Our Healthspan Prospects Update

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(Ver. 2)

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Getting older doesn't have to mean getting sicker. We are committed to discovering the fundamental causes of aging and finding new ways to prevent and treat age-related diseases.

- Salk Institute, La Jolla, CA, inside Salk, Fall 2019 (inside.salk.edu/fall-2019/aging)

Introduction to Our Prospects for a Longer Healthy Life

- **How to Cure Aging During Your Lifetime, Kurzgesagt, 2017, 7m 21s:**

https://www.youtube.com/watch?v=MjdpR-TY6QU

  - **Purge Senescent Cells, accumulated due to telomere shortening and other processes with age, to improve tissue function**
  - **NAD+ for restoring cell maintenance, including DNA repair, and reviving stem cells**
  - **Administration of Stem Cells reinvigorates native stem cells to improve tissue maintenance**
  - **This story is 2 years old but the strategies described, and others, are entering human trials**

What is Aging?: The Hallmarks

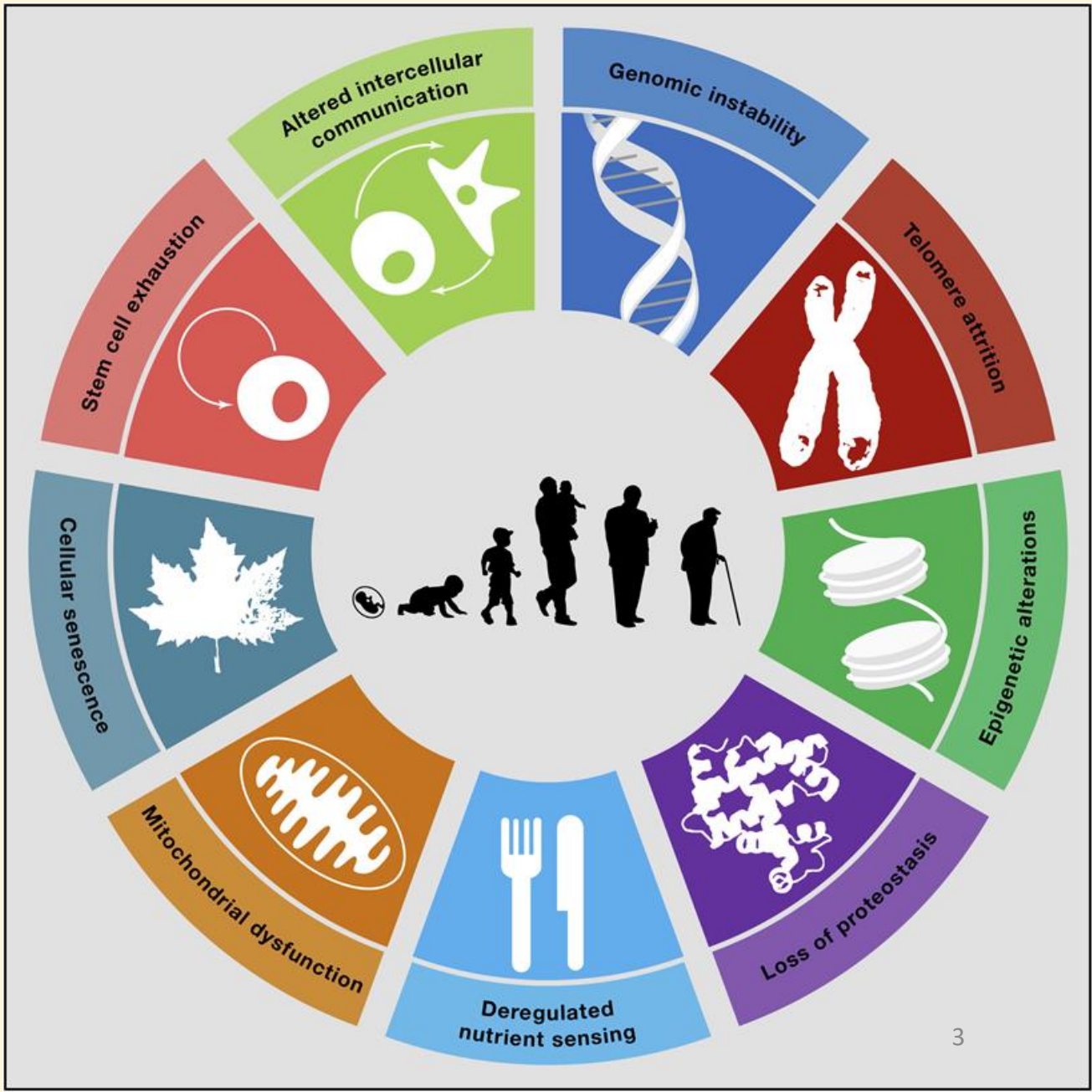
<u>Cell-Level changes</u> associated with aging, or "common denominators of aging" in mammals

What are the interdependencies between the hallmarks?

Which, if any, are more fundamental, closer to root cause(s) of aging?

Which Hallmarks are fundamental to specific age related diseases, e.g. AD, CVD, T2 Diabetes, immune system decline, cancer?

From: Review paper - ***The Hallmarks of Aging***, Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano, Guido Kroemer, *Cell*, Volume 153, Issue 6, Pages 1194-1217 (June 2013)



Healthspan and Lifespan Extension Recent Developments: recap 10/2018 and 2/2019 with updates

In the update of October 2018, I reviewed progress in two major classes of age-related diseases. Here are updates:

1. Alzheimer's and other age-related dementias appear to have multiple causes and may develop over decades without being symptomatic

- **Research thrusts have been to detect early stage (asymptomatic) disease and develop therapies to halt or reverse progress and to identify precipitating conditions, including infections and chronic inflammation, which may be amenable to conventional treatments**

2. Senescent cells, dysfunctional cells which can no longer replicate but have bypassed natural self destruction (apoptosis), cause chronic tissue inflammation, a significant risk for age-related diseases including cardiovascular disease, cancer, and sarcopenia.

- **R&D of senolytics, senescent cell destroyers, continues at numerous academic and pharmaceutical labs.**
- **In June of 2019 Unity Biotechnology reported the results of Phase 1 (safety level) trials of its first senolytic, UBX0101, targeted at osteoarthritis, OA. An apparent success, the next 3 slides are from their report.**

UNITY PIPELINE

Broad therapeutic potential, addressing multiple mechanisms of aging



*Following IPF Outcome

SAFETY AND TOLERABILITY

- UBX0101 was well tolerated up to the maximum administered dose of 4mg
- No serious adverse events
- No AEs led to discontinuation from study
- No dose-dependence in AEs or in clinical laboratory findings in Part A
- The majority of AEs were mild (66% in Part A and 75% in Part B)

Treatment-emergent AE occurring in ≥ 2 patients in Parts A or B

Preferred Term	Part A, 0.1- 4mg (N= 34) n (%)	Placebo (N= 14) n (%)	Part B (4 mg) (N= 20) n (%)	Placebo (N= 10) n (%)
Nasopharyngitis	2 (5.9)	1 (7.1)	0	0
Procedural pain	2 (5.9)	1 (7.1)	2 (10.0)	0
Arthralgia	3 (8.8)	1 (7.1)	0	1 (10.0)
Headache	4 (11.8)	1 (7.1)	0	0

PART A - PAIN – NUMERICAL RATING SCALE

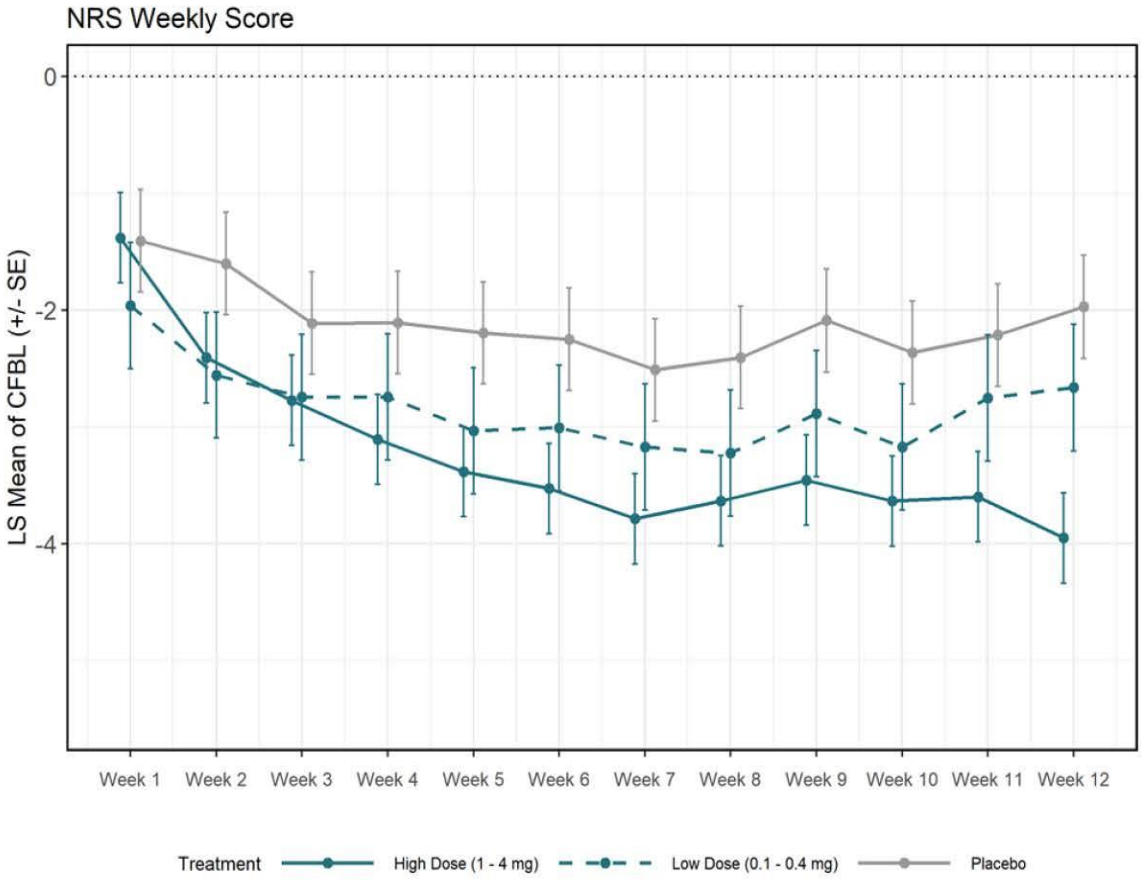
Grouped Dose Cohorts

Low Dose - (0.1, 0.2, 0.4 mg)

High Dose - (1.0, 2.0, 4.0 mg)

MMRM results at Week 12

Treatment	LS Mean	Plc-Adj	p-value
Placebo (vs. All Doses)	-1.96		
Low Doses (0.1 - 0.4 mg)	-2.66	-0.65	0.42
High Doses (1 - 4 mg)	-3.95	-1.98	<0.01



Healthspan and Lifespan Extension Recent Developments: recap 10/2018 and 2/2019 with updates continued

In the update of 2/2019, I reviewed progress in cell reprogramming to counter age-related diseases:

3. Cell Reprogramming: the key to restoring aged body function is epigenetics:

The epigenome is all the chemical modulators of gene activity, sitting on top of the DNA of our genes, which allow a single cell with one set of genes to develop into a trillion cell organism, each cell with the same set of about 20000 genes, but divided into hundreds of tissues with very distinct patterns of gene activity

Analogy: our genome, or suite of genes, is like a cookbook. The genome (cookbook) is replicated in each cell of every tissue (every household), and epigenome is the set of epigenetic marks (bookmarks) on the genes (recipes) actually used in a particular tissue (household).

- **In 2006 Shinya Yamanaka's lab at Kyoto U. published a revolutionary finding (later earning a Nobel Prize)**

  Activation of only 4 genes, shorthand designated OSKM, was sufficient to reprogram differentiated skin cells (fibroblasts) back to a stem cell which can give rise to all tissues in the body, a pluripotent stem cell, in this case an induced pluripotent stem cell or iPS

  Raised the prospect of growing, from a patient's own cells, youthful replacement tissues and organs

- **Over the next 12 years scientists found the gene combinations to reprogram virtually any cell type to any other type without fully understanding the process (optional for medical progress).**

Healthspan and Lifespan Extension Recent Developments: recap 10/2018 and 2/2019 with updates continued

- **Recently research teams at the Salk Institute and Ohio State U have reprogrammed cells in vivo, inside the living body, with the aim of enabling regeneration of damaged or diseased tissue**
- **The research group of Juan Carlos Izpisua Belmonte at the Salk Instit., La Jolla, has made major strides in cell reprogramming using mice.**
  3m31s 2016 video from the Salk Institute:
  https://www.youtube.com/watch?v=3r_p__9EHxU

  In 2017 they demonstrated relief from a progressive genetic disease, return to a youthful form, and erasure of cellular markers of aging without disrupting the epigenetic programming of individual tissues.

  In 2018 they published *In vivo reprogramming of wound-resident cells generates skin epithelial tissue*, the first production of a major organ, the skin, by reprogramming of exposed connective tissue in an open wound.

  They aim for human trials to develop a technique for closing difficult-to-heal open sores without skin grafts. Such sores are a major problem of the elderly and of burn victims.

  The reprogramming genes are engineered into an adeno-associated virus, AAV, which then takes them through the cell membrane to activate inside body cells.

Cell Reprogramming in Vivo, new development

Prof. David Sinclair's research group at Harvard and collaborators authored a 2019 paper "Reversal of Ageing- and Injury-induced Vision Loss by Tet-dependent Epigenetic Reprogramming" (https://www.biorxiv.org/content/10.1101/710210v1)

- **Described a technique for reviving a youthful regeneration capability in nerve tissue of the retina by nudging the cells toward, but not into, a less differentiated state with Yamanaka factors.**
- **Also required were DNA methylation enzymes**
- **The several genes, along with a tetracycline on/off switch, were engineered into an AAV to infect the retina of living mice**
- **Limited operation of the inserted genes promoted healing of a crushed optic nerve and reversed some damage caused by aging**
- **Another result was a more youthful epigenome according to the methylation clocks developed by coauthor Prof. Steve Horvath, UCLA. [a consumer test product is myDNAge]**
- **Results suggest that changes of DNA methylation seen in biological aging are an essential element of biological aging and perhaps a fundamental cause of biological aging.**

Healthspan and Lifespan Extension Recent Development: NAD+ Replacement Therapies

- **Prof. David Sinclair, Harvard, and his mentor Prof. Leonard Guarente, MIT, pioneered research into age regulating sirtuin genes and the key metabolic enzyme NAD+, nicotinamide adenine dinucleotide**
- **In 2018 David Sinclair's group published research describing the mechanisms behind the observed rejuvenation of circulation and musculature in aged mice given NAD+ replacement therapy:**

  Brief video of David Sinclair describing the findings: Rewinding the clock on aging blood vessels, 2m21s: https://www.youtube.com/watch?v=Mf6bQZh_GYs
- **An initial human clinical trial of NAD+ replacement therapy, using a NAD+ precursor nicotinamide mononucleotide (NMN) is underway at Brigham and Women's Hospital near Harvard Medical School. Initial results may be reported in 2019.**
- **Sept 11, 2019 David Sinclair published a popular book outlining his vision for extending human healthspan, Lifespan: Why We Age-and Why We Don't Have To**

  GMA 9_11_2019 video story, 3m31s: https://www.youtube.com/watch?v=MPMCMiAyESw

Summing Up

- **Research in Cell Biology is teasing apart the processes at the heart of biological aging and our risks for major age-related diseases.**
  - **Without fully understanding these complex processes, procedures are being developed to use them to reawaken regeneration mechanisms in our cells.**
  - **The goal is to significantly reduce the individual and social burdens of age-related diseases.**
- **We are developing tools and procedures to directly and simply measure biological age.**
  - **This enables testing of interventions into biological aging in periods much shorter than a lifespan,**
  - **Thereby facilitating selection and optimization of the interventions.**

Speculations about Opportunities

- **Application of this new knowledge expands our healthspan when we have a sound foundation lifestyle including**
  - **movement exercise, an individually optimized diet, and intermittent fasting,**
  - **plus an active desire to live (a powerful medicine/placebo)**
- **Many of those alive today will live much longer healthy lives than is common today,**
  - **with new rejuvenation techniques more than compensating for the toll of the passage of time,**
  - **a situation called exceeding "escape velocity", where we statistically outrun the ravages of biological aging.**
    - **For example, <u>every 5 years</u> we might consult a Lifestyle Coach and undergo outpatient medical/nutritional procedures which roll back our biological age by <u>more than 5 years</u>.**
- **Recently, every month has seen research progress in aging biology which makes such a scenario more credible.**

More Leads

This Healthspan Prospects Update, a single class presentation and discussion, covered only a few of the exciting developments in this field, but you can explore beyond the scope of this presentation on the Internet. Here are a few more leads:

- **For lifestyle optimization (including diet, timing of eating, healthy stress, and exercise) start with Rhonda Patrick's Found My Fitness videos and essays.**
- **For businesses active in aging biology technologies explore a wide variety of sizes and approaches starting with AgeX Therapeutics, Intervene Immune, BioViva Science, and Calico (part of Google).**
- **For frequent news updates on research and development in the lab and clinic and for opportunities to help fund (crowd fund) small high quality research projects at universities and nonprofit institutes, look into the Life Extension Advocacy Foundation.**