\(^2\)

An estimated 25-30 percent of adults age 85 or older suffer from dementia.\(^2\)

The estimated cost of dementia worldwide was $818 billion in 2015 and is expected to grow to $2 trillion by 2030.\(^1\)

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SPECIAL 10TH ANNIVERSARY EDITION
It’s early 2009, and it’s very late at night. Aubrey, Jeff, Sarah, Kevin, and Mike are sitting around a large table covered in papers and half-empty food containers. They are drafting the fundamental plan for a unique organization they hope will change the way the world views the diseases of aging.

That was how we began SRF - SENS Research Foundation - a decade ago. We wrote about raising awareness for an alternative to an increasingly costly and complex pathology chase in medicine, and redefining regenerative medicine as applied to aging.

In some ways, it seems like yesterday, especially as we’ve never for a moment lost sight of that vision. But if you look back through our reports to you, you’ll see how much of a journey it’s been, and how far we’ve come.

Back then, in 2009, we said, “we did this to transform the way you think about medicine.” At the time, I feared that this challenge was beyond the purview of one small group called SRF.

I realize now that I was underestimating the commitment, the energy, the intellectual honesty, and the vision of Aubrey, of our donors, of our supporters and volunteers, and of all the people that I’ve had the good fortune to work with.
It’s early 2019, a bit less late at night. Most of the staff have gone home; though the last week has been a whirlwind of activity.

Greg has just finished up a round of interviews for a Summer Scholars Program, Oki has been chatting with Amutha about the influence her Mito research team has had (Bhavna’s just finished her experiment and Caitlin’s crunching data), all three of the SRF post-baccalaureate grantees are still busy on their projects, Mia is working out the bugs on the new computational chemistry program, our Alliance team on the East coast ought to be asleep, but they’re probably pulling late hours again. Anne and Kelly are working on the layout for this year’s annual report, Maria’s down in LA working out the kinks in a bitcoin donor event, Michael’s away drafting research summaries, and Aubrey’s on the speaker trail somewhere.

Our Forever Healthy partners in Germany will be up soon to put the final touches on what will be another successful Berlin conference, and Lisa’s next door drafting website updates, as I’m writing the statement for this report.

Today, it’s clear that SENS Research Foundation has helped precipitate a real change in medical research. 2019 is, in many respects, the very reality we dreamed of in 2009.

We now see significant energy pouring into the rejuvenation field, and new investment, and many new companies, and new kinds of research arising. That’s in no small part because of all those people noted above, and in no small part because of you.
SPREADING AWARENESS

IF YOU’RE LOOKING FOR A WAY TO HELP SRF, CHECK OUT THESE OPPORTUNITIES TO GET INVOLVED WITH OUR FUNDRAISING AND OUTREACH - AND BE SURE TO HELP SPREAD THE WORD IN YOUR COMMUNITY!

PROJECT FOR AWESOME

A project of the Foundation to Decrease World Suck, a Montana-based 501(c)3 charity, Project for Awesome is a film competition during which community members from around the world make videos about a charity that is particularly important to them. The videos are submitted to the Project for Awesome website, but are also shared, viewed, discussed, and commented on around the internet. You can make your own video or vote for your favorite videos on the Project for Awesome website, which helps determine the charities that receive funding.

Since Project for Awesome began in 2007, they have raised over $1.5 million for different charities around the world. So far, 24 videos supporting SENS Research Foundation have been submitted to Project for Awesome. Keep the momentum going by submitting your own video or by voting for videos in support of SRF this year!

FOR MORE INFORMATION, INCLUDING OFFICIAL RULES AND GUIDELINES, PLEASE VISIT:
WWW.PROJECTFORAWESOME.COM

LONGEVITY FILM COMPETITION

Co-directed by SRF’s Global Outreach Coordinator, Maria Entraigues-Abramson, the Longevity Film Competition was launched in 2018 by SRF, the Healthy Life Extension Society, and the International Longevity Alliance. Filmmakers worldwide were invited to submit their short films focusing on healthy longevity and its potential to positively impact humanity. The longevity film competition is an annual competition.

All 2018 submissions can be viewed at the Longevity Film Competition Vimeo site:
www.vimeo.com/LongevityFilmCompetition.

From left to right, screen shots from: 2018 First Prize Film, “The End of Aging,” by Adam Ford; 2018 Second Prize Film, “8 Years On (My Father),” by Tim Maupin; and 2018 Third Prize Film, “Undoing Aging,” by Charlie Kam.

FOR MORE INFORMATION, INCLUDING OFFICIAL RULES AND PRIZES, PLEASE VISIT:
WWW.LONGEVITYFILMCOMPETITION.COM
LIFESPAN.IO CAMPAIGNS

Lifespan.io is a 501(c)3 nonprofit organization and crowdfunding platform dedicated solely to longevity research projects.

On Lifespan.io, researchers post projects related to longevity or age-related disease, and receive funds from contributors to fulfill their goals. Contributors, in turn, are able to exercise agency in the development of potentially life changing research, as well as receiving rewards specified by the project creators.

From August to October 2015, 400 backers on the Lifespan.io platform raised over $45,000 for SRF's MitoSENS project. From June to September 2016, over 500 backers raised $72,000 for the OncoSENS project.

BE SURE TO CHECK LIFESPAN.IO THIS SUMMER FOR A NEW MITOSENS CAMPAIGN AT:
WWW.LIFESPAN.IO/CAMPAIGNS

SRF ORIGINS: THE METHUSELAH FOUNDATION

“SRF was founded in 2009, but it was founded out of a bifurcation of another foundation – the Methuselah Foundation – which I created with David Gobel in 2003. Back then, we had no money at all - I’d only had the basic scientific idea of SENS a couple of years earlier and had yet to run with it. By about 2005/2006, we were in a position where we were able to spend some money on research. Our first major donor, Peter Thiel, started giving us around a million dollars a year around late 2006, but around 2008, we came to the conclusion that we were really engaged in two different activities.

So in the end, we split the organization in two and formed this new organization, SENS Research Foundation, to pursue research related to SENS. At which point Peter joined us, anted up significant donations for several more years, and set this off on an extremely successful first footing. I’m happy to say it’s all worked out pretty well.”
SRF is committed to the highest standards of transparency and accountability. All accounts are prepared by CCA, LLP accountants and independently audited annually by Wheeler Accountants, LLP.
THANK YOU
TO OUR DONORS, WITHOUT WHOM
WE WOULDN’T BE CELEBRATING
TEN YEARS OF REIMAGINING AGING.

$1,000,000+ DONATED:
The Pineapple Fund

$100,000 - $999,999 DONATED:

$10,000 - $99,999 DONATED:
AntiAging Systems, BMO Charitable Gift Fund, Dalis Foundation, Dennis Rudolph, Donald Olivier, Foundation to Decrease World Suck, Josh Triplett, Mary Ann Liebert Inc., Methuselah Foundation, Network for Good, Peter Harrigan, Porphyry Road Foundation, Singularity University, Vanguard Charitable

“I THINK IT IS ESSENTIAL TO ACCELERATE THE DEVELOPMENT OF THESE EXCITING TECHNOLOGIES AS MUCH AS POSSIBLE. THUS WE FUND SOME OF THE MOST PROMISING RESEARCH IN THIS AREA.”
-MICHAEL GREVE
FOUNDER/CEO, FOREVER-HEALTHY.ORG
“WITHOUT HIM (AUBREY DE GREY) AND THE ORGANISATION (SRF), THE CAUSE OF HEALTHY AGING AND EXTENDING LIFESPAN WOULD BE DECADES BEHIND.”

- JIM MELLON
CO-FOUNDER, JUVENESCENCE

$1,000 - $9,999 DONATED:


“IT’S A LITTLE BIT CRAZY TO IMAGINE A WORLD WHERE AGEING IS A CHOICE, BUT I THINK IT’S EVEN CRAZIER TO IMAGINE THAT HUMANITY WILL NEVER CRACK THIS PROBLEM.”

- PINEAPPLE FUND

$1 - $999 DONATED:

“SENS Research Foundation proposes that we don’t necessarily need to get sick as we age. They created a scientific roadmap to repair the damage caused by aging and eventually keep it under medical control. I can’t think of a more important cause to donate to, than one that could save 100,000 lives a day.”

- Jason Hope, entrepreneur
"I’VE SUPPORTED SENS (RESEARCH FOUNDATION) OVER THE LAST FEW YEARS BECAUSE THEY ARE ON THE FOREFRONT OF MANY SUCH DEVELOPMENTS AND THEIR APPROACH TO REJUVENATION TECHNOLOGIES HAS POTENTIAL TO BOTH IMPROVE AND EXTEND HUMAN LIVES."

- MICHAEL ANTONOV
CO-FOUNDER, OCULUS
FOR THE PAST SEVEN YEARS, SENS RESEARCH FOUNDATION HAS SPONSORED EDUCATIONAL PROGRAMS TO PROVIDE STUDENTS HIGH QUALITY RESEARCH OPPORTUNITIES AND TRAINING EXPERIENCES IN THE FIELD OF AGING RESEARCH.

SRF Summer Scholars Program
2014 - PRESENT

The SRF 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 his or her own research project in such areas as genetic engineering and stem cell research. The Summer Scholars Program has been designed to develop well-spoken, critically thinking future scientists, healthcare professionals, and policy makers.

Since 2014, the number of applications has steadily increased, culminating in 2017-2018 at ~500 applications. The Summer Scholars Program continues to grow in stature and impact. Last year, 488 students from 198 different colleges and universities across the country applied for twelve internship positions. This year, the program was advertised at over 300 colleges and universities.

“It is my privilege to work with some of the brightest young minds from around the country. Through the Summer Scholars Program and the new Postbaccalaurate Fellowship Program, we hope to inspire pursuit of a career in aging research and the training necessary to become visionaries and scientific leaders in the aging field.”

DR. GREGORY CHIN
DIRECTOR OF EDUCATION
In addition to raising SENS awareness with undergraduates across the nation, the program also continues to bolster relationships with SRF research partners.

Summer Scholars projects have been hosted at such prestigious institutions as the Buck Institute for Research on Aging, Harvard Medical School, the Sanford Consortium for Regenerative Medicine, The Scripps Research Institute, the SRF Research Center, the University of Oxford, and the Wake Forest Institute for Regenerative Medicine.

At least twelve Summer Scholars have been hired or extended by mentor labs following completion of their internships.
SENS Foundation Academic Initiative (SENSFAI) was the first student-focused SRF program, prior to the establishment of SRF Education. The SENSFAI began as the Methuselah Foundation Undergraduate Research Initiative (MFURI), founded by Dr. Kelsey Moody, now CEO at Ichor Therapeutics, Inc., and remained active through 2013.

The goal of the program was to provide scholarships and research grants, in addition to networking and internship opportunities, to cultivate a generation of research scientists who would advance the SENS mission. In its first year, the program reached over 50 students in a dozen countries. Its alumni body now boasts numerous peer-reviewed publications and the organization galvanized prestigious partnerships with premier research institutions across the longevity science field.

Multiple members of its alumni body now occupy respected positions throughout the rejuvenation biotechnology space, e.g.: Dr. James Peyer (Managing Partner, Apollo Ventures), Dr. John Schloendorn (CEO, Gene and Cell Technologies), Max Peto (Director, Long Life Labs; Researcher, BioAge Labs), Dr. Igor Bussel (Surgical Fellow, Washing University SOM), and Dr. Aaron Stupple (Manager, Baystate Medical Center).

"When I first read Aubrey's materials at sens.org and the book Ending Aging, I was immediately inspired to contribute to the effort to bring age-related degeneration under complete medical control. I switched gears away from teaching accounting, started studying biochemistry, and began working on a literature review listed at the Academic Initiative's website.

This turned out to be a great way for me to take on a significant research challenge early on in my studies. My literature review, Aluminium and iron in humans: bioaccumulation, pathology, and removal, was published in Rejuvenation Research in 2010. Shortly after publication, Aubrey hired me to work in the SRF lab, and I've been working on rejuvenation biotechnology ever since."
Inspired by the clear need for a more robust training pathway to a career in rejuvenation biotechnology, SENS Research Foundation launched a pilot postbaccalaureate fellowship training program in 2018.

THE POSTBACCALAUREATE FELLOWSHIP PREPARES PARTICIPANTS FOR A CAREER IN REGENERATIVE MEDICINE RESEARCH.

SRF Education is delighted to be able to offer this opportunity to a growing demographic of new scientists who are between undergraduate and graduate programs or longer-term career employment.

Under the guidance of a scientific mentor, each Fellow takes control of their own research project and completes writing assignments that will improve each Fellow’s ability to generate grant proposals, abstracts, and other scientific reports.

Fellows are pursuing projects at the Buck Institute for Regenerative Medicine, The Scripps Research Institute, the SRF Research Center, and the Sanford Consortium for Regenerative Medicine. Topics of study range from stem cell-based regenerative therapies, immunosenescence, heart disease and will in the future encompass many other aging-relevant areas.

Postbaccalaureate Fellow Perspective

HEATHER TOLCHER

PI: EVAN SNYDER
LOCATION: SANFORD CONSORTIUM FOR REGENERATIVE MEDICINE

"Through the SRF Summer Scholars Program, I had the opportunity to go to the University of Oxford in 2017. One thing I enjoyed the most from the SRF Summer Scholars Program was meeting the other students who were just as passionate and enthusiastic about science as I was. The summer program not only improved my ability to write scientific abstracts and grants and to present research in multiple formats but also helped shape my career aspirations and opportunities.

I am now working in the Snyder Lab at the Sanford Consortium for Regenerative Medicine as a postbaccalaureate fellow through the SRF Postbaccalaureate Fellowship that was launched just this past year. I am working on elucidating the molecular basis of neurodegeneration in Alzheimer’s disease using human-induced pluripotent stem cells and developing a diagnostic tool for bipolar and Alzheimer’s disease using machine learning. I am currently applying to MD/PhD programs in neuroscience across the US and hope to continue working on Alzheimer’s research in the future as a physician-scientist."
“The SRF Summer Scholars Program changed my trajectory in science. I feel like I came to the lab with a lot of interest but not a lot of technical skill. Through my internships, I improved my lab skills but also improved my ability to plan and execute quality experiments.

I’m currently working in the Biomedical Engineering Department at the University of Minnesota, in Dr. David K. Wood’s Living Devices Lab. My project is focused on building a 3D ECM-based cell culture platform for high-throughput applications using droplet microfluidics.

I expect to finish my Ph.D. thesis and graduate this coming summer.”

“I started my internship with just a yeast genetics background and learned almost everything with mammalian tissue culture work from Amutha.

Amutha is one of the most detail-oriented and meticulous researchers I ever worked with. She would teach me in great detail really well when I first started, and then let me try it out on my own.

Currently, I am pursuing my PhD at Columbia University Medical Center in the lab of Dr. Shan Zha in the Institute for Cancer Genetics at Herbert Irving Cancer Center.”

“My research as a SRF Summer Scholar was much more similar to my first year in graduate school than to any other research opportunities that I had as an undergraduate.

The structure of the Summer Scholars Internship really pushed me to think deeply about my project beyond what other internships had done and was one of the experiences that better prepared me for my first year in graduate school.

I am now a second year Ph.D. student at New York University studying bacterial evolution dynamics in the Kussell Lab.”
“My mentors helped really reinforce the importance of critical thinking, especially when designing experiments and interpreting results, which in turn refined my understanding of what it means to be a scientist.

After graduating from Rutgers University in 2016, I interned at a shark research lab before moving to Singapore to work at Nanyang Technological University as a Project Officer.

I then joined an incubator program called Entrepreneur First, where I am currently exploring and identifying problems in the areas of biotech/medtech and environmentalism in the hopes of eventually spinning off a company.”

“PI: ANTHONY ATALA, IN KAP KO, JAMES YOO
LOCATION: WAKE FOREST INSTITUTE FOR REGENERATIVE MEDICINE”

“I was a little nervous preparing for my Summer Scholars interview in biochem lab, but when I met [Director of Education] Greg Chin and Dr. Matthew O’Connor, I knew they would be fantastic people to work with.

When I joined SENS Research Foundation as a Summer Scholar for the summer of 2017, Dr. O’Connor encouraged me to find my own path within our atherosclerosis project. I decided to dive into computational biochemistry.

I came away from the summer with a whole new set of skills, friends, and coworkers, and I am happy to say that I am now an employee at SRF. I am thankful to SRF for giving me the opportunity to learn and the space to grow, and I am excited to see what the coming year will bring! Science rules!”

“I think my favorite memory of my Summer Scholar internship is having the day planned to the minute, 3 timers on the bench, and then also having a journal club meeting at the same time. I would check my experiments and then immediately run back not to miss anything from the fun and engaging discussions we had.

I am really passionate about research in the field of regenerative medicine and being part of the SRF Summer Scholars Program helped expose me to a lot of great research that is currently happening not only at the SRF Research Center but also all around the US, and even internationally.

I am currently interviewing for Ph.D. programs while studying Biochemistry and Molecular Biology at the University of Miami.”

“PI: AMUTHA BOOMINATHAN
LOCATION: SRF RESEARCH CENTER”

“PI: MATTHEW O’CONNOR
LOCATION: SRF RESEARCH CENTER”

“ALICIA LEE
2016
PI: ANTHONY ATALA, IN KAP KO, JAMES YOO
LOCATION: WAKE FOREST INSTITUTE FOR REGENERATIVE MEDICINE”

“AMELIA ANDERSON
2017
PI: MATTHEW O’CONNOR
LOCATION: SRF RESEARCH CENTER”

“MARTINA VELICHKOVSKA
2018
PI: AMUTHA BOOMINATHAN
LOCATION: SRF RESEARCH CENTER”
The SENS conference series was the world’s first conference program designed to address the concept of aging as accumulated cellular and molecular damage - based on the SENS damage repair paradigm.

Each SENS conference connected researchers in a broad range of fields related to the aging process, creating unforseen opportunities for collaboration that many delegates cited as a highlight of their experience.

A total of six conferences were held bi-annually at Queen’s College in Cambridge, United Kingdom between 2003 and 2013, with presentations given by speakers from top academic institutions and companies around the world.
The Undoing Aging conference is focused on the cellular and molecular repair of age-related damage as the basis of therapies to bring aging under full control. Scientists, startups, and experts in their chosen fields come together to focus on the diseases of aging.

Topics include stem cells, senescent cells, immunotherapies, biomarkers, and drug discovery. The conference is open to the scientific community, students, media, and any member of the broader rejuvenation movement.

Dr. Aubrey de Grey (left), Chief Science Officer of SENS Research Foundation, alongside Michael Greve (right), Chief Executive Officer of Forever Healthy Foundation, at Undoing Aging 2018.

WWW.UNDOING-AGING.ORG
2018 DONOR EVENT:

IN GRATITUDE TO OUR DONORS, WE HOSTED A MEET AND GREET WITH DR. AUBREY DE GREY AND THE ENTIRE STAFF OF SENS RESEARCH FOUNDATION AT HERBST THEATER IN SAN FRANCISCO, CALIFORNIA ON MAY 8TH, 2018.

REJUVENATION BIOTECHNOLOGY CONFERENCE SERIES:

The Rejuvenation Biotechnology Conference series was SRF’s program of ground-breaking academic/industrial meetings, hosted in California, for three consecutive years from 2014 - 2016.

With a strong focus on translational clinical research and regulatory issues, the tone of these events suggested a world in which the preventative application of regenerative medicine to age-related disease and disability is no longer a contentious theory, but instead a rapidly growing commercial enterprise.
OVER 60 SPEAKING ENGAGEMENTS, IN 40+ DIFFERENT CITIES, AND 20 DIFFERENT COUNTRIES.
During 2018, the Alliance has focused on the development of infrastructure to support the adoption of novel therapeutics and diagnostics for age-related disease, digital health tools, and regulations and standards. This included supporting clinical trials for digital health tools and medical devices, along with a number of industry academic partnerships and multi-stakeholder events.

2018 Alliance Events at the University of Oxford in Oxford, England:
1. International Research Symposium and Fundraiser at St. Edmund Hall, University of Oxford
2. “Improving Development of Health Apps & Standards (IDEAS)” Research Seminar at University of Oxford

2018 Alliance Clinical Studies:
1. ChroniSense National Early Warning Score Study (CHESS)
2. Utility of the Cardiac Electrical Biomarker (VECTRA)
Paediatric Obesity Digital Health Application: A Feasibility Study
Health Education England
E. Meinert, Sir David Cooksey Fellow
The purpose of this project is to evaluate a patient education and engagement application made for young people, centered on health promotion to combat obesity.

The Impact of Climate Change on Public Health
European Institute of Innovation and Technology: EIT Health
E. Meinert, Sir David Cooksey Fellow
Climate change is negatively impacting health through direct and indirect effects and is considered today to be a major public health concern. It is predicted that through effective empowerment of local communities, combating climate change and reversing man-made damages will be achieved provided we act immediately. This sub-activity will engage the issue of climate change through two challenge-based cases.

Japanese Society for Science Promotion
M. van Velthoven, Sir David Cooksey Fellow
Health services are increasingly expected to deliver better value healthcare equally to all of those in need (regardless of gender, age, background, socio-economic status, religion etc.), and to embrace and harness mobile tools given the rapid uptake of smartphones and apps. The planned work will fill this gap in the literature by providing an overview of how health apps are used by the public, patients, and healthcare workers in low- and middle-income countries.

European Network for the Joint Evaluation of Connected Health Technologies
E. Meinert, Sir David Cooksey Fellow
ENJECT is a 4-year research coordination programme funded by COST - the longest running European framework that supports trans-national cooperation among researchers, engineers, and scholars across Europe. ENJECT falls within the realm of Connected Health research which focuses on a new technology-enabled model of healthcare delivery and encompasses terms such as wireless, digital, electronic, mobile, and tele-health. ENJECT will help to learn how to connect therapies, patients, and care-givers to deliver optimum health results in an era of stretched resources and increasing demands.

Data Science for Health: Real World Evidence
European Institute of Innovation and Technology: EIT Health
E. Meinert, Sir David Cooksey Fellow
This course will introduce participants to the intersection of real-world evidence (RWE) and healthcare, and provide the opportunity to understand and develop new methods for data analysis. Real World Data (RWD) defines the substantial quantity of data that falls outside the boundaries of controlled clinical trials -- data that is increasingly being used to inform decision-making in healthcare.

Digital Activity Line Coordination and Strategy
European Institute of Innovation and Technology: EIT Health
E. Meinert, Sir David Cooksey Fellow
The purpose of this sub-activity is to complete landscape analysis on the use of digital education technology for medical education and patient engagement. This research will inform strategic recommendations for the implementation of digital technology for EIT Health CAMPUS education programmes.
In this section, we put the spotlight on some of the companies and founders that SRF has empowered to become key players in making the first SENS-strand-relevant technologies a reality for patients sooner rather than later.

**COVALENT BIOSCIENCE:**

Transthyretin (TTR), a protein involved in the transport of vitamin A and thyroid hormones, is susceptible to becoming a sticky amyloid, which deposits in the joints, carpal tunnels, and most importantly the heart, where it causes senile cardiac amyloidosis (SCA) — a major contributor to heart failure, and the most important contributor to the deaths of supercentenarians.

Catabodies are catalytic antibodies: fragments of IgM antibodies that target aberrant proteins for destruction. Conventional therapeutic antibodies targeting aggregated proteins bind tightly to their target amyloid, with the aim of mobilizing it from the tissue for eventual excretion or degradation. However, this need for conventional antibodies to bind their target for an extended period is inefficient and it may be responsible for the side-effects that have plagued most immunotherapies targeting beta-amyloid in the brain, as the antibody-aggregate complex becomes snared in the blood-brain barrier, leading to damage to brain blood vessels.

Because catabodies catalytically cleave their target instead of binding it, one catabody molecule can cleave multiple aggregate targets before being degraded, and the risk of cerebral vascular side-effects is reduced because antibody-aggregate complexes only exist transiently.

**REVEL LLC:**

Adjacent strands of proteins in aging tissues accumulate crosslinks that limit their ability to move independently, leading the tissues to become stiff and lose their elasticity. This contributes to strokes, renal failure, and other end-target pathologies. Cleaving these crosslinks would allow these adjacent strands of protein to move freely again, partially restoring tissue elasticity and reducing these devastating outcomes. Crosslinking by glucosepane — a kind of Advanced Glycation Endproduct (AGE) crosslinking — is thought to be a major contributor to tissue crosslinking with age.

The Yale group behind Revel has developed reagents to enable the development of glucosepane-cleaving agents and its own candidate agents.
Oisín Oncology, Inc.

The tumor-suppressor gene p53 is the single most frequently mutated gene in human cancer, being involved in roughly 50% of all invasive tumors and in more than 80% of some of the most difficult-to-treat ones. These mutations are considered “undruggable” because most p53 mutations’ contribution to cancer comes from the absence of a functional protein, with no change in the expression of the gene in most cases, so there is an absence of anything with which a drug might interact.

Oisín’s platform technology uses non-integrating genetic “suicide switches” that overcome this problem by providing the cancer cell with a functional p53 promoter, whose activation by the cancer cell’s primed transcription factors acts as the “on switch” that drives the expression of a cellular apoptotic factor such as caspase 8, eliminating the cancerous cell.

Oisín’s platform technology uses non-integrating genetic “suicide switches” that can be induced and withdrawn from the body entirely at will. In this case, the promoter for p16 (a gene expressed in many senescent cells and not normal ones) acts as the “on switch” that drives the expression of a cellular apoptotic factor, leading to the selective destruction of senescent cells.
ARIGOS BIOMEDICAL:

Every year, thousands of people die waiting for a needed organ transplant, even as tens of thousands of donated organs are discarded. The key problem is time: organs can only be kept viable for a matter of hours after they are harvested, and distance and logistics often conspire to prevent a potential match. Technologies to substantially lengthen organ storage time could save many lives and reduce a great deal of worry and suffering.

Arigos is developing a novel organ and tissue storage solution that will overcome the barriers to vitrification, the extreme low-temperature conversion to a stable glass state, which would dramatically extend organ shelf life.

By replacing blood with a gas, Arigos can eliminate the tendency of freezing biological fluids to crystalize and damage cells, without the use of the toxic “antifreeze” chemicals that have hitherto been the strategy to prevent this damage.

“Mike and Aubrey hired me in January 2010 to take on operations for SENS Foundation. The lab was located in an incubator space. We had a downstairs and an upstairs, lab benches on the ground floor with a deathtrap of a meeting space above. It didn’t take long to realize that the incubator was not going to be a suitable environment for the kind of research we wanted to do. [SRF CEO] Mike gave me a budget, and I went looking for a new home for the Foundation.

Four months of searching for the right home and a mere $50k was enough to get the team the tools they needed to get to work in their new home. I am proud of that accomplishment. At SRF, I helped to build my first happy, productive research lab. Then, I helped it to grow as the needs of the organization evolved.

In the early days, the research agenda was also somewhat controversial, and it has been delightful to watch acceptance grow over time. Today, I am building my second happy, productive research lab; and it’s a hard thing. After 25 years of non-profit work, I’ve learned that startups are a very different challenge.

Our mission at Arigos is also the extension of healthy human lifespan, and we’re using cryobiology at temperatures so low that our NASA colleagues insist they can only be considered “hostile”. SRF gave me an educational experience that helped me considerably in building this new lab [for Arigos]. It gave us funding when we would otherwise have had to shut the doors. And it gave me people who will forever be friends.”
ICHOR THERAPEUTICS: ANTIXERENE/RECOMBIPURE

Some protein-protein interactions that could theoretically be targeted by small molecule drugs as a means of indirectly eliminating aging damage are difficult to target in practice, because the target proteins themselves cannot be manufactured at sufficient purity and scale as to enable high-throughput screening. p53 is a good example, both for cancer and senescent cells: in both cases, the offending cell type is able to survive because p53 is inactivated through interactions with another protein (the Mdm2 oncoprotein and FOXO4, respectively). Drugs that could interrupt these interactions could therefore nudge these age-related aberrant cell types to self-destruct.

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.

ICHOR THERAPEUTICS: LYSOCLEAR

Age-related macular degeneration (ARMD) is the leading cause of blindness in persons over the age of 55 in developed countries. It is caused by the death of photoreceptors in the back of the eye, which in turn is the result of the death and dysfunction of the Retinal Pigmented Epithelium (RPE) cells. RPE are killed or rendered dysfunctional by the accumulation of intracellular aggregates, the most important of which is A2E, a toxic derivative of vitamin A that accumulates in RPE lysosomes.

LYSOCLEAR is a classic application of the lysoSENS strategy of identifying enzymes from microbes and other sources that are capable of degrading a material that the cell is not equipped to handle (in this case A2E and other RPE aggregates), and targeting modified versions of those enzymes to the affected cells, enabling them to eliminate the waste product and return to function.
Distinguished specialists and world-renowned experts guide our research budget and ensure focus on projects with the greatest potential to make major breakthroughs in age-reversing biomedicine.
We built a team, collected the tools we needed to do the work, and the rest is history.

- DR. MATTHEW O’CONNOR

“In terms of science, the goals were clearly to pursue the development of medicines that would turn back the clock of aging, to actually develop medicines that would genuinely rejuvenate the body by restoring the molecular and cellular structure and composition of the body to something like how it is in early adulthood. We would be the pioneers; we would be the kind of engine room of all of this.”

- DR. AUBREY DE GREY
Mitochondria are the tiny cellular “power plants” in our cells, and like other power plants, they generate waste in the process — free radicals, which over time damage mitochondrial DNA. As a result, a small but rising number of our cells get taken over by such dysfunctional mitochondria as we age. These damaged cells in turn export toxic molecules to far-flung tissues, contributing to Parkinson’s disease, age-related muscle dysfunction, and other conditions.

The MitoSENS program exists to pursue the goal of achieving a grand engineering solution to the problem of accumulation of cells with these mutation-bearing mitochondria: allotopic expression of functional mitochondrial genes. Allotopic expression involves placing “backup copies” of all of the protein-coding genes of the mitochondria in the cell’s nucleus. From this “safe harbor”, the copied genes can then direct the cell’s machinery to produce engineered versions of the missing mitochondrial proteins and deliver them to the mitochondria. With their full complement of proteins restored, mitochondria can resume producing energy normally, despite lacking the genes to produce them on their own.

"Mitochondria are such interesting little creatures, and I couldn’t be happier with what we’ve done so far. The thing that blows my mind is that, 8 years later, I’m still learning so much about mitochondria every week! It’s a constant adventure. Since our initial breakthrough - moving two targeted mitochondrial genes to the cell nucleus - that we published in 2016, the progress has been exponential."

- DR. MATTHEW O’CONNOR

In 2016, the MitoSENS team achieved a major breakthrough in successfully demonstrating efficient replacement of the missing mitochondrial ATP8 gene in cells from a human patient with an ATP8 mutation, restoring their ability to produce energy using the most efficient pathway.

After significant work to extend 2016’s breakthrough to other genes, the team discovered that an established method already widely used in biotechnology could also be applied to enable significantly more consistent production of allotopically-expressed protein. To test this novel method more broadly, the MitoSENS group first briefly allotopically expressed each of the thirteen vulnerable mitochondrial genes via a transient loop of DNA located in the cytosol. Versions of the genes engineered the new way produced a great deal more RNA than the same genes engineered in the way that all previous investigators have used.

All thirteen of the genes engineered in this new way were able to produce actual protein, versus only a fraction of the conventionally-engineered genes. This milestone achievement is being prepared for publication in a scientific journal as of this writing, and tests are now underway to verify that all proteins thus expressed are properly incorporated into the mitochondria’s energy-production system.
The team has compared performance between 'traditional' and novel systems for producing allotopic ATP8 in cells derived from FVB mice, which bear a minor but significant mutation in ATP8. The cells engineered using the novel method produced significantly more actual ATP8 protein than those engineered the conventional way – and it is important to note that in this experiment, the new genes were cemented into the nucleus and expressed from there, thus mimicking the goal for human MitoSENS therapies. The allotopically-expressed protein works as intended when using the improved system: it enters the mitochondria, incorporates properly into the energy-producing machinery, and significantly enhances these cells’ ability to survive when they are forced to rely on the mitochondria’s primary energy-generation mechanism.

Next, the MitoSENS team plans to demonstrate efficacy in living, breathing mice – specifically, Maximally Modifiable Mice (MMM), a novel line of mice created by Stanford researchers with SRF funding (see Page 36). The new MMM-derived mouse model will have the allotopic ATP8 construct engineered into their nuclear genomes from conception, but will have mitochondria (and thus mitochondrial DNA) derived from FVB mice, with their mutant ATP8 gene.

This work, in conjunction with behavioral studies to be performed in collaboration with the Brand lab at the Buck Institute, is expected to prove that the allotopic gene actually functions in vivo, restoring the mice’s ability to generate cellular energy efficiently.

“In 2009, just as I’d finished my postdoctoral work, Aubrey pitched me to join the MitoSENS project at the new research center that he and the new ‘SENS Foundation’ were creating. At first I was nervous to take on the project because I had no experience at all working with mitochondria! But Aubrey wanted someone with a general background in aging research, who would be able to think about the problems from the SENS damage repair perspective. That convinced me that I was the right person for the job.

The double challenge of learning a new field and taking on an inherently difficult project was a tall hill to climb. We have a huge amount of results that we want to publish in the next year, and way more new ideas to test than time to work on them. We expect that progress will be swift from here on out!”
LYSSENS

A SMALL MOLECULE APPROACH TO REMOVAL OF TOXIC OXYSTEROLS AS A TREATMENT FOR ATHEROSCLEROSIS
SENS RESEARCH FOUNDATION RESEARCH CENTER
PRINCIPAL INVESTIGATOR: MATTHEW O’CONNOR
RESEARCH TEAM: AMELIA ANDERSON, CAROLYN BARNES, ANGIELYN CAMPO, ANNE CORWIN, SIRISH NARAYANAN

Many diseases of aging are driven in part by the accumulation of “junk inside cells.” These are waste products derived from the metabolic processes particular to specific cell types. The accumulation of these wastes disables the cell type in question and leads to their dysfunction; after decades of silent accrual, a critical number of these cells become dysfunctional, causing diseases of aging characteristic of that tissue to erupt. For example, atherosclerotic lesions form when immune cells called macrophages take in 7-ketocholesterol (7-KC) and other damaged cholesterol byproducts in an effort to protect the arterial wall from their toxicity, only to ultimately fall prey to that same toxicity themselves. These macrophages — now dysfunctional “foam cells” — become immobilized in the arterial wall and release inflammatory molecules that in turn promote advanced atherosclerosis, heart attack, and stroke. In other organs, the accumulation of damaged molecules inside vulnerable cells drives Alzheimer’s and Parkinson’s diseases, as well as age-related macular degeneration.

In an exciting development, the team has engineered a lead compound following evaluation of data from human blood sample tests in conjunction with computer modeling to predict the likely behavior of rationally-designed molecules. Preliminary testing indicates performance consistent with enhanced activity relative to the existing family of compounds: specifically, the candidate molecules exhibit selective targeting of 7KC, with significantly reduced affinity for native cholesterol. A patent application for this lead compound and others to be derived from it has now been submitted.

The LysoSENS team has created a family of small molecules that may be able to selectively remove toxic forms of cholesterol from early foam cells and other cells in the blood. If effective, these small molecules could serve as the basis for a groundbreaking therapy that would prevent and potentially reverse atherosclerosis and, possibly, heart failure. The team has developed an automated assay to quickly testing candidate drugs against 7KC, as well as testing for potential off-target effects.

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The LysoSENS team is now working to advance their existing molecules through traditional pre-animal drug-testing regimens, as well as continuing to create new versions of the drug that may be even more specific for 7-KC. Meanwhile, they are also working with partners to begin testing the absorption, circulation to tissues, and routes and rates of metabolism and excretion of their lead candidate, and to perform toxicity assays. The Research Center has also recently acquired a new robotic system to render their assays even faster and more precise, which our in-house engineer Anne Corwin is working to set up and program; the end result should be an increase in throughput that allows for faster testing of more molecules.

SRF PAST AND PRESENT: LYSSENS ORIGINS

“AlysoSENS - like MitosSENS - originated in 2005, in two different locations: Rice University and Arizona State University, headed up by two PhD students: Jacques Mathieu and John Schloendorn, respectively. At Rice, Jacques was working on atherosclerosis and in Phoenix, most of the work was on macular degeneration -- that work subsequently came here to the RC.

We continued the macular degeneration work at the research center for about four years; eventually it was picked up by Kelsey Moody, who worked with us for a while and then went to start his own company - Ichor Therapeutics. Meanwhile, the atherosclerosis work has recently been revitalized as another internal LysoSENS program, and is now also doing very well.”
ENHANCING INNATE IMMUNE SURVEILLANCE OF SENESCENT CELLS
BUCK INSTITUTE FOR RESEARCH ON AGING & SRF RESEARCH CENTER
PRINCIPAL INVESTIGATOR: JUDITH CAMPISI (BUCK INSTITUTE)
RESEARCH TEAM: ABHIJIT KALE (BUCK INSTITUTE), MATTHEW O’CONNOR (SRF), MATTHEW STOCKER (SRF)

When cells acquire DNA damage that puts them at risk of becoming cancerous, they are programmed to enter a new state called senescence in which they lose their ability to replicate and undergo various metabolic changes. Over time, senescent cells accumulate in aging tissues, spewing off a cocktail of inflammatory and growth factors, as well as enzymes that break down surrounding tissue (the “senescence-associated secretory phenotype” (SASP)). The charge sheet against senescent cells has expanded into a remarkable litany of age-related diseases. Multiple studies have documented that the converse is also true: “senolytic” drugs and gene therapies that destroy senescent cells exert sweeping rejuvenating effects in aging, both in “normally” aging laboratory animals and in animal models of multiple diseases of aging. In theory, however, senolytic therapies shouldn’t be necessary. The body’s immune system is on continuous patrol against senescent cells: our natural killer (NK) cells recognize senescent cells as abnormal, bind to them, and release substances that trigger the senescent cells to self-destruct.

In an SRF-donor-funded collaboration between Dr. Judith Campisi’s lab at the Buck Institute and the SRF Research Center, this project seeks to answer the critical question of why senescent cells are able to accumulate with age despite the existence of this immune surveillance system, and what we might do to enhance immune surveillance and elimination of these cellular saboteurs.

Dr. Campisi has found that about ten percent of senescent cells are resistant to being killed, even by fresh NK cells, suggesting that these resistant cells are the ones that escape immunosurveillance and accumulate in aging tissues. Her research team and other scientists have developed preliminary data suggesting mechanisms whereby senescent cells can make themselves invisible to NK cells, thus protecting themselves from destruction. The Buck-SRF collaboration is seeking to drill further down into these questions and test possible means to intervene in the process. The Campisi lab is looking into further elaborating the biology of one of senescent cells’ two self-protective mechanisms, and testing a potential role for another kind of immune cell (macrophages) in defending the body against senescent cell accumulation.

At the SRF-RC, we are perfecting the method of co-culturing NK and senescent cells and controlling the killing process, and will begin testing two potential therapeutic targets identified in the Campisi lab.

The team is also developing an algorithm for the SRF-RC’s automated microscope imaging system to rapidly analyze stained plates of cells for quantitative analysis of senescent cell-killing ability - a job hitherto done by laborious human visual microscopy.

FUNCTIONAL NEURON REPLACEMENT TO REJUVENATE THE NEOCORTEX
ALBERT EINSTEIN COLLEGE OF MEDICINE (AECOM)
PRINCIPAL INVESTIGATOR: DR. JEAN HÉBERT
RESEARCH TEAM: HIROKO NOBUTA, JOANNA KRZYSPIAK, ALEXANDER QUESADA, MARTA GRONSKA-PESKI, JAYLEECIA SMITH

Of all the challenges in cell therapy, replacement of neurons in the neocortex is both the most important (being the seat of consciousness and identity) and perhaps the most formidable. Only recently have any researchers succeeded in integrating new neurons into this area of the brain. The vast majority of transplanted cells in these cases have failed to survive, and the few survivors have achieved only limited function and integration into existing circuits.

SRF is now supporting Dr. Jean Hébert’s work to advance two innovative strategies to address different aspects of this grand challenge. First, Dr. Hébert’s team will work to extend their preliminary data showing that neuronal precursor cells survive and integrate better when they are accompanied by vascular precursor cells to ensure that neurons have the nutrients and oxygen they need. This will be done in young mice, old mice, and mice who have suffered an induced stroke, and using both mouse-derived cells and cells derived from human embryonic stem cells and lines.

Second, because new neurons will be needed throughout the aging neocortex but transplanting neurons throughout the entire tissue would be extremely invasive and risk injury to a tissue we cannot afford to damage, the AECOM team will engineer microglia (which, unlike neurons and their precursors, are highly mobile cells) to disperse widely from the site of transplant and then be reprogrammed into cortical projection neurons at their destination. The team will characterize the integration of the transplanted microglia-cum-neurons into host circuits, and determine whether depleting host microglia enhances these processes in different models.
Dr. Hébert’s team has made remarkably quick early progress. It appears that — at least for mouse precursor cells — neuronal precursor transplant into young mice is only very minimally aided by the addition of vascular precursor cells, because the host is able to supply most of the vascular precursors itself. By contrast, far more of the transplanted vascular cells are used in the stroke model because of the much greater need for total vascular precursors to support the large number of neuronal precursors needed to repair a large lesion. The AECOM team have shown that the human-derived cells can also be successfully transplanted into the mouse models; the team can proceed to do similar cell-mix tests using those cells.

Dr. Hébert’s team has also demonstrated that transplanted mouse microglia will spread across broad areas of the mouse cortex after it is transiently depleted of its own microglia. Demonstrating the same thing using human-derived microglia is going to take longer, as the mouse brain is not able to produce an important growth factor these cells need to survive. They are overcoming this problem by using a line of transgenic mice that express this human factor.

Finally, the team has successfully reprogrammed mouse and human microglia into neurons with adequate efficiency, using a combination of four transcription factors. This will allow them to transform the transplanted and dispersed microglia into neurons all across the neocortex, potentially taking a major step toward brain-wide neuronal circuit maintenance and repair.

In 2018, the Yale team scaled up this pilot-level method to produce glucosepane in quantities useful for industrial production, and also to synthesize three conformational variants (diastereomers) of glucosepane that may occur in vivo. They are working on two more such variants; they have also used their synthetic glucosepane to develop glucosepane-targeting antibodies capable of labeling glucosepane in aging tissues (which they are working up into a monoclonal antibody for mass production that will be compatible with human metabolism) and tracking the effects of potential glucosepane-cleaving drugs.

They have identified a lead candidate glucosepane-cleaving biocatalyst, and completed the evaluation of seven significant variants and their AGE-breaking mechanism. Today, work continues on synthesizing pentosinane (another common AGE crosslink) and additionally on the AGE-related compounds imidazole and 2-aminoimidazole.

MAXIMALLY MODIFIABLE MOUSE
APPLIED STEM CELL, INC.
PROJECT DIRECTOR: DR. RUBY YANRU CHEN-TSAI

The CRISPR/Cas9 gene editing system has the ability to make precisely-targeted changes in the genetic sequence – a clear strength of the platform – but is limited in its lack of an obvious delivery mechanism. It’s reasonably easy to use CRISPR/Cas9 to modify individual cells, but there is no known (or clearly-foreseeable) way to deliver the system to human tissues in vivo while still retaining strong precision and without the risk of either silencing or mutating introduced or non-targeted genes.

CRISPR/Cas9 is only able to make relatively small changes to an existing gene. That’s great for correcting small but catastrophic mutations in existing genes, or rendering genes with a toxic gain-of-function inoperable — but it’s not much use for delivering the new genes that will be necessary to take advantage of it for delivery of rejuvenation biotechnologies.

The Maximally-Modifiable Mouse project aims to overcome this problem by allowing us to make use of a powerful gene insertion system (the integrase) used by phages — viruses that target bacteria as their hosts. The mycobacteriophage Bxb1 catalyzes precisely-targeted, one-way insertion of even very large genes into the host genome. Unfortunately, mammals lack the genetic “docking sites” that this integrase targets.

To enable the development of models of diseases of aging and the rapid testing and eventual human delivery of rejuvenation biotechnologies, SRF has been funding Stanford gene therapy...
spinoff Applied StemCell (ASC) to create a line of Maximally-Modifiable Mice (MMM). The MMM will have two of the needed docking sites engineered directly into their genomes, which will then be ready for the insertion of new therapeutic transgenes at any time during the lifespan.

Currently, ASC is testing the ability of the system to deliver and integrate convenient test genes into the mice’s cells in vivo. They will then test the expression and functional protein production of those genes. We are especially excited by the potential to use this technology to both develop better models in which to test the allotopically-expressed mitochondrial genes that our in-house Mito team has been testing in cells, and to deliver those genes and actually test them in such mice.

**REMEDICATION OF ABBRENT INTRACELLULAR TAU**

**BUCK INSTITUTE FOR RESEARCH ON AGING**

**PROJECT DIRECTOR: DR. JULIE ANDERSEN**

**RESEARCH TEAM: CYRENE ARPUTHASAMY, MANISH CHAMOLI, ANAND RANE**

Aging brains accumulate aggregates composed of aberrant forms of the protein tau, both inside and outside of neurons. These aggregates are an important driver of “normal” age-related cognitive decline, as well as neurodegenerative diseases of aging like Parkinson’s (PD) and Alzheimer’s (AD) diseases. A number of rejuvenation biotechnologies targeting aberrant tau outside of cells are currently in clinical trials, with the idea that capturing these “seeds” of tau aggregates will interrupt its “infectious” cell-to-cell transmission. To prevent the problem entirely — and eventually reverse it — requires new strategies to target aberrant tau inside of brain neurons.

SRF is funding Dr. Andersen’s team to test the idea that this tau accumulation may result from age-related dysfunction of the cellular “recycling centers” (lysosomes) due to the buildup of other kinds of intracellular aggregates, such as beta-amyloid, the other major damaged protein characteristic of the AD brain. If this is the case, then the most effective remediation method for aberrant tau could entail using rejuvenation biotechnology to target these primary aggregates, thus allowing the cell to clear out its own burden of aberrant tau once lysosomal function is restored.

Neurons of patients with AD and other neurodegenerative aging diseases are often full of autophagosomes (APGs), the vesicles that form around targets for autophagy and in which they are dragged to the lysosome for degradation. This buildup is thought to result from a failure of lysosomal function, as the already-overburdened organelle refuses to take up any more cargo.

The Andersen lab has developed lines of human and rat neuronal cells that produce APGs with molecular tags that allow them to track the production and disappearance of APGs in neurons. They can use these tags to screen for compounds that increase the successful trafficking of APGs and their cargo to the lysosome. Compounds that pass this preliminary test will be evaluated in neurons treated with small, soluble beta-amyloid aggregates, to see if these compounds will prevent or reverse the formation of insoluble aggregates of both beta-amyloid and tau.

**TARGET PRIORITY OF TISSUE CROSSLINING**

**THE BABRAHAM INSTITUTE**

**PRINCIPAL INVESTIGATOR: JONATHAN CLARK**

**RESEARCH TEAM: MELANIE STAMMERS**

As discussed in the project summary for “Glucosepane Crosslinks and Undoing Age-Related Tissue Damage”, adventitious crosslinking of collagen (and elastin) contributes to the slow stiffening of our arteries and other tissues with age. Some of these crosslinks represent the kind of chemistry that can happen spontaneously (like AGE crosslinking), but others are the unintended consequences of metabolic processes that modify collagen — either as “collateral damage,” or to help us get through short-term problems at the cost of contributing to the long-term burden of crosslinking damage that eventually compromises function.

Recognizing the importance of prioritizing our targets, SRF is funding a systematic study of this question in the tissues of “normally”-aging, nondiabetic mice at the Babraham Institute in Cambridge. The mice have been administered labeled building blocks for protein, which are then incorporated into extracellular matrix proteins, whose turnover can then be studied. The study has required the development and validation of new experimental methods and assays, which were published in a Royal Society of Chemistry journal in 2018.

An early and surprising finding is that crosslinks which are considered permanent in tissue are continuously being broken apart and re-forming under the stress and strain of normal activity: it is the balance between these reversible crosslinks and the truly irreversible ones that gives rise to many of the changing mechanical properties of aging collagen. They have also confirmed the expectation that the crosslink profile in each tissue is distinct from others (which is only partially explained by the tissue-specific mixture of elastin and collagen), and that both the mixture of proteins and the pattern of protein-specific crosslinks changes with age.

Importantly, some of the crosslinks that have been reported by others to accumulate in aging tissues were not detected. They are also complementing chemical analysis of the tissues with functional tests of the effect of these crosslinks on tissue mechanical function. Drilling down into these issues will be critical to identifying the next targets as glucosepane crosslink-breakers enter into animal testing.
2018 PUBLICATIONS

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