sens research foundation

reimagine aging

annual report

sens research foundation

reimagine aging

SENS Research Foundation funds research at institutions around the world and at our own Mountain View Research Center. Our research is integrated with our wide-ranging outreach and education programs. We are committed to the creation of the Rejuvenation Biotechnology Industry which will play a pivotal role in curing the diseases of aging.

Many things go wrong with aging bodies, but at the root of them all is the burden of decades of unrepaired damage to the cellular and molecular structures that make up the functional units of our tissues. Faced with the diseases and disabilities caused by this damage, today's medicine is too often reduced to crisis management in the emergency room, painfully harsh treatments for diseases such as cancer, or best efforts at palliative care for diseases such as Alzheimer's disease.

SENS Research Foundation is transforming the way the world researches and treats age-related disease.

PARKINSON'S KIDNEY FAILURE CANCER MACULAR DEGENERATION

HORMONAL IMBALANCE STROKE OSTEOPROPOSIS INCONTINENCE

ALZHEIMER'S DISEASE HEART DISEASE SARCOPENIA PNEUMONIA

DIABETES EMPHYSEMA OSTEOARTHRITIS

In contrast, rejuvenation biotechnologies are targeted therapies that apply the principles of regenerative medicine to the entire scope of the damage of aging. These therapies will restore the normal functioning of our cells and essential biomolecules, preventing, age-related disease.

In other words, instead of merely slowing down the accumulation of aging damage in our tissues, rejuvenation biotechnologies will remove, repair, replace or render harmless our damaged cellular and molecular machinery, returning aging tissues and organs to health.

Cover photo: Siah St. Clair (allofnature.blogspot.com). Used with permission.

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letter from ceo & cso

Since SENS Research Foundation's founding in 2009, we've worked toward bringing our vision of a world free of age-related disease from concept to reality. In challenging ourselves on this front, we have likewise challenged you, our supporters. We've asked a lot of all of you, and not only have you accepted this challenge, you have delivered. The rejuvenation biotechnology community that has emerged over the past several years owes its existence to each and every one of you.

We asked you to "Reimagine Aging". You did. The members of our community have embraced the concept and come together in many amazing ways – on Facebook and Twitter, on Reddit, at our Rejuvenation Biotechnology Conferences, in our education programs and at events held around the world. You have become our most vocal advocates. Over 2000 of you have become our funders.

We asked you to help us change how the world researches and treats age-related disease. You did. Through the efforts of our donors, collaborators, and our advisory board, world-renowned institutions are pursuing age-related disease research specifically focused on the damage-repair paradigm.

We asked you to help us move from basic research to translational research and clinical trials. You did. In 2016 we launched Project|21, our five-year plan to help move rejuvenation biotechnologies from concept to human clinical trials. Project|21 is now backed by a number of generous and forward-thinking individuals, such as our long-time major donor, the Thiel Foundation, and new major donors like entrepreneur Michael Greve and the Forever Healthy Foundation, investor Harry McPike, and even EDM star Steve Aoki.

You asked us to follow through. We did. In lending your support, you place not only resources in our hands, but trust. We know that a world-changing nonprofit cannot operate on the power of vision alone; and we are here not just to inspire, but to deliver results. The purpose of this report is to demonstrate concrete examples of those results to you, including:

- **Research and Alliance programs that have resulted in over 25 publications over the past two years (page reference);.**
- **Our most successful Summer Scholars program to date (page reference);**

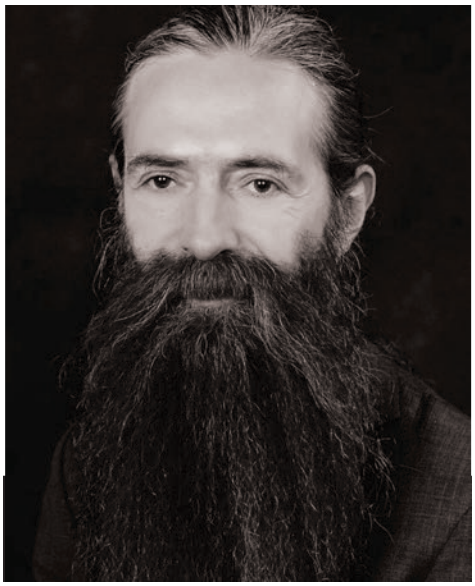
- **Successes at our internal laboratories that include patentry on the identification of ALT cancers, and a MitoSENS team publication on the nucleic relocation and rescue of mitochondrial genes (page reference(s));**
- **The establishment of three new research programs at the Buck Institute, a next step in the development of critical mass in rejuvenation biotechnology (page reference); and**
- **Technology transfer achievements which include a private company raising funding for the first-ever clinical trial of a technology originating at the SRF lab, which may put us far ahead of schedule on the most important of our Project 21 goals (page reference).**

With your help, we have taken great steps toward the establishment of a robust rejuvenation biotechnology industry and the realization of our vision. And every step we are able to take is proof of the power of your community. Thank you, and we hope you enjoy this report.

Sincerely,

Mike Kope
CEO

Aubrey de Grey
CSO



project|21 Building the Bridge to Human Clinical Trials for Rejuvenation Biotechnologies

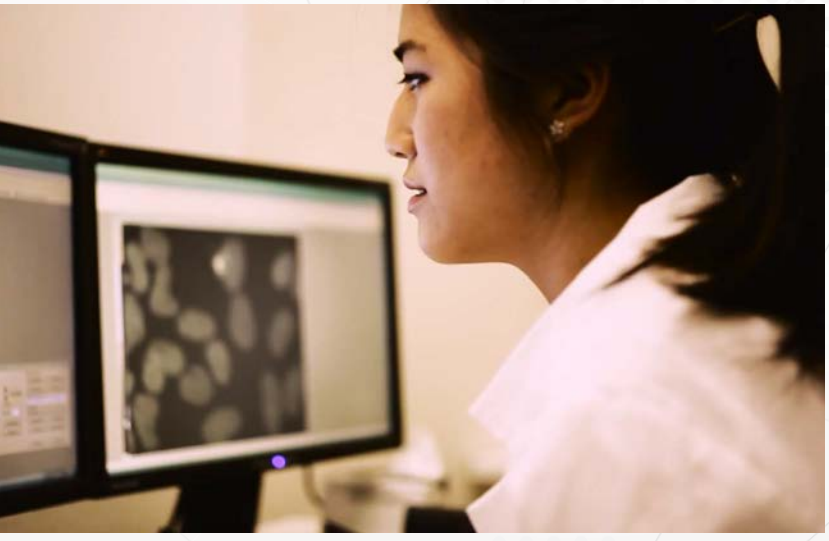
Ending aging will require large-scale investment to flow into a globally-recognized rejuvenation biotechnology industry. SENS Research Foundation has put all the pieces in place – core research groups, key players, shared knowledge, underlying tools – for the creation of this industry.

Through our new Foundation programs, Project|21 will deliver the perfect environment for the critical marriage of opportunity and investment. By properly stewarding this emerging industry, we can create an environment where the first damage repair interventions addressing specific age-related diseases will be brought to human clinical trials within five years. Project|21 will work to overcome the three major barriers to the development of truly effective rejuvenation therapies:

- **Funding to convert promising basic research programs is scarce**
- **There are too few opportunities for dynamic collaborations with mainstream regenerative medicine**
- **There is little understanding of the regulatory pathways and clinical infrastructure these technologies will require.**

Project|21 will require $50 million in total funding, at least half of which will come from the members of SENS Research Foundation's Group|21. Group|21 will bring together philanthropists, each donating between $500,000 and $5 million. Grants, grassroots efforts and matching-fund strategies will provide the remaining support.

To learn more about Project|21 and how to join Group|21 go to www.SENSProject21.org.



fundraising highlights

German Internet Entrepreneur Michael Greve and his Forever Healthy Foundation committed $5 Million in philanthropic support over the next five years to support the SENS Research Foundation. In addition, Michael Greve's company KIZOO Technology Ventures will be committing seed investments of $5 million in startups focused on bringing rejuvenation biotechnology treatments to market.

The Thiel Foundation donated $1 million in philanthropic unrestricted support to SENS Research Foundation in December 2016. The Thiel Foundation is a long time supporter of SENS Research Foundation, providing some of the original funding for the Foundation in 2009. This new funding will help support the growth of the Foundation's research that will lead to major progress in the fight to cure age related diseases.

The Foster Family Foundation donated $500,000 to SENS Research Foundation with a majority committed to supporting the MitoSENS program.

Harry McPike donated $300,000 in unrestricted funding to SENS Research Foundation.

SENS Research Foundation has partnered with Lifespan.io to raise funds for our research programs. The OncoSENS Program 2016 Crowdfunding Campaign – Control ALT, Delete Cancer -- yielded $72,008. The 538 donors have enabled the OncoSENS Team to complete a critical project enabling high throughput screening of a diverse library of drugs to find treatments for ALT based cancers.

The MItoSENS Program's 2015 Crowdfunding Campaign raised $46,128 from 400 donors. The campaign was focused on engineering backup copies of mitochondrial genes to place in the nucleus of the cell, aiming to prevent age-related damage and restore lost mitochondrial function.

> "My goal is to provide support for the critical research of the SENS Research Foundation and to facilitate the development of the rejuvenation biotech industry and ecosystem. I think we should have more people contribute to the step-by-step creation of cures for the root causes of all age-related diseases. And we should have a whole rejuvenation industry based on the SENS treatment model including the self-accelerating feedback-loop of success stories and amazing opportunities for scientist, entrepreneurs and VC investors. This will truly accelerate both research and therapies. I have decided to lead by example and make this $10 million commitment.
>
> MICHAEL GREVE

outreach

SENS Research Foundation has continued to build a widening community of informed and enthusiastic stakeholders throughout 2015 and 2016. We have also continued to reach out to organizations and individuals to form valuable links within our community.

highlights

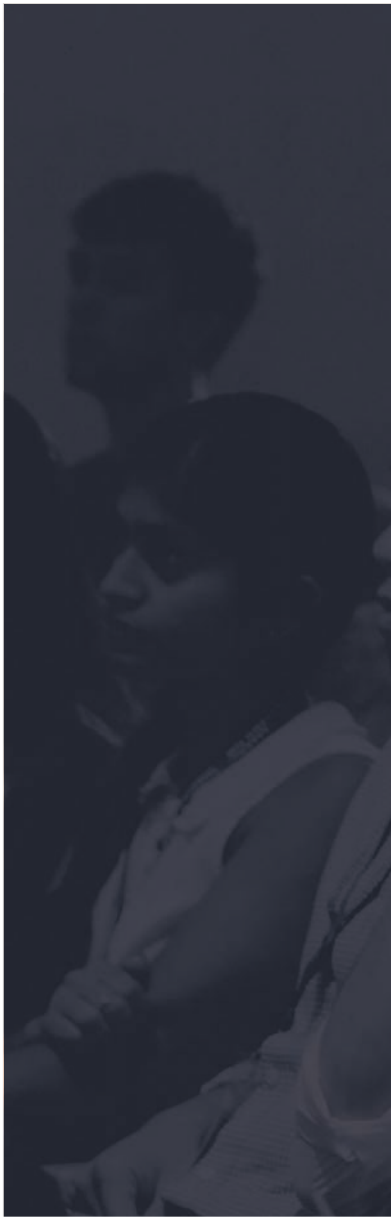
SENS Research Foundation's activities have been covered by many media outlets globally including

American Society of Cell Biology, Financial Times, NPR, Hindustan Times, National Geographic, El Mundo, GeekWire, The New Statesman, Scientific America, The Scientist, BBC4, BBC Science, Nature, and Nature Communications

SENS Research Foundation, Aubrey de Grey, and our research have been featured in documentaries around the world in 2015-2016 including Sweden, Italy, France, England, and the United States.

Over the past year representatives of SENS Research Foundation have addressed audiences around the world including in the United States, Argentina, Vietnam, United Kingdom, India, Italy, Brazil, Russia, Canada, South Korea, France, Croatia, Turkey, The Netherlands, Scotland, Romania, Singapore, Denmark, Spain, Switzerland, Portugal, Luxembourg, and Ireland.

Our Newsletters are delivered to almost 9000 subscribers. Our Facebook pages have over 20,000 Likes and Members. Our Twitter, @SENSTweet, has almost 25,000 followers.



2016 rejuvenation biotechnology conference

The 2016 Rejuvenation Biotechnology Conference was focused on taking the Rejuvenation Biotechnology Industry to the next level by addressing the question: what will it take to push emerging breakthroughs in regenerative medicine from proof-of-concept to implementation?

This conference sought to answer this critical inquiry by covering all the stages from securing funding, to production, to navigating regulation, to clinical evaluation and adoption of new treatments. Industry leading experts presented real-life examples drawn from their own work followed by open panel discussions and Q&A. Dr. Pinchas Cohen, Dean of USC Leonard Davis School of Gerontology keynoted the first day of the conference. As with our previous conferences, we provided ample time for networking with industry leaders, funders and researchers.

The 2016 Rejuvenation Biotechnology Conference was hosted at the Buck Institute for Research on Aging in Novato California. We would like to thank the Buck Institute for their generous support in hosting our event.

Due to our limited space, the 2016 Rejuvenation Biotechnology Conference was an invitation-only event. We had 250 registered attendees. In order for our entire community to be able to participate, we live streamed the conference. The conference was streamed to 62 countries around the world, and a full recording of that stream is now available on our website. Videos from the conference and the stream have been viewed over 10,000 times since the conference.

Education is an essential component of SENS Research Foundation's mission, allowing us to accelerate the pace of turning laboratory discoveries into real-world health benefits. Our goal is to train not only future scientists who will develop life-saving therapeutics, but also the health care professionals and policymakers who will ensure those therapeutics are safely and efficiently brought to patients suffering from age-related diseases.

Summer Scholars Program

In collaboration with leaders of the rejuvenation biotechnology field at the Buck Institute for Research on Aging, the Harvard Stem Cell Institute, the Sanford Burnham Prebys Medical Discovery Institute, The Scripps Research Institute, the University of Oxford, and the Wake Forest Institute for Regenerative Medicine, SENS Research Foundation's Summer Scholars Program offers undergraduate students the opportunity to gain valuable experience in biomedical research, combating diseases of aging such as cancer and Parkinson's disease.

Students who have participated in the program have not only learned valuable technical and communication skills, but also made tangible contributions to the rejuvenation biotechnology field. Summer Scholars have been authors on three publications in 2015 and five in 2016. As the Summer Scholars Program continues to grow, we look forward to expanded support of both young rejuvenation biotechnology scientists as well as the discoveries and therapeutic development of our research partners.

New Oxford–CASMI Partnership

While the Summer Scholars Program provides an immersive experience between academic sessions, our new crowdsourced SRF-Oxford-CASMI Research Program will run year-round. Developed in collaboration with the University of Oxford and its Centre for the Advancement of Sustainable Medical Innovation (CASMI), this program will offer students with limited access to research facilities and laboratory experience an opportunity to participate remotely in inquiry-based research.

This work will focus on investigating the obstacles blocking or slowing the development and research of therapeutics. Such studies could entail the exploration of the shortcomings in drug and device regulation in the United States, examination of obstacles and possible improvements to patenting therapeutics, or analysis of the effectiveness of new regulatory pathways for regenerative medicine products.

publications

These publications are the result of research funded by SENS Research Foundation.

Boominathan A, Vanhoozer S, Basisty N, Powers K, Crampton AL, Wang X, Friedricks N, Schilling B, Brand MD, O'Connor MS. 2016. Stable nuclear expression of ATP8 and ATP6 genes rescues a mtDNA Complex V null mutant. Nucleic Acids Res 44: 9342-9357.

Draghici C, Wang T, Spiegel DA. 2015. Concise total synthesis of glucosepane. Science 350: 294-298.

Gaspar J, Mathieu J, Alvarez PJJ. 2016. A Rapid Platform to Generate Lipofuscin and Screen Therapeutic Drugs for Efficacy in Lipofuscin Removal. Materials, Methods & Technologies. 10: 1-9.

Gravina S, Dong X, Yu B, Vijg J. 2016. Single-cell genome-wide bisulfite sequencing uncovers extensive heterogeneity in the mouse liver methylome. Genome Biol 17: 150.

Rebo J, Mehdipour M, Gathwala R, Causey K, Liu Y, Conboy MJ, Conboy IM. 2016. A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood. Nat Commun 7: 13363.

Alliance Publications

These publications were the result of the work from Alliance-funded researchers. Many of these publications included contributions from our SRF Summer Scholars.

Arshad Z, Karmen L, Choudhary R, Smith J, Branford O, Brindley D, Pettitt D, Davies B. 2016. Cell assisted lipotransfer in breast augmentation and reconstruction: A systematic review of safety, efficacy, use of patient reported outcomes and study quality. JPRAS Open. 10: 5–20.

Arshad Z, Smith J, Roberts M, Lee WH, Davies B, Bure K, Hollander GA, Dopson S, Bountra C, Brindley D. 2016. Open Access Could Transform Drug Discovery: A Case Study of JQ1. Expert Opin Drug Discov 11: 321-332.

Brindley DA, Arshad Z, Luo D, Dopson S, Hollander G, Frost S, Bountra C, Smith JA. 2015. 21(st) Century Cures Act: An Act of Cure or Diagnosis? Rejuvenation Res 18: 295-298.

Bure K, Ball A, Biagioni K, Mehta S, Choudhary R, Arshad Z, Pettitt D, Holländer G, Al-Mossawi H, Faulstich F, Reeve B, Smith J, Brindley D. 2016 Automation of CAR-T cell adoptive immunotherapy bioprocessing: Technology opportunities to debottleneck manufacturing. Bioprocess International.

Lannon K, Smith J, Bure K, Brindley D. 2015 Quantitative Risk Assessment of Bioaccumulation Attributable to Extractables and Leachables in Cellular Immunotherapy Biomanufacturing. Bioprocess International.

Luo D, Smith JA, Meadows NA, Schuh A, Manescu KE, Bure K, Davies B, Horne R, Kope M, DiGiusto DL et al. 2015. A Quantitative Assessment of Factors Affecting the Technological Development and Adoption of Companion Diagnostics. Front Genet 6: 357.

Meier A, Faulkner SD, Schoonderbeek C, Jong B, Kung J, Brindley D, Barker R. 2016. An assessment of implications of adaptive licensing for pharmaceutical intellectual property and regulatory exclusivity rights in the European Union. Clin Pharmacol Ther 100: 743-753.

Merks P, Swieczkowski D, Byliniak M, Drozd M, Krupa K, Jaguszewski M, Brindley D, Naughton B. 2016. The European Falsified Medicines Directive in Poland: background, implementation and potential recommendations for pharmacists. Eur J Hosp Pharm.

Naughton B, Vadher B, Smith J, Smith G, Chapman S, Dopson S, Brindley D. 2016. EU Falsified Medicines Directive mandatory requirements for secondary care: A concise review. J Generic Med Bus J Generic Med Sect 12: 95–101.

Naughton BD, Smith JA, Brindley DA. 2016. Establishing good authentication practice (GAP) in secondary care to protect against falsified medicines and improve patient safety. Eur J Hosp Pharm Sci Pract 23: 118-120.

Naughton B, Smith J, Ohanjanyan A, Smith G, Dopson S, Horne R, Brindley D. 2016. EU FMD: hospital pharmacy challenges and opportunities. European Journal of Hospital Pharmacy: Science and Practice.

Pettitt D, Anandan SM, Kulkarni MK. 2016. Novel intraoperative applications for the metal suction cannula. Ann R Coll Surg Engl 98: 344-345.

Pettitt DA, Pai A, Bradbury E, Anandan S, Kulkarni M. 2016. An unusual finger injury. BMJ 353: i2680.

Pettitt D, Pettitt A, Roberts M, Smith J, Brindley D. 2016. Legal Framework on the Scientific Use of Animals in Research. in Basic Science Methods for Clinical Researchers (eds. M Jalali, F Saldanha and M Jalali). Academic Press.

Pettitt D, Smith J, Fuerstenau-Sharp M, Bure K, Holländer G, Predki P, Slade A, Jones P, Mitrophanous K, Brindley D. 2016. Emerging platform bioprocesses for viral vectors and gene therapies. Bioprocess International.

Pettitt D, Smith J, Meadows N, Arshad Z, Schuh A, DiGiusto D, Bountra C, Holländer G, Barker R, Brindley D. 2016. Regulatory barriers to the advancement of precision medicine. Expert Rev Precis Med Drug Dev 1: 319–329.

Pettitt D, Raza S, Naughton B, Roscoe A, Ramakrishnan A, Ali A, Davies B, Dopson S, Hollander G, Smith J, Brindley D. 2016. The Limitations of QALY: A Literature Review. J Stem Cell Res Ther. 9.

Rekhi R, Smith J, Arshad Z, Roberts M, Bountra C, Bingham I, Bure K, Brindley D. 2016. Decision-Support Tools for Monoclonal Antibody and Cell Therapy Bioprocessing Current Landscape and Development Opportunities. Bioprocess International.

Smith J, French A, Hurley H, Davies B, Dopson S, Fairchild P, Roberts M, Riley P, Reeve B, Williams D, Daheron L, Bure K, Carr A, Karp J, Wall I, Brindley D. 2016. Challenges and Opportunities in the Development of Induced Pluripotent Stem Cell Therapeutics. in Frontiers of Stem Cell and Regenerative Medicine Volume II (eds. A Rahman and S Anjum), pp. 145-175. Bentham Science.

Smith J, Dopson S, Davies B, Wartolowska K, Karp J, Carr A, Brindley D., 2016. Borderline Regulation of Stem Cell Technologies: Therapies, Devices and Combination Products. in Global Medical Device Regulatory Strategy (eds. M Gropp and PT Takes), pp. 237-248. Regulatory Affairs Professionals Society.

srf alliance program 2016

The SENS Research Foundation (SRF) Alliance Program was founded to support the translation of SRF's basic science programs from the laboratory to the bedside. Specifically, the Alliance has delivered substantial international research impact in the domains of regulation, open access drug development and regenerative medicine.

Core to the Alliance's mission is supporting the implementation of human clinical studies for SRF supported programs by 2021.

The SRF Alliance Program Research capitalizes on three core areas, namely:

1. **Clinical Trial Structures & Regulatory Science (Prof. Chas Bountra, Sir John Bell, Prof. Russ Altman)**
2. **Open Drug Innovation (Prof. Chas Bountra, Prof. Richard Barker, Sir David Cooksey)**
3. **Regenerative Medicine (including Cell & Gene Therapy) (Brock Reeve, Prof. Evan Snyder, Prof. Georg Hollander)**

Presently, this consists of a restricted grant from SRF, with disbursement contingent upon evidence of matched funding and an academically rigorous research focus that must have a clear positive impact on therapeutic development. This has been realized through a number of PhD studentships, Post-Doc Fellowships and Impact Grants, in addition to events organization and awareness.

Dr David Brindley, the Director of Alliances, and James Smith, an Alliance Associate, are robustly supported by the SRF Core Team, with close synergies to existing SRF Education programs. They have provided supported to all functions within the SRF-delivered Alliance events.

These events include:

- **Washington DC Sartorius-Phacilitate Cell & Gene Therapy World**
- **ISCT Singapore event (guest speaker, ex-CEO Invida (now Menarini Asia-Pacific)**
- **IBC Life Sciences' BioProcess International Conference & Exhibition, Boston**
- **Cell Therapy Manufacturing & Gene Therapy Congress, Amsterdam**

To date, expenditure has been sustained as per the planned schedule, and three PhD students have been offered support subject to matched contributions. Two students have so far commenced their studies - David Pettitt and James Smith. David Pettitt is currently researching the commercialization of cellular based therapeutics [add supervisors], and is specifically examining regenerative medicine clinical trial models and viable reimbursement mechanisms. He has presented his research to date at a number of international conferences, in addition to authoring a number of high-impact publications. He was also the recipient of the GTCbio Scholarship, awarded in recognition of outstanding achievements and promise in Stem Cell research. James Smith's research focuses on the use of intellectual property as a resource for measuring innovation in the life sciences, and the construction of computational models to predict drug success at an earlier stage in development.

2017 will see the Alliance focus on supporting an international program of events, incumbent PhD students (matched funding via The Oxford Martin School), and three Post-Doctoral Fellows (matched funding via the Oxford Academic Health Science Centre).

Since July 2016, the SRF Alliance Program has supported a number of high-impact publications, which are detailed in the Publications section.

finances

Committed to the highest standards of transparency and accountability

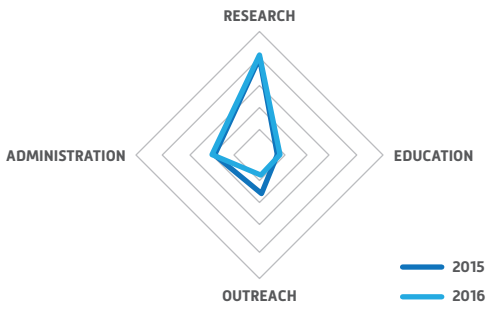
Yr. 2015 and Yr. 2016

SRF accounts have been prepared by MKR Accounting and independently audited every year by LMGW Certified Public Accountants, LLP. We strive for the highest standards in our management of the generous donations given to us each year, and each dollar is directed towards the area of our organization in which it will provide the greatest benefit to our mission.

Funding Sources

In addition to the ongoing support from the 2012 restricted grant from SENS Foundation EU, we have also received large grants from the Thiel Foundation in support of the organization, the Foster Foundation in support of our MitoSENS research program, and the Forever Healthy Foundation in support of ongoing research programs. It is with the strong support of these Foundations and the generosity of our many supporters worldwide that allow SRF to continue advancing rejuvenation biotechnologies.

REVENUE	Yr. 2015	Yr. 2016
Individual	$ 403,245.00	$ 332,950.00
Corporate	$ 34,203.00	$ 69,414.00
Grants	$ 992,341.00	$ 2,282,177.00
Other	$ 148,787.00	$ 17,022.00
Total Revenue	**$ 1,578,576.00**	**$102.345**



EXPENSES	Yr. 2015		Yr. 2016	
Research	$ 1,934,371.00	48%	$ **4,060,680.00**	50%
Education	$ 309,130.00	8%	$ 397,379.00	10%
Outreach	$ 811,858.00	20%	$ 428,787.00	11%
Administration	$ 1,005,321.00	25%	$ 1,050,282.00	26%
Total Expenses	**$ 4,060,680.00**		**$ 3,907,561.00**	

sens research foundation advisory board

Pedro Alvarez, PhD, Chair, Department of Civil and Environmental Engineering, Rice University

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

Anthony Atala, MD, Director, Wake Forest Institute for Regenerative Medicine

Maria A. Blasco, PhD, Director, Molecular Oncology Programme, Spanish National Cancer Research Centre (CNIO)

Judith Campisi, PhD, Professor, Buck Institute for Research on Aging; Senior Scientist, Lawrence Berkeley National Laboratory

George Church, PhD, Professor, Department of Genetics, Harvard Medical School

Irina Conboy, PhD, Assistant Professor, Department of Bioengineering, UC Berkeley, and Berkeley Stem Cell Center

Marisol Corral-Debrinski, Research Director, Fondation Voir et Entendre, Institut de la Vision, Universite Pierre et Marie Curie

Gabor Forgacs, PhD, Professor, Biophysics Laboratory, University of Missouri-Columbia; Founder, Organovo, Modern Meadow

Leonid Gavrilov, PhD, Senior Research Scientist, Center on the Demography and Economics of Aging, NORC and the University of Chicago

S. Mitchell Harman, PhD, Director and President of Kronos Longevity Research Institute

William Haseltine, PhD, Chair, Haseltine Global Health

Jay Jerome, PhD, Director, Graduate Program in Cellular and Molecular Pathology, Vanderbilt University Medical Center

Brian Kennedy, PhD, Professor, Buck Institute for Research on Aging

Daniel Kraft, MD, Executive Director, FutureMed, Singularity University

Jeanne Loring, PhD, Director of the Center for Regenerative Medicine, The Scripps Research Institute

Chris Mason, PhD, Chair of Regenerative Medicine Bioprocessing, University College London

Stephen Minger, PhD, Director, SLM Blue Skies Innovations Ltd.

Janko Nikolich-Zugich, MD, PhD, Chair, Department of Immunobiology and Co-Director, Center on Aging, University of Arizona

Graham Pawelec, PhD, Professor of Experimental Immunology, Tübingen University

Bruce Rittmann, PhD, Director, Swette Center for Environmental Biotechnology, Biodesign Institute, Arizona State University

Nadia Rosenthal, PhD, Director, Australian Regenerative Medicine Institute

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Vladimir Skulachev, ScD, Director, A.N. Belozersky Research Institute of Physico-Chemical Biology, Moscow State University

David Spiegel, PhD, Associate Professor of Chemistry, Yale University

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Rudolph Tanzi, PhD, Director, Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease, Harvard University

Fyodor Urnov, PhD, Head, Advanced Genomics Technologies, Sangamo Biosciences; Associate Adjunct Professor, UC Berkeley

Jan Vijg, PhD, Chair, Department of Genetics, Albert Einstein College of Medicine

Michael West, PhD, CEO, Biotime Inc.

Death-Resistant Cells: Toward Neutralizing the SASP

Buck Institute for Research on Aging
Principal Investigator: Judith Campisi
Research Team: Kevin Perrott

Non-dividing "senescent" cells in our bodies resist signals for apoptosis (programmed cell death) and secrete numerous inflammatory signaling molecules and protein-degrading enzymes into their local environment. The latter phenomenon is called the senescence-associated secretory phenotype, or SASP, and is thought to play a role in the chronic disease-promoting inflammation widespread in aging tissues. Additionally, although activation of the senescence program in cells at risk of becoming cancerous can pre-empt the initiation of cancer, the long-term effects of the SASP may make the local tissue environment more vulnerable to the spread of cancer. With SENS Research Foundation funding, the Buck Institute senescent cell project has been screening small molecules for their effects on fibroblasts (a type of skin cell) rendered senescent by ionizing radiation and other causes of DNA damage, including replicative stress. Their goal is to identify agents that can selectively kill senescent cells or interrupt the SASP.

Work by the Buck team revealed that a compound called apigenin suppresses the secretion of a representative constituent of the SASP. They furthermore determined that the root of apigenin's ability to shut down the vicious cycle that enforces ongoing SASP is IRAK4, a key part of the signaling cascade activated inside cells when the SASP component IL-1α engages its receptor. In the last year, they have taken advantage of this potent suppressive effect on cells in culture to tease out the role of the SASP in driving the known and newly-discovered harmful effects of senescent cells.

In earlier studies, Buck researchers led by Dr. Judith Campisi had shown that the presence of senescent cells alongside cancer cells can stimulate those cells to both multiply more rapidly and to spread to other parts of the body — the metastasis process, which ultimately makes most cancers so deadly. Repeating these studies in cell culture while inhibiting the SASP with apigenin almost completely nullified the proliferation-stimulating and pro-metastatic effects of senescent cells on breast cancer cells.

Additionally, growing relatively nonaggressive cancer cells in culture medium taken from senescent cells makes them adopt a more aggressive character, in a process known as the epithelial-to-mesenchymal transition (EMT). Surprisingly, when apigenin is added to that same SASP-containing culture medium before using it to bathe the cancer cells, two of the hallmarks of the EMT are prevented, suggesting that in addition to inhibiting the release of SASP factors from senescent cells, apigenin may have some direct effect on SASP signaling.

These studies give us further insights into why senescent cells are so harmful to the aging body. Human studies conducted with apigenin suggest that the concentrations required to achieve the effects on the SASP in senescent cells cannot be obtained from dietary supplements, but drugs based on parts of its structure could dampen some of the harmful effects the SASP in senescent cells. Removing these cells is the ultimate solution to these problems, and in the last year several groups have made rapid progress toward this goal. In the meantime, these studies using apigenin may demonstrate important principles from which senescent-cell-focused rejuvenation biotechnologies may be derived.

Target Prioritization of Tissue Crosslinking

The Babraham Institute
Principal Investigator: Jonathan Clark

Our arteries slowly stiffen with age, in substantial part because of random crosslinking of the structural proteins collagen and elastin. Some of these crosslinks are the result of purely stochastic chemical reactions, including those with blood sugar and other fuels in the circulation.

Other crosslinks arise from enzymatic processes that modify collagen — either as "collateral damage," or for purposes that help with short-term survival but whose cumulative burden over time eventually compromises function. Developing rejuvenation biotechnologies to break these crosslinks is key to restoring youthful arterial function.

To tease out the effects and relative importance of all of these different sources of crosslinking in aging tissues, the Babraham Institute team has been studying the crosslinking process in the tissues of aging mice. This has required the development and validation of new experimental methods and assays, which are now ready for use in elucidating these questions. In particular, a new HPLC methodology that is better suited to the analysis of crosslinks within tissues (as opposed to isolated in vitro systems) has been successfully implemented. In addition to this, a new, faster and improved method for the analysis of glucosepane has been developed.

Using these new tools, the team has evaluated multiple tissues for crosslink presence. Importantly, some of the crosslinks that have been reported by others to accumulate in aging tissues were not detected. This was not because the new method was unable to detect such crosslinks when present, because it had no problem detecting the same crosslinks were added directly to the samples. While further studies are needed to confirm it decisively, these results suggest that several crosslinks now believed to accumulate in aging tissues may actually be experimental artifacts.

The team also noted that increased non-enzymatic glycation with age is clearly evident, and that a number of glycation structures can be seen in the mass spectral data. Preliminary mechanistic studies have been done to determine the key factors driving this process. The strain of mouse that we chose to use in these studies is known to not easily develop diabetes. As much of the work into Advanced Glycation Endproduct (AGE) crosslinks has been carried out in diabetic models, this makes investigating the effects of age on these animals especially important in understanding the effects of aging itself on tissue crosslinking.

The Babraham team is now preparing and studying tissues from a wide range of ages in non-diabetic mice in preparation for a full analysis on the observed changes. As part of this work, they are also looking at tissues from mice that have been fed diets containing special tracers, whose incorporation into and disappearance from tissue proteins will help reveal the rate at which these proteins are broken down and replaced in aging tissues — information still missing from crosslink studies, counteracting the effects of early chemical processes in aging tissues that could lead to the formation of irreversible crosslinks. Over the next year, the team aims to be able to demonstrate which crosslinks show significant changes with age and gain insight into the controlling factors for these changes.

Engineering New Mitochondrial Genes to Restore Mitochondrial Function

SENS Research Foundation Research Center
Principal Investigator: Matthew O'Connor
Research Team: Amutha Boominathan, Bhavna Dixit, Kathleen Powers, Shon Vanhoozer

Free radicals derived from our energy-producing mitochondria can mutate the organelle's DNA, leading to deletions of large stretches of the mitochondrial genome. These deletion mutations prevent the mitochondria from building various pieces of the electron transport chain (ETC), with which mitochondria generate most cellular energy. The accumulation of deletion-mutation-containing cells is a significant consequence of aging, and is implicated in age-related disease as well as in several currently incurable and extremely debilitating inherited mitochondrial disorders. The rescue of mitochondrial DNA mutations therefore has tremendous potential for restoring the health of aging people and treating the victims of inherited mitochondrial disease.

A potential rejuvenation biotechnology to recover ETC function is the allotopic expression of functional mitochondrial genes: placing "backup copies" of all of the protein-coding genes of the mitochondria in the "safe harbor" of the nucleus, thereby giving the mitochondrion all of the proteins it needs to continue producing energy normally even when the original mitochondrial copies have been mutated. However, demonstration of efficient functional rescue via allotopic expression has long been a research challenge.

This year, the SRF MitoSENS team reported a tremendous success: for what they believe is the first time, they have used allotopic expression to rescue the complete loss of a mitochondrially-encoded protein in a mammalian cell.

Achieving this landmark success required several key steps. First, because of its ancient evolutionary history as a separate organism, the mitochondrial genome actually uses a different genetic code from the one used by the genes in the cell's nucleus, so the "lettering" of the mitochondrial genes had to be "rewritten" to function in the nucleus. Next, in order to allow the proteins that the allotopically-expressed genes encode to enter into the mitochondria, the team had to engineer in versions of the targeting sequences that permit such entry from the proteins that are naturally encoded in the nucleus but destined for the mitochondria. And finally, they had to demonstrate in ways that would finally convince a skeptical scientific community that their engineered proteins could achieve the functional rescue of mitochondrial mutations.

For the proof-of-concept, the SRF group has focused on the smallest mitochondrially-encoded protein, a component of the last Complex of the ETS called ATP8. To demonstrate rescue, they used cells derived from a patient who suffered from a rare mutation in the ATP gene that completely prevented the production of the ATP8 protein. However, the patient's original cells contained a mixture of mitochondria, only a subset of which carried this otherwise-fatal mutation. So in order to decisively prove the effectiveness of allotopic expression, the group had to perform additional work to make a derivative completely free of wild-type ATP8 genes, so that there would not be any competing endogenous ATP8 protein that might otherwise be thought responsible for the rescue of the cells.

A publication in the prestigious scientific journal Nucleic Acids Research announced their success in the fall of 2016. The results show that their targeted and recoded ATP8 protein can be expressed from the nucleus, turned into protein in both normal and mutant cells, and efficiently targeted to the mitochondria. Furthermore, they can demonstrate functional rescue of the null cells. Under conditions where mutant cells die for lack of ability to produce energy, the cells with engineered allotopically-expressed proteins were able to survive and replicate. Drilling down further, they additionally show that the allotopically-expressed protein is successfully localized to Complex V of the ETS where it belongs, and that mitochondria from such cells consume oxygen, which is required for the ETC to produce energy but which does not occur in mutant cells lacking the allotopically-expressed genes. Lastly, they show that the Complex V of mitochondria from such cells is capable of recharging ATP, the cell's energy currency.

In addition to ATP8, the SRF MitoSENS team has further demonstrated expression and targeting of a second re-engineered protein, ATP6, simultaneously in the same cells (which are also deficient – though not completely lacking – in ATP6 protein). Adding allotopically-expressed ATP6 to ATP8 in such cells has further enhanced the benefits of ATP8 alone on most of the measures noted above. And most importantly, it is proof-of-concept that ATP8 is not a special case: other mitochondrially-encoded proteins can simultaneously be expressed from the nucleus, targeted to and imported into the mitochondria, and function appropriately in the ETC.

We are hopeful that these results are an important step towards proof-of-concept of future allotopic expression gene therapies.

Identification of the Genetic Basis of ALT in Cancer

SENS Research Foundation Research Center
Principal Investigator: Haroldo Silva
Research Team: David Halvorsen, Melissa Bonner

The prevalence and death from cancer increase dramatically with age. The final barrier standing against cancer cells' ability to divide to grow tumors to a sufficient degree as to be harmful to patients is the erosion of the repetitive DNA sequences present at the end of every chromosome (telomeres). Telomeres shorten every time a cell divides, and thus all cancers have to find a way to keep their telomeres long enough to prevent senescence (which occurs when cells can no longer divide) or death.

Most cancers use an enzyme called telomerase for this purpose, but about 10-15% of cancers use a telomerase-independent mechanism known as Alternative Lengthening of Telomeres (ALT). The ALT mechanism remains largely a mystery, although we do know that components of the DNA damage repair and homologous recombination machinery do play essential roles in the ALT pathway. The presence of ALT in cancers is often associated with lower patient survival compared with tumors that rely on telomerase, since it is prevalent in clinically-challenging cancers occurring in the brain, lung, bone and soft tissue.

Therefore the OncoSENS team at SENS Research Foundation is working hard to find new ways to attack ALT cancers.

First, the team has developed and established two separate high-throughput assays measuring different ALT-specific biomarkers. In particular, the team optimized a microscopy-based assay to quantify a newly-identified potential ALT-associated biomarker termed single-stranded C-rich templates or simply ssC by the SRF team. Meanwhile, the team has combined the ssC assay with an assay for detecting a more well-known ALT biomarker known as ALT-associated promyelocytic leukemia bodies (APB), enabling simultaneous detection of both biomarkers. The third and most reliable ALT cancer biomarker is composed of partially double-stranded circular DNA pieces originated from telomeres and known as C-circles. These C-circles can now be easily detected by a novel technique developed by the team in collaboration with researchers in Australia. The SRF Research Center team has also adapted their assays to work at the 384-well plate level (i.e. 384 different samples can be tested simultaneously) using the Biomek 2000 robotic liquid handler, which should greatly improve experimental efficiency and speed.

These assays will finally enable cancer researchers to screen hundreds of thousands of compounds across multiple drug libraries, or even test every single one of the more than 20,000 genes in the human genome, for ways to shut down ALT cancers as well as learn more about the mechanisms behind the ALT pathway so that it can be decisively deactivated. Such large-scale studies are unprecedented in the field of ALT cancer research.

In addition to their biomarker work, the team is also pursuing more targeted methods to kill ALT cancer cells by taking advantage of particular structures present at the telomeres of these cells. Such structures can serve as targets for specially designed molecules that can potentially destroy cancer cells while leaving healthy cells virtually unharmed.

Finally, the team has several ongoing international collaborations aimed at understanding the molecular mechanisms behind the ALT pathway. On that front, the team is testing for evidence of ALT activation in mortal human fibroblasts after X-ray irradiation treatment and in transgenic zebrafish strains that grow tumors without a functional telomerase gene. The team also continues to investigate the role of the enzyme HDAC5 and its associated complexes on the ALT pathway, using both RNA interference and small molecule drug inhibitor techniques.

Glucosepane Crosslinks and Routes to Cleavage

Yale University
Principal Investigator: David Spiegel
Research Team: Matthew Streeter, Venkata Reddy, Robert Hale, Egor Chirkin, Nam Kim

Our arteries slowly stiffen with age. One of the key drivers of this stiffening process is the accumulation of molecular crosslinks that are formed between adjacent strands of structural proteins of the large arteries. One major cause of crosslink accumulation in aging is Advanced Glycation Endproducts (AGE), and one AGE in particular, called glucosepane, is currently thought to be the single largest contributor to tissue AGE crosslinking. The Yale AGE team is studying the role

of AGEs in aging, and developing novel tools and strategies for reversing AGE-mediated protein damage and develop new antibodies and reagents to enable rejuvenation research.

In earlier SRF-funded research, our pilot lab at Cambridge University found that all of the commercially-available antibodies for the major AGE-related molecules are actually highly unreliable. This is a serious impediment to detecting such molecules in tissue samples and in evaluating the effects of interventions targeting them, whether in high-throughput screening or in later studies in vivo. The Yale glucosepane team is now tackling this problem via the novel chemistry and methods they have developed.

In the last twelve months, the Yale team has made exciting progress in their work. Most notably, they have developed the first synthetic route to produce glucosepane. Their novel synthetic strategy is the first ever to provide high yields of pure samples of glucosepane, putting them (and soon other scientists) for the first time in a position to explore mechanisms through which crosslinks can be broken.

In collaboration with a colleague at Yale, they have also developed a high-throughput assay for screening proprietary libraries of organic catalysts for agents capable of breaking synthetic glucosepane. One of these libraries has already been taken forward for proof of concept, which led to the identification of several leads for catalysts that could be capable of converting glucosepane back to free lysine in arginine. The Yale team's ongoing work aims to identify and characterize the mechanisms by which they induce glucosepane cleavage. Insights gained from this work offer a potential route to the development therapeutically viable crosslink-breaking rejuvenation biotechnologies.

Beyond that, the Yale group has successfully generated proteins containing their synthetic glucosepane that can be used to identify antibodies that label glucosepane-containing proteins. These antibodies will enable the immunochemical detection of glucosepane crosslinks for a wide range of applications, including Dr. Jonathan Clark' complementary work at the Babraham Institute at Cambridge measuring the burden of such crosslinks in aging tissue, and for testing of candidate glucosepane-breaking drugs.

En route to the synthesis of glucosepane, the team also developed a new chemical method for forming a class of organic molecules known as substituted imidazoles, solving a long-standing problem in heterocyclic chemistry and creating a platform for work on other AGE crosslinks. They are applying this newly designed iso-imidazole methodology toward the synthesis of a variety of biomedically important molecules, including the neglected tissue crosslink pentosinane and the methylglyoxal-derived hydroimidazolones (MG-H). This work will allow them to expand their knowledge of crosslinks and, for the first time, evaluate pentosinane's role in aging biology.

Finally, the Yale team has now generated and characterized the first selective antibodies against all three isomers of MG-H. These efforts were enabled by their laboratory's success in developing efficient syntheses for each of these isomers as both isolated amino acids and as bound to peptide structures. This publication is the first to demonstrate the generation of selective antibodies against individual MG-Hs, which are valuable for the visualization and characterization of MG-H modifications in biological samples.

Tissue-Engineered Thymus

Wake Forest Institute for Regenerative Medicine (WFIRM)
Principal Investigator: John Jackson
Research Team: Shay Soker, James Yoo

The thymus gland is responsible for the development of a class of immune cells called T-cells. As part of the degenerative aging process, the thymus shrinks in size, and the structure and function of the remaining tissue decays, with the critical thymic epithelial tissues responsible for maturing T-cells giving way to fat cells and collagen. This process of thymic atrophy prevents the body from maturing new T-cells, progressively weakening the immune system's ability to fight off never-before-encountered infections. Engineering new, healthy thymic tissue would help to restore the vigorous immune response of youth.

SENS Research Foundation has therefore funded this WFIRM group to apply tissue engineering techniques to the creation of functional thymic tissue to fortify or replace the aging thymus. Engineering new tissues requires a "scaffold" in which to embed cells to give them structure and functional cues, and the WFIRM group has tested different scaffolding systems: decellularized donor scaffolds and hydrogels.

In the hydrogel approach, cell aggregates are cultured in a 3D collagen-based hydrogel system. Hydrogel structures resemble soft tissues more closely than any other purely human-made structure, and are highly biocompatible, making them unlikely to trigger an immune rejection response. To generate the cells to seed into the hydrogel scaffold, the WFIRM group cultured thymus epithelial cells and bone marrow progenitor cells in microscopic wells that encouraged them to cluster together into spherical structures. These spheroids were then placed in a basic hydrogel scaffold, where they have so far remained viable for several weeks at a time. During the first three weeks, small numbers of mature T-cells begin to develop from the bone marrow stem cells.

In the decellularized scaffold paradigm, an organ of the type that is needed is taken from a donor, but is then stripped of its original cells and DNA, leaving behind a protein structure with low potential for immunological rejection that can be repopulated with cells taken from the new organ recipient. This results in a new organ with the native structure and growth factors already present in the transplanted original organ, but with all the cells and most of the DNA and proteins of the recipient, eliminating the potential for immune rejection.

The WFIRM group initially began work in this paradigm using mouse organs, but they found that once decellularized, mouse thymuses lacked the rigidity to serve in that role. They accordingly moved on to the pig thymus — a species that not only worked well as an experimental system, but has some clinical potential as well. The pig is closer to humans both immunologically and in terms of size, giving it a widely-recognized potential for use as a source of donor organs for human patients, since organs from young human donors are in severely short supply and older organs are too degenerated to be useful. Such porcine scaffolds are low in immunological risk, and can be made even less so with some genetic techniques being developed by SENS Research Foundation Science Advisory Board member George Church and others. They then tested different protocols for stripping donor material from scaffolds, and optimizing for their ability to support the growth and the specialization of seeded T-cell precursors.

In an attempt to move this project to a more translational level over the past year, a human thymus was obtained from a 29-year-old donor for epithelia cell isolation and culture as well as histological analysis. Already at this relatively young age, the donor thymus showed significant characteristics indicative of age-related involution, including shrinkage, loss of structural organization, and infiltration with fat cells. Epithelial cells were then isolated and cultured with a porcine thymus tissue powder that they have found to preserve the epithelial character of mouse thymus epithelial cells in culture. This worked very well: human thymic epithelial cells not only continued to express cell-surface markers consistent with retained epithelial character, but they also expressed FOXN1, a gene that is critical for the proper function of thymus epithelial cells whose absence leads to the failure of thymus development in the womb. These results suggest that adult human thymuses can be used to isolate and culture thymic epithelial cells that can be used in the engineering of human thymus tissue constructs.

Catalytic Antibodies Targeting Transthyretin Amyloid

University of Texas-Houston Medical School (UTHMS)
Principal Investigator: Sudhir Paul
Research Team: Stephanie A. Planque

As part of the degenerative aging process, proteins that normally remain dissolved in bodily fluids become damaged, and adopt a misfolded form called amyloid. Amyloid composed of the transporter protein transthyretin (TTR) deposits in the heart and other organs with age, beginning to impair heart function in 20-25% of individuals over the age of 80, with increasing prevalence and severity at later ages. These deposits impair the heart's ability to relax and take in blood to pump to the rest of the body, contributing to the single most common form of heart failure as well as to a more purely amyloid-driven form of heart disease. TTR amyloids have also been found in many other aging organs, including the kidney, digestive organs, and spleen, and researchers have implicated them in several degenerative joint and ligament conditions. No therapies exist to remove wild-type TTR amyloids from the aging body, and no other organization is funding research to develop such therapies. This makes wild-type TTR a critical-path target for SRF research.

With SRF funding, the UTHMS extracellular aggregate team is working to develop novel catalytic antibodies ("catabodies") that would recognize and cleave TTR amyloid deposited in the heart and other tissues. Catabodies have the potential to be safer and more effective than conventional antibody-based immunotherapies: their catalytic activity minimizes the amount of antibody required to clear deposits from tissues, and the fact that they don't form stable complexes with their targets or engage immune cells is expected to minimize the inflammatory side-effects seen with other experimental antibody therapies. The UTHMS team has developed a system to identify native catabodies and engineered catabody fragments with more powerful amyloid-cleaving capacity, which can be used to augment the body's natural catabody defense system and prevent or reverse diseases of aging driven by extracellular aggregates.

In research published last year, the UTHMS group identified TTR aggregate-targeting catabodies and catabody fragments present in serum samples from young volunteers with Waldenstrom's macroglobulinemia (WM), a cancer involving hyperproliferation of the antibody-producing B cells. These catabodies were able to specifically cleave misfolded TTR, leaving TTR in its native conformation untouched. They also confirmed that healthy human serum also contains TTR-cleaving catalytic potential. Surprisingly, however, they subsequently found that even the best of the catabodies present in WM serum worked no better than randomly-picked Immunoglobulin M (IgM) antibodies from healthy humans. They therefore sought to identify the best of the IgM catabodies present in such serum, using a system of identifying B-cells whose IgM-type receptors recognize misfolded wild-type TTR and then deriving the underlying IgM antibodies.

This search resulted in the identification of two powerful TTR-cleaving catabodies, which they named 5E8 and 10E10. When tested for their ability to degrade misfolded wild-type TTR, these candidates were able to hydrolyze both soluble aggregates and deposit-like particulates, while having no effect on either TTR in its healthy, normal conformation or on a selection of fourteen other physiologically important proteins. Remarkably, these catabodies broke down TTR amyloid an astounding 500 times faster than IgM 1802, the best of the WM-derived candidates! Based on the catabodies' rapid kinetics and anticipated half-life in the blood, the researchers project that each one of these new IgMs could buzzsaw its way through more than 40,000 misfolded TTR molecules before they are themselves eliminated by physiological processes. And the concentrations required to disintegrate 80% of a sample of amyloid were many hundreds of times lower than those routinely achieved in the blood using other infused antibodies.

The UTHMS team have now identified the DNA sequences that encode IgM catabodies 10E10 and 5E8, and cloned the key domains along with a generic human IgM core structure into the commonly-used human cell line HEK293 for experimental production. From this, the establishment of stable cell lines will enable larger-scale production, as they work to develop these candidates into functional rejuvenation biotechnologies.

Rejuvenation of the Systemic Environment

University of California, Berkeley
Principal Investigator: Irina Conboy
Research Team: Justin Rebo, Keith Causey

In "heterochronic parabiosis," the circulation of an aged animal is joined to that of a young one, so that the aged organism's tissues are exposed to a youthful systemic environment (and vice-versa). Striking rejuvenating effects occur on old animals, even as "premature aging" phenomena emerge in their young parabiotic pairmates. To potentially adapt this phenomenon for rejuvenation therapies, scientists have been hunting for decades for the specific rejuvenating factors supposed to be present in the "young blood," but have not yet yielded consistent or reproducible results,

Dr. Conboy and the UC Berkeley systemic environment team realized that there might be a misunderstanding of what was really going on in parabiosis. When animals are connected, they are not just given reciprocal blood transfusions, but are surgically joined together. So in addition to receiving young blood, the old animals also have their old blood filtered through the young animals' livers and kidneys, and diluted with the young pairmate's own blood. Might the effects of parabiosis mostly come from the removal of toxic or suppressive factors from the old animals' sluggish circulation instead of from the delivery of active rejuvenating factors?

To test this possibility — and to accelerate identification and testing of potential pro- and anti-rejuvenation factors in the exchanged blood — SENS Research Foundation funded the team's development of a novel technological platform. Using a mixture of off-the-shelf and custom 3-D printed parts, this platform enables the group to easily and safely extract blood from small animals and transfuse it quickly and directly into another animal, without the reciprocal exchange of its blood or the passage of its blood through the pairmate's system. It thus separates the effects of the young animals' metabolic and excretory systems from the pure effects of their blood.

The team then used the new system to repeat key parabiosis experiments from Dr. Conboy's and others' labs. As compared with the impact of full-on parabiosis, the effects of isolated young blood on old muscles' ability to repair an injury were still substantial: the stem cells recovered significant regenerative powers, and less residual fibrosis remained after the wound was resolved. But by contrast, previously-reported benefits of parabiosis in the brain and the liver were either not present, or were far more modest, when young blood was administered without the confounding effects of full surgical conjoining. Most notably, the effects of young blood alone on neurogenesis (the birth of new neurons in the brain) were negligible, contrary to the effects of full-on parabiosis.

Another critical finding was the confirmation of suppressive factors in the old animals' blood, which inhibited neurogenesis and other regenerative responses of young animals transfused with it. Strikingly, many of these suppressive effects persisted for days after the young animals were disconnected from the old animal's blood supply. Notably, one or more yet-unidentified factors in old blood somehow trigger the young animals to produce more beta-2-microglobulin (B2M) — an immune factor already linked to suppressive effects in previous parabiosis research, and suspected to be a contributor to several kinds of cognitive impairment and dementia in humans, including Alzheimer's disease.

While this clearer picture of the basis of the "parabiosis effect" indicates a lower likelihood of isolating true pro-rejuvenation factors in the blood of young mice, we are nonetheless closer to being able to filter out factors responsible for suppressing the regenerative potential of an older body. With these suppressive factors removed, people receiving therapies derived from this work could more fully benefit from rejuvenation biotechnologies that repair their cellular and molecular aging damage.

New Research and Moving to Clinical Trials

SENS Research Foundation will be funding three new research projects at the Buck Institute for Research on Aging.

The "Maximally Modifiable Mouse"

Brian Kennedy, PhD, Professor, Buck Institute for Research on Aging

Many components of SENS require the addition of new genes to the genome of cells in the body. This technology, known as somatic gene therapy, has been a goal of medicine for decades, but it is still very far from perfect. Difficulty in controlling the precise location of gene insertion is a significant barrier to these efforts, as insertion in the "wrong" location could result in the cell becoming cancerous. To mitigate this difficulty, we have devised a new method for inserting genes into a pre-defined location. In the clinic, this will be done as a two-step process, in which first CRISPR is used to create a "landing pad" for the gene, and then the gene is inserted using an enzyme that only recognizes the landing pad. We have created mice that already have the landing pad, and now we plan to evaluate how well the insertion step works in different tissues.

Destroying Alzheimer's-associated neurofibrillary tangles

Julie K. Andersen, PhD, Professor

In recent years we have made great progress in enhancing cells so that they can destroy waste products that otherwise accumulate and poison them. Our past work in this SENS strand is now being taken forward by two spin-out companies, Human Regenerative Biotechnologies and Ichor Therapeutics, which are pursuing this approach against atherosclerosis and age-related macular degeneration respectively. But equivalent problems also appear in all the major age-related neurodegenerative diseases, including Alzheimer's, where the waste collects in aggregates termed "tangles". We will seek to eliminate tangles, initially in cell culture models, by introducing genes that reinforce the ability of the cell's "incinerator" (the lysosome) to maintain its function.

Killing dysfunctional white blood cells

Judith Campisi, PhD, Professor

The immune system works less well in the elderly, and it is believed that two factors contribute to this decline: the depletion of a type of white blood cell known as a naive T cell, and the accumulation of another type known as an effector memory T cell. We and others have made good progress in solving the former problem by regenerating or replacing the organ that makes naive T cells early in life (the thymus), but there has been little progress on the latter problem. We will seek to eliminate these unwanted cells using a genetic technique called suicide gene therapy, which has already been shown to work well in eliminating other types of unwanted cell.

Two of the companies SENS Research Foundation has supported are beginning to raise funding to move their research from the lab to clinical trials.

Ichor Therapeutics, a biotechnology company that focuses on developing drugs for age-related diseases, announced a series A offering to bring its LYSOCLEAR product for age-related macular degeneration and Stargardt's macular degeneration through Phase I clinical trials. In 2014, Ichor Therapeutics completed a material and technology transfer agreement for rights to concepts and research pioneered by SENS Research Foundation. In 2017 Ichor announced LYSOCLEAR, a recombinant enzyme product that selectively localizes to the lysosomes of RPE cells where A2E accumulates, and destroys it. Ongoing studies suggest that LYSOCLEAR is safe and effective at targeting A2E, eliminating up to 10% with each dose. This product would be the first clinical candidate based on concepts and research pioneered by the SENS Research Foundation.

Oisin Biotechnologies reports that they have made significant progress in showing that their vector works, efficiently transducing cells and delivering their DNA construct which can kill targeted cells on command. Oisin closed a $500K oversubscribed convertible debt round in mid-December and are working towards a substantial Series A in the next few months that would go towards a Phase 1 Clinical Trial.

$100,000 Plus
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SENS Foundation EU (continuing grant)
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