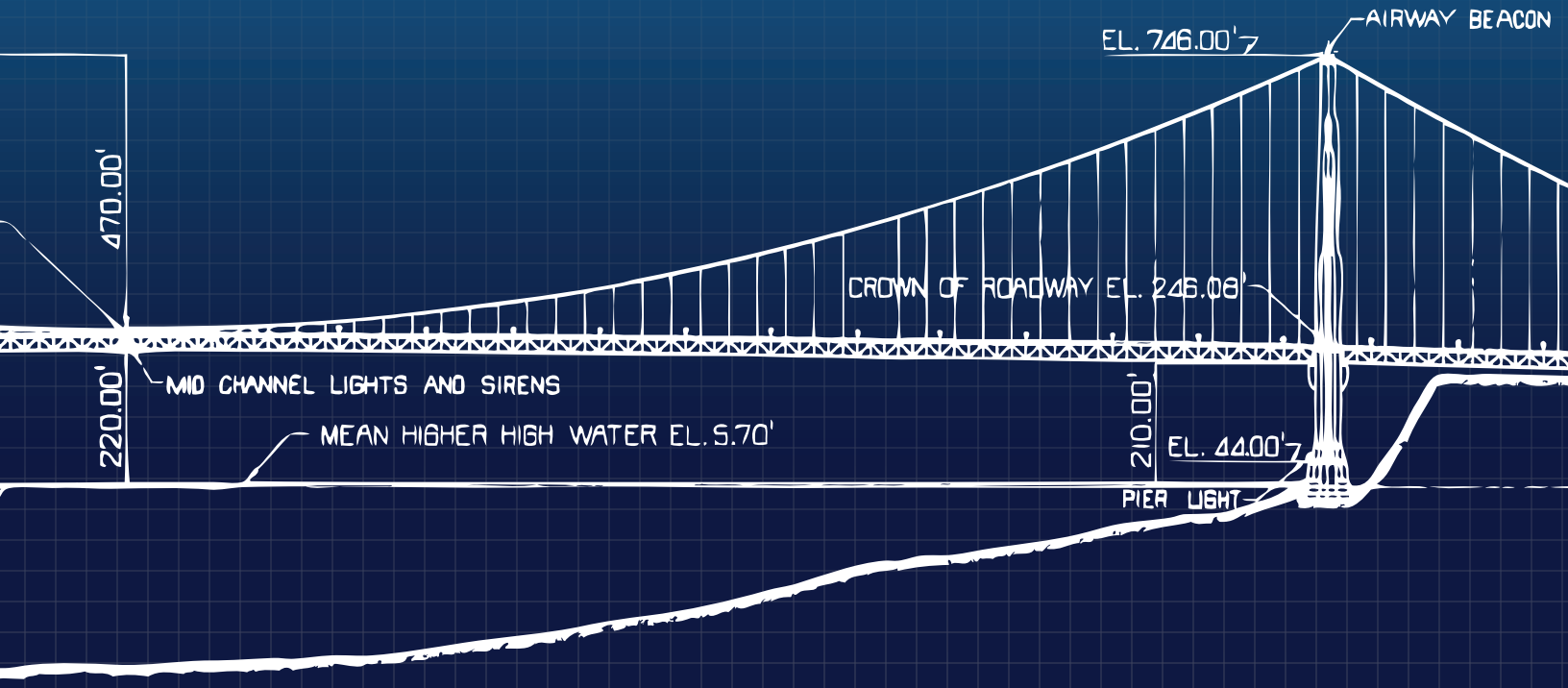
sens research foundation

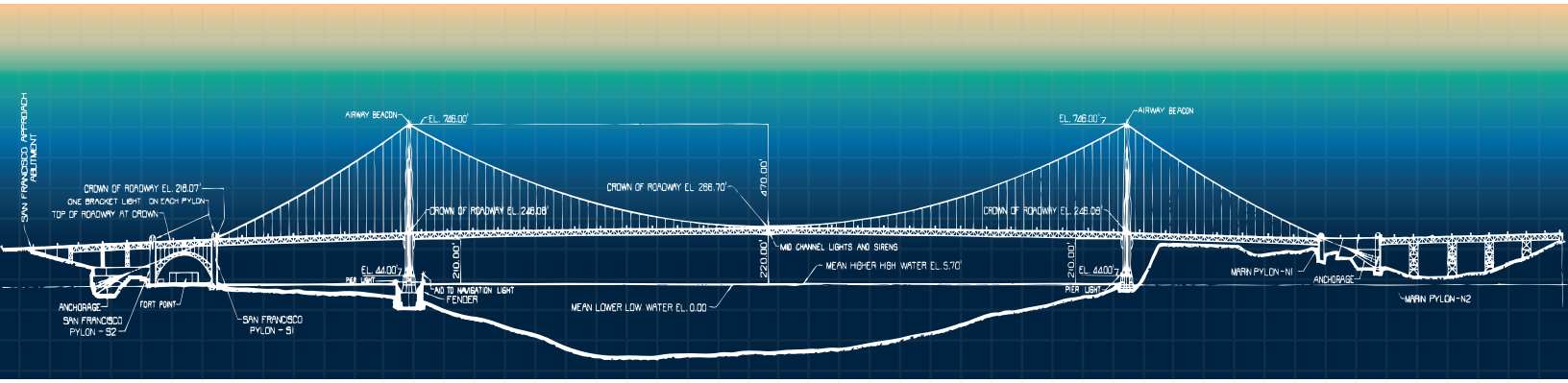
reimagine aging



2018 ANNUAL REPORT

EST 2009 • 501(C)(3) • RESEARCH • EDUCATION • OUTREACH

CONTENTS



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Dr. Aubrey de Grey
Chief Science Officer

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LETTER FROM CEO & CSO

The valley of death – the chasm between innovation and availability that has become such a common theme in drug development – is especially wide for the field of rejuvenation biotechnology. Besides the time and resources required to develop any medicine, the few who initially strove to develop this field faced the added challenge of demonstrating that we could feasibly intervene to prevent age-related disease by redressing the underlying damage that causes such disease.

Photo by Erin Ashford

There is scarcely a biotech organization that hasn't used, at some point, a 'bridging the gulf' metaphor to address the valley of death. But it has been such an integral part of our identity that we built it into our brand; the multi-colored ribbon of our logo having been designed to evoke both double-helix and suspension bridge imagery (and yes, it's always had seven twists).

Upon the launch of his project to build the Golden Gate Bridge, Chief Engineer Joseph Strauss had this to say:

"It took two decades and two hundred million words to convince people the bridge was feasible."

We have at times wondered whether even that would be sufficient. But with the diligent efforts of our own research teams and those of a growing number of institutions, the question of feasibility has increasingly fallen away. Today we see our research programs successfully translating into development, our former students becoming rejuvenation biotechnologists and developers, new collaborative energy from the investment arena, and the groundwork being laid for regulatory models for rejuvenation interventions.

For the opportunity to make our contribution to this blueprint and this bridge, we have all of you, our supporters, partners, and stakeholders, to thank. We know there is considerable construction work ahead, but together with you and our collaborators, we've no doubt we will create a new kind of span to connect our biotech hub to the broader community.

When the Golden Gate Bridge was conceived, it was deemed impossible. By the time of its completion, Mr. Strauss and his team had fostered an engineering revolution.

We're with you, Mr. Strauss.

Cheers and best regards,

Aubrey Mike

BUILDING A WORLDWIDE NETWORK

2017 Student Internship Locations:

- SRF Research Center, Mountain View, CA, USA
- University of Oxford, Oxford, England, UK
- Sanford Consortium for Regenerative Medicine, La Jolla, CA, USA
- Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
- The Scripps Research Institute, San Diego, CA, USA
- Buck Institute for Research on Aging, Novato, CA, USA

2017 Researcher/SRF Staff-Attended Events:

- *EuroMit* - Cologne, Germany
- *Mitochondrial Quality Control* - Xi'an, Shanxi Province, China
- *The 14th meeting of the Asian Society of Mitochondrial Research and Medicine* - Xi'an, Shanxi Province, China
- *Cell & Gene Meeting on the Mesa Scientific Symposium*, Salk Institute for Biological Sciences, La Jolla, CA USA

2017 Research Project Locations:

- Yale University, New Haven, CT, USA
- The Babraham Institute, Cambridge, UK
- Buck Institute of Research on Aging, Novato, CA, USA
- Applied Stem Cell, Inc., Milpitas, CA, USA

Dr. Aubrey de Grey's 2017 Speaking Engagements:

- Basel, Switzerland - *4th Annual Life Sciences R&D Data Intelligence Leaders Forum*
- São Paulo, Brazil - *Campus Party Brazil*
- Toronto, Canada- *World Affairs Conference*
- Tech Museum of Innovation, San Jose, CA, USA - *Technology and the Ethical Imagination*
- Saint Gallen, Switzerland - *START Summit*
- Manchester, UK - *ReThinkX MedX Future of Healthcare Conference*
- Bucharest, Romania - *Innovation Summit*
- Toronto, Canada - *Ideacity*
- San Diego, California, USA - *Festival of Genomics*
- London, England - *TEMPLE Talks - How To Deafeat Aging*
- Berlin, Germany - *Tech Open Air Conference*
- Amsterdam, Netherlands - *Dept Festival 2017*
- Boston, Massachusets, USA - *Connected Health Conference*
- New York, New York, USA - *The Economist - The Business of Longevity*
- Royal Danish Opera, Copenhagen, Denmark - *SingularityU Denmark Summit*
- Boston, Massachusets, USA - *Connected Health Conference*
- Kuala Lumpur, Malaysia - *iCapital Global Investor Week*
- Congress Center, Basel, Switzerland - *Swiss Innovation Forum*
- Miami, Florida, USA - *IFATS Miami 2017*

Research Advisory Board

Research Advisory Board member locations are represented by white pins

Pedro Alvarez, PhD
Rice University

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

Anthony Atala, MD
Wake Forest Institute for Regenerative Medicine

Maria A Blasco, PhD
Spanish National Cancer Research Centre

Judith Campisi, PhD
Buck Institute for Research on Aging

George Church, PhD
Harvard University and MIT

Irina Conboy, PhD
UC Berkeley and Berkeley Stem Cell Center

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SLM Blue Skies Innovations, Ltd.

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University of Arizona

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Tübingen University

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Arizona State University

Nadia Rosenthal, PhD
Jackson Laboratory for Mammalian Genetics

Jerry Shay, PhD
University of Texas Southwestern Medical Center

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Moscow State University

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Yale University

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Loughborough University

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Harvard University

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UC Berkeley and Altius Institute for Biomedical Sciences

Jan Vijg, PhD
Albert Einstein College of Medicine

Michael West, PhD
Biotime, Inc.

2017 REJUVENATION BIOTECHNOLOGY SHOWCASE

On September 11, 2017, at the UCSF Mission Bay Conference Center in San Francisco, SENS Research Foundation partnered with the California Life Sciences Institute (CLSI) to leverage the opportunities presented at this unique point in our history. **The emergence of the rejuvenation biotech industry represents a shift in medical research and development** overall toward a "preventative maintenance" approach to age-related disease. This has implications from the laboratory to the clinic to the business sphere, and there are significant opportunities for investment. More Bay Area startups are emerging in this space, and SRF's applied research programs are creating more tech transfer opportunities than ever before.

SRF partnered with CLSI because it supports California's leadership in life sciences innovation through its entrepreneurship, education, and career development programs. CLSI's FAST (Fellows All-Star Team) Accelerator provides select entrepreneurs with intensive team review and coaching to perfect their business model and product development plans, and to build a compelling commercialization strategy.

The event brought together a selection of FAST companies with a rejuvenation biotechnology focus and SRF translational research projects, all of which will become the rejuvenation biotech companies of tomorrow. The event furthermore facilitated information-sharing between key players poised to directly impact the direction and growth of these companies and the healthcare industry.

2017 REJUVENATION BIOTECH SHOWCASE PRESENTATIONS:

- *Killing Dysfunctional Cells* - Judith Campisi, Buck Institute for Research on Aging
- *Engineering New Mitochondrial Genes to Restore Mitochondrial Function* - Matthew O'Connor, Vice President of Research, SRF
- *Glucosepane Crosslinks and Routes to Cleavage* - David Spiegel, Yale University
- *ALTerran*, Haroldo Silva, Co-Founder
- *SyntheX*, Maria Soloveychik, CEO
- *Eidos*, Isabella Graef, Co-Founder
- *HepatX Corporation*, Eric Schuur, CEO
- *SciBac*, Jeanette Mucha, Chief Science Officer

SRF-CASMI-AHSC OXFORD SYMPOSIUM

In June 2017, **leading experts in rejuvenation biotechnology** and healthcare translation gathered with major donors and investors at Oxford for a symposium to celebrate the success of the SRF-CASMI Alliance and announce the launch of the Sir David Cooksey Fellowships in Healthcare Translation.

The symposium began at St. Anne's College with introductory comments from Dr. David Brindley, Senior Research Fellow in Healthcare Translation, Department of Paediatrics, University of Oxford, Mike Kope, CEO of SENS Research Foundation, and Dr Richard Barker, Founder and Director of CASMI.

St. Anne's College, Oxford

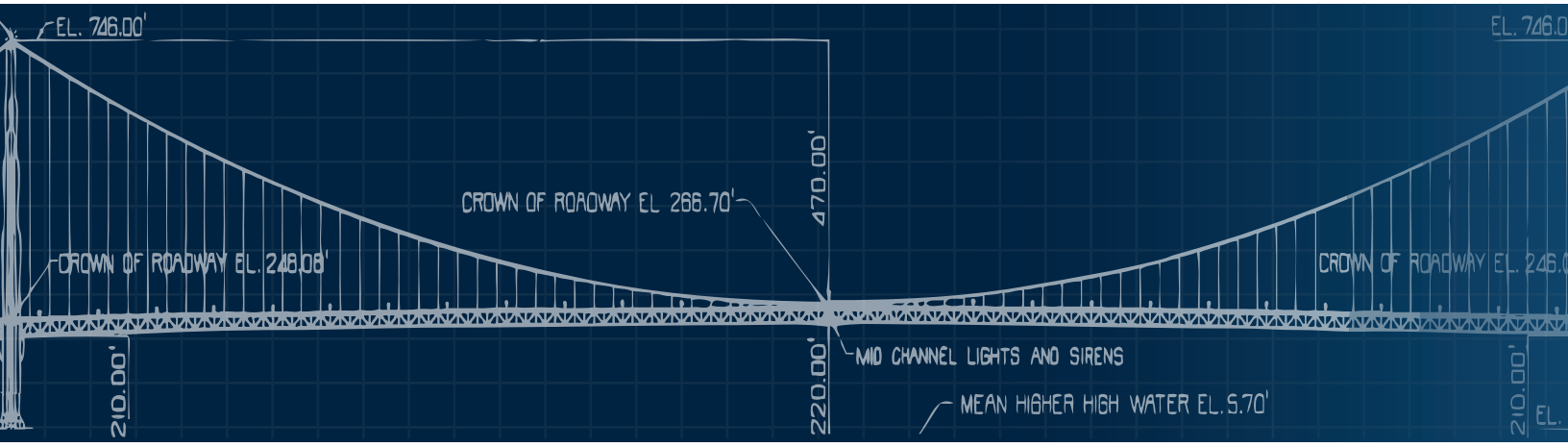
St. Hilda's College, Oxford

Presentations from program leads and Alliance-supported students addressed the identification of current barriers to deployment for new therapies, along with strategies to address these barriers and generally improve the practical effectiveness of rejuvenation biotechnology research. The afternoon sessions culminated in the Sir David Cooksey Fellowship announcement.

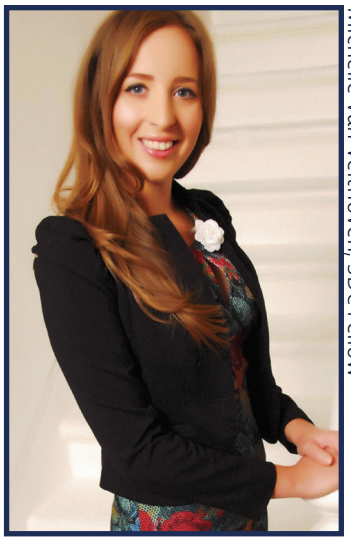
Evening sessions took place at St. Hilda's College and began with presentations by leading Oxford academics: an overview of translation of developmental and regenerative medicine at Oxford and introductions to some of the specific work being performed in this realm. The event concluded with remarks from major donor, Michael Greve, Founder and CEO of Forever Healthy Foundation. We are thankful to all who took part in this event and look forward to realizing the potential of these exciting collaborative efforts.

ALLIANCE

Reflecting on the SRF Alliance Program in 2017, one key theme emerges: **continuity.**



The University of Oxford currently hosts two students who have traversed the full SRF continuum from Summer Scholar intern to SRF-funded Ph.D student. In 2017, this continuum of support extended to SRF's first Post-Doctoral program: the Sir David Cooksey Fellowships in Healthcare Translation, named for the 'Father of Healthcare Translation', Sir David Cooksey GBE.



Michelle van Velthoven, SDC Fellow

Edward Meinert, SDC Fellow

The inaugural class of Cooksey Fellows have brought with them unique perspectives in cell and gene therapy and digital health and have initiated the SRF Alliance's first clinical trials, CHESS and VECTRA, in collaboration with industrial partners. The Alliance maintains its commitment to publishing all outputs in open access journals, wherever possible, and now has more than 25 peer-reviewed publications in high impact journals including *Nature Biotechnology, Molecular Therapy,* and *Science Advances*.

KEY ACHIEVEMENTS OF 2017

Clinical Trials: Two

PhD Students: Three

Publications: Twenty-five

Funding: Total matched and in-kind funding greater than $500,000

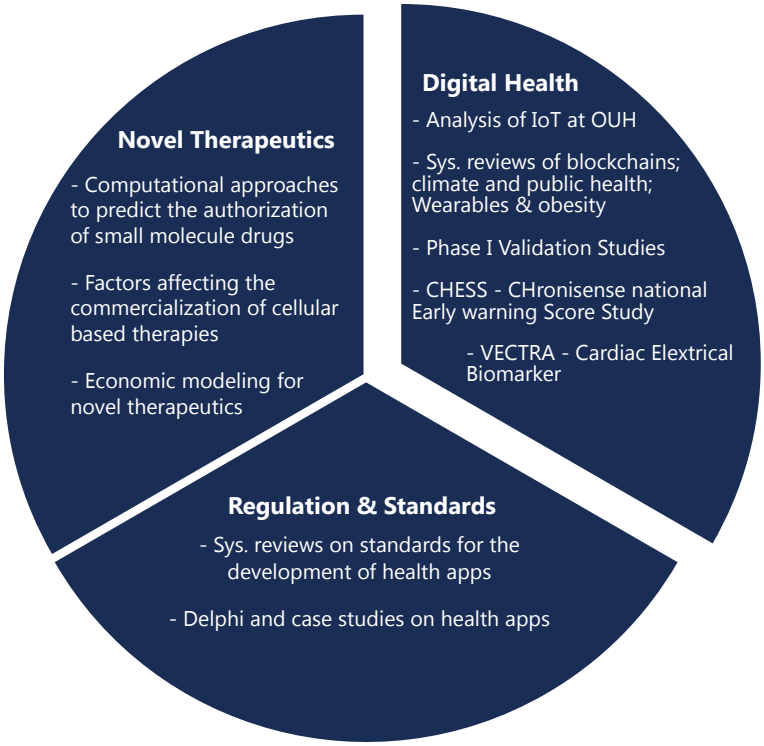
Fellowship: Launched Post-Doc Program with three post docs at University of Oxford

Looking ahead to 2018, Alliance seeks to maintain and build upon this theme of continuity. Its successful matched funding program will enable multiple new research programs, will publish the first international guidelines pertaining to digital health development and implementation, and will deliver deeper collaborative programs in the coming year and beyond.

DR. DAVID BRINDLEY, DIRECTOR OF ALLIANCE

See a list of publications from the Healthcare Translation Research Group on page 23!

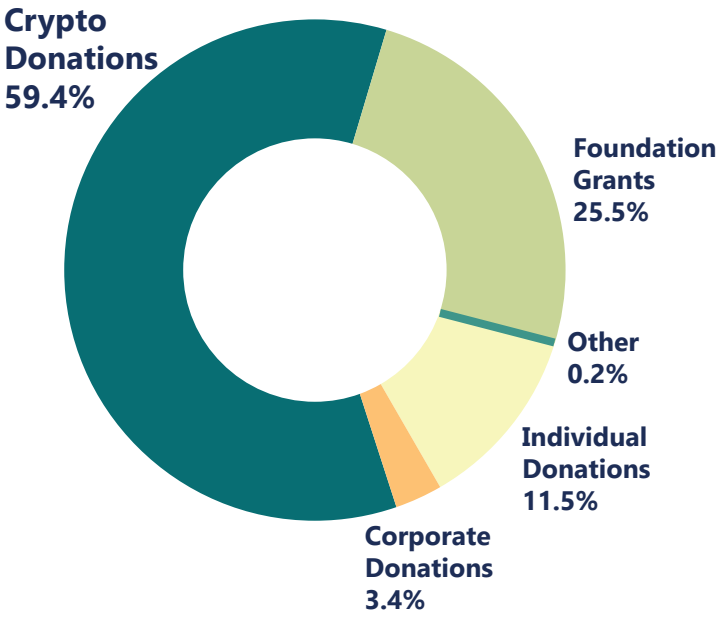
THE HEALTHCARE TRANSLATION GROUP: RESEARCH THEMES

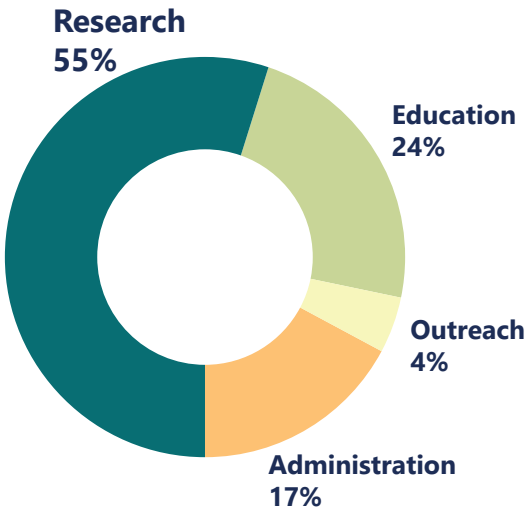


FINANCES

COMMITTED TO THE HIGHEST STANDARDS OF TRANSPARENCY AND ACCOUNTABILITY

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.





In previous years, our primary source of funding was due to large foundational grants; Foundations such as SENS Foundation EU, Forever Healthy Foundation, Foster Foundation, McPike Zima Foundation, and the Antonov Foundation gave SRF just over $2 million in 2017, significantly more than in past years.

In addition to the foundation grants, we received well over 50% of our income from donors invested in various crypto currencies. With the influx of crypto currency donors joining the support of our Foundational donors and the immense generosity of our many individual supporters world-wide, SRF is able to continue advancing rejuvenation biotechnologies and increase the breadth and scope of our Research and Education programs in the coming year.

2017 Revenue		
Individual Donations	$ 908,836	12%
Corporate Donations	$ 268,241	3%
Crypto Donations	$ 4,672,532	59%
Foundation Grants	$ 2,006,335	25%
Other	$ 15,586	0%
Total Revenue	**$ 7,871,530**	

2017 Expenses		
Research	$ 2,146,412	55%
Education	$ 920,533	24%
Outreach	$ 172,38	24%
Administration	$ 676,534	17%
Total Expenses	**$ 3,915,862**	

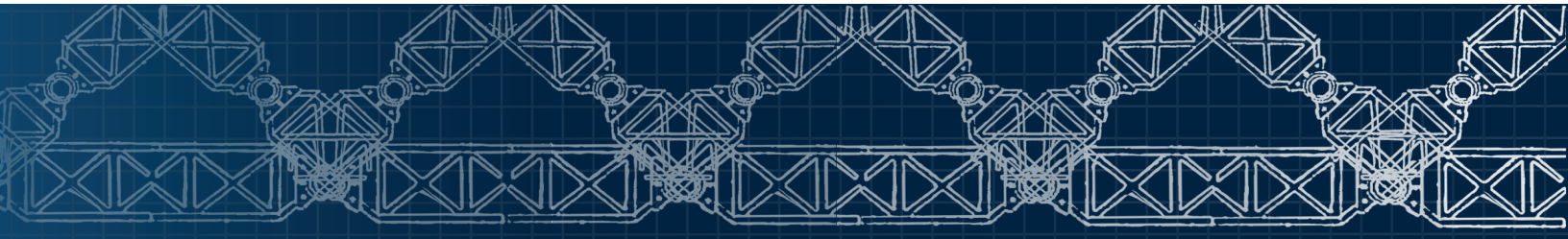
FUNDRAISING FOCUS

SENS Research Foundation experienced a number of significant donations during 2017 which resulted in a total of $7,871,530 in revenue.

- Cryptocurrency expert and co-founder of Ethereum and co-founder of Bitcoin Magazine Vitalik Buterin donated over $2.41 Million in Ethereum.
- In December 2017, the Pineapple Fund announced its intention to donate $86 million to charity. SENS Research Foundation submitted an appeal and within hours received word it would receive $1 million in Bitcoin.
- The Forever Healthy Foundation and founder Michael Greve continued its five year commitment to funding critical SENS Research Foundation research and education programs.
- SENS Research Foundation raised $5,020,000 during its ten week, year-end fundraising campaign, including over a million dollars in anonymous donations. Over 1400 donations were received during the campaign from SRF's generous donors.
- SRF received a generous bequest of over $135,000 from the estate of George Abramson. George left his estate to leading research organizations across the US that are working to cure the diseases of aging.
- Reason, Josh Triplett, and Christoph Cornuejols came together to provide a $3000/month matching grant for our year end subscriber drive.
- Enthusiastic SRF Fans posted 23 videos about why they support SRF in the Project4Awesome's annual funding competition. People from all over the world voted and SRF became one of 20 organizations to receive funding.

> "I've been a fan of Aubrey's work since I first read Ending Aging when I was a teenager, and I am happy to have been blessed with the opportunity to personally support SENS's efforts. Their focus on creating solutions to the diseases of aging, one of the greatest problems facing humanity, is very much in line with my goal to positively impact the lives of millions of people around the world."
>
> -Vitalik Buterin, Co-founder of Ethereum and Bitcoin Magazine

> "When I was a little kid, I was going on a trip with my grandmother. I had hoped that before she passes away, it would be possible to take a pill to live longer. Regenerative medicine for ageing will be transformative to medicine and humanity, and I'm excited to be supporting SENS Research Foundation!"
>
> - Founder of Pineapple Fund



THANK OUR SUP

A.J. Tomczynski, Aaron Brown, Aaron Davidson, Aaron Morgan, Aaron Vollrath, Adalberto Foresti, Adam Baker, Adam Cham, Adam Herrman, Adam Hruby, Adam Osborn, Adam Perrotta, Adam Starkey, Adam Summerfield, Adrian Scott, Adrian Wolf, Agatha Piskorski, Aidan Sices, Ake Brannstrom, Alain Nacouzi, Alan Forrester, Alan Mims, Alben Weeks, Alejandro Kondrasky, Aleksandar Djuricic, Aleksey Yeschenko, Alessandro Ermon, Alex Carro Queijeiro, Alex Edelman, Alex Jurkat, Alex Le, Alex Neill, Alex Samuelsson, Alex Schiltmans, Alex Starr, Alex Tarnava, Alexa High, Alexandar Mechev, Alexander Aas, Alexander Green, Alexander Hubbard, Alexander Pilmeister, Alexander Sommers, Alexander Turner, Alexandra Watt, Alexandrian Negrila, Alfonso Padovano Sorrentino, Alireza Alidousti, Alistair Turnbull, Allan Hill, Allan Kirchhoff, Allen Hoskins, Allison Koberstein, Allstate the Giving Campaign, Alvaro Gomez, Amanda Gately, Amazon Smile, America Online Giving Foundation, Amund Hov, Anar Ismailov, Anat Paskin-Cherniavsky, Andre Heinonen, Andrea Giuriolo, Andreas Hoelzl, Andreas Svensson, Andreea Haseganu, Andrej Tusicisny, Andrew Carter, Andrew Davis, Andrew Hall, Andrew Hamler, Andrew Larke, Andrew Loshe, Andrew Monda, Andrew Pavelchek, Andrew Reeves, Andrew Schindler, Andrzej Ukasik, Angelo Russoniello, Angus Gillott, Anita Ellis, Anji Greene, Ann Abbey, Anne and Ian Nowland Charitable Fund, Annie Jalota, Anthony Carew, Anthony Davies, Anthony Francis, Anthony Southworth, Antoine Lindsey, Anton Pols, Antonio Estrada, Antony Mellor, Antti Peltonen, Aram Sargsyan, Aran Morgan, Ariah Mackie, Arieh Chichireen, Ariel Feinerman, Arkadi Prokopov, Arne Frank, Artur Saraiva, Artur Tomczyski, Arya Pourtabatabaie, Aseem Sachdeva, Ash Weeks, Austin Landry, B. 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Jay Forbes, Jacob Arambula-Wright, Jacob Mabey, Jacob Perkins, Jaime Chavez-Riva, Jake Rubin, Jakob Branger, Jakob Elmgren, Jamal Abdisalam, James Anderson, James Briscoe, James Carr, James Ellis, James Erik Elliott, James Joyce, James McGettigan, James Mellon, Jan Grmeyer, Jane Rieder, Janet Melk, Janice LeCates, Janis Elsts, Jared Bender, Jaring Huijnen, Jason Defretas, Jason Moore, Jason Morton-McKay, Jean Reotutar, Jeanette Acton, Jean-Marc Gruninger, Jeff Fuja, Jeffrey Foust, Jeffrey Hochderffer, Jeffrey Hook, Jeffrey Long, Jeffrey Zaroyko, Jelle Geerts, Jeremy Brown, Jeremy Elser, Jeremy Wilkins, Jeroen Dombeek, Jerry Searcy, Jesse Halbig, Jessica Jamner, Jewish Communal Fund, Jim Fehrle, Joan Jorquera Grau, Joe Beaman, Joe Kalfus, Joel Kehle, Joey Katz, Johan Edstrom, Johan Katalanc, Johannes Damarowsky, John Burke, John de Boer, John Duignan, John Loffeld, John Mariani, John Navilliat, John Tennant, John Young III, Johnny Courmontagne, Jon langford, Jon Maier, Jon Schermann, Jonathan Arnon, Jonathan Cain, Jonathan Cogan, Jonathan Godley, Jonathan Mannella, Jonathan Wood, Jonathon Sellers,

Jone Haugland, Jonno Meindert, Jordan Duncan, Jose Luis Ricon, Jose Maria Moruno Navarro, Josep Bru, Joseph Dandridge, Joseph Dushkewich, Joseph McManus, Joseph Meisenhelder, Joseph Miners, Joseph Oliva, Joseph Purcell, Josh Burgess, Josh Triplett, Joshua Ball, Joshua Bernheim, Kevin Secretan, Kevin Williams, Kim Steadman, Kimberley Williams, Kristopher McHale, Kristy Thornton, Kriszti Ipacs, Kriszti Pinter, Kuo-Fang Chen, Kyle Bledsoe, Kyle Litwin, Kyle Swigert, Lachlan Glaskin, Lajos Adam, Lance Jackson, Lars Claussen, Lasse Simonen, Laszlo Czako, Laszlo Fernekesz, Laura Murison, Laurel Holmgren, Laurent Hamers, Lauryn Denton, Lee Thomas, Leeland Deney, Lei Ding, Leigh Jevon, Lemuel Eleda, Len Nguyen, Leonid Velikovich, Leony Merks, Leroy Arellano, Lev Reyzin, Lewis Carney, Lewis Grozinger, Li Li, Liam Shore, Libor Behounek, Lincoln Mayer, LinkedIn Matching Gifts, Linus Petersson, Lisa McCormick, Lorinc Vegh, Louis Burke, Louis Yu, Louise Stout, Lucas Pearson, Ludvig Larsson, Luis Rosias, Lukas Arvidsson, Lukas Henschke, Luke Webster, M G Dillner, Magnus Esbjorner, Magnus Ulstein, Malene Sondergaard Nielsen, Mallory Sherman, Manuel Carmona de la Cuesta, Marat Karpeka, Marc Palmer, Marcel Gill, Marcelo Oliveira, Marco Servetto, Margo Hennig, Mario Guzman, Marion Holtz, Marius Alksnys, Mark Borbely, Mark Bruce, Mark Horn, Mark Jaskula, Mark Kerr , Mark Mastro, Mark Milburn, Mark Ruben, Mark Sackler, Mark Sanger, Mark Suddens, Mark Whelan, Mark Williams, Mark Zykin, Markus Rigler, Markus Wolf, Marlon Kruizinga, Marsha Kai, Marten Hein, Martin Precek, Martin Stolz, Martin Therrien, Martin Towner, Martin Volejnik, Martyn Brewer, Mary Ann Liebert, Masha Sergeeva, Mathias Soeholm, Mathieu Cloutier, Mathieu Roy, Mats Andersson, Matt Kruger, Matt Lewis, Matthew Calero, Matthew Dancer, Matthew Draghi, Matthew Graves, Matthew Huson, Matthew O'Connor, Matthew Opdyke, Matthew Ostroskie, Matthew Preston, Matthew Smith, Matthias Andre, Matthias Schwarz, Mattias Wallander, Maurice Koutoukalis, Maurice Mullenders, Maurits Luyben, Max Comess, Max Kanwal, Max Kopych, McPike Zima Foundation, Mhael Falcon, Micha Szymacha, Michael Beasley, Michael Calhoun, Michael Campbell, Michael Debus, Michael Everhart, Michael Falk, Michael Gardner, Michael Haerpfer, Michael Hart, Michael Huemer, Michael John Sato, Michael Lombardi, Michael Long, Michael Marquardt, Michael Marye, Michael McCutchan, Michael Pateras, Michael Puleo, Michael Rae, Michael Schulz, Michael Sherman, Michael Smiley, Michael Thompson, Michael Whalen, Michael Willis, Michela Biancini, Michele Giannotti, Michele Primmer, Mihkel Lukats, Mikael Cluseau, Mikaela Harris, Mike Barraclough, Mike Bosse, MIke Bryan, Mike Cottrill, Mike Dussault, Miles Clark, Mirza Ibrahimovic, Mitja Lustrek, Mohamed Chmeis, Moncomble Florian, Myles Berdock, Nathan McKaskle, Nathan Meryash, Nathan Wailes, Nathaniel Hwang, National Philanthropic Trust, Neal Conner, Neal Strobl, Ned Ilincic, Neil Guild, Network for Good, Nextera Energy, Nicholas Drotthammar, Nicholas Kerrison, Nicholas Martin, Nicholas W. 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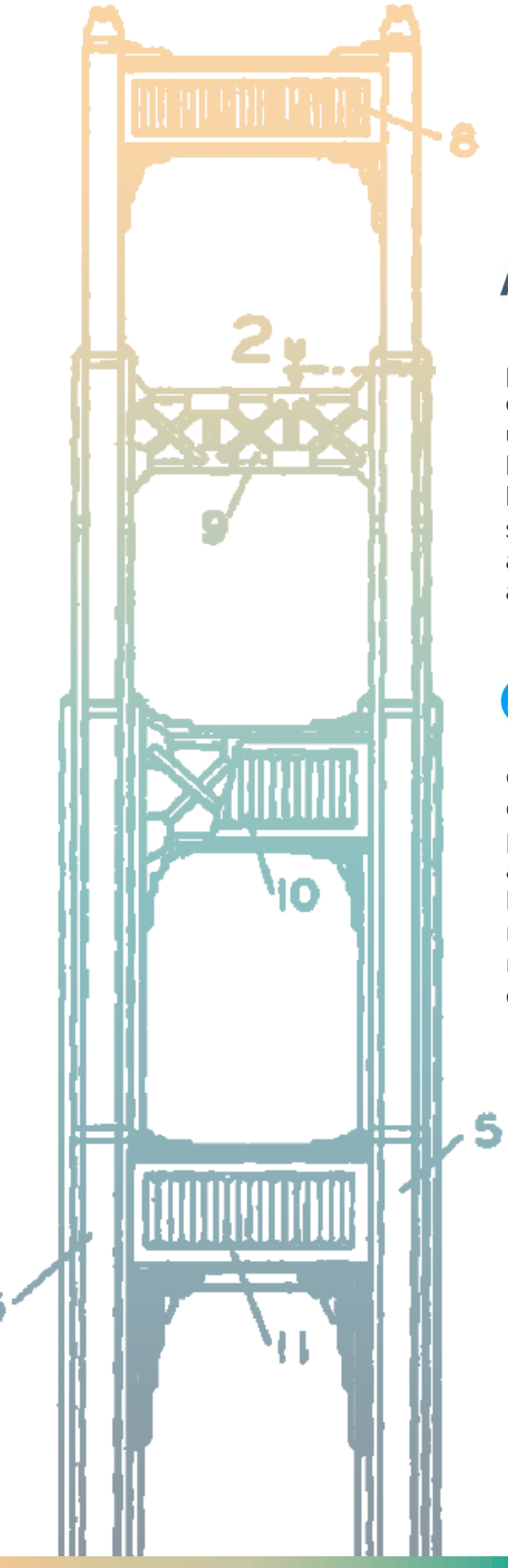
YOU TO PORTERS

PROGRAMMATIC INVESTMENTS



ICHOR THERAPEUTICS™

ANTOXERENE

Antoxerene, a portfolio company of Ichor Therapeutics, is a small molecule drug discovery company that focuses on molecular pathways of aging. Using patent-pending RP-tag technology, the company manufactures full-size bioactive protein targets on scale for use in small molecule high throughput screening applications. To our knowledge, Antoxerene is the first and only company with small molecule hits on the p53/FOXO4 pathway, which has been implicated in cellular senescence. Antoxerene is developing these hits for eventual clinical use and is also pursuing strategic partnerships with drug discovery teams across the globe to further deploy its platform technology.

LYSOCLEAR

Lysoclear, a portfolio company of Ichor Therapeutics, is an ophthalmology company developing an enzyme therapy for age-related macular degeneration and Stargardt's disease. In 2017, the company completed pivotal proof-of-concept studies with its first generation enzyme lead and conducted extensive mechanistic work to clarify the role of retinal lipofuscin in the onset and progression of macular degenerations. These results have been submitted for peer-reviewed publication. Lysoclear is now optimizing its enzyme into a drug candidate in preparation for IND enabling studies.

KELSEY MOODY, CEO, ICHOR

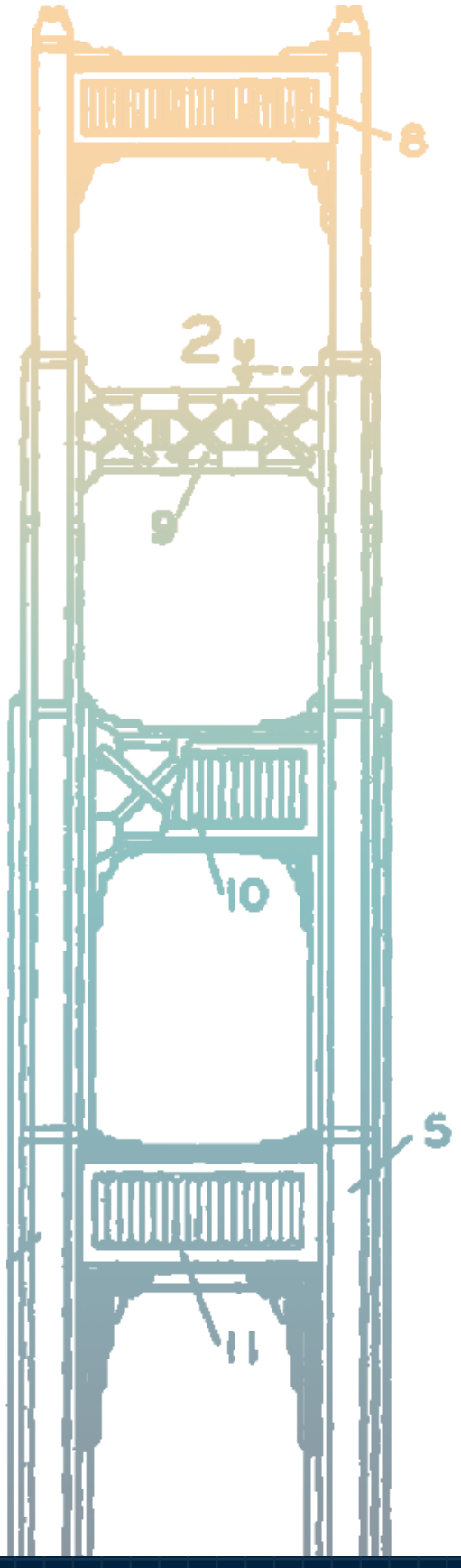
Oisín is developing a highly precise, patent-pending, DNA-targeted intervention to clear senescent cells. These cells secrete molecules that cause inflammation in an effort to attract immune cells that would usually clear them. But for reasons that are not fully known, as we age, persistently senescent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

There are two major challenges to clearing senescent cells using this approach: Designing and creating the DNA construct that recognizes that a cell has become senescent and then destroys it, and safely and efficiently delivering this construct into cells throughout the body. Both goals have been achieved in pioneering proof of concept experiments in 2016.

Oisin has demonstrated the ability to transduce cells both in vitro (cell culture) and in vivo (in aged mice), then showed that p16 positive senescent cells can be killed on demand in both *in vitro* and *in vivo* environments. Now they are embarked on experiments that will show improvements in both healthspan and lifespan in model organisms from mice to primates.

Thousands of people die each year for lack of an organ transplant, while tens of thousands of organs are discarded for reasons that include the absence of a suitable match or distance from the recipient. The problem is that organs are viable for mere hours once harvested for transplant and long-term organ banking is only available for very small samples, like embryos. We need similarly stable banking for larger tissue structures and organs. This could more than double the number of transplants performed each year and would eliminate five of the current organ waiting lists within a few years. Arigos is developing a technology to do just that.

Arigos has made great strides towards the banking of human organs, demonstrating functional and structural recovery of similarly-sized tissues from below -120°C. Their ability to cryopreserve large, complex tissue structures is a breakthrough in medical research; and their team is passionate about bringing this technology from the lab benches to the patient's bedside as quickly as possible.



EDUCATION

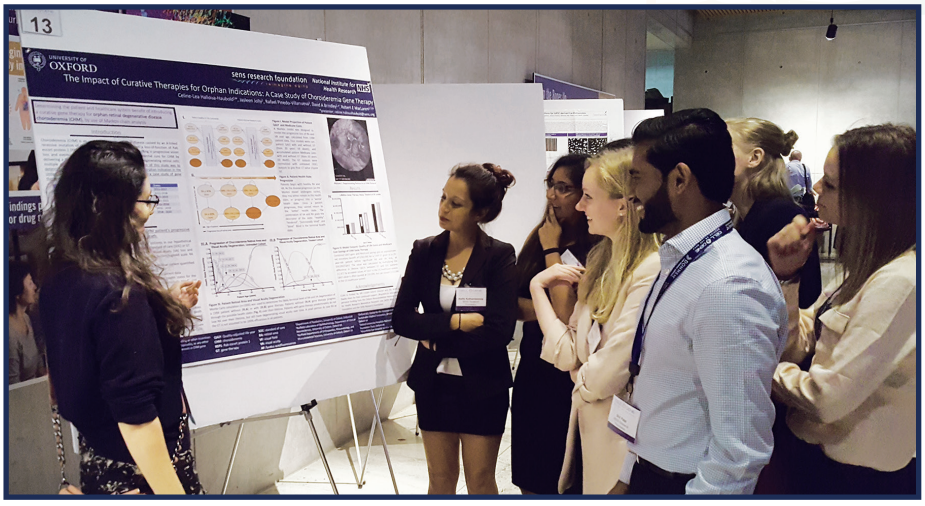
Education continues to be an important component of SENS Research Foundation's mission. As the rejuvenation biotechnology industry continues to grow, it will become more and more important to produce a workforce of scientists, doctors, and policy makers trained in the therapeutic possibilities of rejuvenation biotechnology. SRF Education sponsors several programs aimed at fulfilling this need.

SUMMER SCHOLARS PROGRAM

Summer Scholars Sumedh Sontakke, Shil Patel, Heather Tolcher, Anja Schempf, Aashka Patel, Alefia Kothambawala, and Srinidhi Venkatesan Kalavi at the Salk Institute for Biological Sciences.

The SRF Summer Scholars Program continues to grow in reputation and scope. In 2017, 550 students from over 200 different universities and colleges applied for the twelve positions in the program. The 2017 SRF Summer Scholars were hosted by the Brigham and Women's Hospital/ Harvard Medical School, the Buck Institute for Research on Aging, the Sanford Consortium for Regenerative Medicine, the Scripps Research Institute, the University of Oxford, and the SRF Research Center.

The 2017 Summer Scholars attended the 12th Annual Cell and Gene Meeting on the Mesa Scientific Symposium at the Salk Institute for Biological Sciences. In addition to learning about exciting new regenerative medicine discoveries, they presented the results of their summer projects to each other and their mentors at a symposium at the Sanford Consortium hosted by Dr. Evan Snyder.



Former Summer Scholar Celine-Lea Halioua-Haubold presenting her poster to 2017 Summer Scholars Alefia Kothambawala, Aashka Patel, Heather Tolcher, Anja Schempf, Shil Patel, and Amelia Anderson at the Cell & Gene Meeting on the Mesa Scientific Symposium.

SRF-OXFORD-CTSCC RESEARCH PROGRAM

The new partnership with the University of Oxford and the Centre for the Advancement of Sustainable Medical Innovation (CASMI) Translational Stem Cell Consortium (CTSCC) has offered students with limited access to research facilities and laboratory experience an opportunity to participate remotely in non-bench research projects.

Over the course of 2017, twenty student volunteers worked as a team to contribute to SRF-supported research at the University of Oxford.

The goal of the 2017 SRF-Oxford-CTSCC research project is to better predict the eventual success of early drug candidates with greater accuracy to help reduce the exceptionally high cost of new drug development.

Student volunteers helped collect literature, patent, and other drug therapeutic information as well as provided critical analysis of the methodologies identified. In particular, the collective effort of the volunteers helped to generate code, which is now being used to collect drug data more efficiently.

This endeavor was spearheaded by Project Lead and former Summer Scholar James Smith (pictured above), who plans to publish the results of the project in 2018.

Along with Project Associate and former Summer Scholar Zeeshaan Arshad (pictured below), several volunteers will receive acknowledgements or authorship for their contribution to the research.

RESEARCH

Engineering New Mitochondrial Genes to Restore Mitochondrial Function (MitoSENS)
SENS Research Foundation Research Center
Principal Investigator: Amutha Boominathan
Research Team: Matthew O'Connor, Bhavna Dixit, Caitlin Lewis, Jasmine Zhao, Michaela Copp

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 indispensible components of the electron transport chain (ETC), which mitochondria use to generate most cellular energy. When the ETC is disrupted, cells are denied their most efficient energy source, and mitochondria become dysfunctional, which is probably why the accumulation of cells overtaken by such mutant mitochondria are closely linked to Parkinson's disease, age-related muscle dysfunction, and other debilities of aging.

The MitoSENS team is working on a potential rejuvenation biotechnology to sustain and recover ETC function: allotopic expression of functional mitochondrial genes. Allotopic expression involves placing "backup copies" of all of the protein-coding genes of the mitochondria in the "safe harbor" of the nucleus, which can then deliver the proteins mitochondria need to build their ETC and continue producing energy normally, even when the original mitochondrial copies have been mutated.


Photo: SRF-RC Lab

In 2016, the MitoSENS team successfully demonstrated the efficient functional rescue of the ATP8 gene in cells from a human patient with an ATP8 mutation via allotopic expression. In 2017, they successfully translated this rescue to cells from mice with mitochondrial mutations. Stable expression of allotopic ATP8 in mouse cells with such mutations allows them to grow more rapidly, both under normal conditions and in a special medium that forces them to rely exclusively on the ETC for energy.

The team is working to establish a "landing pad" in mouse cells to enable reliable and safe gene therapy for animal studies (see the Maximally-Modifiable Mouse Project on page 22). They expect to soon begin preliminary *in vivo* testing of allotopic ATP8 in transgenic mice. Meanwhile, they are also looking to expand the strategy to other mtDNA genes and further improve allotopic expression of the ATP6 gene.

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

As discussed in the project summary for "Glucosepane Crosslinks and Routes to Cleavage", our arteries slowly stiffen with age, in substantial part because of adventitious crosslinking of the structural proteins collagen and elastin. Some of these crosslinks are the result of purely stochastic chemical reactions (like AGE crosslinking), but others are the result of physiological 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.

Amidst all of this, it's not obvious that the mere quantity of a given kind of crosslink makes it the most important one to go after, since crosslinks may have a disproportionate effect on tissue elasticity depending on where in the protein strand they bind and how tightly, and they likely also vary in how much they interfere with the body's ability to turn the tissue over.

These are the challenges we put to the Babraham team, which for the first time - with SRF funding - is studying the question systematically in the tissues of aging mice. 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 are now ready for use in elucidating these questions.

Using these new tools, the team has evaluated multiple tissues for crosslink presence, in a strain of mice that is minimally at risk for diabetes to avoid confounding "pure" aging effects with those of extreme levels of blood sugar and fats. They have largely completed the chemical analysis of tendon and skin and have started the analysis of aorta, creating a list of "prime suspect" crosslinks, which will need to be analyzed statistically for significance.

Importantly, some of the crosslinks that have been reported by others to accumulate in aging tissues were not detected. The Babraham team is also complementing chemical analysis of the tissues with careful tests of their mechanical properties. By conducting the tests on the same tissue samples, rather than separately as is often done, conclusions can be draw more directly linking changes in crosslinks and the physical properties of the tissues. Thanks to Dr. Clark's painstaking work, we'll soon have a much better idea of what our challenges are in preventing and reversing age-related tissue stiffening and what our next therapeutic targets should be.

Glucosepane Crosslinks and Routes to Cleavage
Yale University
Principal Investigator: David Spiegel and Jason Crawford
Research Team: Matthew Streeter, Venkata Reddy, Robert Hale, Egor Chirkin, Nam Kim, Tyler Goddard

Our arteries slowly stiffen with age, leading to rising systolic blood pressure, increased risk of stroke, and kidney damage. 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. A 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. A rejuvenation biotechnology capable of cleaving glucosepane crosslinks would allow bound arterial proteins to move freely again, maintaining and restoring the elasticity of the vessels and helping prevent the risks of stiffening vessels.

The Yale team is developing new reagents and approaches to accelerate glucosepane research. They now are able to synthesize all three conformational variants (diastereomers) of glucosepane that may occur in vivo. They are also working to generate antibodies that can then be used to label glucosepane crosslinks in tissue samples and *in vivo*.

COMING IN 2018

The Yale team has identified some potential glucosepane-breakers, about which we hope to be able to make further announcements this year pending publication in a peer-reviewed journal.

Unleashing Immune Clearance of Senescent Cells
Buck Institute for Research on Aging
Principal Investigator: Judith Campisi
Research Team: Abhijit Kale

When cells suffer stresses that put them at risk of becoming cancerous, a program is activated that forces them into senescence, a state of growth arrest that prevents the cell from endangering the rest of the body. But senescent cells also secrete inflammatory cytokines, proteinases, growth factors, and other factors collectively termed the *senescence-associated secretory phenotype* (SASP).

One of the reasons why the SASP exists in the first place is to exude chemical signals that attract Natural Killer (NK) immune cells, which then clear senescent cells from the tissue. Despite this, senescent cells accumulate over the course of the lifespan, leading to age-related disease and frailty due to the ongoing secretion of SASP long after it has stopped serving this useful self-limiting role. A critical question is therefore that of how some senescent cells are able to escape immune surveillance and what might be done to overcome their defenses.

Dr. Judith Campisi, a renowned pioneer in senescence research, is answering this question and developing strategies to enhance immune clearance of senescent cells. Campisi's group has already discovered that one of the key NK cell binding markers on the surface of senescent cells begins to disappear within weeks of the cell becoming senescent. Without this marker ligand, NK cell binding cannot occur, and the NK cells' killing ability cannot be unleashed. Worse yet, when these ligands are shed from the senescent cell surface, they act as a kind of "decoy:" NK cells bind to the free-floating ligands instead of the actual senescent cells, keeping them distracted with a dummy target while senescent cells persist in wreaking their havoc. To validate these results, the Campisi lab is now working to extend them to studies of NK cells from young and old blood donors. These early results suggest some potential strategies for restoring NK cell immunosurveillance of senescent cells.

COMING IN 2018

SRF is preparing to expand this project with a complementary intramural project at the SRF Research Center with research focused on overcoming the effects of shed immune markers to restore NK cells' ability to target senescent cells for destruction.

Photo: Campisi Lab, Buck Institute for Research on Aging

Meanwhile, the Campisi team has extended their work to macrophages (another kind of immune cell), with preliminary results indicating that one or more components of the SASP interfere with the macrophages' ability to break down NAD+, an important energy carrier molecule. The team is currently exploring the mechanism(s) by which this interference occurs.

Remediation of Aberrant Intracellular Tau
Buck Institute for Research on Aging
Project Director: Dr. Julie Andersen
Research Team: Georgia Woods, Anand Rane, Natalia Schowe

Aggregates composed of aberrant tau protein accumulate with age, both inside and outside of neurons. These aggregates are an important driver of neurodegenerative diseases of aging, such as Parkinson's and Alzheimer's diseases, as well as of age-related neurodegeneration. Several immunotherapies that aim to capture the extracellular tau aggregates and prevent cell-to-cell transmission are currently in clinical trials, but even if effective, these therapies would offer an incomplete solution as they would not degrade tau aggregates that accumulate inside the cytosol of individual cells.

One possible basis for this intracellular accumulation may be as a consequence of age-related lysosomal dysfunction that is driven by the accumulation of other kinds of intracellular aggregates. As such, this deleterious accumulation might be reversed if lysosomal function could be restored. This line of investigation will inform strategy: do we need a custom solution just for intracellular tau aggregates, or will clearing other age-related lysosomal junk be sufficient to restore an existing capacity to eliminate these aggregates? The Andersen lab is testing this possibility using neurons that express mutant versus wild-type human tau.

To date, they have found that when such neurons are exposed to increasing levels of the cellular stressors that drive tau aggregation (okadaic acid or beta-amyloid), a tipping point is reached when previously-soluble tau begins to clump inside the cell; if the cellular stress is removed, otherwise-healthy cells are still able to clear the aggregated tau. The Andersen lab is investigating whether drugs known to inhibit lysosomal function prevent otherwise-healthy cells from clearing accumulated tau aggregates under these conditions and if this ability returns after lysosomal function is restored. They propose to expand this study by screening for small molecules that enhance the formation of autophagy-related vacuoles known as autophagosomes (APGs) as a novel therapeutic approach for tau removal, confirming these experiments with neurons derived from reprogrammed cells from patients with Alzheimer's disease.

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: Navneet Ramesh, Amelia Anderson, Henry Vilas, Sirish Narayanan, Anne Corwin

Many diseases of aging are driven in part by the accumulation of intracellular aggregates derived from the metabolic waste products particular to specific cell types.

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 but ultimately fall prey to that same toxicity themselves, converting to a disabled, immobilized form called foam cells. Alzheimer's and Parkinson's are also, in part, lysosomal diseases.

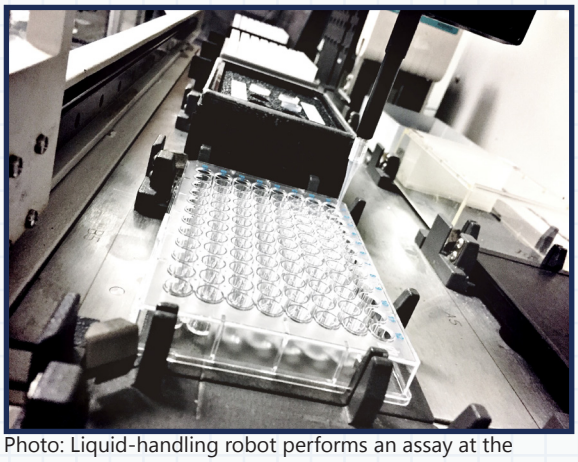
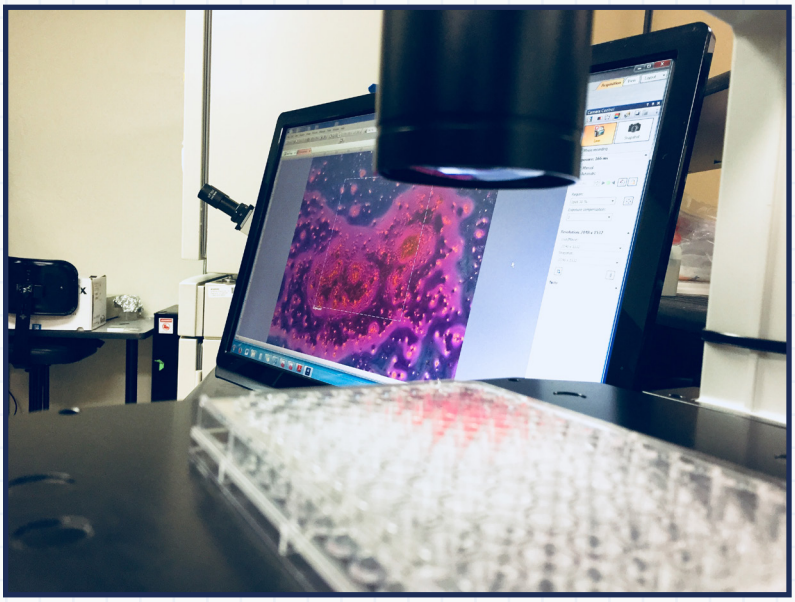


Photo: Liquid-handling robot performs an assay at the SRF-RC Lab

Dr. O'Connor's team has identified a family of small molecules that may be able to selectively remove toxic forms of cholesterol from human blood, which would help combat the development of atherosclerosis. They have been testing its effects and those of closely-related compounds in human blood samples and using computer modeling to predict the likely behavior of different admixtures and chemical cousins of these compounds, seeking potential modifications and combinations that would maximize selectivity for toxic cholesterol byproducts while leaving native cholesterol alone.

The Maximally-Modifiable Mouse
Applied StemCell, Inc.
Project Director: Dr. Ruby Yanru Chen-Tsai
Research Team: Dr. Qi Zheng, Dr. James Luo

Gene therapies are critically important to the future of rejuvenation biotechnologies: they both enable early proofs-of-concept in mice and will be either essential or desirable for the delivery of many rejuvenation biotechnologies in humans. However, current gene therapy has its problems, including that the vectors for delivery of such transgenes integrate the gene into the recipient genome in random locations, posing the risk that the therapeutic gene will be silenced or will disrupt the neighboring gene, causing cancer or other mutations. The CRISPR/Cas9 system has raised a lot of justified excitement because of its precision, but while it can make relatively small edits in existing genes, it is very limited in its ability to deliver entirely new ones — useful for correcting mutations, for instance, but not for introducing entirely new capabilities.



The Maximally-Modifiable Mouse project aims to overcome these problems by allowing the use of the phage integrase from the mycobacteriophage Bxb1 — a powerful gene insertion system that catalyzes precisely-targeted, one-way insertion of large genes into the host genome. Unfortunately, mammals lack the genetic "docking sites" that this integrase targets.

Applied StemCell (ASC) has created a line of Maximally-Modifiable Mice with 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. This will help us determine how to make the same modification in humans, which would then allow us to safely and reliably deliver rejuvenation biotechnologies for human use.

Currently, ASC is beginning initial tests to confirm that the mice's engineered "docking sites" are functional by inserting the convenient gene for Green Fluorescent Protein (GFP). Once the sites are validated, they can be used for expression of desirable therapeutic genes and the creation of more realistic models of human diseases of aging. This work could enable us to safely and reliably deliver allotopically-expressed mitochondrial genes, new lysosomal enzymes, and other rejuvenation biotechnologies to tissues all across the human body.

2017 LIST OF PUBLICATIONS

Pettitt D, Roberts M, Smith J, Brindley DA. 2017. Legal Framework on the Scientific Use of Animals in Research. Basic Science Methods for Clinical Researchers. 2017 Elsevier Academic Press (Book Chapter).

Fuerstenau-Sharp M, Pettitt DA, Bure K, Smith J, Ware J, Brindley D. 2017. Scalable purification of viral vectors for gene therapy: An appraisal of downstream processing approaches. BioProcess International.

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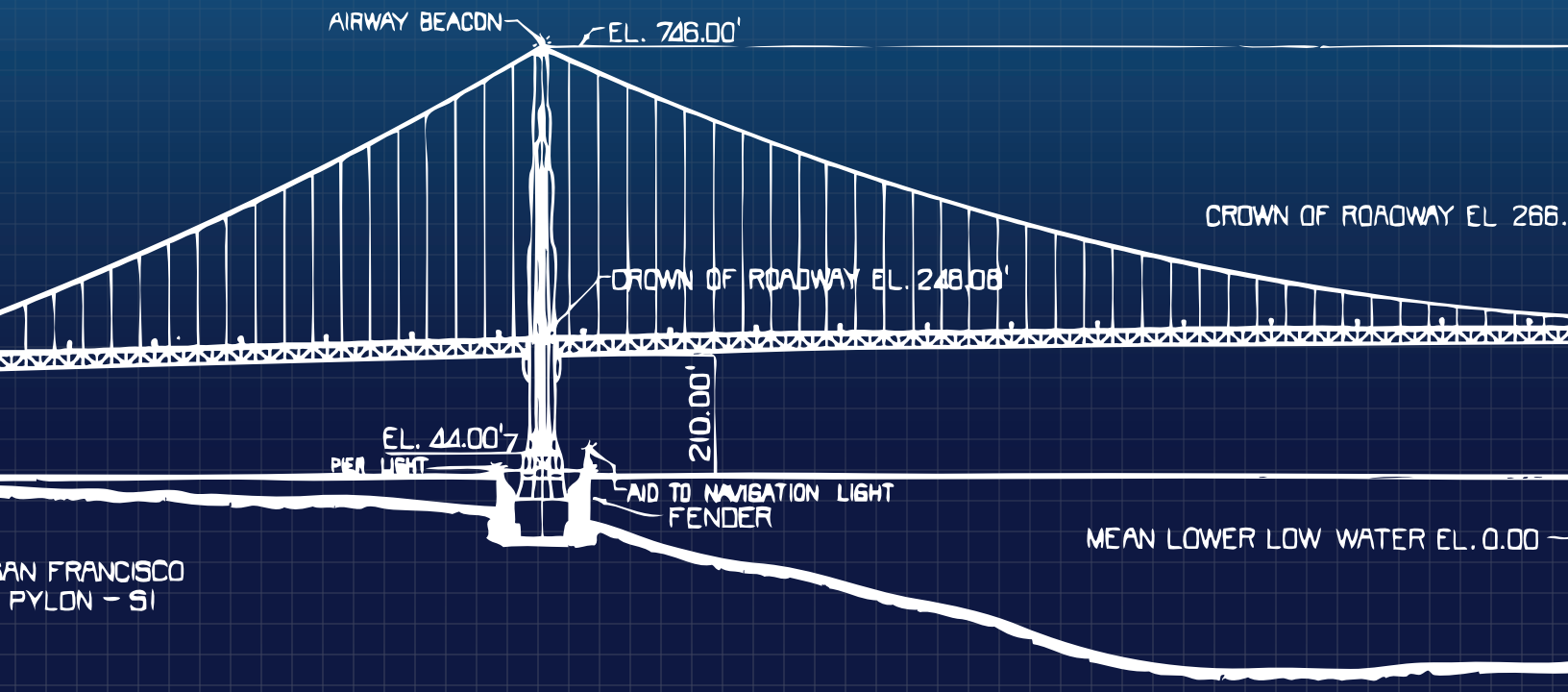

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