2-DAY CONFERENCE

ENDING AGE-RELATED DISEASES

INVESTMENT PROSPECTS & ADVANCES IN RESEARCH

CONFERENCE PROGRAM & ABSTRACTS

THURSDAY JULY 11TH - FRIDAY JULY 12TH 2019

COOPER UNION

FREDERICK P. ROSE AUDITORIUM

NEW YORK

WELCOME

Keith Comito
President Lifespan.io

Dear participant,

I welcome you to our second annual Ending Age-Related Diseases: Investment Prospects and Advances in Research conference at the historic Cooper Union.

This conference brings together researchers, biotech companies, investors, regulators, medical doctors, and longevity advocates in order to foster the development of next-generation drugs and therapies that directly target the processes of aging.

While bringing aging under medical control is an ambitious goal, it is a feasible one, and one whose humanitarian importance requires our collective and full attention. Let us all work together in a unified effort that will eventually free mankind from the burden of chronic, age-related diseases. Every moment matters, and every action counts.

Thank you for your involvement in this field, and I wish you a productive conference!

Keith Comito

ABOUT LIFESPAN.IO

In 2014, the Life Extension Advocacy Foundation was established as a 501(c)(3) non-profit organization dedicated to supporting the development of advanced biotechnologies that seek to cure age-related diseases and engaging the public about the exciting possibility of ending these diseases.

In 2015, we launched Lifespan.io, the first nonprofit crowdfunding platform focused on aging research, in order to enable the general public to directly aid research efforts. To date, we have successfully supported seven research projects aimed at investigating aging and developing therapies to treat age-related diseases.

In 2016, we launched our news and educational website, which brings you the latest biotech news, interviews with leading researchers, and articles explaining the processes of aging and the social benefits of controlling them.

In 2017, we began the monthly livestreamed Journal Club, in which Dr. Oliver Medvedik of the Cooper Union explores the latest research papers. In 2018, we created the Longevity Investor Network, a group focused on identifying promising new biotech startups, reviewing their concepts and business models, and connecting them with potential investors. We also held our first Ending Age-Related Diseases conference, the success of which convinced us to make this an annual event.

This year, we introduced the LifeXtenShow, a weekly episodic production that popularizes rejuvenation biotechnology, making the topic understandable for a wider audience.

Our Lifespan Heroes are monthly patrons who support our advocacy and promotional work. As Lifespan Heroes are the driving force behind our progress, we offer event discounts and other perks. Consider becoming a Lifespan Hero and supporting us as a monthly patron so that, together, we can end age-related diseases sooner!

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PROGRAM

DAY 1 - JULY 11TH

8:00 - 9:00	**REGISTRATION**
9:00 - 9:10	**KEITH COMITO (LIFESPAN.IO)** Welcome Talk
9:10 - 9:15	**OLIVER MEDVEDIK (KANBAR CENTER FOR BIOMEDICAL ENGINEERING)** Welcome Talk
9:15 - 9:45	**AUBREY DE GREY (SENS RESEARCH FOUNDATION)** Keynote: Estimating the true complexity of comprehensive rejuvenation
9:45 - 11:30	**SESSION 1: FUNDAMENTALS ON BIOMARKERS**
	MORGAN LEVINE (YALE CENTER FOR RESEARCH ON AGING) DNA Methylation Landscapes in Aging and Age-Related Diseases **ALEX ZHAVORONKOV (INSILICO MEDICINE)** Multi-Modal Biomarkers Of Aging **DOUG ETHELL (LEUCADIA THERAPEUTICS)** Predicting Alzheimer's disease with deep learning **MICHAEL LUSTGARTEN (TUFTS UNIVERSITY)** Role of the gut microbiome on muscle strength in older adults; My n=1 data and the quest for optimal health and lifespan.
11:30 - 11:40	**SPONSOR PRESENTATIONS**
11:40 - 12:00	**COFFEE BREAK**
11:50 - 13:30	**SESSION 2: FUNDAMENTAL STUDIES ON THE ROOT MECHANISMS OF AGING, PART 1**
	GEORGE CHURCH (HARVARD MEDICAL SCHOOL) Aging-related gene, cell, & organ therapies **JUDITH CAMPISI (BUCK INSTITUTE FOR RESEARCH ON AGING)** Puzzles and promises of cellular senescence **ANDREI GUDKOV (ROSWELL PARK COMPREHENSIVE CANCER CTR)** 'Retrobiome' in aging: Intrinsic mechanisms of systemic DNA damage by retroelements and therapeutic approaches to prevent it **VERA GORBUNOVA (UNIVERSITY OF ROCHESTER)** From long-lived species to anti-aging interventions

DAY 1 - JULY 11TH

13:45 - 14:30	**LUNCH**
14:30 - 15:20	**SESSION 3: FUNDAMENTAL STUDIES ON THE ROOT MECHANISMS OF AGING, PART 2**
	VADIM GLADYSHEV (HARVARD MEDICAL SCHOOL) From longevity signatures to longevity interventions **AMUTHA BOOMINATHAN (SENS RESEARCH FOUNDATION)** Remediation of mitochondrial DNA defects via allotopic expression
15:20 - 16:00	**PANEL DISCUSSION: UNLOCKING FUNDING FOR BASIC RESEARCH ON THE MECHANISMS OF AGING (CHAIR: OLIVER MEDVEDIK)**
16:00 - 18:40	**SESSION 4: ENCOURAGING PROGRESS IN AGING RESEARCH**
	MICHAEL GREVE (FOREVER HEALTHY FOUNDATION) Accelerating the availability of rejuvenation therapies **JOÃO PEDRO DE MAGALHÃES (UNIVERSITY OF LIVERPOOL)** Prospects, problems and pitfalls in developing aging therapeutics **HUDA SULIMAN (ICARIA LIFE SCIENCES)** Icaria Life Sciences, Inc. – Your partner for aging research **PAUL SPIEGEL (ECLECTIC LAW)** California Healthy Aging Initiative: allocating funding for aging research **JUSTIN REBO (BIOAGE)** Building a pipeline of therapies that treat aging

DAY 2 - JULY 12TH

8:00 - 9:00	**REGISTRATION**
9:00 - 9:10	**OLIVER MEDVEDIK (KANBAR CENTER FOR BIOMEDICAL ENGINEERING)** Welcome Talk
9:10 - 9:40	**RONALD KOHANSKI (NATIONAL INSTITUTE ON AGING)** *Keynote:* Concepts and perspectives in geroscience
9:40 - 11:30	**SESSION 5: CREATING INTERVENTIONS AGAINST AGING, PART 1**
	MARÍA BLASCO (CNIO) Telomere-based therapeutic strategies for cancer and age-related diseases **MICHAEL WEST (AGEX THERAPEUTICS)** The reversal of the aging of human cells: strategies for clinical implementation **GREG FAHY (INTERVENE IMMUNE)** Intervene Immune: Reversing human aging right now! **REASON (REPAIR BIOTECHNOLOGIES)** Developing therapies for thymus regeneration and atherosclerosis reversal
11:30 - 11:40	**SPONSOR PRESENTATIONS**
11:40 - 12:00	**COFFEE BREAK**
12:00 - 13:45	**SESSION 6: CREATING INTERVENTIONS AGAINST AGING, PART 2**
	KELSEY MOODY (ICHOR THERAPEUTICS) Towards enzyme augmentation therapy (EAT) for macular degeneration **PAM MAHER (SALK INSTITUTE FOR BIOLOGICAL STUDIES)** Novel anti-aging compounds based on natural products for the treatment of Alzheimer's disease **JOHN LEWIS (OISIN BIOTECHNOLOGIES)** Systemic senolysis in naturally aged mice **JARED FISCHER (OREGON HEALTH AND SCIENCE UNIVERSITY)** Rationally designed FOXO4-p53 interfering peptide selectively kills chemo-therapy-induced senescent and dormant cancer cells in vivo

DAY 2 - JULY 12TH

13:45 - 14:30	**LUNCH**
14:30 - 15:50	**SESSION 7: CREATING INTERVENTIONS AGAINST AGING, PART 3**
	KEVIN STRANGE (NOVO BIOSCIENCES) Rethinking regenerative medicine: developing small molecule drugs that unlock our innate regenerative potential **JAY SARKAR (TURN.BIO)** Epigenetic reprogramming for multifaceted reversal of aging phenotypes **PETER FEDICHEV (GERO)** Hacking aging: a data-driven approach to healthy life extension
15:50 - 16:30	**PANEL DISCUSSION: UNLOCKING A FUTURE WITHOUT AGE-RELATED DISEASES: A FORECAST (CHAIR: KRIS VERBURGH)**
16:30 - 17:00	**COFFEE BREAK**
17:00 - 18:15	**SESSION 8: INVESTORS' PERSPECTIVES ON DEVELOPING A REJUVENATION INDUSTRY**
	JOE BETTS-LACROIX (YCOMBINATOR) The law of the instrument **JAMES PEYER (KRONOS BIOVENTURES)** Addressing the most challenging problems in longevity with a VentureLabs model **SREE KANT (LIFE BIOSCIENCES)** Novel investment paradigms in aging research
18:15 - 18:55	**PANEL DISCUSSION: DIALOGUE BETWEEN INVESTORS AND REJUVENATION BIOTECH (CHAIR: BILL CHERMAN)**
18:55 - 19:00	**KEITH COMITO (LIFESPAN.IO)** Closing remarks

ABSTRACT

ESTIMATING THE TRUE COMPLEXITY OF COMPREHENSIVE REJUVENATION

Even though comprehensive damage repair is the common sense approach to maintaining health in old age, the question of whether it is a practical approach depends on how complex it is.

Dr. Aubrey de Grey

SENS Research Foundation
aubrey@sens.org

I will discuss this issue at multiple levels: the complexity of the damage itself, the thoroughness with which it must be repaired in order to achieve longevity escape velocity, and the overlap of the advances required to implement different repair therapies, among other things.

ABSTRACT

SYSTEMS-LEVEL MODELING OF AGING ACROSS BIOLOGICAL LEVELS OF ORGANIZATION

Dr. Morgan Levine

Department of Pathology,
Yale University School of Medicine
morgan.levine@yale.edu

Aging is associated with numerous changes at all levels of biological organization. Harnessing this information to develop measures that accurately and reliably quantify the biological aging process will require incorporation of functioning/failure at various levels that can be integrated using systems-level approaches.

This talk will provide illustrations on how DNA methylation data (DNAm) can be integrated with cellular, physiological, proteomic, and clinical data to model age-related changes that propagate up the levels—finally manifesting as age-related disease or death.

We will also show how network modeling can be used to generate a 'diseasome' model in order to identify hub methylation signatures with implications for multiple pathways and outcomes.

Given the complexity of the biological aging process, modeling of systems dynamics over time will both lead to the development of better biomarkers of aging and inform our conceptualization of how alterations at the molecular level propagate up levels of organization to eventually influence morbidity and mortality risk.

ABSTRACT

DEEP MULTI-MODAL BIOMARKERS OF AGING FOR HEALTHCARE, FINANCE, AND INSURANCE

Dr. Alex Zhavoronkov

Polina Mamoshina, Qingsong Zhu, Alex Zhavoronkov

Insilico Medicine, Hong Kong Science and Technology Park
Insilico Medicine, Johns Hopkins University
Buck Institute for Research on Aging
alex@insilico.com

Since 2014, deep learning systems have demonstrated superhuman performance on multiple tasks, including image, text, and voice recognition. The predictors of chronological and biological age developed using deep learning are rapidly gaining popularity in the aging research community.

These deep aging clocks can be used in a broad range of applications in the pharmaceutical industry, spanning target identification, drug discovery, data economics, and synthetic patient data generation. The first biological aging clocks utilizing deep learning techniques were first presented by the scientists at Insilico Medicine in 2015 and published in 2016 (Putin, Zhavoronkov 2016). Deep aging clocks were since used to predict specific- and all-cause mortality, evaluate population-specific differences (Mamoshina, 2018), perform quality control of diverse data sets, generate synthetic data, and function in many other applications (Zhavoronkov, 2018).

Age is a universal, biologically relevant feature ubiquitously present in most data sets. It is now possible to train the various architectures of deep neural networks on specific data types and multiple data types. In theory, a deep neural network trained on every feature known about the population and an individual subject during the course of that person's life can predict age- and health-associated features and provide the best representation of that individual's health status.

Here, we will cover the deep aging clocks trained on blood biochemistry, imaging, activity, transcriptomic, and macrobiotic data sets individually and in combination. We will discuss the applications of these aging clocks in actuarial science for prediction of mortality and health hazards.

ABSTRACT

PREDICTING ALZHEIMER'S DISEASE WITH DEEP LEARNING

Dr. Doug Ethell

Leucadia Therapeutics Inc.
dethell@leucadiatx.com

Alzheimer's disease afflicts 40M people worldwide... and there's no cure! Another 200M people walking around today will get this disease by 2050, threatening the solvency of healthcare systems across the globe.

Over the past 25 years, therapeutic efforts have incurred an unbroken string of failed clinical trials that couldn't reverse, stop, or even slow the relentless progression of Alzheimer's disease pathology. An effective treatment for Alzheimer's disease remains the largest unmet need of our generation.

Leucadia Therapeutics has a completely novel approach to tackling Alzheimer's disease. After throwing out the current dogma, we used Occam's Razor to ask if a simpler explanation could account for the extraordinary prevalence of Alzheimer's among elderly patients.

We discovered an age-dependent change that disrupts the clearance of toxic metabolites from the region of the brain where Alzheimer's disease strikes first. The company is developing a diagnostic/prognostic algorithm to evaluate the status of this age-dependent change in anyone by using non-invasive CT scans—years before cognitive impairment begins.

Our LT-CA algorithm uses a 20-second scan to predict when the age-dependent slowing of this clearance mechanism will hit a critical level, after which toxic metabolites accumulate to seed Alzheimer's disease pathology. Currently, Project Cribrose is collecting CT scans from 2000 participants to feed Deep Learning algorithms in order to roll out LT-CA by 2020.

Further, Leucadia Therapeutics is preparing to test an implantable device (Arethusta) to restore the clearance of toxic metabolites from that region of the brain in an effort to prevent Alzheimer's disease before it starts.

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Arethusta will be implanted in an outpatient procedure under twilight anesthesia—similar to a wisdom tooth extraction procedure. After implantation, the device will restore CSF-mediated clearance, thereby reversing mild cognitive impairment and preventing progression to Alzheimer's disease. If successful, Arethusta will become more common than pacemakers. A clinical trial is set to begin in 2020.

Leucadia Therapeutics was founded by Professor Doug Ethell in 2015, and he left academia to run the company full-time in 2017. In this talk, Dr. Ethell will explain Leucadia's technology and discuss the company's plan to end Alzheimer's disease.

ABSTRACT

ROLE OF THE GUT MICROBIOME ON MUSCLE STRENGTH IN OLDER ADULTS; A PERSONALIZED APPROACH FOR OPTIMIZING BIOLOGICAL AGE

Dr. Michael Lustgarten

Jean Mayer Human Nutrition Research Center on Aging, Tufts University
michael.lustgarten@tufts.edu

Evidence in support of a gut-muscle axis has been reported in rodents, but studies in older adults are limited.

Accordingly, the goals of the present study were to compare gut microbiome composition and functions between high-functioning (HF, n=18) with low-functioning (LF, n=11) older adults (average age: 76 years) that were different in terms of body composition and physical functioning and to test the causative role of the gut microbiome on the maintenance of these variables by transferring fecal samples from HF and LF older adults into germ-free mice.

Family-level Prevotellaceae, genus-level Prevotella and Barnesiella, and the bacterial species Barnesiella intestinihominis were significantly increased in HF when compared with LF older adults at the initial study visit and at a 1-month follow-up visit, when comparing HF with LF human fecal donors, and when comparing HF- with LF-colonized mice. Grip strength was significantly increased by 6.4% in HF- when compared with LF-colonized mice.

Collectively, these data suggest a causative role for gut bacteria on the maintenance of muscle strength, evidence that helps eludicate the gut-muscle axis in older adults.

In the second half of my presentation, I'll explain how I've maintained a biological age that is 15-20 years younger than my chronological age. To do that, I use aging.ai in conjunction with regular blood testing and daily dietary nutrition tracking.

ABSTRACT

AGING-RELATED GENE, CELL & ORGAN THERAPIES

Dr. George Church

Blavatnik Institute, Wyss Institute,
Harvard University
MIT
PersonalGenomes.org
church_lab_admin@hms.harvard.edu

We are using gene editing plus in vitro differentiation of human iPSCs to explore the impact of causative genetic and epigenetic loci on age-related diseases such as Alzheimer's (PMID: 30699343).

We are also exploring engineered animal organs for xenotransplants (PMID: 28798043) with enhanced resistance to pathogens, senescence, cancer, and cryopreservation.

We have recently increased the multiplex-editing limit from 31 to 13,000 edits per genome (doi.org/10.1101/574020).

Using machine learning (AI-ML, Manifoldbio) and over a million specific synthetic genome designs, we have improved AAV vectors (Dyno, Ally) and are employing AAV for delivery of known age-related genes (Rejuvenatebio).

ABSTRACT

PUZZLES AND PROMISES OF CELLULAR SENESCENCE

Dr. Judith Campisi

Buck Institute for Research on Aging
Lawrence Berkeley National Laboratory
jcampisi@buckinstitute.org

Cellular senescence is a complex cell fate that leads to a tripartite phenotype: an essentially irreversible arrest of cell proliferation, a multi-faceted secretory phenotype, and relative resistance to apoptosis.

The senescent state is induced by both stressful and physiological stimuli. The growth arrest is known to be a potent tumor-suppressive mechanism, whereas the resistance to apoptosis is thought to partly explain why senescent cells increase with age. The senescence-associated secretory phenotype (SASP) is thought to drive many of the beneficial effects (e.g., pro-wound healing) of senescent cells as well as many of their deleterious effects (e.g., pro-aging phenotypes and age-related pathologies).

Both effects may be due to the pro-inflammatory nature of the SASP. Transgenic mouse models in which senescent cells can be selectively eliminated have established that senescent cells are indeed causal for a growing number of aging phenotypes and diseases. Thus, clearing senescent cells can prevent, ameliorate, or, in some cases, reverse the deleterious effects of senescent cells. These findings have led to a surge in the search for small molecules that can mimic the mouse transgenes. Indeed, several such 'senolytics' have now been identified. While these drugs hold promise for improving health in humans, they also reveal unexplained complexities in the senescence response.

The composition of the SASP, for example, depends on the cell type, inducer, and timing. In addition, senescent cells are surprisingly heterogeneous, even when controlling for genotype, cell type and inducer. It is not at all clear which senescent subtypes senolytics target. Thus, the field is still at an early stage, and much basic knowledge is still needed before safer and more efficacious senolytics are developed.

ABSTRACT

'RETROBIOME' IN AGING: INTRINSIC MECHANISMS OF SYSTEMIC DNA DAMAGE BY RETROELEMENTS AND THERAPEUTIC APPROACHES TO PREVENT IT

Aging in mammals is associated with a progressive accumulation of cells with damaged genomes, and this is considered to be a major cause of systemic chronic inflammation as well as a driver of growing frailty and increasing risk of age-related diseases.

Dr. Andrei Gudkov

Genome Protection, Inc. & Roswell Park Comprehensive Cancer Center
andrei.gudkov@roswellpark.org

In our studies, we address both the nature of intrinsic genotoxic stress and the mechanisms of its control that malfunction in the elderly. We define the DNA "retrobiome" as a collection of repetitive retroelements in the mammalian genome expanded via a process driven by reverse transcriptase of the L1 family of DNA repeats.

Our studies elucidate the retrobiome's role as an intrinsic genotoxic stress generator and show that, together with age-related decline in certain immune system functions (immunosenescence), it could be responsible for the progressive accumulation of cells with damaged DNA.

According to our paradigm, species-specific lifespan is a function of genetically determined retrobiome activity and time of immunosenescence onset. Luckily, both appear to be potentially druggable traits, so we have established a program aimed at developing two classes of anti-aging therapies: one class targeting retrobiome activity (inhibitors of L1 reverse transcriptase functions, etc.) and another counteracting immunosenescence. Specifically, we have found that TLR5 agonists could mitigate immunosenescence and exhibit considerable efficacy in preclinical models of chronological aging.

Our findings allow for quick clinical validation. Specifically, together with Mayo Clinic, we are launching a clinical trial to test our novel TLR5 agonist's potential as a rejuvenating immunotherapy while using immunosenescence as an aging biomarker.

ABSTRACT

FROM LONG-LIVED SPECIES TO ANTI-AGING INTERVENTIONS

Dr. Vera Gorbunova

Rochester Aging Research Center,
University of Rochester
vgorbuno@ur.rochester.edu

Animals have evolved a dramatic diversity of aging rates. Even within mammals, lifespans differ over 50-fold, from four years for a mouse to 211 years for a bowhead whale.

This natural diversity of lifespan can be exploited to understand the mechanisms of longevity. With modern technological advances now available, it has become possible to undertake a comparative study of aging at the molecular level.

Our goal is to identify mechanisms that allow such exceptionally long-lived animals to live long and healthy lives and then use these mechanisms to benefit human health. I will talk about our recent progress in developing anti-aging interventions that are based on the research of long-lived animal species.

ABSTRACT

FROM LONGEVITY SIGNATURES TO LONGEVITY INTERVENTIONS

The rate of aging varies significantly across species and cell types and is further modified by genetic and environmental factors. We employ this diversity to shed light on general principles and mechanisms of lifespan control.

Dr. Vadim Gladyshev

Brigham and Women's Hospital,
Harvard Medical School
vgladyshev@rics.bwh.harvard.edu

We apply comparative genomics approaches to short- and long-lived species and carry out analyses across panels of mammals. We sequenced the genomes of several mammals with exceptional lifespan and identified genes that may contribute to their longevity.

We also carried out analyses of gene expression, metabolites, and elements across large panels of mammals. These studies point to both lineage-specific and common adaptations to longevity involving various pathways.

In addition, these analyses identify patterns of gene expression and metabolite levels, which we term longevity signatures, that characterize species lifespan and the effects of interventions that adjust lifespan within species.

Using these signatures, one may identify new pharmacological, dietary and genetic interventions with the potential to increase lifespan. To characterize longevity interventions in mice, we also developed blood and multi-tissue DNA methylation clocks. Together, these genomics approaches and tools offer a platform for unbiased discovery and validation of longevity interventions in mammals.

ABSTRACT

REMEDIATION OF MITOCHONDRIAL DNA DEFECTS VIA ALLOTOPIC EXPRESSION

Mitochondrial dysfunction is identified as one of the primary hallmarks of aging under the damage accumulation paradigms. The kidney-shaped organelle, present in numbers ranging from 100s to 1000s per cell, orchestrates the oxidative phosphorylation (OxPhos) process, generating ATP to power cellular functions.

Dr. Amutha Boominathan

Caitlin J. Lewis, Bhavna Dixit, Carter J. Hall, Matthew S. O'Connor, and Amutha Boominathan
SENS Research Foundation
amutha.boominathan@sens.org

Biogenesis of mitochondria involves the coordinated transcription and translation of its constituent components encoded by both the mitochondrial and nuclear genomes. Human mitochondrial DNA encodes 13 important genes, all protein products of the OxPhos machinery. The remaining mitochondrial proteins (~1400) are encoded by nuclear DNA and must be cytosolically synthesized and imported into mitochondria. Several factors predispose the mtDNA to accumulate mutations with time, including: 1) The proximity of mtDNA to sites of free radical generation, 2) the absence of DNA protective factors such as histones, and 3) inefficient DNA repair mechanisms within in the organelle.

Accumulated mtDNA damage exists as both point mutations or partial deletions that compromise organelle function and manifest as diseases in pediatric and adult populations. Defects in oxidative phosphorylation can result in disease states in nearly every tissue type, though symptoms are disproportionally severe in neurological, cardiovascular, and skeletal muscle tissues due to their high metabolic burden. Current treatments for mitochondrial diseases are focused on managing symptoms or slowing the disease progression, however, and do not address the root causes of the disease.

The long-term goal of our lab is to express the mtDNA protein-encoding genes from the nucleus via a process known as “allotopic expression” and to achieve functional incorporation of target proteins into their respective complexes in the OxPhos chain.

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This strategy may serve as a viable treatment option for conditions related to mitochondrial damage and dysfunction, and demonstration of its feasibility is a requisite of preclinical studies in animal models. Previous studies from our lab have demonstrated that by re-engineering the ATP8 and ATP6 genes for nuclear expression, allotopic expression could rescue a patient disease cell line that is defective for Complex V of the OxPhos relay.

Here, our recent progress will be discussed along with some of the avenues being explored to improve the expression of additional mtDNA genes and to overcome challenges inherent to the allotopic approach. Gene therapy technology may subsequently allow this technology to be employed therapeutically for diseases arising from inherited or acquired mutations in mtDNA.

ABSTRACT

ACCELERATING THE AVAILABILITY OF REJUVENATION THERAPIES

Senolytics, NAD+ Restoration, Lipid Replacement, Decalcification, mTOR Modulation, Geroprotectors, ... - the first generation of human rejuvenation therapies is available today.

Michael Greve

Forever Healthy Foundation
hello@forever-healthy.org

However, the field is still very young, and information often spotty. New therapies are emerging, and existing ones are updated or replaced.

Many of us can not or do not want to wait for decades until we have all the knowledge, perfect therapies, and a lifetime of experience on how to implement such therapies.To take advantage of these exciting developments right now, we need to navigate this time of transition and make very personal decisions about which treatments to apply and when. Arming ourselves with the best knowledge about therapeutic options is vital.

To rise to this challenge, we have created our “Rejuvenation Now" initiative to:

- continuously identify potential new rejuvenation therapies
- systematically evaluate new and existing therapies on benefits, risks, procedures, and potential applications
- evaluate providers for specialized therapies (such as stem cell treat ments)
- freely share our evaluations, protocols, and learnings

ABSTRACT

PROSPECTS, PROBLEMS AND PITFALLS IN DEVELOPING AGING THERAPEUTICS

João Pedro de Magalhães

Institute of Ageing and Chronic Disease, University of Liverpool
aging@liverpool.ac.uk

Age-related conditions are the leading causes of death and healthcare costs. Reducing the rate of aging would have enormous medical and financial benefits.

A large number of potential longevity-extending drugs and drug targets already exist, fostering a new crop of anti-aging companies. In this talk, I will discuss the prospects but also the challenges and pitfalls of developing aging therapeutics. The latter include reliance on findings from short-lived model organisms, a poor biological understanding of aging, and hurdles in performing clinical trials for aging.

ABSTRACT

ICARIA LIFE SCIENCES, INC. YOUR PARTNER FOR AGING RESEARCH

Huda Suliman

Icaria Life Sciences, Inc.
Ichor Therapeutics, Inc.
hsuliman@icarialifesciences.com

Icaria Life Sciences, Inc. is a dedicated preclinical contract research organization by Ichor Therapeutics, Inc. that concentrates on the discipline of aging. We provide results-focused research services with the ability to understand and meet the needs of our clients on an individual basis.

We offer a broad range of services tailored for aging research, including protein engineering, drug discovery, senolytic research, rodent husbandry, surgical models, xenograft models, and lifespan studies. Icaria fills in capability gaps to help industry and academic clients move promising technologies from a discovery stage into a product pipeline, allowing progression to the clinic. Specifically, we have the ability to navigate the complex pathways of aging and characterize the nuances that lead to promising drug targets. Once targets are identified, we characterize the structure-activity relationship (SAR) determining the effects of the biophysical properties of compounds to identify potential drugs.

When in-vitro models for studying aging pathway targets are not readily available, we create processes for developing and validating assays tailored for our testing needs. Advanced studies using aged animals are very challenging because basic husbandry for handling older animals is more complex than handling a regular colony. With our highly experienced husbandry group, we are able to readily determine how old mice clinically appear in order to define healthspan and determine the effects of interventions. Icaria Life Sciences, Inc. is committed to advancing the study of aging and shares the vision of delivering next-generation therapies for age-related diseases.

ABSTRACT

CALIFORNIA HEALTHY AGING INITIATIVE: THE PEOPLE'S EFFORT TO FUND AGING RESEARCH

Paul Spiegel

Walter Crompton, Michael Conboy, Paul Spiegel, Aubrey de Grey, Carter Hall
Eclectic Law, Life Extension Advocacy Foundation (LEAF) International Longevity Alliance American Longevity Alliance Center for Research and Education on Aging (CREA).
pspiegel@eclecticlaw.com

Inadequate funding impedes our ability to develop new therapeutics targeting root-cause aging mechanisms. A dedicated group is mounting an ambitious California ballot initiative to fund aging research.

This measure, the California Healthy Aging Initiative ("CHAI"), will authorize the issuance of $12 billion in government bonds over a 18-year period to fund research and translation into therapies that will delay and reverse age-related diseases. If approved, CHAI would create the single largest research fund to date aimed at enabling people to live longer, healthier lives. This talk will present and discuss CHAI and the need for greater public funding of longevity research.

ABSTRACT

CONCEPTS AND PERSPECTIVES IN GEROSCIENCE

As a field of research, geroscience deals with the points of intersection between the biology of aging and the biology of disease. The biology of aging is conceptualized through "hallmarks of aging".

Ronald A. Kohanski

National Institute on Aging
ronald.kohanski@nih.gov

There has been broad agreement around seven to nine such hallmarks, but when accounting for activities of daily living (at one end of the physiology spectrum) and cellular functions (at the other end), the hallmarks of aging appear to multiply. Despite this increasing complexity in what we know about aging, it is understood that aging is the major risk factor for chronic diseases and degenerative conditions that encumber the lives of older adults; taken in combination, these are morbidity. However, decades of research have conclusively demonstrated that there are both genetic and environmental risk factors that contribute to morbidity.

Yet, we also know that genes and the environment impact how we age. Importantly, we now know that aging is a malleable risk factor because we can slow the rate of aging – and slowing the rate of aging will compress the period of morbidity in older adults, which is, in effect, the geroscience hypothesis. In this talk, I will: 1. outline concepts for the hallmarks of aging, 2. provide examples of the intersection between these hallmarks and other risk factors for morbidity, and 3. conclude with suggestions about leveraging these findings in the development of anti-aging therapies that emerge from geroscience.

ABSTRACT

TELOMERE-BASED THERAPEUTIC STRATEGIES FOR CANCER AND AGE-RELATED DISEASES

María A. Blasco

Molecular Oncology Program,
Spanish National Cancer Research Centre (CNIO)
mblasco@cnio.es

Over the past years, our laboratory has contributed to dissecting the roles of telomerase and telomere length as key molecular pathways underlying cancer and aging, and it has addressed the potential use of telomerase activation as a therapeutic strategy for telomere syndromes and age-related diseases (Blasco et al., Cell, 1997; Tomás-Loba, Cell, 2008).

More recently, we have developed a telomerase-based gene therapy strategy that allows telomerase activation in adult organisms (Bernardes de Jesus et al., EMBO Molecular Medicine, 2012) and that has shown therapeutic effects in age-related pathologies in mice, such as myocardial infarction (Bär et al., Nature Communications, 2014) as well as in mouse models for the telomere syndromes aplastic anemia (Bär et al., Blood, 2016) and pulmonary fibrosis (Povedano et al., Cell Reports, 2015; Povedano et al., eLife, 2018).

More recently, we have also demonstrated that telomerase gene therapy does not induce cancer incidence in mouse models even in the presence of an activated oncogene. Finally, I will discuss telomere elongation and life extension in mice in the absence of genetic manipulations.

ABSTRACT

IMPLEMENTATIONTHE REVERSAL OF THE AGING OF HUMAN CELLS: STRATEGIES FOR CLINICAL

Michael D. West

AgeX Therapeutics, Inc.
jpeabody@agexinc.com

Unlike the negligible senescence observed in many primitive metazoans, mammalian somatic cells show evidence of a developmentally programmed loss of immortal regeneration over time, leading to an exponential rise of the risk of mortality (aging). Some triggering events, such as the repression of the immortalizing gene for telomerase, can occur very early in development with deleterious consequences only in late life.

To apply the full power of modern molecular technologies to the problem of aging, we therefore need robust laboratory models providing diverse cell types from the entire span of life from its earliest stages to old age. The culture of human immortal pluripotent stem cells and their mortal derivatives provide, for the first time, a comprehensive in vitro system to analyze the molecular biology of early development, where many of these somatic restrictions behind aging may be initiated [1]. In addition, facile protocols to reprogram the aging of cells in the laboratory back to immortality [2] provide in vitro models of human cell age reversal that allow the analysis of the critical molecular regulators.

This discovery research is providing evidence of leads for potential therapeutic development, such as “partial reprogramming” protocols, or as designated in our lab, “induced Tissue Regeneration” (iTR). Interestingly, these insights may significantly unify many of the diverse observations related to aging, including the role of dietary restriction and growth-related pathways involving AMPK and mTOR in aging and regeneration.

Furthermore, these insights highlight the importance of epigenetic modifications to the genome in the clockwork of cell aging. Clinical applications of emerging technologies to directly target pivotal regulators of cell aging may be unusually broad, including common age-related degenerative conditions, such as heart failure, osteoarthritis, and stroke, or even systemic aging itself.

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In addition, as is the case in telomerase regulation, embryonic regenerative pathways frequently reappear in cancer; there may, therefore, be important applications for the diagnosis and treatment of cancer as well.

[1] West MD, Binette F, Larocca D, Chapman KB, Irving C, Sternberg H. 2016. The germline/soma dichotomy: implications for aging and degenerative disease. West MD. Regen Med 11(3): 331-334.

[2] Vaziri H, Chapman KB, Guigova A, Teichroeb J, Lacher MD, Sternberg H, Singec I, Briggs L, Wheeler J, Sampathkumar J, Gonzalez R, Larocca D, Murai J, Snyder E, Andrews WH, Funk WD, West MD. 2010. Spontaneous reversal of the developmental aging of normal human cells following transcriptional reprogramming. Regen Med 5(3): 345-63.

ABSTRACT

THYMUS REGENERATION LEADS TO MULTIFACETED AGING PROTECTION AND AGING REVERSAL IN HUMANS

Gregory M. Fahy

Gregory M. Fahy, Robert T. Brooke, Steve Horvath
Intervene Immune, Inc.
fahy@interveneimmune.com

Intervene Immune carried out a clinical trial of thymus regeneration from 2015 to 2017. Nine volunteers aged 51-65 at trial onset were treated for one year, and six volunteers were followed up six months after the end of treatment. Thymic fat was replaced with non-adipose mass in all volunteers ($p<10^{-13}$), and this was accompanied by an increase in the thymic output of CD4 T cell recent thymic emigrants and an increase in circulating naïve CD4 and CD8 T cells.

Thymus regeneration treatment also led to reduced CRP levels, lowered PSA levels, increased percentage of free PSA, a reduction ($p=0.002$) in a cancer rejection checkpoint inhibitor that has been a target of recent blockbuster drugs costing $150,000/yr, and an increased lymphocyte-to-monocyte ratio (LMR). Higher LMR values are associated with protection against 8 different types of cancer, independently supporting our other suggestions of reduced cancer risk, and are also associated with protection against heart disease, atherosclerosis, stroke, and inflammation. Remarkably, the improvement in LMR remained undiminished 6 months after discontinuing treatment and was correlated with an improvement in thymic fat-free mass ($p<0.02$).

The increase in LMR was driven by a decrease in monocytes, most of which are CD38+. Increases in CD38+ immune cells are thought to drive age-related tissue NAD depletion, which, in turn, drives many aging phenotypes; this might explain why higher LMRs are so generally protective. Repletion of tissue NAD owing to depletion of CD38+ monocytes should thus have global aging reversal effects. We investigated this possibility using four different epigenetic clocks (the Horvath, Hannum, PhenoAge, and GrimAge clocks). Global linear mixed-model analysis showed an overall reduction in volunteer epigenetic age that was significant at the $p<10^{-11}$ level.

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To quantify this effect for each volunteer, we subtracted out the pre-treatment difference between epigenetic age (EA) and chronological age (A) as (EA-A)0, computing the treatment effect as (EA-A)-(EA-A)0. Although our healthy volunteers appeared to be biologically younger than their chronological ages at baseline [(EA-A)0 <0], they were, based on the mean of four epigenetic clock results, 1.5 years younger after 12 months of treatment than they were at baseline or, relative to their 1-year increase in chronological age, they were 2.5 years younger than they would have been without treatment [(EA-A)-(EA-A)0 = -2.5 years].

We note that the concept of "longevity escape velocity" would prescribe that [(EA-A)-(EA-A)0 = -1 year after 1 year of treatment. Furthermore, the GrimAge clock, which is the best epigenetic predictor of lifespan, showed a 2-year improvement that did not diminish 6 months after discontinuing treatment. Remarkably, epigenetic aging reversal accelerated from a mean of -1.5 year/year of treatment after 9 months to -6.5 years/year between 9 and 12 months ($p<0.005$). Epigenetic aging reversal was not diminished by higher pretreatment ages or by younger pretreatment epigenetic ages. Thus, thymus regeneration

ABSTRACT

THYMUS GROWTH AND REGENERATION THROUGH FOXN1 UPREGULATION

Reason

Jayanta Mukherjee; Marc Ridilla; David Mackenzie-Liu; Bill Cherman; Reason
Repair Biotechnologies, Inc.
reason@repairbiotechnologies.com

Human thymus glands shrink at an accelerated pace with age, leading to decreased naive T cell production and a compromised immune system. FOXN1 is a transcription factor that regulates thymic activity and production of naive T cells.

Repair Biotechnologies is developing a gene therapy that safely and effectively upregulates FOXN1 in thymic epithelial cells, targeting indications such as cancer, HIV, and naive T cell shortage. Early mouse studies showed a 39% increase in thymus weight after a single dose of our first candidate therapy.

ABSTRACT

TOWARDS ENZYME AUGMENTATION THERAPY (EAT) FOR MACULAR DEGENERATIONS

Kelsey Moody

Ichor Therapeutics, Inc.
kelsey.moody@ichortherapeutics.com

Age-related macular degeneration and Stargardt's macular degeneration are progressive diseases that clinically manifest as the progressive loss of central vision.

A molecular hallmark of both indications is the accumulation of lipofuscin within the lysosomes of retinal pigmented epithelial (RPE) cells, essential support cells of the posterior eye segment. Drawing inspiration from enzyme replacement therapy development pipelines, Lysoclear, an Ichor portfolio company, has demonstrated proof-of-concept for using an enzyme therapy to augment RPE lysosomes with the ability to degrade lipofuscin. This presentation will provide an update on recent efforts to move from proof-of-concept studies towards a clinical candidate.

ABSTRACT

FISETIN AND ITS DERIVATIVES FOR THE TREATMENT OF AGE-ASSOCIATED NEURODEGENERATIVE DISEASES

Pamela Maher

Pamela Maher and Antonio Currais
The Salk Institute for Biological Studies
pmaher@salk.edu

There are no drugs that halt the progression of any age-associated neurodegenerative disease. This is likely due to the failure of drug developers to recognize that, while there are mutations that predispose individuals to disease as they get older, the vast majority of neurodegenerative diseases arise from a confluence of multiple, toxic insults associated with aging.

Thus, the identification of multi-target lead compounds is needed, and their selection should be based upon a requirement for their efficacy in phenotypic screening assays that reflect the biology of the aging brain. This approach to neurodegenerative disease drug discovery is likely to produce safe and effective drugs. Plant secondary metabolites (natural products) are the ideal source of lead compounds because they have evolved to interact at low affinity with multiple enzymes. Indeed, the chemical scaffolds of the majority of drugs in the clinic are based upon those of natural products. My laboratory has completed a series of proof-of-principle experiments demonstrating that some polyphenolic natural products are exceptionally effective in halting disease progression in a wide variety of animal models of age-associated neurodegenerative diseases and that the potency and medicinal chemical properties of these compounds can be dramatically improved without losing their multi-target activities.

Using this approach, we initially identified the flavonol fisetin (3,7,3',4' tetrahydroxyflavone) as an orally active, novel neuroprotective and cognition-enhancing molecule. Further studies demonstrated that fisetin can prevent learning and memory deficits and neuroinflammation in APPswe/PS1dE9 (huAPP/PS1) double transgenic Alzheimer's disease (AD) mice. More recently, using rapidly aging SAMP8 mice, a model of sporadic AD and dementia, fisetin was found to reduce cognitive deficits while restoring multiple markers associated with impaired synaptic function, stress, and inflammation.

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However, we recognized that there was room for medicinal chemical improvement of fisetin. Using structure-activity relationship (SAR)-driven iterative chemistry, we synthesized more than 160 derivatives of fisetin based on several different chemical scaffolds. We used our phenotypic screening assays to identify fisetin derivatives with significantly enhanced neuroprotective activity while, at the same time, maintaining other key activities. Using this approach, we identified CMS121 as being highly effective at reversing deficits in cognitive function in double transgenic AD mice when administered at a late stage in the disease process, when pathology is already present. Moreover, in the SAMP8 mice, not only is CMS121 effective at preventing further cognitive decline when administered to aged mice, but it also has an overall anti-aging effect.

ABSTRACT

SYSTEMIC SENOLYSIS IN NATURALLY AGED MICE

John D. Lewis

John D. Lewis, Arun Raturi, Douglas Brown, Prakash Bhandari, Liliya Grin, Henry Garcia, Matthew Scholz, Gary Hudson
Oisín Biotechnologies, Inc.
Department of Oncology, University of Alberta, Edmonton,
Entos Pharmaceuticals
john.lewis@oisinbio.com

Over the past years, our laboratory has contributed to dissecting the roles of telomerase and telomere length as key molecular pathways underlying cancer and aging, and it has addressed the potential use of telomerase activation as a therapeutic strategy for telomere syndromes and age-related diseases (Blasco et al., Cell, 1997; Tomás-Loba, Cell, 2008).

Therapeutic approaches to eliminate senescent cells (SCs) in vivo using transgenic mouse models have demonstrated significant improvements in lifespan, reduction of cancer, and amelioration of age-related degeneration. Unfortunately, this approach requires that the organism be genetically engineered from the embryo and thus cannot be implemented in humans. We describe a clinically viable gene therapy consisting of a suicide gene under a senescent cell promoter delivered in vivo with fusogenic lipid nanoparticles (LNPs). These LNPs employ fusion-associated small transmembrane (FAST) proteins that can efficiently transduce a wide range of cells in vivo without observed toxicity or off-target effects. Selective ablation of target cells is then achieved through the expression of a potent pro-apoptotic transgene driven by a senescence-associated promoter such as p16Ink4A or p53.
Here, we describe targeting of p16Ink4A-positive or p53-positive cells in vitro and in vivo using this method and the in vivo clearance of SCs in a dose-dependent manner. Results of repeated dosing using constructs targeting various promoters are presented, including biodistribution and toxicity of LNPs in non-human primates. We will also present results of a lifespan/healthspan study in a cohort of naturally aged C57BL/6 mice (105 week-old at start of trial), where we observe significant improvements in median lifespan as well as improvements in associated health indicators such as bone density. In summary, this approach represents a first-in-class therapeutic that targets cells based on transcriptional activity rather than surface markers or metabolism.

ABSTRACT

RATIONALLY DESIGNED FOXO4-P53 INTERFERING PEPTIDE SELECTIVELY KILLS CHEMOTHERAPY-INDUCED SENESCENT AND DORMANT CANCER CELLS IN VIVO

Interference with the FoxO4-p53 complex has been recognized as an efficient way of blocking senescence and steering cells' fate toward apoptosis. We conducted a comprehensive modeling study to unravel the structure of the FoxO4-p53 complex, leading to the rational design of the senolytic peptide Eterone, which selectivity binds to FoxO4 but not to other potential targets. Preliminary binding assays confirmed the selective design of Eterone, which binds to FoxO4 20 times stronger than p53. Next, we studied the roles of Eterone on eliminating chemotherapy-induced senescence cells and dormant cancer cells in vivo.

Jared M. FIscher

Jared M. Fischer*, Emel Timucin*, Elise Manalo, Michelle Gomes, Süleyman Selim Cinaroglu, Ugur Sezerman, and Yavuz Ahiska
Cancer Early Detection Advanced Research Center, Knight Cancer Institute, Oregon Health and Science University
Eternans Ltd.
fischerj@ohsu.edu

* *equal contribution*

First, we studied the effects of Eterone on orthotopically injected, senescent A375 human melanoma cells expressing luciferase. A375 cells were induced to senescence with doxorubicin in culture then injected intradermally into the ears of NSG mice. Eterone was injected locally to the left ear and saline injected locally to the right ear (one injection per day for 2 days). Not only did the local injection of Eterone eliminate 100% of the chemotherapy-induced A375 senescent cell signal within 48 hours, we also found no obvious damage to the surrounding normal ear tissue, suggesting that Eterone can specifically eliminate senescent cancer cells in vivo.

Second, a genetically engineered mouse model of melanoma was used to study the effects of Eterone +/- a Braf inhibitor via intratumoral injection. We found that the Braf inhibitor resulted in cell senescence without any apoptosis, and this senescence was overcome after removal of the Braf inhibitor.

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Next, we delivered the Braf inhibitor first and waited 3 days to deliver Eterone, and we found no apoptosis and tumor growth. However, when we delivered the Braf inhibitor plus Eterone concomitantly, we found >95% apoptosis of the cancer cells within 48 hours and no tumor growth over two weeks.

This result suggests that Eterone treatment concomitant with a targeted pro-senescence therapy can completely eliminate early melanoma cells. Finally, the effects of systemic delivery of Eterone were tested on dividing A375 luciferase+ cells. Although Eterone had no effect on dividing A375 cells at the site of primary injection, we found a 1000-fold reduced signal in metastatic liver and lung tissues, suggesting that Eterone can eliminate the dormant cancer cells that initially seed metastases. Overall, our results show that Eterone can (i) completely eliminate chemotherapy-induced senescent cancer cells, (ii) combine with a safe chemotherapeutic to eradicate early cancer, and (iii) prevent metastases by eliminating the dormant cancer cells residing in tissues.

ABSTRACT

RETHINKING REGENERATIVE MEDICINE: DEVELOPING SMALL MOLECULE DRUGS THAT UNLOCK OUR INNATE REGENERATIVE POTENTIAL

Diverse non-mammalian animals readily regenerate and repair complex tissues and organs after injury or amputation. A growing body of evidence indicates that mammals, including humans, also have significant regenerative capacity that is inactivated during the aging process.

Kevin Strange

Kevin Strange and Viravuth Yin
Novo Biosciences, Inc.
kevin.strange@novobiosciences.com

Novo Biosciences is a late-stage, pre-clinical regenerative medicine company driving a paradigm shift in the field by developing first-in-class small molecule therapies that unlock our innate regenerative potential. Our lead small molecule MSI-1436 slows chronic degenerative changes and stimulates regeneration of injured heart, skeletal muscle, skin, bone, nerve, connective and vascular tissues in lower vertebrates and mammals (Smith et al, 2017; Strange and Yin, 2019). MSI-1436 is a natural, readily synthesized aminosterol that selectively inhibits Protein Tyrosine Phosphatase 1B (PTP1B). PTP1B is expressed ubiquitously and is a master regulator of Receptor Tyrosine Kinase (RTK) signaling. Upon ligand binding, RTKs are activated by tyrosine autophosphorylation, which, in turn, activates downstream signaling cascades. PTP1B inhibits those signaling cascades by dephosphorylating and inactivating RTKs. RTKs control multiple cellular processes that must function in a coordinated manner for regeneration to occur.

These cellular processes include immune system responses, metabolism, cell proliferation, cell differentiation and programmed cell death. Inhibition of PTP1B by MSI-1436 thus enhances the activity of diverse cellular pathways required for tissue regeneration. Importantly, MSI-1436 has previously been tested in humans for other indications and has been shown to be well-tolerated. Doses of MSI-1436 that stimulate regeneration in animal models are 50 times lower than the maximum well-tolerated human dose. Stem cell transplants to treat devastating diseases and injuries have failed.

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Development of viable and cost-effective regenerative medicine therapies requires a systems-level understanding of regenerative biology and recognition that our genomes encode the machinery required for repair and regeneration of complex tissues and organs. MSI-1436 represents proof-of-principle of these concepts and a promising regenerative medicine drug candidate.

EPIGENETIC REPROGRAMMING FOR MULTIFACETED REVERSAL OF AGING PHENOTYPES

Jay Sarka

Jay Sarkar, Vittorio Sebastiano and Marco Quarta
Turn Biotechnologies, Inc.
jay.sarkar@turn.bio

Though aging is generally associated with tissue and organ dysfunction, these can be considered the emergent consequences of fundamental transitions in the state of cellular physiology.

These transitions have multiple manifestations at different levels of cellular architecture and function, but the central regulator of these transitions is the epigenome, the most upstream dynamic regulator of gene expression. Reproduction is the only general phenomenon in nature where the age of (parental) cells is truly reset - to produce an embryo and ultimately an age 0 offspring - and core to this process is a dramatic reprogramming of the epigenome. Here, we present a technology that captures part of this age reset mechanism but uses transient reprogramming to drive more youthful phenotypes without the full reset back to an embryo.

This reprogramming technology is distinct from previous anti-aging/pro-longevity interventions, as instead of just modulating a few identified aging pathways, reprogramming engages a global and balanced state transition in the case of reproduction, or state perturbation in our transient approach, which we show leads to a multifaceted age reversal effect at the DNA, metabolic, whole cell, and local environmental levels. We further discuss the emergent tissue-

ABSTRACT

REVERSE ENGINEERING OF AGING IN BIG MEDICAL DATA FOR RATIONAL DESIGN OF LIFE-EXTENDING INTERVENTIONS

The mortality rate in humans doubles approximately every eight years, as described by the Gompertz law of mortality. The incidence of specific diseases, such as cancer or stroke, also accelerates after the age of about 40 and doubles at a rate that mirrors the mortality-rate doubling time.

Peter O. Fedichev

Gero
Moscow Institute of Physics and Technology
peter.fedichev@gero.ai

We demonstrated how the combination of big data from large-scale longitudinal studies and state-of-the-art machine learning tools can be used to reveal mechanisms of aging acceleration and produce novel biomarkers of aging (1). We investigated the organism state variability in populations representing the healthy aging and frail individuals, and we observed the interplay between aging, frailty, and resilience along with the evidence for limiting human lifespan (2). In the largest available mouse dataset from Jackson's lab, the same approach revealed the dynamic origins of aging acceleration and yielded a biomarker of aging for mouse longevity studies. We report how the discrimination between the aging phenotypes allowed us to identify novel life-extending interventions (3) and demonstrate experimental validation of treatments providing lasting rejuvenative effects.

1. Fedichev, P.O. (2018). Hacking aging: a strategy to use big data from medical studies to extend human life. Frontiers in Genetics, 483(9). DOI:10.3389/fgene.2018.00483
2. Pyrkov, T.V., Avchaciov, K., Tarkhov, A., Menshikov, L.I., Gudkov, A.V. Fedichev, P.O. (2019). Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts ultimate limit of human lifespan. bioRxiv. DOI:10.1101/618876
3. Tarkhov, A., Alla, R., Ayyadevara, S., Pyatnitskiy, M., Menshikov, L., Shmookler Reis, R.J., Fedichev, P.O. A universal transcriptomic signature of age reveals the temporal scaling of Caenorhabditis elegans aging trajectories. Scientific Reports, 9. DOI:10.1038/s41598-019-43075-z

ABSTRACT

THE LAW OF THE INSTRUMENT

Joe Betts-Lacroix

YCombinator
VIUM
jbettslacroix@gmail.com

A Silicon Valley perspective: when the known instrument of progress is the startup, we look everywhere for types of possible progress responsive to it. With that cognitive bias in place, we consider the present nail: developing cures based on mechanisms related to aging, and we wonder about the various instruments: government labs, pharmaceutical company R&D, academia, non-profits -- and none of them seems so like a hammer as the startup company. We will discuss the properties of compelling nails.

ABSTRACT

ADDRESSING THE MOST CHALLENGING PROBLEMS IN LONGEVITY WITH A VENTURELABS MODEL

To create and approve the first medicines that will enhance human healthy longevity, we will have to create new companies. For the first time in the history of drug development, most approved drugs originate from small biotech companies instead of large biotech and pharmacos.

Dr. James Peyer

Kronos BioVentures
james@kronos.vc

There has been an interesting bifurcation in the ecosystem of biotech companies into “West Coast” and “East Coast” models of financing. The East Coast model is exemplified by a venture building approach, in which scientists and entrepreneurs work hand in hand with a specialized investment group to bring more capital to bear on an interesting scientific issue early on and then leverage the scalability of investor syndicates to accelerate new drugs towards pharma partnerships. Dr. Peyer discusses the pros and cons of the two models in biotech and lays out the considerations that longevity entrepreneurs must make in thinking about financing and designing their efforts from the earliest stages.

ABSTRACT

LIFE BIOSCIENCES: A NOVEL PARADIGM FOR INVESTMENT AND R&D IN AGING

Sree Kant

Life Biosciences
Sree@lifebiosciences.com

The talk will explore the Life Biosciences approach to solving the key issues in investing and operationalizing aging-related R&D. The problem is multifaceted, with questions involving science, preclinical models, and regulatory pathways. Conventional pharma models and VC models are challenging to apply in this context.

A matrix problem would need a matrix solution. Life Biosciences has built an integrated approach across multiple hallmarks/pathways of aging that are analogous to the biology of aging itself. The Life model encompasses multiple investments across diverse biological approaches and the ability to drive and exploit interconnectedness between these approaches.

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Tax EIN: 46-5328762
Website: www.leafscience.org / www.lifespan.io
E-mail: info@lifespan.io


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