Summer Scholar placements:

Students who are selected for interviews, based on their application, will be contacted to rank their interest in the host lab placements. At this time, they will be able to express locational restrictions.

PI	Affiliation	City	State	Associated SENS strand
Amutha Boominathan	SENS Research Foundation	Mountain View	California	MitoSENS
Hadi Rebbaa	SENS Research Foundation	Mountain View	California	RepleniSENS
Amit Sharma	SENS Research Foundation	Mountain View	California	ApoptoSENS and RepleniSENS
Polina Lishko	Washington University	St. Louis	Missouri	bioactive lipids in aging
Khalid Shah	Harvard University	Boston	Massachusetts	OncoSENS
Chris Wiley	Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University	Boston	Massachusetts	ApotoSENS
Tong Zheng	Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University	Boston	Massachusetts	ApotoSENS
Jean Hebert	Albert Einstein, College of Medicine	Bronx	New York	RepleniSENS
Evan Snyder	Sanford Burnham Prebys (SBP) Medical Discovery Institute	La Jolla	California	RepleniSENS
Gino Cortopassi	University of California, Davis	Davis	California	MitoSENS
Elastrin	Elastrin	Greenville	South Carolina	GlycoSENS

Amutha Boominathan (SENS Research Foundation, Mountain View, CA): Mitochondria are power plants of the cell and are also the only cellular organelle that possess their own DNA in mammals. In humans, mitochondrial DNA (mtDNA) codes for 13 important proteins, all of which assemble into the oxidative phosphorylation relay. Mutations in mtDNA occur as a consequence of constant exposure to reactive oxygen species produced by the mitochondrial energy generation process as well as mistakes in mtDNA replication. These mutations accumulate over time due to inefficient repair mechanisms and compromise respiratory chain function. Inherited and acquired mutations in mtDNA result in impaired energy generation and are the cause for several pathologies such as Leber's hereditary optic neuropathy (LHON), Myoclonic Epilepsy with Ragged Red Fibers (MERRF), Kearns-Sayre syndrome and Leigh syndrome. Age-associated mitochondrial dysfunction has been implicated in several neuromuscular diseases including sarcopenia, Alzheimer's, and Parkinson's disease.

The Boominathan lab at SENS Research Foundation is utilizing gene therapy approaches to develop translational avenues in treating inherited and acquired mutations in the mitochondrial

DNA.. Using the allotopic approach, we have identified specific targeting elements/ sequences that can improve the expression of these essential genes from the nuclear DNA and their transport to the correct location in mitochondria. The summer scholar/ Postbaccalaureate Fellow selected will use a computational approach to design and test a library of constructs in model patient cell lines with specific mutations in mtDNA. The ability of re-engineered genes to rescue function will be evaluated through various techniques, such as protein gels, qPCR, and activity assays, with the potential of extending the studies to animal models.

Amit Sharma (SENS Research Foundation, Mountain View, CA):

Goal 1: Natural killer cells are primary drivers of immune surveillance of senescent cells. This project involves isolation and characterization of age-dependent changes in the phenotypes of Natural Killer cells. This is to investigate if the age of subjects effects the ability of NK cells to eliminate senescent cells in vitro and in vivo.
Goal 2: We have identified several unique antigens expressed on the surface of senescent cells. The goal of this project is the targeted elimination of senescent cells by CAR-NK therapy. We are characterizing the surface an antigen on senescent cells and investigate if targeting this antigen can enhance NK cell-mediated clearance of senescent cells from patient-derived primary endothelial cells and foetal lung fibroblasts. The ultimate goal of the project is to demonstrate that the CAR-NK cells that are capable of eliminating senescent cells in ex vivo and mouse models.
Goal 3: develop a novel way to remove abnormally aggregated tau as a therapeutic intervention with potential relevance to mitigating normal age-dependent cognitive decline, as well as for tauopathies like Alzheimer's disease and related dementias.

Hadi Rebbaa (SENS Research Foundation, Mountain View, CA):

Research at the RepleniSENS program aims at developing new approaches to extend health span. Toward this goal, we are developing new agents (senolytics) that selectively eliminate senescent cells, optimized stem cells with improved potential for tissue regeneration, and biomarkers to assess the efficacy of senolytics and stem cells either alone or in combination.

Jean Herbert (Albert Einstein College of Medicine, New York, NY):

The neocortex is the part of our brain that performs our highest cognitive functions. In recent years, the mechanisms underlying how stem cells in the embryo generate the neocortex have become better understood. Armed with this knowledge, the Hébert Lab is developing approaches to replace and repair adult neocortical tissue after age-related degeneration. The Hébert lab offers its members excellent training opportunities in a multidisciplinary research area

Polina Lishko (Washington University in St. Louis, School of Medicine, St Louis, MO):

Our lab studies bioactive lipid signalling in the reproductive tissues and brain epithelia with the focus on how it impacts ion channels and electrogenic transporters in these tissues during aging. We have two research projects: first project focuses on the physiology of brain/eye epithelia and the changes they undergo during aging, and the second project focuses on steroid regulation of female reproductive tract and placenta. Here is a short description of the projects that are compatible with SENS research goals. Project 1. The

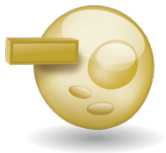
slow onset of cognitive decline and gradual deterioration of physiological functions with age goes hand in hand with changes in the levels of circulating steroids. Recent studies indicate that women bear a heavier burden of Alzheimer's disease, and there is a correlation between early onset of menopause (and hence an earlier decline in sex steroid levels) with increased susceptibility to Alzheimer's disease. Additionally, age-related macular degeneration (AMD) which is a leading cause of blindness, also disproportionally affects women. The decline in physiological functions encompasses the changes in the levels of sex steroids that exert potent effect on brain and eye epithelia, i.e., choroid plexus (CP) and retinal pigment epithelium (RPE). Both tissues, CP and RPE are essential for maintenance of the healthy brain and retina. Our goal is three-prong: a) to describe a comprehensive proteo-ionic landscape of CP/RPE and its regulation by ion channels and electrogenic transporters during a lifespan. We are specifically interested in the ion channels that are regulated by steroid hormones; b) to determine the changes in bioactive lipids/steroid landscape of CP/RPE with age; c) to search for non-steroid activators of ion channels in CP/RPE that are implicated in age-related dysfunction of these tissues to develop novel therapeutics tools. Understanding effect steroid hormones impose on the function of CP/RPE and reproductive tissues and revealing molecular bases behind their pathophysiology is important to develop appropriate therapeutical intervention and address the needs of millions of people worldwide.

Project 2. Preterm labor poses a significant threat to maternal well-being and the health of the baby. One of the factors that initiates preterm labor is excessive uterine contractions that cause the cervix to open prematurely. The uterine myometrium, made up predominately by the most powerful smooth muscle cells in the human body, can switch between quiescent and active states to house the developing fetus and push it out during labor. One of the major factors that maintains uterine quiescence during gestation is steroid hormone progesterone. Due to progesterone's pro-gestational effects, supplementations of progesterone or intramuscular injections of the synthetic progestins are currently the only treatments administered to pregnant patients at risk of preterm labor. However, there is a lack of understanding of the biological processes underlying preterm labor and the heterogeneity of the population studied. Therefore, greater understanding of the specific molecular mechanisms underlying uterine contractions is essential for prevention of preterm labor. Until now, the molecular mechanism of progesterone's rapid effects on uterine contractility were not understood. Recently, we have found that progesterone, as well as other selective progestins specifically and potently activates a membrane receptor which expression is upregulated in uterine myometrium and placenta. Our results provide strong insight into a non-genomic mechanism behind the rapid progesterone-driven control of uterine excitability and further support current evidence for this receptor as a promising novel therapeutic target for controlling uterine contractions.

This research is expected to unveil the mechanisms by which steroids regulate CP/RPE physiology as well as the function of myometrium and placenta and will help identify new molecular targets and molecular therapeutics that has the potential to lead to treatments for neurodegenerative diseases, age-related macular degeneration and preterm birth.

Christopher Wiley (Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA): Cellular senescence is a process by which a cell undergoes a permanent proliferative arrest - coupled to the secretion of a myriad of inflammatory cytokines, growth factors, proteases, and oxylipins collectively known as the senescence-associated secretory phenotype (SASP). Molecules that allow elimination of senescent cells, known as senolytics, prevent several age-related diseases. In our lab, the SENS Scholars will study the

metabolic signatures of senescent cells, potentially working to identify therapies that target these signatures. These will include genetic and pharmacological manipulation of lipid metabolism, and outcomes will include cellular senescence, the SASP, and cell survival. Overall, the scholar will contibute to the identification of new therapies for aging and age-related diseases.



Tong Zheng (Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA): Our lab studies how foods benefit the aging brain, especially in maintaining mobility and cognitive function and slowing the progression of neurological disease. Specifically, we look at the ways nutrients can counteract the changes in the aging brain that make it more susceptible to neurological disorders. We focus on the persistent activation of pathways that reduce brain plasticity and, over time, contribute to destructive cellular changes which affect cell survival and functioning such as their ability to generate new cells and to adapt to new experiences. We also investigate behavioral and performance changes due to oxidative stress and inflammation, in conjunction with changes in cellular function, signal transduction. and possible amelioration of these effects with nutrition.

Khalid Shah (Harvard University, Boston, MA): Cell based therapies are emerging as a promising strategy for cancer. We have developed cell surface receptor targeted adult stem cells, cancer cells and T cells expressing novel bi-functional immunomodulatory proteins. Using our recently established tumor models that mimic clinical settings, we have explored the fate and efficacy of different engineered cell based therapies. Our findings demonstrate the strength of using innovative approaches and clinically relevant preclinical models that pave a path for clinical translation. Recent projects in the Dr. Shah's Center are focused on combined stem cell and T cell based therapies for the treatment of solid tumors.

Gino Cortopassi (University of California, Davis, Davis, CA): **1) Novel non-rapalog mTORC1 inhibitors for longevity**. mTORC1 inhibitors such as rapamycin and rapalogs are the single best validated drug target for longevity. We have identified the first non-rapalog mTORC1-specific inhibitors since rapamycin was identified in 1974 (Allen Cortopassi et al. 2018; Sandoval Cortopassi et al. 2020). Recently we showed one representative of this novel class meclizine extends lifespan in yeasts and mice. This project could include screening molecules for mTORC1 specificity by biochemical assays, or also computer work: docking/fitting by AutoDoc Vina and Molecular Dynamics by Gromacs or equivalent studies of molecules for their ability to inhibit mTORC1, or both.

2) The Ketogenic Diet and 'Ketodrugs' for longevity and resistance to Alzheimer's disease. We showed in 2017 (Rogers Ramsey Cortopassi et. al) that the Ketogenic Diet (KD) significantly extends lifespan 13% in mice, a human equivalent would be 10 years of extension from 78 average lifespan to 88yrs. Mice on the KD or 'Ketodrugs' resist memory loss in two mouse models of Alzheimer's disease. We find the KD & Ketodrugs inhibit age-related inflammation in brain and other tissues. The successful student could perform QRTPCR studies of inflammatory genes in brain and other tissues of animals on KD/Ketodrugs, to test explicit

hypotheses of KD/Ketodrug beneficial mechanism in traditional wet lab research. Also computer based projects are available testing novel Ketodrug's binding to their Shc target, with docking/fitting by AutoDoc Vina and Molecular Dynamics by Gromacs or equivalent studies of molecules.

Evan Snyder (Sanford Burnham Prebys (SBP) Medical Discovery Institute, La Jolla, CA):

We believe the study of stem cell biology will provide insights into many areas: developmental biology, homeostasis in the normal adult, and recovery from injury. Indeed, past and current research has already produced data in these areas that would have been difficult or impossible via any other vehicle. We have engaged in a multidisciplinary approach, simultaneously exploring the basic biology of stem cells, their role throughout the lifetime of an individual, as well as their therapeutic potential. We have taken two disparate organ systems, the brain and the lung, and are discovering parallels in their development, response to infections and molecular functions. Taken together, these bodies of knowledge will glean the greatest benefit for scientists and, most importantly, for patients. All of our research to date has been performed in human stem cells and verified in animal models with the ultimate goal of bringing them to clinical trials as soon as possible.

Possible research project options include:

1. Model brain development using human induced pluripotent stem cells (hiPSCs).
2. Model lung development using human induced pluripotent stem cells (hiPSCs).
3. Search for molecules that confer a resistance to age-related degeneration.
4. Determine the effects of tobacco related products on lung stem cells and aging.
5. Discover what directs the homing of neural stem cells to areas of pathology.
6. Explore how SARS-CoV-2 impacts lung and brain cells.

Elastrin (Greenville, SC):

https://www.elastrin.com