INVESTMENT PROSPECTS & ADVANCES IN RESEARCH

PROGRAM AND BOOK OF ABSTRACTS

Lifespan.io

CROWDSOURCING THE CURE FOR AGING

Keith Comito
President Lifespan.io

This unique moment in history shows that our collective work to overcome the root causes of age-related diseases has never been more relevant. Together we can build a future that brings the benefits of true and lasting health to as many people as possible, in solidarity with all humankind.

The time for the longevity dividend is now.

ENDING AGE-RELATED DISEASES 2020

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DAY 1 - AUGUST 20th

TIME ZONE: EDT

09:00-09:10 **WELCOME TALK**
Keith Comito *(Lifespan.io)*

09:10-09:20 **WELCOME TALK**
Oliver Medvedik *(Lifespan.io, The Maurice Kanbar Center for Biomedical Engineering)*

09:20-10:05 **OPENING KEYNOTE:**
Maximizing the pace of biomedical gerontology in a pandemic-conscious world
Aubrey de Grey *(SENS Research Foundation)*
Q&A

10:05-10:15 **LIFESPAN DOCUMENTARIES PREMIERE**
Tim Maupin *(Lifespan.io)*

10:15-11:45 **SESSION 1: BIOMARKERS OF AGING**
Epigenetic Clocks for Clinical and Preclinical Applications
Steve Horvath *(UCLA)*
Deep Biomarkers of Human Aging
Polina Mamoshina *(Insilico Medicine)*
Alternative RNA processing: a new senotherapeutic target?
Lorna Harries *(University of Exeter)*

11:45-12:30 ***INTERVIEW:*** **THE NIA'S SYSTEMIC APPROACH TO EXTENDING HEALTHY LIFESPAN**
Ronald Kohanski *(NIA)* and **Keith Comito** *(Lifespan.io)*

11:45-12:30 PREMIUM **PANEL DISCUSSION: BIOMARKERS OF AGING: SIGNIFICANCE FOR R&D AND THERAPEUTIC APPLICATION**
Chair: **Vadim Gladyshev**
Participants: **Steve Horvath** *(UCLA)*, **Kristen Fortney** *(BioAge Labs)*, **Stanislav Skakun** *(BioData)*, **Peter Fedichev** *(GERO)*

12:30-2:00 **SESSION 2: FUNDAMENTAL STUDIES OF THE ROOT MECHANISMS OF AGING, PART 1**

Targeting senescent cells to alleviate aging: A simple task?
Judith Campisi *(The Buck Institute for Research on Aging)*

Genetic mechanisms of aging and longevity on the Drosophila model
Alexey Moskalev *(Institute of Biology of the Komi Science Centre of the Ural Division of RAS)*

A new perspective on the changes in tendon collagen crosslinking with age and the impact on function
Jonathan Clark *(Babraham Institute)*

2:00-2:30 **POSTER SESSION**

Collagen glycation: beyond vascular stiffness and hypertension
Alexander Fedintsev *(Institute of Biology of the Komi Science Centre of the Ural Division of RAS)*

SynergyAge: a curated database for synergistic and antagonistic interactions of longevity-associated genes
Gabriela Bunu *(Institute of Biochemistry of the Romanian Academy)*

2:00-2:45 PM **PANEL DISCUSSION: PUBLIC PERCEPTION OF RESEARCH ON AGING**

PREMIUM

Chair: **Elena Milova** *(Lifespan.io)*
Panelists: **Daria Khaltourina** *(International Longevity Alliance)*, **Roey Tzezana** *(XPRIZE)*, **Maria Entraigues Abramson** *(SENS Research Foundation)*

2:30-3:00 ***INTERVIEW:*** **DOES AGING MEET THE WHO CRITERIA FOR CLASSIFICATION AS A DISEASE?**

Daria Khaltourina*(International Longevity Alliance)* and **Elena Milova** *(Lifespan.io)*

3:00-4:30 **SESSION 3: FUNDAMENTAL STUDIES OF THE ROOT MECHANISMS OF AGING, PART 2**

Preventing, attenuating and reversing diseases of old age as a class: young blood is not required
Irina Conboy *(UC Berkeley)*

Quantifying and manipulating the aging process
Vadim Gladyshev *(Harvard Medical School)*
Endogenous Retrobiome and Immunosenescence as Targets for Antiaging Therapies
Andrei Gudkov *(Roswell Park Comprehensive Cancer Center)*

4:30-5:10 ***INTERVIEW:*** **HUMANITY AND LONGEVITY: PAST, PRESENT AND FUTURE**
David Wood *(London Futurists)* and Steve Hill *(Lifespan.io)*

5:10-5:55 **PANEL DISCUSSION: ACCELERATION OF HUMAN REJUVENATION TRIALS: THE PATH FROM RESEARCH TO APPLICATION**

Chair: **Michael Geer** *(Humanity)*
Panelists: **Aubrey de Grey** *(SENS Research Foundation)*, **Gregory Fahy** *(Intervene Immune)*, **Kevin Perrott** *(OpenCures)*, **Sajad Zalzala** *(AgelessRx)*, **Steve Horvath** *(UCLA)*

5:55-6:00 **DAY ONE ROUNDUP**
Keith Comito *(Lifespan.io)*

DAY 2 - AUGUST 21st

TIME ZONE: EDT

09:00-09:05 **WELCOME TALK**
Oliver Medvedik *(Lifespan.io, The Maurice Kanbar Center for Biomedical Engineering)*

09:05-09:50 **OPENING KEYNOTE:**
Preventive Medicine in an Ageing Society (Beyond Healthcare to Health)
Brian Kennedy *(National University of Singapore)*

Q&A

9:50-10:00 **KIDS AND LIFE EXTENSION**

Tim Maupin *(Lifespan.io)*

10:00-11:00 **SESSION 4: INVESTING IN REJUVENATION, PART 1**

We need to get back to the future - The Poison Squad vs the Nuremberg Code
David Gobel *(Methuselah Foundation)*
Biotech VC meets Impact Investing with the Mission to Enhance Human Health
Alexandra Bause *(Apollo Ventures)*

11:00-11:15 ***INTERVIEW:*** **REJUVENATION NOW - SHARING VITAL KNOWLEDGE WITH THE PUBLIC**

Michael Greve *(Forever Healthy Foundation)* and **Elena Milova** *(Lifespan.io)*

11:15-11:45 ***INTERVIEW:*** **FACTORS THAT INFLUENCE PUBLIC VIEWS ON REJUVENATION**

Mair Underwood *(University of Queensland)* and **Elena Milova** *(Lifespan.io)*

11:00-11:45 **PANEL DISCUSSION: ROLE OF MEDIA IN ENGAGING EARLY ADOPTERS**

PREMIUM

Chair: Keith Comito *(Lifespan.io)*
Panelists: Sonia Arrison *(100 Plus Capital)*, **Pat Graziosi** *(Life Noggin)*, **Greg Grinberg** *(ActualFood, Life+)*, **Tim Maupin** *(TWOCOATS Film Production, Lifespan.io)*

11:45-12:45 **SESSION 5: INVESTING IN REJUVENATION, PART 2**

Why Longevity Is the Next Trillion Dollar Opportunity
Sergey Young *(Longevity Vision Fund)*
The Longevity Impact Fund - Funding Translational Longevity Research
Javier Noris *(Lifespan.io)*

12:45-1:30 **PANEL DISCUSSION: HOW TO OVERCOME THE VALLEY OF DEATH?**

Chair: Javier Noris *(Lifespan.io)*
Panelists: Patrick Burgermeister *(Kizoo Ventures)*, **Reason** *(Repair Biotechnologies)*, **Sergio Ruiz** *(Methuselah Fund)*, **Ronjon Nag** *(Institute R42)*

1:30-3:00 **SESSION 6: TARGETING AGING WITH INTERVENTIONS, PART 1**

A Comprehensive Therapy for Cancer and other Aging-Associated and Degenerative Diseases - Attacking Senescent Cells and Cancer Cells Simultaneously
Lewis Gruber *(SIWA Therapeutics)*

Aging, Senescent Cells, and Senolytics
James Kirkland *(Mayo Clinic)*

Targeted senolytic systemic treatments for geriatric syndromes
Marco Quarta *(Rubedo Life Sciences)*

3:00-3:40 ***INTERVIEW:*** **THE POWER OF QUANTIFIED SELF FOR CREATING A LONGEVITY STRATEGY**

Stanislav Skakun *(BioData)* and
Elena Milova *(Lifespan.io)*

3:40-5:10 **SESSION 7: TARGETING AGING WITH INTERVENTIONS, PART 2**

Towards Reversal of Atherosclerosis
Reason *(Repair Biotechnologies)*

Harnessing the Regenerative Secretome of Pluripotent Stem Cells to Rejuvenate Aged Tissues
Hanadie Yousef *(Juvena Therapeutics)*

Engineering drugs for the removal of toxic metabolites with aging
Matthew O'Connor *(SENS Research Foundation, Underdog)*

5:10-5:15 **THE LAST GENERATION TO DIE (TRAILER)**

Tim Maupin *(Lifespan.io)*

5:15-6:15 **SESSION 8: TARGETING AGING WITH INTERVENTIONS, PART 3**

Engineering rejuvenation therapeutics with AI
Peter Fedichev *(GERO)*

Are Methylation Clocks a Reliable Gauge of Anti-Aging Interventions?
Joshua Mitteldorf *(School of Medicine, Washington University in St. Louis)*

6:15-6:20 **CLOSING REMARKS**

Keith Comito *(Lifespan.io)*

LIFESPAN FACTORY ("ON DEMAND" PROGRAM) 1 / 2

KELSEY MOODY *ICHOR THERAPEUTICS*

2019 Workshop: Developing a Biotechnology Startup in the Rejuvenation Field

ISABELLE SCHIFFER (*FOREVER HEALTHY FOUNDATION*)

Rejuvenation therapies from bench to bedside - where are we now?

THOMAS WELDON *(PONCE DE LEON HEALTH)*

How to reverse your epigenetic age now

SAJAD ZALZALA *(AGELESSRX)*

Phase IV Rapamycin Longevity Trial: a Paradigm Shift in Human Longevity Clinical Trials

RONJON NAG *(R42 GROUP)*

AI and Aging

TYLER GOLATO *(MOLECULE)*

Molecule: Decentralized Drug Development and a New Financing Pathway for Longevity Therapeutics

ERIC LEIRE *(GENFLOW)*

Genflow Biosciences: A Disruptive Approach to Longevity Therapies

GORDAN LAUC *(GLYCANAGE)*

Using Glycans as a Tool to Prevent Age-Related Diseases

LIFESPAN FACTORY ("ON DEMAND" PROGRAM) 2 / 2

PAUL SPIEGEL *(ECLECTIC LAW)*

Beyond Retirement: A New Social Compact for the Age of Longevity

EDWARD LAYNE *(AGEMETER)*

Testing Functional Age and Screening for Covid-19

EVAN SNYDER *(NATIONAL INSTITUTE OF HEALTH)*

Using Stem Cells & Machine Learning to Model & Diagnose Complex Neurological Disorders & the Aging Brain

MICHAEL GEER *(HUMANITY.HEALTH)*

Collaborating to Increase the Healthspan of Humanity

KRIS VERBURGH *(NOVOS)*

The high-tech and low-tech approach to longevity: overview and ways to identify promising longevity technologies and approaches

GREG GRINBERG *(ACTUALFOOD)*

Rejuvenation research as a documentary: Life+

Maximizing the pace of biomedical gerontology in a pandemic-conscious world

Aubrey de Grey
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COVID-19 is disproportionately dangerous for the elderly, to a greater degree even than seasonal flu. Thus, to those of us who already understand that aging is the world's foremost medical problem, it has the silver lining that maybe key policy-makers worldwide will now see the true value of investing in preventative medicine and the research needed to make it work better. However, the intensely deep-seated conviction that aging is "not a disease" remains a huge barrier. I will discuss my view of how we might best navigate the political landscape and have the greatest influence on the key public spending decisions that will be made as this pandemic recedes and policy-makers turn their attention to the possibility of another one.

Epigenetic Clocks for Clinical and Preclinical Applications

Steve Horvath
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In mammals, DNA methylation is an epigenetic mark that regulates gene expression by serving as a maintainable mark whose absence marks promoters and enhancers. Recent epidemiological studies demonstrate that DNA methylation levels are associated with aspects of biological aging in humans. We present several universal mammalian epigenetic clocks that lend themselves for measuring aging across mammalian species.

We leverage these epigenetic clocks to evaluate several promising anti-aging treatments in humans, preclinical models (mouse, rat), and in vitro.

Alternative RNA processing: a new senotherapeutic target?

Lorna Harries
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L.W.Harries@exeter.ac.uk

Common, chronic diseases associated with age have common roots. Rather than each disease arising from a unique set of causes, it is now apparent that many such disorders have their origins in the age-related decline of a number of basic health maintenance mechanisms, termed the 'hallmarks of ageing'. Interventions targeting ageing hallmarks ('senotherapeutics') are now the subject of intense study to treat the causes, rather than the consequences of ageing. I present here evidence that the age-related dysregulation of alternative splicing (AS) comprises a new, druggable, hallmark of ageing. Splicing factors; transcripts involved in temporal or tissue specific regulation of AS are amongst the most deregulated mRNAs in human populations and aged cells, demonstrate associations with median strain lifespan and dietary restriction in animal models, and are similarly dysregulated in young fibroblasts from individuals suffering from progeroid symptoms.

Finally, drugging this new hallmark in senescent (aged) human skin, lung or endothelial cells using small molecules or targeted genetic interventions is capable of restoring splicing factor levels to those comparable with young cells, and rescuing multiple features of cellular senescence. Drugs that target the regulation of splicing factors may therefore represent promising novel anti-degenerative therapies in the future.

Collagen glycation: beyond vascular stiffness and hypertension?

Alexander Fedintsev
Institute of Biology of the Komi Science Centre of the Ural Division of RAS
alexanderfedintsev@gmail.com

Glycation of the proteins of an extracellular matrix (ECM) is a widely known feature of aging, however many scientists think that the role of the collagen glycation is only limited to vascular stiffness and the aging of the skin. Here I will present evidence that ECM glycation may go far beyond that and cause stem cell depletion, cellular senescence and decline of neuroplasticity.

SynergyAge: a curated database for synergistic and antagonistic interactions of longevity-associated genes

Gabriela Bunu[1], Dmitri Toren[1,2], Catalin-Florentin Ion[1], Robi Tacutu[1]
1 Systems Biology of Aging Group, Institute of Biochemistry of the Romanian Academy 2 The Shraga Segal Department of Microbiology, Immunology and Genetics, Center for Multidisciplinary Research on Aging, Ben-Gurion University of the Negev
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Interventional studies on genetic modulators of longevity have significantly changed gerontology. Understanding the causal relationship between genes and the aging process is however still restricted by the lack of information regarding epistasis, in general, and non-linear interactions between longevity-associated genes. Unfortunately, based on observations so far, there is no simple method to predict the cumulative impact of genes on lifespan. This project contributes to the progress in this field by providing researchers with the necessary information for predictive methods and with a guided design for epistasis lifespan experiments.

With this aim in mind, we developed SynergyAge - a database containing genetic and lifespan data for animal models obtained through multiple longevity-modulating interventions. The studies included in SynergyAge focus on the lifespan of animal strains which are modified by at least two genetic interventions, with single-gene mutants included as a reference. SynergyAge, which is publicly available at www.synergyage.info, provides an easy to use web-platform for browsing, searching, and filtering through the data, as well as a network-based interactive module for visualization and analysis.

Targeting senescent cells to alleviate aging: A simple task?

Judith Campisi

Buck Institute for Research on Aging and Lawrence Berkeley National Laboratory

Cellular senescence is a multi-faceted cell fate into which cells enter upon receiving both physiological and stress or damage signals. Senescent cells are now recognized as a significant driver of a large number of age-related phenotypes and pathologies. Consequently, there are now many strategies that are being developed to selectively eliminate senescent cells from organisms, including humans. Many of these strategies, including activating or harnessing the immune system, hold promise for postponing, mitigating or even reversing certain age-related diseases. However, it is also now clear that senescent cells are not always deleterious. Are there targetable differences between beneficial vs deleterious senescent cells? Are beneficial senescent cells always beneficial and are the deleterious variants always deleterious? I will discuss some recent insights into the complexities of senescent cells, the understanding of which may be essential for the development of safe anti-senescent strategies as therapies for age-related phenotypes and diseases.

Geroprotective properties of carotenoid fucoxanthin

Alexey Moskalev [1,2] , Mikhail Shaposhnikov [1] , Zulfiya Guvatova [2] , Anastasiya Snezhkina [2] , Anna Kudryavtseva [2] , Ekaterina Lashmanova [1]
1 Institute of biology of Russian Academy of Sciences, Molecular radiobiology and gerontology 2 Engelhardt Institute of Molecular Biology of Russian Academy of Sciences, Postgenome Technologies
amoskalev@list.ru

Fucoxanthin is a xanthophyll, accessory pigment in the chloroplasts of brown and some other algae, giving them a brown or olive-green color. In our experiments, it increases the median lifespan of Drosophila melanogaster and Caenorhabditis elegans. In the Drosophila model, increased fucoxanthin had a positive effect on fecundity, fertility, intestinal barrier function, and nighttime sleep. The whole fly transcriptome analysis revealed 57 differentially expressed genes involved. Among the most represented molecular pathways induced by fucoxanthin, most are related to longevity pathways, including MAPK, mTOR, Wnt, Notch, and Hippo signaling pathways, autophagy, translation, glycolysis, oxidative phosphorylation, apoptosis, immune response, neurogenesis, sleep, and response to DNA damage. Then we studied fucoxanthin effects in young and senescent human embryonic lung fibroblasts. There was no significant difference in β-galactosidase activity between cells treated with fucoxanthin and untreated young cells. Fucoxanthin at a concentration of 5 μM caused the pronounced antioxidant effect in the late passage cells. Moreover, transcriptomic data on human cells showed the increased expression levels of genes related to the antioxidant Nrf2/ARE pathway. According to the analysis of enriched KEGG pathways, fucoxanthin altered in fibroblasts processes like ribosome biogenesis, lipid metabolism, and cell cycle regulation including some age-related pathways such as Wnt, JAK-STAT, and FoxO signaling pathways. We suggest that fucoxanthin may have therapeutic potential for treating age-related diseases.

Preventing, attenuating and reversing diseases of old age, as a class: young blood is not required.

Irina Conboy
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Heterochronic blood sharing rejuvenates old tissues, and most of the studies on how this works focus on young plasma, its fractions, and a few youthful systemic candidates. However, it was not formally established that young blood is necessary for this multi-tissue rejuvenation. Here, using our recently developed small animal blood exchange process, we diluted specifically the plasma factors of old mice, and replenished the albumin that would be diminished if only saline was used. Our data demonstrate that a single neutral age blood exchange, NBE, suffices to meet or exceed the rejuvenative effects of enhancing muscle repair, reducing liver adiposity and fibrosis, and increasing hippocampal neurogenesis in old mice, all the key outcomes seen after blood heterochronicity in heterochronic parabiosis. Comparative proteomic analysis on serum from NBE, and from a similar human clinical procedure of therapeutic plasma exchange (TPE), revealed a molecular re-setting of the systemic signaling milieu, interestingly, elevating the levels of some proteins, which broadly coordinate tissue maintenance and repair and promote immune responses.

Moreover, a single TPE yielded functional blood rejuvenation, abrogating the typical old serum inhibition of progenitor cell proliferation. Ectopically added albumin does not seem to be the sole determinant of such rejuvenation, and levels of albumin do not decrease with age nor are increased by NBE/TPE. A model of action (supported by a large body of published data) is that significant dilution of autoregulatory proteins that crosstalk to multiple signaling pathways (with their own feedback loops) would, through changes in gene expression, have long-lasting rejuvenative molecular and functional effects. This work improves our understanding of the systemic paradigms of multi-tissue rejuvenation and suggests a novel and immediate use of the FDA approved TPE for improving the health and resilience of older people. Phase 2B and Phase 3 clinical trials and commercialization (clinical services) of this approach are being actively developed; these will expand our findings and extend these to prevention, attenuation and reversal of inflammatory, fibrotic, degenerative and metabolic diseases, as well as improved immunity and resilience to viral illnesses.

Endogenous Retrobiome and Immunosenescence as Targets for Antiaging Therapies

Andrei Gudkov
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Aging is associated with a gradual accumulation of cells with damaged DNA, progressive decline in immune functions (immunosenescence) accompanied with a rise in systemic inflammation, an increase of frailty, and risk of numerous aging-related diseases. Since each mammalian species has a clearly defined lifespan, the mechanisms underlying longevity and aging are genetically determined and programmed by endogenous factors. Experimentally accumulated evidence allows for the identification of the components of this "timer". Thus, sporadic activation of endogenous retroelements occupying nearly half of the mammalian genome ("retrobiome") drives spontaneous age-related mutagenesis and interferon-mediated inflammation. This process is normally balanced by the immune system that eradicates cells with activated retrobiome. We hypothesize that aging results from a disbalance of this equilibrium and, therefore, can be prevented and treated by either pharmacological inhibition of retrobiome activity or reversion of immunosenescence. Genome Protection is developing therapies targeting both processes. We will present evidences of efficacy of our drug candidates.

Preventive Medicine In An Ageing Society (Beyond Healthcare To Health)

Brian Kennedy
NUHS Centre for Healthy Longevity
Yong Loo Lin School of Medicine, National University of Singapore
Buck Institute for Research on Aging

We now know that ageing is the biggest risk factor for a range of late onset chronic conditions that drive morbidity and mortality, and dramatically increase healthcare costs. Considerable effort has been expended to identify effective therapies for these conditions, which include metabolic, neurodegenerative, cardiac and other syndromes. Yet therapies have been hard to identify. A new strategy is to target the biggest risk factor – ageing itself. Slowing ageing is relatively easy in animal models, including mice, and when done effective, not only lifespan but healthspan is extended. The question now is how to develop interventions and test them in humans. I will discuss known and novel interventions, including those affecting amino acid metabolism and discuss strategies for measuring and delaying ageing in humans. A major reason we are effective at treating metabolic and cardiac symptoms is that we have identified risk factors (e.g hyperglycemia, hypercholesterolemia, etc.) and treat these before the diseases develop to later stages. Ageing is the ultimate risk factor and treating it effectively may revolutionize medicine.

We need to get back to the future - The Poison Squad vs the Nuremberg Code

David Gobel
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In the early days of the 20th century there was no AMA, no FDA, no NIH, and no food nor drug labelling. Meat packers and food manufacturers put whatever they thought was good for business into their cans and bottles and sold them to the public - and the public health suffered as a result. Were these manufacturers evil? Maybe...but nobody had any scientific basis for knowing what was bad for you or good for you. So, a brave group of folks in the US Dept. of Agriculture decided to test these foods systematically on themselves. These people became known as "The Poison Squad". Since they were human, the results of these experiments were immediately and directly applicable to society, and resulted in huge benefits to public health - our health. Then, thanks to NAZI human experimentation atrocities in the early 1940's, human medical experimentation was virtually criminalized via the Nuremberg Code which (correctly) favored animal based experimentation. With the advent of 3d printing of human tissues we have an emerging opportunity to dramatically accelerate our rate of discovery and delivery of drugs and biologics that can attack aging and disease.

Biotech Investing with the Mission to Enhance Human Health

Alexandra Bause
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The remarkable increase in human life expectancy over the past century unveiled a devastating decline in human health as we age. The current healthcare system is primarily set up to react to existing health conditions, which are often only detected once the majority of the underlying damage has already occurred. With an ever-advancing understanding of age-related pathophysiology, the need to intervene much earlier in this process becomes undeniably clear. Importantly, over the past decades, there has been tremendous progress in identifying the fundamental biological mechanism that drive the age-related decline in health and performance. However, the translation and commercialization of these discoveries is facing challenges, as the drug development and regulatory frameworks have been primarily focussed on assessing clinical endpoints in established disease conditions.

Fortunately, there is growing ambition for identifying and establishing predictive biomarkers that can help detect emerging health conditions before they manifest, and can act as surrogate clinical endpoints. At the same time, technological progress is improving the generation of large data sets that can expedite such discoveries. These trends may enable the development of interventions to prevent and reverse age-related health decline within the existing frameworks, and to apply a biotech investment approach with a high impact-goal: enhancing healthy lifespan.

Why Longevity is the Next Trillion Dollar Opportunity

Sergey Young
Longevity Vision Fund

In his talk Sergey Young explains why he believes that Longevity is the next Trillion Dollar Opportunity. As founder of Longevity Vision Fund, Sergey gives an insider view on the latest developments in the quest for accessible and affordable longevity technologies, as well as driving forces of the longevity sector on the whole.

A rapidly aging population and the rise of age-related diseases, coupled with unhealthy lifestyles, create demand for healthcare transformation. At the same time, innovations in science and technology, a growing inflow of capital, and regulatory changes join forces to accelerate this revolution in health and longevity.

Sergey also highlights the pain-points in longevity research, including the lack of an economic model for commercialization of scientific breakthroughs in aging. He also demonstrates how simple policy changes can resolve some of the most challenging healthcare problems such as rare diseases (affecting 400m patients worldwide) and groups at high risk throughout the global coronavirus pandemic.

Dysfunctional/Aging Cell Removal Antibody Immunotherapy

Lewis S. Gruber
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Based upon the integral involvement of oxidative stress in aging and in aging-related and disabling diseases, our research at SIWA Therapeutics, Inc. is advancing the treatment of aging and aging related diseases by immunotherapy to remove damaged and dysfunctional cells. Our proprietary humanized mAb, 318H, is basis for our immunotherapy. 318H selectively targets a biomarker on cells exhibiting a combination of: (a) an abnormally high level of glycolysis and (b) oxidative stress. 318H is designed to bind to and provoke immune destruction and removal of senescent, cancer and virally-infected cells, including cells infected by Influenza A and SARS-CoV-2 (COVID-19).

Our focus is on treating certain life-threatening diseases eligible for FDA fast-tracking:
(1) Aggressive cancers qualifying for FDA fast-tracking – We are partnering with a major institution in pancreatic cancer (in vivo study with 318H in humanized mice is in process). We believe 318H can become a comprehensive cancer therapy as it reduces cancer cells as well as the SCs protecting the cancer cells in the tumor micro-environment.

(2) Kidney Disease – we have shown binding of 318H to diseased kidney cells. We also have ongoing exploratory studies with an animal health partner in chronic kidney disease.
(3) Infectious Disease – 318H binds in vitro to Influenza A-infected cells as well as SARS-CoV-2 infected cells; Since 318H removes SCs and SCs are associated with conditions that are complications of COVID-19, 318H also could be effective in treating complications of COVID-19 with which SCs are strongly associated.

We have completed a 318H tolerability study in non-human primates. No adverse effects were observed. A PK study will be completed next month. In February 2020, SIWA was named a "key player" in Anti-Aging Drugs by the MIT Technology Review in its list of the 10 Breakthrough Technologies of 2020. In September 2018, Forbes named SIWA as one of 3 senolytics companies to watch. Our CEO, Lewis Gruber, was named to the Aging Analytics Agency's list of 1000 Longevity Leaders for his work in developing SIWA's 318H.

Aging, Senescent Cells, and Senolytics

James L. Kirkland

Mayo Clinic Kogod Center on Aging

Aging processes such as cellular senescence might make a "root cause" contribution to chronic diseases. Senescent cells (SC) accumulate with aging and at sites of etiology of many chronic diseases. SC are resistant to apoptosis. SC can release factors that are pro-apoptotic, inflammatory, pro-fibrotic, cause stem cell dysfunction, and spread senescence, the senescence-associated secretory phenotype (SASP). Transplanting small numbers of SC into young mice, so that only 1/10,000 cells in recipients are transplanted SC, is sufficient to cause frailty, accelerated age-related disease onset, and early mortality.

We developed senolytics drugs that selectively clear SC by inhibiting survival pathways that protect SC from apoptosis due to their SASP. In mice, intermittent senolytic administration alleviated many conditions, including among others, age- or diet-related cardiovascular dysfunction, liver fat and fibrosis in steatosis, bleomycin-induced pulmonary fibrosis, radiation damage, cognitive dysfunction, and osteoporosis. Senolytics delayed frailty, chronic diseases, and early death caused by transplanting SC. In old mice, senolytics improved physical function, delayed age-related diseases, and extended remaining lifespan. In early clinical trials, senolytics reduced fat tissue SC in patients with diabetic kidney disease, decreased circulating SASP factors, and alleviated physical dysfunction in patients with idiopathic pulmonary fibrosis. Senolytics could hold promise for delaying, preventing, or treating age-related disorders, but further study is needed before they are used outside the context of clinical trials.

Gene Therapy for Cholesterol Catabolism in Atherosclerosis

Marc Ridilla, David Mackenzie-Liu, Garrett Strough, **Reason**, Bill Cherman, and Mourad Toporsian
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We have engineered a new mammalian enzyme that confers cells the ability to degrade cholesterol, which we refer to as Cholesterol Degrading Protein (CDP). Transfection of CDP DNA into mouse RAW264 macrophages prevented excess accumulation of cholesterol and the ensuing "foamy appearance" of these cells when exposed to cholesterol-rich LDLs. Cells stably expressing CDP converted cholesterol to a catabolite that could readily exit the cell and one that could be measured in the cell culture media by ELISA. Interestingly, CDP converted the oxidized form of cholesterol, 22-hydroxycholesterol (22HC), with significantly greater efficiency (~500 fold) compared to cholesterol. Intravenous administration of the CDP gene using adeno-associated virus 6 (AAV6-CDP) was very well tolerated by mice and resulted in a decrease in free liver cholesterol concentrations.

This CDP-mediated breakdown of cholesterol resulted in a concomitant and significant rise in serum levels of CDP-dependent cholesterol catabolite levels in CDP therapy treated mice compared to control untreated mice. These data provide preliminary evidence that CDP therapy can efficiently break down cholesterol and its oxidized form to a catabolite that can be readily eliminated from the cell. Systemic administration of CDP into mice is safe, well-tolerated and can be potentially implemented as an efficient treatment for advanced atherosclerosis via either targeted and cell-specific administration of the CDP gene or the use of CDP-expressing monocyte/macrophage cell therapy.

Harnessing the Regenerative Secretome of Human Pluripotent Stem Cells to Rejuvenate Aged Tissues

Hanadie Yousef, Thach Mai, Rami Jaafar, Katelyn Busse, HeeJu Kim, Tara Paglino, Jeremy O'Connell
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Age-induced tissue degeneration is caused in part by the decline of stem and precursor cell function driven by dysregulation of the local stem cell niche and systemic environment. At Juvena Therapeutics we are harnessing the regenerative secretome of human pluripotent stem cells (hPSCs) to develop biologics that reverse age-related degenerative diseases, with an initial focus on skeletal muscle rejuvenation. Juvena's proprietary ML-enhanced discovery platform is based on the efficient identification of lead candidates through proteomics, high-throughput screening for restored stem cell function, and validating targets in a preclinical development pipeline. hPSC-secreted proteins enhance the activity of aged human and mouse muscle precursor cells.

In an acute injury model, they promote skeletal muscle regeneration by inducing extracellular matrix remodeling, myogenic signaling, and proliferative homeostasis. Juvena has identified several key proteins from the hPSC secretome that when injected systemically or locally in preclinical models of sarcopenia, glucocorticoid-induced atrophy and acute injury, rejuvenate aged skeletal muscle to promote strength and function. By ultimately developing a pipeline of signaling protein therapeutics that can treat age-related diseases by revitalizing tissue-specific stem and precursor cell function, we can avoid a looming healthcare crisis by promoting healthspan for our increasing aged population.

A Practical, Safe, Effective Drug for Removing a Toxic Oxysterol From Aged Cells and Tissues

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Underdog Pharmaceuticals is a SENS Research Foundation spinout company dedicated to reversing age-related disease by removing 7-ketocholesterol (7KC) from aging cells and tissues. 7KC is a toxic oxysterol produced by the non-enzymatic oxidation of cholesterol that accumulates over time in cell membranes causing serious dysfunctions [1]. 7KC toxicity is implicated in several diseases of aging including atherosclerosis and age-related macular degeneration. Cyclodextrins (CDs) are naturally occurring, non-toxic, cyclic oligomers of glucose that are typically utilized to encapsulate and improve the aqueous solubility of small, hydrophobic molecules in drug delivery, materials sciences, and other industrial applications. Some modified CDs probed their ability to extract sterol molecules from membrane cells. We use a combination of in silico methods (molecular docking and molecular dynamics simulations) and in vitro and ex vivo target engagement assays to implement a synergistic rational drug design strategy aimed at developing CDs with high affinity and specificity for 7KC over cholesterol. The CDs engineered by Underdog are being developed as therapeutics to treat atherosclerosis and other debilitating diseases of aging by efficiently extracting 7KC from cells and tissues.

[1] Anderson et al 7-Ketocholesterol in Disease and Aging. Redox Biol. 2020 Jan;29:101380. doi: 10.1016/j.redox.2019.101380.

Are Methylation Clocks a Reliable Gauge of Anti-Aging Interventions?

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Traditionally the gold standard for evaluating anti-aging interventions has been the survival curve. As we move from short-lived lab animals to mammals and humans, this takes too long. Thus, there is an important role for surrogate markers for aging. Since 2013, algorithms based on methylation patterns in nuclear DNA have been leading candidates for this role, based on the fact that (1) they have the tightest correlation with chronological age, and (2) some are actually more accurate than chronological age for predicting future mortality and morbidity. But we require more than accuracy in order to accept a surrogate for measured survival curves. In evaluating interventions, we don't want tests that reward cosmetic benefits, or any downstream correlates of aging. We must have confidence that an intervention is addressing the upstream cause of aging. In this presentation, I discuss an empirical reason and a theoretical reason for believing in methylation clocks as good surrogates for aging. The empirical argument is that interventions known to prolong lifespan (e.g. caloric restriction) also retard the methylation clocks. The theoretical argument is that changes in gene expression are a primary driver of aging. Methylation patterns are by far the best-understood among dozens of known epigenetic mechanisms, and methylation changes can persist over periods sufficiently long to account for aging. We have good reason to hope that methylation will be a useful epigenetic marker for a primary cause of aging. Granted that it is not possible to distinguish the direction of causation with certainty, and that there are probably some methylation patterns that are upstream of aging and some that are downstream, how can we gain confidence that the sites used in a particular methylation clock are likely to be upstream? I will argue that searching for sites correlated to smoking status (as in the Horvath/Lu Grim Age clock) is biased toward downstream sites and is less useful. But searching for sites that are correlated with chronological age but are better predictors of mortality than chronological age itself (as in the Horvath/Levine PhenoAge clock) is a sound strategy for finding markers that are upstream of aging.

Mitteldorf, J. 2016. An epigenetic clock controls aging. Biogerontology 257:265
Horvath, S. & Raj, K. 2018. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nature Reviews Genetics 19(6):371

AgelessRx Launches First Large-scale Placebo-controlled Clinical Trial into the Effects of Rapamycin on Longevity

LIFESPAN FACTORY

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AgelessRx is an online telemedicine clinic dedicated to helping humans live longer and healthier. Rapamycin is an FDA-approved antifungal agent, most used to prevent organ transplant rejection. Rapamycin targets the mTOR signaling pathway, which is associated with many aging-related diseases. We are a launching a double-blind, randomized, placebo- controlled trial entitled Participatory Evaluation of Aging with Rapamycin for Longevity, or PEARL (ClinicalTrials.gov Identifier: NCT04488601). PEARL will be our first nationwide telemedicine trial and is the first large-scale intervention trial on longevity.

The study will consist of two phases. In the first phase, we will evaluate safety and efficacy of rapamycin in a double-blind, randomized, placebo-controlled matter. In the second phase we will launch an even larger-scale study (1,000 patients) to which we can add extra trial arms assessing combination strategies (e.g. rapamycin and metformin), to assess synergy between these longevity drugs.We will evaluate a low dose (1.5mg 3x/week and 5mg once/week), medium dose (2.5mg 3x/week), and high dose (5mg twice/week) of intermittent rapamycin. This schedule allows caloric restriction recovery each week and the total dose would not exceed the dose transplant patients receive. Eligible patients include those aged 50-85 of any sex, any ethnicity, in relatively good health, with only well-managed, clinically stable chronic diseases.

Our objectives are: I) Establish a long-term 12-month safety profile for a single dose of rapamycin administered three times a week, bi-weekly, or weekly in a healthy adult population with a 6-month interim analysis of the data; II) Assess the long-term efficacy of rapamycin in altering the clinical signs of aging as well as the biophysical endpoints associated with declining health and aging in healthy older adults. III) Roll out rapamycin therapy on a much broader scale using our established telemedicine platform.

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To monitor any reduction of aging-related decline symptoms in this elderly population, we will assess bone, muscle, and immune aging, and determine the accumulation of visceral fat(primary endpoint) and biomarkers of aging (such as the Levine Biomarker Aging Clock and the PhenoAge DNA methylation clock) (secondary endpoints). Safety profiles will include registration of side effects and monitoring of blood markers (CBC, electrolytes, liver function, renal function, lipids, glucose).

PEARL will allow AgelessRx to build a research infrastructure and platform to accelerate the practical clinical investigation of longevity therapies, allowing us roll out these therapies to vast populations across the world to make a significant and meaningful impact on human health and longevity.

AI and Aging

LIFESPAN FACTORY

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Globally, the number of persons aged 60 or over is projected to double by 2050, from 1 billion in 2015 to 2.1 billion in 2050. By 2100 it is expected to increase to 3.1 billion, nearly 3 times its value in 2017. Seeing the growth prospects of an aging population worldwide, it is no surprise that we now look to technology to attracting innovations at a rapid pace. These innovations are becoming increasingly important as the countries of the world deal with the elderly population explosion in the coming decades. They are likely to face fiscal and political pressures to reform public systems of healthcare monitoring, pensions, and social protections for a growing older population.

In this context, Artificial Intelligence approaches could be transformative toward identifying strategies for preservation of good health with advancing age. AI researchers can exploit computationally intense algorithms to assist humans in making sense of large, complex data sets with patterns that may not be detected using parametric statistical methods. An overarching question now in the aging field is whether AI, machine learning (ML), or deep learning (DL) approaches would be useful tools for identifying the genetic basis of exceptional health and life span.

With this background, the third webinar in the series will look to:

Can AI make you live longer with better, smart diets?
Can AI help you exercise better?
Can AI detect cancerous cells and destroy them?
Can you upload your brain in a machine and live forever?
Can AI assist us as we get older?

Molecule: Decentralized Drug Development and a New Financing Pathway for Longevity Therapeutics

LIFESPAN FACTORY

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Molecule is a radical new approach to funding drug development efforts out of academia, allowing investigators working in translational drug discovery the opportunity to move their therapies towards commercialisation without the need to found a startup company. We help investigators with promising ideas secure private and public investment in the earliest stages of a project, and work with them to help move the therapeutic closer to market. We employ innovative funding/financing mechanisms that allow for the distribution of intellectual property to fundraise for drug development, with a long-term goal of allowing broad patient and public participation. We are applying this model to financing and commercialising projects in the longevity space, with a focus on decentralized funding models that realign incentives through novel ownership dynamics.

This presentation introduces one of our pilot projects with the Scheibye-Knudsen Laboratory, focused on the creation of therapeutics to extend human lifespan. The Scheibye-Knudsen Lab has identified 10+ molecules that have a very significant effect on lifespan & aging by analyzing health and prescription records containing over 1.5 billion data points, covering 40 years of data on 4.8 million individuals. This is the first study of its kind, and the lab was provided exclusive access to the Danish population's health and prescription records to carry out this work. The project focuses on repurposing and reformulating the 3 drugs with the most statistically significant effect on lifespan.

Using Glycans as a Tool to Prevent Age-Related Diseases

LIFESPAN FACTORY

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The majority of proteins that evolved after the appearance of multicellular life are glycosylated and glycans significantly affect structure and function of these proteins. However, due to structural complexity of glycans and the absence of a direct genetic template, the analysis of protein glycosylation is much more complicated than the analysis of DNA or proteins. Consequently, the knowledge about the importance of individual variation in glycans for both normal physiological processes and diseases is still limited.

In the last few years it is becoming increasingly clear that variations in a DNA sequence are only a beginning of the understanding of complex human diseases. Genetic polymorphisms have to be put in the context of complex biology of life and a more elaborate approach that combines different 'omics phenotypes is needed to understand disease mechanisms and perform patient stratification that transcends genomics. Glycomics, as by far the most complex posttranslational modification, has an immense potential in this respect, which is only beginning to be investigated.

By generating glycomic data for over 150,000 individuals from some of the best characterized clinical and epidemiological cohorts, we enabled glycomics to meet other 'omics. The analysis of this rich gold mine is painting a picture of a very complex genetic and epigenetic regulation of glycosylation that fine tunes protein activity in multiple biological systems and also contributes to ageing at the molecular level. In particular, the evidence is accumulating that in cardiometabolic diseases, changes in glycosylation are not only biomarkers, but functional effectors that change up to a decade before initial disease diagnosis and in the meantime they actively participate in disease development.

Since glycans are under significant environmental influence, lifestyle and pharmacological interventions can be used to preventively correct these disease-causing age-related changes and in this way delay, or even completely avoid disease onset.

The high-tech and low-tech approach to longevity: overview and ways to identify promising longevity technologies and approaches

LIFESPAN FACTORY

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To live longer and healthier lives there are high-tech and low-tech approaches. High-tech approaches involve new biotechnologies that are currently in development, such as viral therapies, gene editing, transcriptomic and epigenetic drugs. These approaches have the potential to not only slow down, but even partially reverse aging. However, we should not ignore the importance of low-tech approaches, such as nutrition, nutraceuticals, food supplements and over-the-counter drugs, which can enable fast adoption and can slow down the aging process during the lifetime of the individual, substantially reducing the risk of aging-related diseases and symptoms.

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