People Unlimited
Winter Super Longevity Week
December 2018

Today's age reversal options

Brian M. Delaney

AGE REVERSAL NETWORK

Suggested sequence of age reversal interventions, *September 2018*

- **Step 1: mTOR inhibition (rapamycin)**
- **Step 2: NAD^+ restoration (infusions/patches)**
- **Step 3: Eliminate senescent cells (senolytics)**
- **Step 4: Young plasma/umbilical cord stem cells**

Suggested sequence of age reversal interventions: New, expanded edition, *December 2018*

- **Step 1a: Lifestyle factors: conventional.**
- **Step 1b: Lifestyle factors: radical dietary interventions.**
- **Step 1c: Lifestyle-mimetics: rapamycin, metformin, etc.**
- **Step 2: NAD^+ restoration (infusions/patches/etc.).**
- **Step 3: Senotherapy (senolytics, senomorphics).**
- **Step 4: Biologics from young sources.**
- **Step 5: Gene-editing (available now, to some).**

Well-known, conventionally recommended lifestyle options

- Dietary quality (broccoli instead of cupcakes, and so on)
- Macronutrient optimization (< sugar, ≥ protein)
- Aerobic exercise
- Strength training[1]
- Good sleep
- Psychological well-being
- Social well-being
- Having purpose

} *Makes sense evolutionarily*

[1] Exp Gerontol. 2015 Oct;70:105-10. doi: 10.1016/j.exger.2015.07.008. Epub 2015 Jul 13.
Effects of different types of physical activity on the cognitive functions and attention in older people: A randomized controlled study.
Iuliano E[1], di Cagno A[2], Aquino G[3], Fiorilli G[4], Mignogna P[5], Calcagno G[6], Di Costanzo A[7].

Journal of
Alzheimer's Disease & Parkinsonism
Case Report Open Access

Bredesen et al., J Alzheimers Dis Parkinsonism 2018, 8:5
DOI: 10.4172/2161-0460.1000450

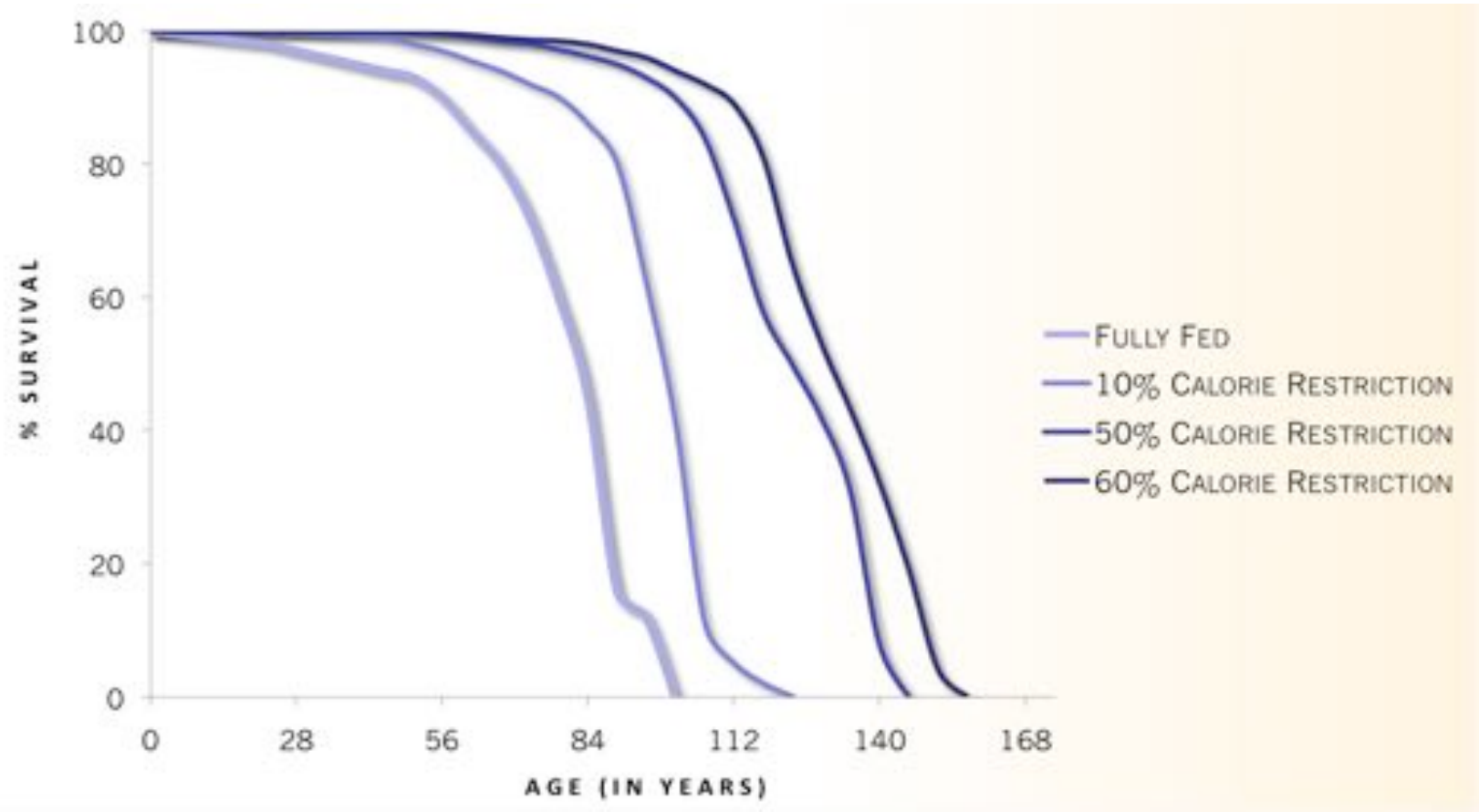
Reversal of Cognitive Decline: 100 Patients

In the current set of 100 patients, for those evaluated by MoCA, MMSE, or SLUMS pre- and post-treatment (72 of the 100), there was a mean improvement of 4.9 points, with a standard deviation of 2.6 and a range of 1-12.

Extreme lifestyle factor

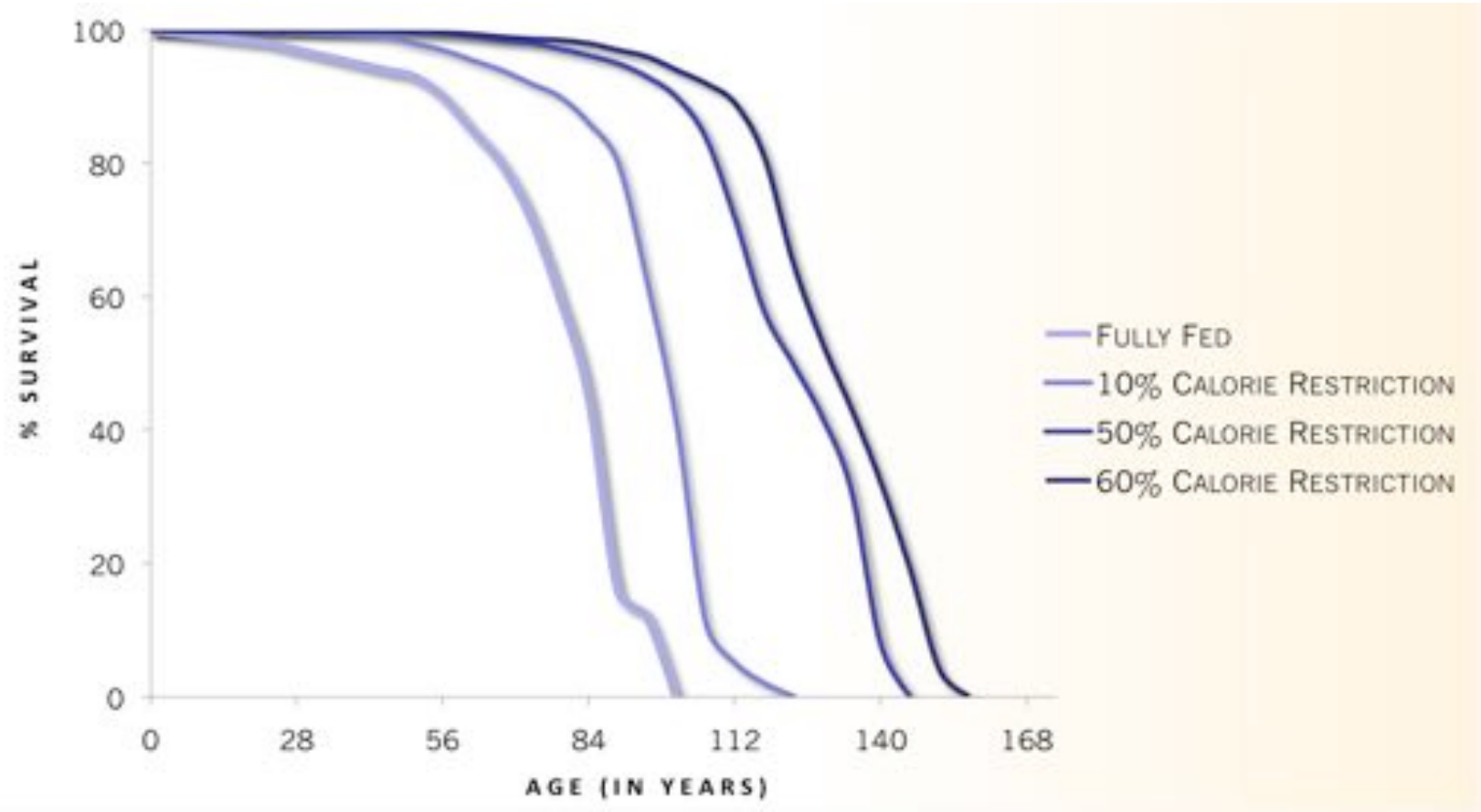
- Rigorous dietary restriction!

Possible survival of normally fed humans and humans on varying degrees of DR?



(Adapted from *Beyond the 120-Year Diet*.)

Possible survival of normally fed humans and humans on varying degrees of DR? *Almost certainly unrealistic.*



(Adapted from *Beyond the 120-Year Diet*.)

Possible downsides to *traditional, daily* DR

- Feeling cold.
- Bone loss?
- Cessation of menses?
- Low testosterone.
- Social challenges and resulting isolation.
- Hunger. *(Rodents need to be caged individually . . . .)*
- Looking (in some cases) too scrawny, not “virile”/“fertile”.

(Much less likely to apply to alternate forms of DR.)

False "Decision Monumentalism"

The choice is *not* :

1. Eat 3000+ calories of whatever I want, never have to think about what I'm eating.

vs.

2. Eat 1400 calories of boring rabbit food for the rest of my life, have to sit down with a computer program every time I want to take a bite of food.

DR- or lifestyle-mimetics

- Resveratrol
- AMPK-activating supplement(s)

  (Gynostemma pentaphyllum)
- Klotho
- Rapamycin
- Metformin
- NAD^+ restoration therapy

Rapamycin

- antifungal
- immunosuppressant
- anti-cancer
- antiaging!

2009 study was first to show lifespan extension in mammals of both sexes with rapamycin treatment

Published in final edited form as:
Nature. 2009 July 16; 460(7253): 392–395. doi:10.1038/nature08221.

Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

David E. Harrison[*,1], Randy Strong[*,2], Zelton Dave Sharp[3], James F. Nelson[4], Clinton M. Astle[1], Kevin Flurkey[1], Nancy L. Nadon[5], J. Erby Wilkinson[6], Krystyna Frenkel[7], Christy S. Carter[8], Marco Pahor[8,†], Martin A. Javors[9], Elizabeth Fernandez[2], and Richard A. Miller[*,10]

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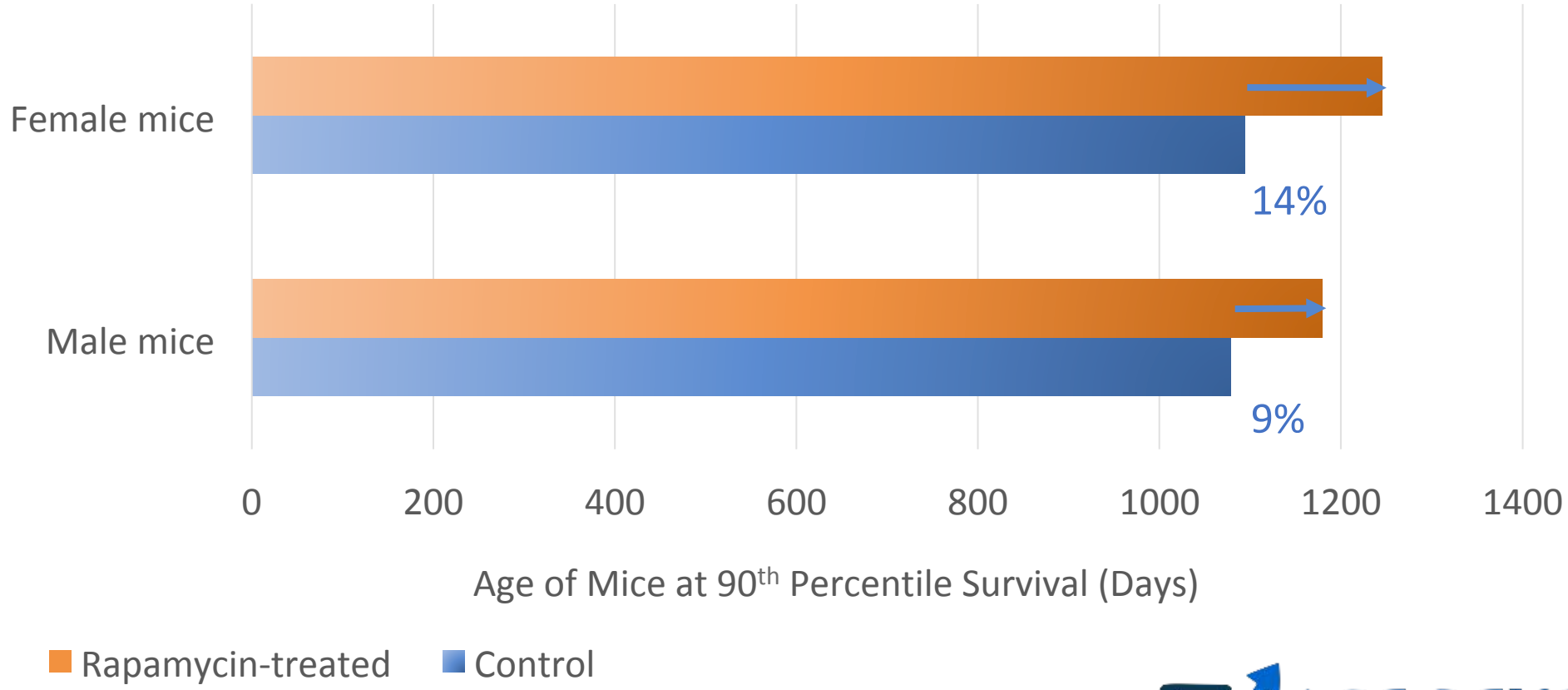
Harrison 2009: Maximum lifespan increased in male and female mice with rapamycin treatment



Harrison DE, Strong R, Sharp ZD, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. *Nature.* 2009;460(7253):392-395.

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Reviews/Analyses of rodent data

- Arriola Apelo 2016 – in 36 rodent trials, various mouse strains, dosing schedules, and sample sizes
  - Range of lifespan extension of 5.7 - 121%
    - But includes some very short-lived mice that could skew results

- Swindell 2016 – In 29 mouse studies :
    - Rapamycin treatment reduced age specific mortality by about half
    - Rapamycin-treated mice are 3.97 times more likely to reach “Advanced Age”
    - Mortality decreased more (59%) in females than in males (37%)

Swindell WR. Meta-Analysis of 29 Experiments Evaluating the Effects of Rapamycin on Life Span in the Laboratory Mouse. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2016.
Arriola Apelo SI, Lamming DW. Rapamycin: An InhibiTOR of Aging Emerges From the Soil of Easter Island. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2016;71(7):841-849.

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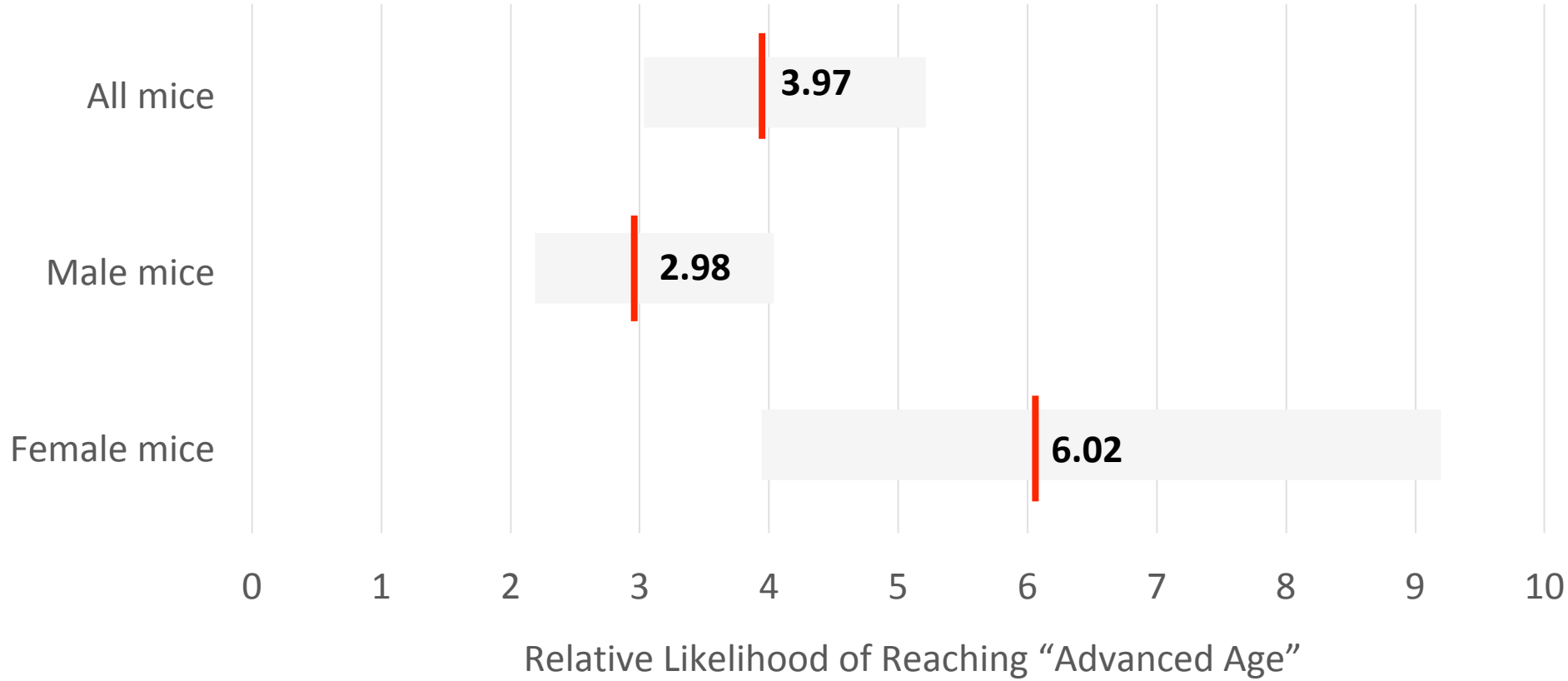
Rapamycin-Treated Mice Nearly Four Times as Likely to Reach “Advanced Age”; Female Mice Six Times as Likely



Swindell WR. Meta-Analysis of 29 Experiments Evaluating the Effects of Rapamycin on Life Span in the Laboratory Mouse. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2016.

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mTOR – Functions and potential influence on longevity

A protein *kinase* that can move mountains

"You have an old building you want to renovate. You don't want to find an electrician, then a plumber, then a carpenter... You hire a general contractor. Same thing with the body and targeting mTOR."

-David Sabatini.

mTORC1 Functions

- mTORC1 Activation:
  - Induces cell growth and proliferation
  - Represses autophagy
  - Promotes lipid formation
  - Alters mitochondrial metabolism

(Activation good when still growing – function; later: hyperfunction.)

- mTORC1 Inhibition (Rapamycin/DR)
  - Inhibits cellular growth
  - Induces autophagy
  - Extends lifespan in mice
  - Anti-aging effects in mice
  - Decreased cellular senescence

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Kaeberlein M. mTOR Inhibition: From Aging to Autism and Beyond. *Scientifica.* 2013;2013:849186.
Ehninger 2014
Fischer 2015

mTORC2 – functions and rapamycin

- Inhibition of mTORC2 is believed to largely account for the adverse effects of rapamycin, including deleterious effects on the insulin pathway
- Short-term rapamycin treatment has little effect on mTORC2
- Prolonged, chronic rapamycin administration inhibits mTORC2 in most tissues, including liver, adipose tissue, skeletal muscle, and immune cells, by suppressing mTORC2 assembly.
- However, “The sensitivity of mTORC2 to rapamycin varies by cell line and tissue type, with mTORC2 in liver, adipose tissue, and muscle being sensitive to chronic exposure to rapamycin, but with mTORC2 in other tissues (e.g., thymus, kidney, and stomach) being completely resistant to rapamycin.”

Sarbassov DD, Ali SM, Sengupta S, et al. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. *Molecular cell.* 2006;22(2): 159-168.
Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *Cell.* 2012;149(2):274-293.
Arriola Apelo SI, Lamming DW. Rapamycin: An InhibiTOR of Aging Emerges From the Soil of Easter Island. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2016;71(7):841-849.
Arriola Apelo SI, Neuman JC, Baar EL, et al. Alternative rapamycin treatment regimens mitigate the impact of rapamycin on glucose homeostasis and the immune system. *Aging Cell.* 2016;15(1):28-38.

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Translation to humans: dosage

- 126 ppm rapamycin in chow (viz. Bitto et al) is the human equivalent of 87 mg/day
- 14 ppm (viz. Harrison and others) is the human equivalent of 9.7 mg/day
- A standard maintenance immunosuppressive dosage is 2 to 5 mg/day
- Thus, Bitto et al's dosage is roughly **17-43 times** the standard medical (organ transplant) dose associated with severe and sometimes critical side effects, and which requires expert supervision and management
- However, Matt Kaeberlein's dog study used much lower human equivalent doses, and saw benefits in heart health.

http://reference.medscape.com/drug/rapamune-sirolimus-343206
https://www.clinicalkey.com/#!/content/drug_monograph/6-s2.0-802

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Translation to humans: treatment duration

- 90 mouse days ≠ 90 human days
- Bitto's single ("transient") 90-day mouse intervention likely correlates with years- or decades-long treatment in older humans
- Similarly, a 30 day human trial is roughly equivalent in duration to a single rapamycin injection in a mouse.

Dutta, S., & Sengupta, P. (2016). Men and mice: Relating their ages. *Life Sci, 152*, 244-248.
Bitto et al. Transient rapamycin treatment can increase lifespan and healthspan in middle-aged mice. *Elife*, 2016;5:e16351

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Rapamycin: pro

- Mouse studies show health benefits.
- Mouse studies show lifespan benefits.
- Dog studies show health benefits.
- All the above even when started in old age!
- It's *easy* to take one pill once a week or so.

http://reference.medscape.com/drug/rapamune-sirolimus-343206
https://www.clinicalkey.com/#!/content/drug_monograph/6-s2.0-802

Rapamycin: contra

- Untested (in humans) high doses needed to have an effect?
- How well does the mice research translate?
- Pulse dosing needed, but not clear on what timescale.

(Some people trying high doses on their own.)

Stay tuned: (much) more research is underway

http://reference.medscape.com/drug/rapamune-sirolimus-343206
https://www.clinicalkey.com/#!/content/drug_monograph/6-s2.0-802

Metformin

Metformin improves healthspan and lifespan in mice

- Increased mean lifespan
- Decreased inflammation
- Delayed onset of cataracts
- Improved exercise performance
- Improved markers of metabolic health

Nat Commun. 2013; 4: 2192. Metformin improves healthspan and lifespan in mice. Alejandro Martin-Montalvo, et al.

Metformin vs. rapamycin

- Mouse models have found a range of lifespan extension by metformin from 5-40%, varying by sex, age, and disease model.
- Metformin has a much better safety profile and established history of use.

Martin-Montalvo A, Mercken EM, Mitchell SJ, et al. Metformin improves healthspan and lifespan in mice. *Nature communications.* 2013;4:2192.
Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a Tool to Target Aging. *Cell Metab.* 2016;23(6):1060-1065.

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Metformin: good choice for many

- As with all DR- and lifestyle-mimetics: possibly not needed if on restricted diet and exercising well.
- Particularly helpful for people who eat a lot of carbohydrates.
- Consider seriously, especially if having difficulty with glucose control.

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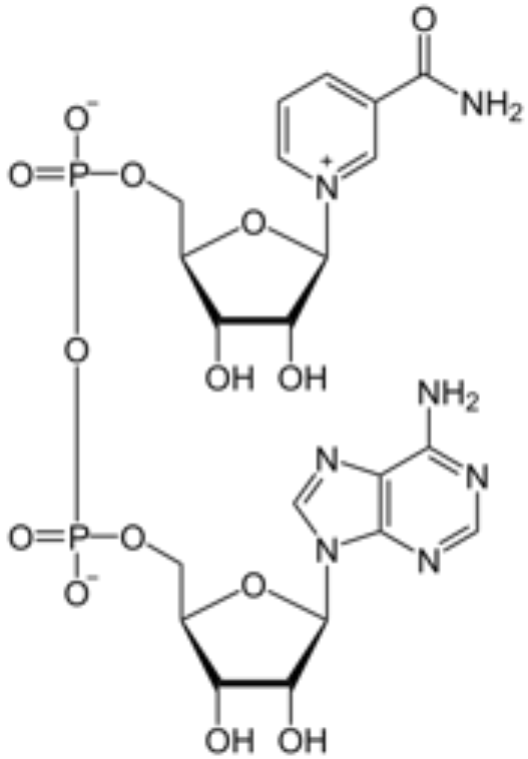
NAD^+ therapy



https://en.wikipedia.org/wiki/Nicotinamide_adenine_dinucleotide

Benefits of high NAD^+ levels

- Chromosome stability
- DNA repair
- Improved immune cell signaling
- Essential for sirtuin function (deacetylation)
- Improved cardiac function
- Longer telomeres?
- Energy production
- Protein folding

Findings from pilot studies measuring NAD+ plasma Levels

Healthy Americans

Age	NAD+ Plasma Levels
20-40 years	**50-60** ng/mL
41-60 years	**36-39** ng/mL
> 60 years	**4-8** ng/mL

Unhealthy Americans (aged 72-80)

Average level under 1 ng/mL

Young unhealthy people can have low NAD+ plasma levels

Factors that Lower NAD+ Beyond Normal Aging

1) Mental Stress
2) Physical Stress
3) Ethanol (alcohol) ingestion
4) Underlying pathologies

"The Plasma NAD+ Metabolome is Dysregulated in 'normal' Ageing" Rejuvenation Research. 2018 Aug 19. and unpublished clinical observations

Findings from human NAD^+ infusion trials

- Systolic blood pressure drop
- Arthritis pain subsides
- Depression alleviates
- Improved sleep
- Tremors dissipate
- Blood lipids normalize
- Neurological improvements
- Improved exercise endurance

How to restore youthful NAD^+

- **Step 1:** Test baseline **NAD^+ blood levels** (if practical).
- **Step 2:** **NAD^+ infusion** (**300-500** mg IV every other day/3 times).

  or **NAD^+ patch** (1 to 3 **400 mg** patches/day/every other day/3 times).

  or **sublingual, buccal, IM**... delivery systems.

  Or – <u>especially</u> if levels not so bad – i.e., are > 20 ng/mL:

  - **precursors (nicotinamide riboside)**
  - **non-precursor drugs/nutraceuticals (NCD201, available soon)**
  - **DR**
  - **ketogenic diet**[1]

- **Step 3:** **Maintain** youthful **NAD^+** with oral precursor or other simple means

  (250-500 mg/day of **nicotinamide riboside**, for example).

- **Step 4:** Test **NAD^+ blood levels** after **4 or so weeks**.

  (Repeat Step 2 if **NAD^+ blood levels** are not at least 40 ng/mL.)

Or: If it feels good do it?

[1] Elamin et al., 2017. Ketone-Based Metabolic Therapy: Is Increased NAD^+ a Primary Mechanism?

Caveat for cancer patients

Those being actively treated for cancer should not aggressively boost NAD^+ because this might repair DNA that chemotherapy and/or radiation is seeking to destroy. Here are some important points for cancer patients:

- NAD^+ facilitates DNA repair. Radiation and most chemotherapy **destroy** cell DNA.
- Those undergoing treatment for cancer might **delay** boosting NAD^+.
- However, those suffering "chemo-brain" or bone marrow toxicity* from chemo may consider NAD^+ after complete response.

* Rejuvenating Aged Hematopoietic Stem Cells Through Improvement of Mitochondrial Function. Ann Lab Med. 2018 Sep;38(5):395-401. doi: 10.3343/alm.2018.38.5.395

Combining lifestyle-mimetics

- Almost no research on combinations (general problem with real-world age-reversal regimens).
- Hence much is speculative.

Combining lifestyle-mimetics: Examples

- Resveratrol plus NAD^+ restoration
- Rapamycin plus metformin

Senotherapy:

The most important
age management treatment
available today.

Senescent cells accumulate with age and:

- Impede organ function
- Create chronic inflammation
- Emit protein-destroying enzymes
- Shorten healthy lifespan

Why retain *dysfunctional*, aged, "zombie" cells?

nature

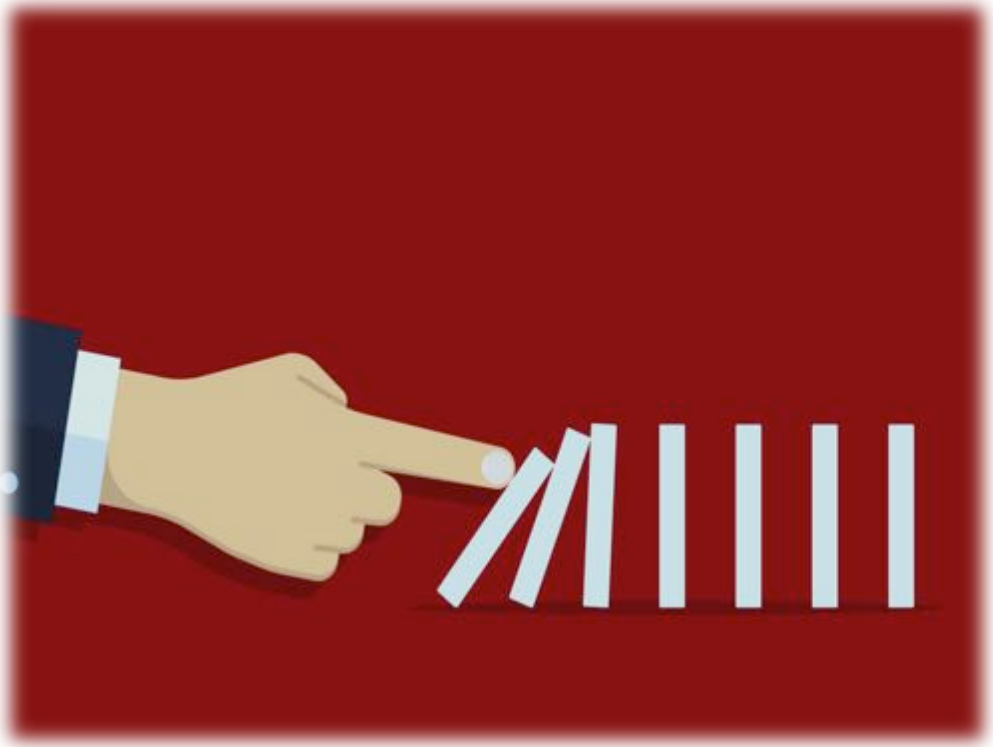
July 9, 2018

Deadly impact of senescent cells

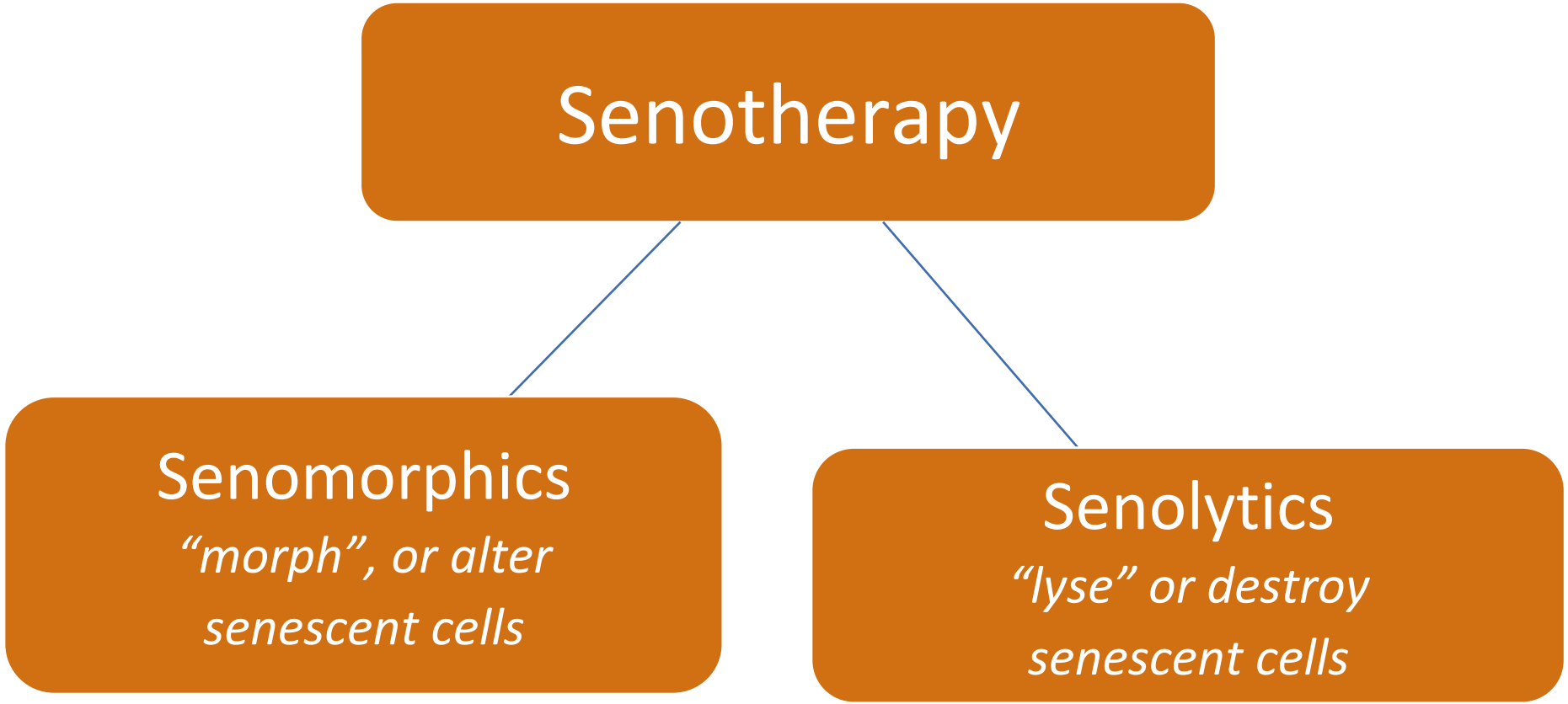
Transplanting small numbers of senescent cells into young mice causes:

1) Persistent physical dysfunction.

2) Spread of cell senescence to host tissues.



"Senolytics improve physical function and increase lifespan in old age." Nature Medicine, July 9th, 2018


Senotherapy
Senomorphics
“morph”, or alter senescent cells
Senolytics
“lyse” or destroy senescent cells

Senomorphics

- rapamycin
- resveratrol
- apigenin
- metformin (mild senomorphic effect)
- some statins (can reduce the expression of pro-inflammatory cytokines
- glucocorticoids
- JAK1/2 inhibitors (under development for inflammatory diseases)
- NF-κB inhibitors ("")

Senolytics

- dasatinib + quercetin
- fisetin
- piperlongumine
- (More coming soon.)

Preliminary data from human senolytic study

Two doses of dasatinib + quercetin in osteoarthritis patients:

- ✓ 90% of subjects see relief of osteoarthritis pain + improved joint function
- ✓ Most subjects want to re-dose (after 6 months) to see better results
- ✓ Follow-up MRI of joints and aging biomarkers to be completed in Dec 2018

(Most study subjects had severe bone-on-bone osteoarthritis.)

Senolytic dose schedule: d+q

Quercetin

25 mg per kilogram of
body weight is approximately:

100 pounds = **1,125 mg**

165 pounds = **1,875 mg**

220 pounds = **2,500 mg**

275 pounds = **3,000 mg**

330 pounds = **3,750 mg**

Dasatinib

2.5 mg per kilogram of
body weight is approximately:

100 pounds = **112 mg**

165 pounds = **187 mg**

220 pounds = **250 mg**

275 pounds = **305 mg**

330 pounds = **375 mg**

Take first dose of quercetin/dasatinib (preferably on empty stomach) then repeat same dose one week later.
(May repeat this protocol in 6-12 months, or sooner as your doctor may direct.)

Possible side effects include: Mild flu symptoms, diarrhea, headache, fatigue for 12-24 hours.

Caution: Take in presence of qualified medical doctor in case of severe allergic reaction.
Do not engage in strenuous exercise during or for one week after the dosing schedule.

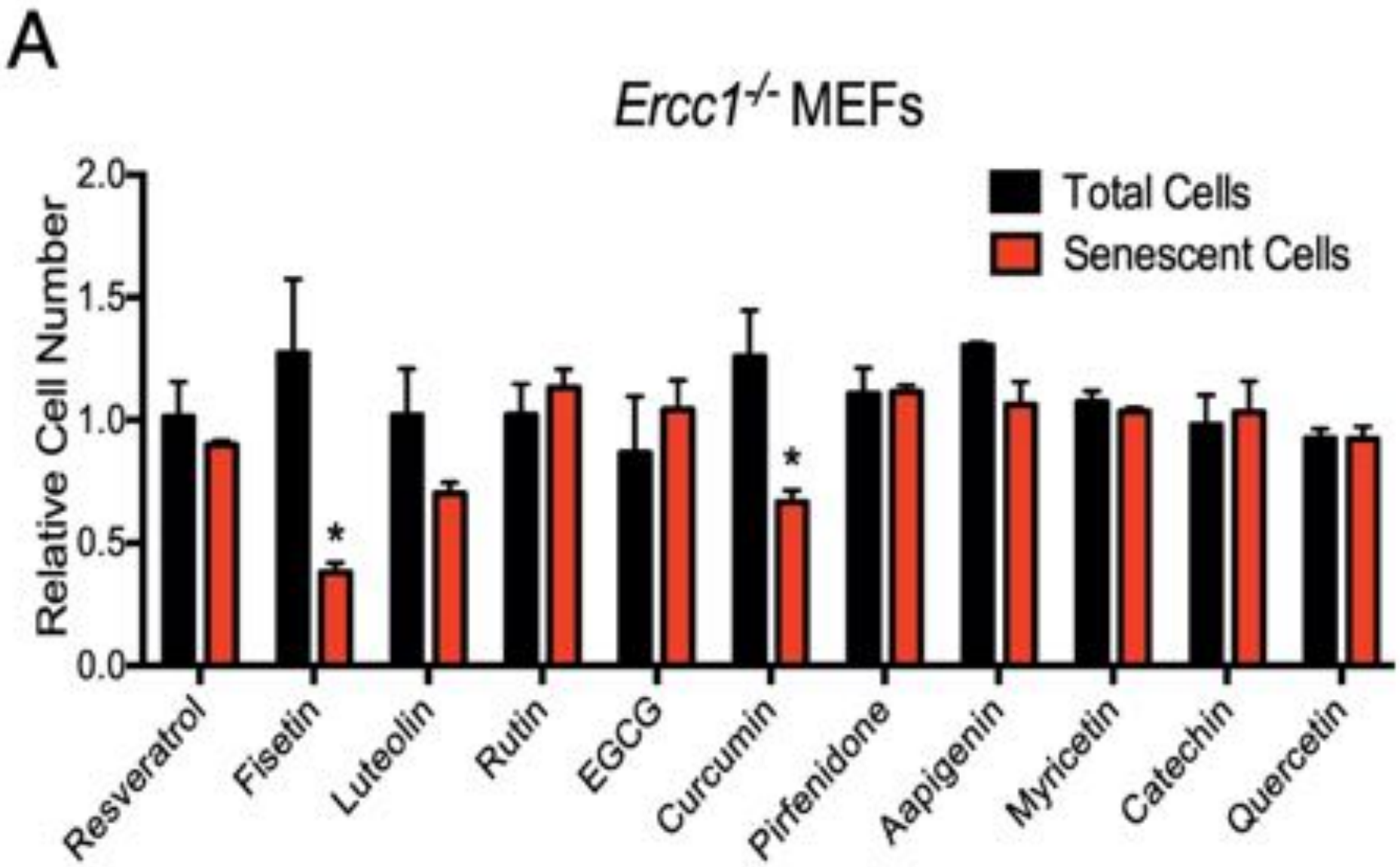
Fisetin: new, promising, safe senolytic

https://haleplushearty.org/2018/10/04/how-to-slow-aging/

University of Minnesota Medical School Researchers Have Discovered How to Slow Aging

Laura Niedernhofer, Paul Robbins

https://www.med.umn.edu/news-events/university-minnesota-medical-school-researchers-have-discovered-how-slow-aging



EBioMedicine 2018 36, 18-28DOI: (10.1016/j.ebiom.2018.09.015)

FINDINGS:

Of the 10 flavonoids tested, **fisetin was the most potent senolytic**. Acute or intermittent treatment of progeroid and old mice with fisetin **reduced senescence markers in multiple tissues**, consistent with a hit-and-run senolytic mechanism. Fisetin reduced senescence in a subset of cells in murine and human adipose tissue, demonstrating cell-type specificity. Administration of fisetin to wild-type mice late in life restored tissue homeostasis, reduced age-related pathology, and **extended median and maximum lifespan**.

EBioMedicine 2018 36, 18-28DOI: (10.1016/j.ebiom.2018.09.015)

https://clinicaltrials.gov/ct2/results?cond=&term=fisetin+mayo

Status	Study Title	Conditions	Interventions	Locations
Not yet recruiting	Alleviation by **Fisetin** of Frailty, Inflammation, and Related Measures in Older Adults	• Frail Elderly Syndrome	• Dietary Supplement: **Fisetin** • Drug: Placebo oral capsule	• **Mayo** Clinic in Rochester, Minnesota, United States
Recruiting	Alleviation by **Fisetin** of Frailty, Inflammation, and Related Measures in Older Women	• Frail Elderly Syndrome	• Dietary Supplement: **Fisetin** • Drug: Placebo oral capsule	• **Mayo** Clinic in Rochester, Minnesota, United States
Recruiting	Inflammation and Stem Cells in Diabetic and Chronic Kidney Disease	• Chronic Kidney Diseases • Diabetes Mellitus • Diabetic Nephropathies	• Dietary Supplement: **Fisetin** • Drug: Placebo oral capsule	• **Mayo** Clinic in Rochester, Minnesota, United States

Senolytic Dose Schedule: fisetin, Mayo trial

Fisetin

20 mg per kilogram of
body weight is approximately:

100 pounds = **910 mg**

165 pounds = **1,500 mg**

220 pounds = **2,000 mg**

275 pounds = **2,500 mg**

Take first dose (preferably on empty stomach?) then repeat same dose next day.
(May repeat this one month later, and repeat the whole two-month treatment in 6-12 months, or sooner as your doctor may direct.)

Possible side effects *may* include: Mild flu symptoms, diarrhea, headache, fatigue for 12-24 hours.
Caution: Take in presence of qualified medical doctor in case of severe allergic reaction.
Do not engage in strenuous exercise during or for one week after the dosing schedule.

Cautions on senolytics

- All-purpose cautionary note: need more trials.
- Off-target effects?
- Could senescent cells be useful?[1,2]
- Wait until consumer test available for presence of senescent cells?
- Extreme dietary restriction instead as safer option?
- Wait until we can “de-senesce” senescent cells?

[1] Mosteiro L et al., **Tissue damage and senescence provide critical signals for cellular reprogramming in vivo**. Science. 2016 Nov 25;354(6315).

[2] Muñoz-Espín D, Serrano M, **Cellular senescence: from physiology to pathology.** Nat Rev Mol Cell Biol. 2014 Jul;15(7):482-96.

nature > cell research > letter to the editor > article

Cell Research

Letter to the Editor | OPEN | Published: 05 June 2018

Embryonic senescent cells re-enter cell cycle and contribute to tissues after birth

Zhou B, et al.

Cell Research **volume 28**, pp. 775–778 (2018)

Recommendations

For everyone:

- Practice seno-*prevention* (DR, healthy lifestyle, antiaging in general).

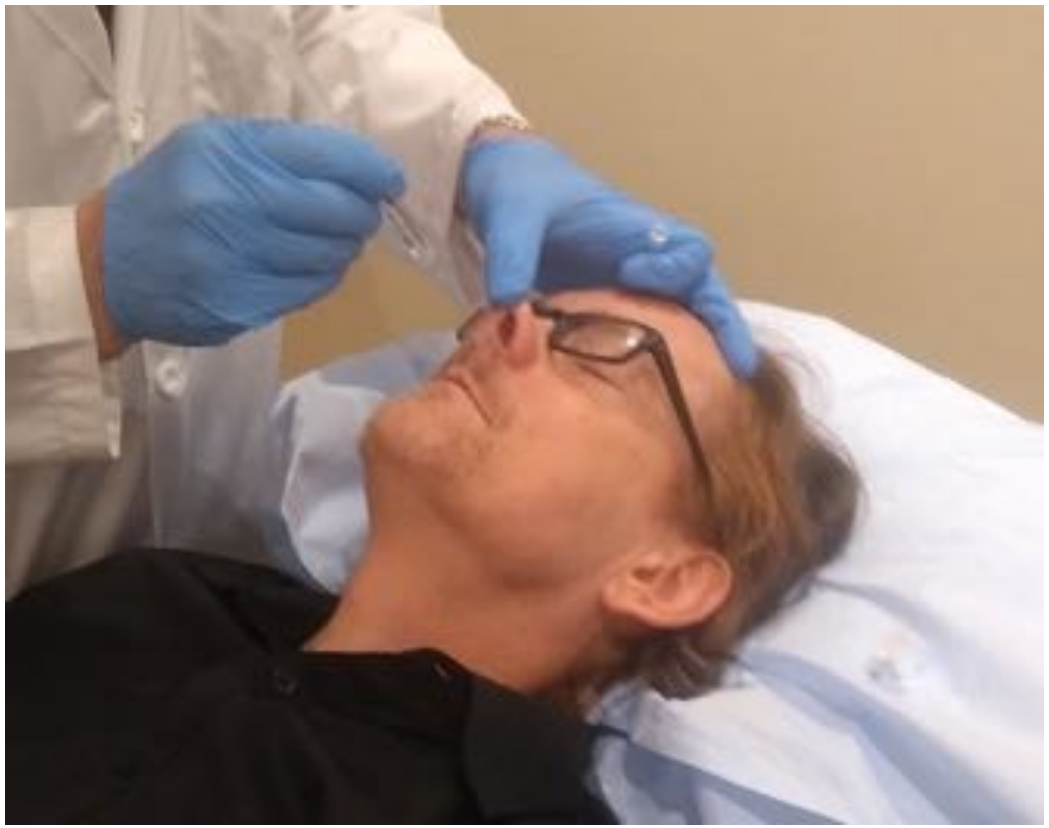
If you're under 40 or 45, or want to be cautious

- Wait for more trials.
- Wait for validated ways of measuring senescent cell burden.
- Possibly try one round of fisetin (if past age 35 or so). Fisetin appears very safe.

If you're over 40 or 45:

- Consider dasatinib + quercetin.
- Consider fisetin (at least several months before or after the d+q).

“Living Medicine”/“New Biologics”



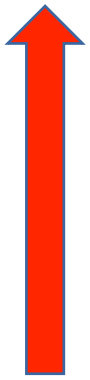
Living Medicine/New Biologics

- **Stem cells as building blocks**
- **Medicinal signaling cells (MSCs): “stem cells” as sources of youthful factors**
- **Young blood/plasma (including plasma exchange)**
- **Exosomes (and other extracellular vesicles)**
- **Isolated/extracted signaling factors**

Youthful signaling factors: Delivery mechanisms

More frequent treatment needed

- **Medicinal signaling cells**
- **Young blood/plasma**
- **Exosomes (and other EVs)**
- **Signaling factors**



Risk

- Pathogens
- Immune reaction
- Inefficiency (MSCs – trapped in capillaries)
- “Clumping” (MSCs)

Before we bypass 1990s “building block” thinking about stem cells...

- Academic researchers continue focusing on stem cells as replacement cells for damaged tissues.

  Classic example: Parkinson’s research.

- Some clinics offer partly differentiated stem cells to repair tissue under the rationale “like treats like”.

  Example: Mike Chan’s European Wellness clinics: fetal cell xeno-transplantaton.

(Fairly) young plasma (teens and twenties)

Ambrosia Trial: Still waiting for evidence to be published.

But what about the amazing parabiosis experiments?

- This involved a *continual* infusion of young blood and continual removal/filtering of old.

Really young plasma (umbilical cord plasma)

Growing body of pre-clinical evidence (mice), mostly for neurodegenerative diseases

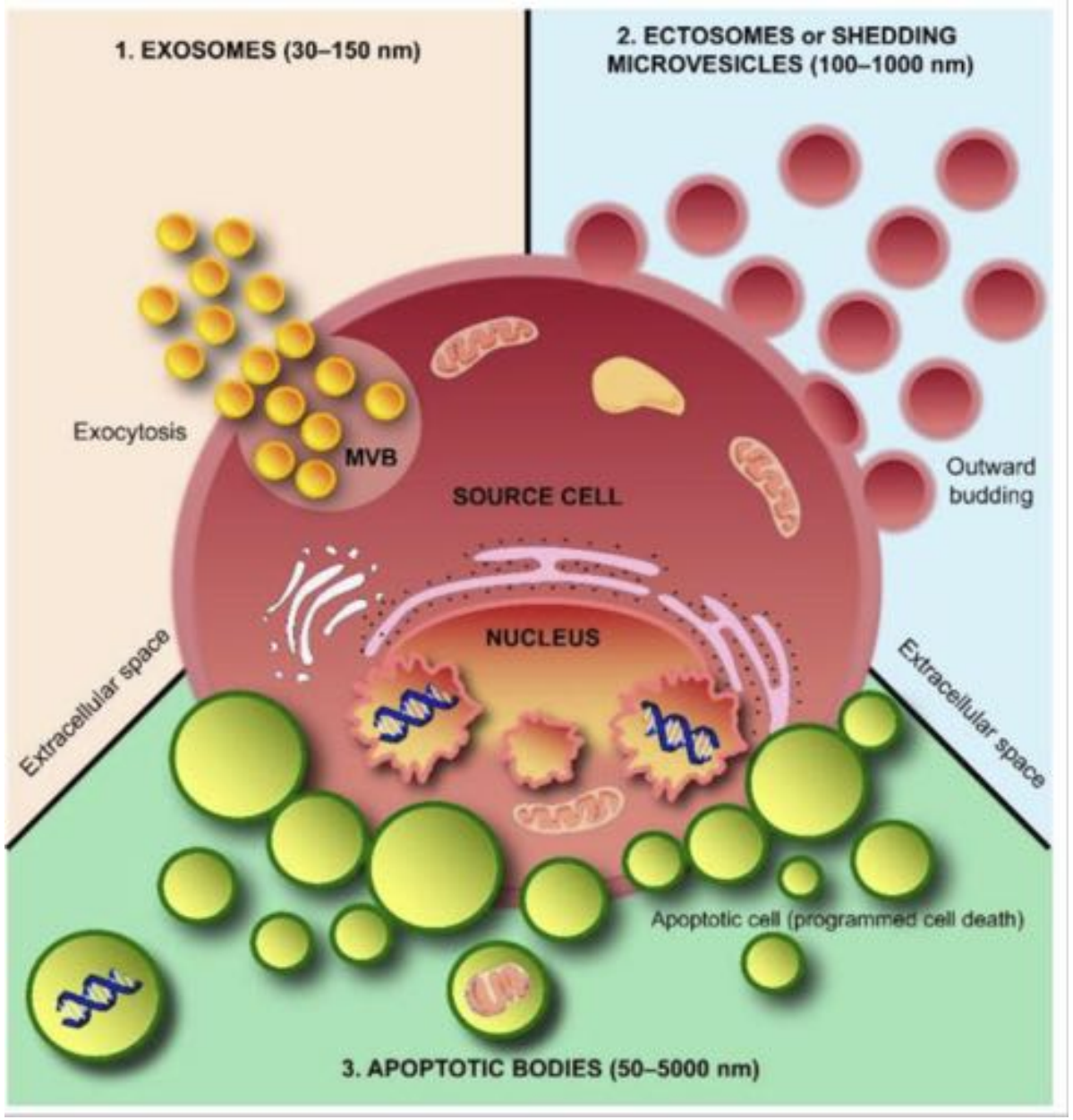
Clinical trials now starting:

- University of Southern Florida, Tampa
- Republic of Korea
- China

Phase I Clinical Safety Study About Human Umbilical Cord Blood Monocyte in the Acute Ischemic Stroke

Sponsor:
China Medical University Hospital
Collaborators:
StemCyte, Inc.
University of South Florida
Saneron CCEL Therapeutics, Inc.
Buddhist Tzu Chi General Hospital

Exosomes and (other) extracellular vesicles



https://www.clinicaltrials.gov/ct2/results?cond=&term=exosomes

102 Studies found for: *exosomes*

Status	• Study Title	• Conditions	• Interventions	• Locations
Unknown	Study of Molecular Mechanisms Implicated in the Pathogenesis of Melanoma. Role of**Exosomes**	• Metastatic Melanoma	• Biological: blood test	•CHU de Nice ^Hôpital de l'Archet Nice, France
Not yet recruiting	Allogenic Mesenchymal Stem Cell Derived**Exosome** in Patients With Acute Ischemic Stroke	• Cerebrovascular Disorders	• Biological: **exosome**	
Enrolling by invitation	Effect of Plasma Derived **Exosomes** on Cutaneous Wound Healing	• Ulcer	• Other: plasma-derived **exosomes**	•Department of Dermatology and Plastic Surgery, Kumamoto University Kumamoto, Japan
Active, not recruiting	Study Investigating the Ability of Plant**Exosomes** to Deliver Curcumin to Normal and Colon Cancer Tissue	• Colon Cancer	• Dietary Supplement: curcumin • Dietary Supplement: Curcumin conjugated with plant **exosomes** • Other: No intervention	•James Graham Brown Cancer Center Louisville, Kentucky, United States
Not yet recruiting	Combined Diagnosis of CT and **Exosome** in Early Lung Cancer	• Early Lung Cancer	• Procedure: Surgery	
Recruiting	Interrogation of **Exosome**-mediated Intercellular Signaling in Patients With Pancreatic Cancer	• Pancreatic Cancer • Benign Pancreatic Disease	•	•Memorial Sloan Kettering Cancer Center New York, New York, United States

Exosomes carry signaling molecules, both good and bad

- proteins
- lipids
- cytokines
- mRNA
- miRNA[1] (including xeno-miRNA)[2]
- siRNA
- mtDNA
- mitochondria[3]
- etc.

[1] ASEMV, 2018. Milk exosomes accumulate in the intestinal mucosa and peripheral tissues in wild-type pups nursed by exosome and cargo tracking dams. Janos Zempleni.

[2] Sci Rep. 2017; 7: 5933. Bovine milk-derived exosomes from colostrum are enriched with proteins implicated in immune response and growth. Samuel, et al.

[3] Redox Biol. 2018 Sep; 18: 54–64. Exosomal transfer of mitochondria from airway myeloid-derived regulatory cells to T cells. Hough, et al.

Exosomes: regulatory status

- Currently (more or less) unregulated in the US.
- This will likely change soon.
- If done under FDA Public Health Service Act Section 361, would be considered “minimally manipulated”, easy to gain access.
- If under Section 351, more stringent.

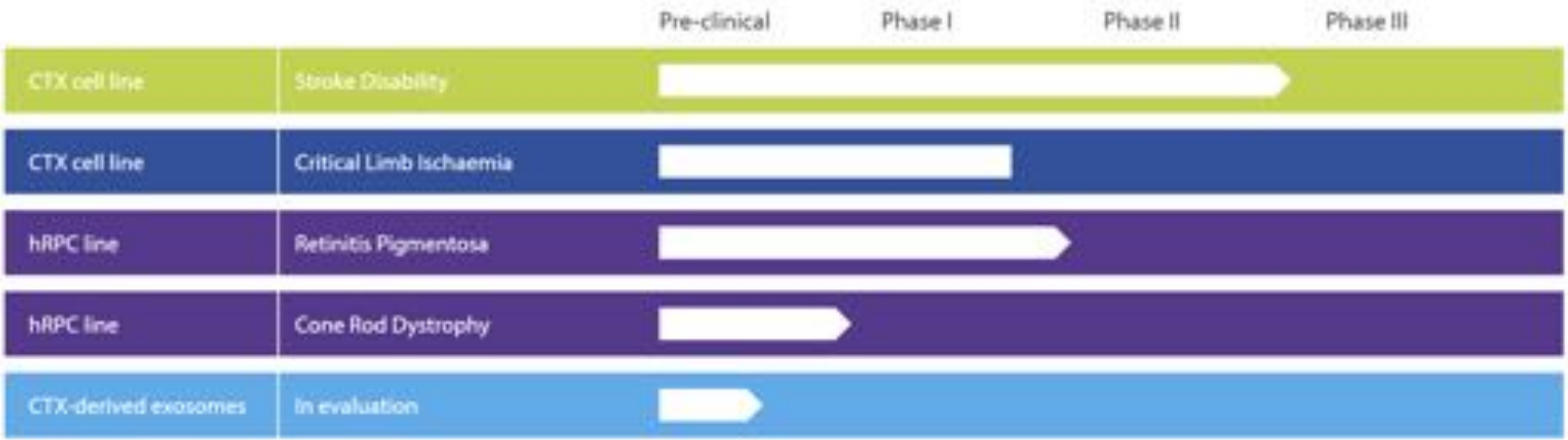
Exosomes: where to get them

- Kimera Labs
- Off-shore?

Soon:

- ReNeuron
- (Many others will follow.)

ReNeuron



http://www.reneuron.com/products/products-technologies/#products

Signaling molecules: Individual factors available now

- Oxytocin[1]
- GDF-11? (Risky. Narrow dose window?)
- IL-10 – anti-inflammatory cytokine
- Proprietary exosome contents from NovoMax[2]

[1] Nat Commun. 2014; 5: 4082. Oxytocin is an age-specific circulating hormone that is necessary for muscle maintenance and regeneration. Elabd, et al.

2 http://www.novomax.us/. NovoMax® Exosomes.

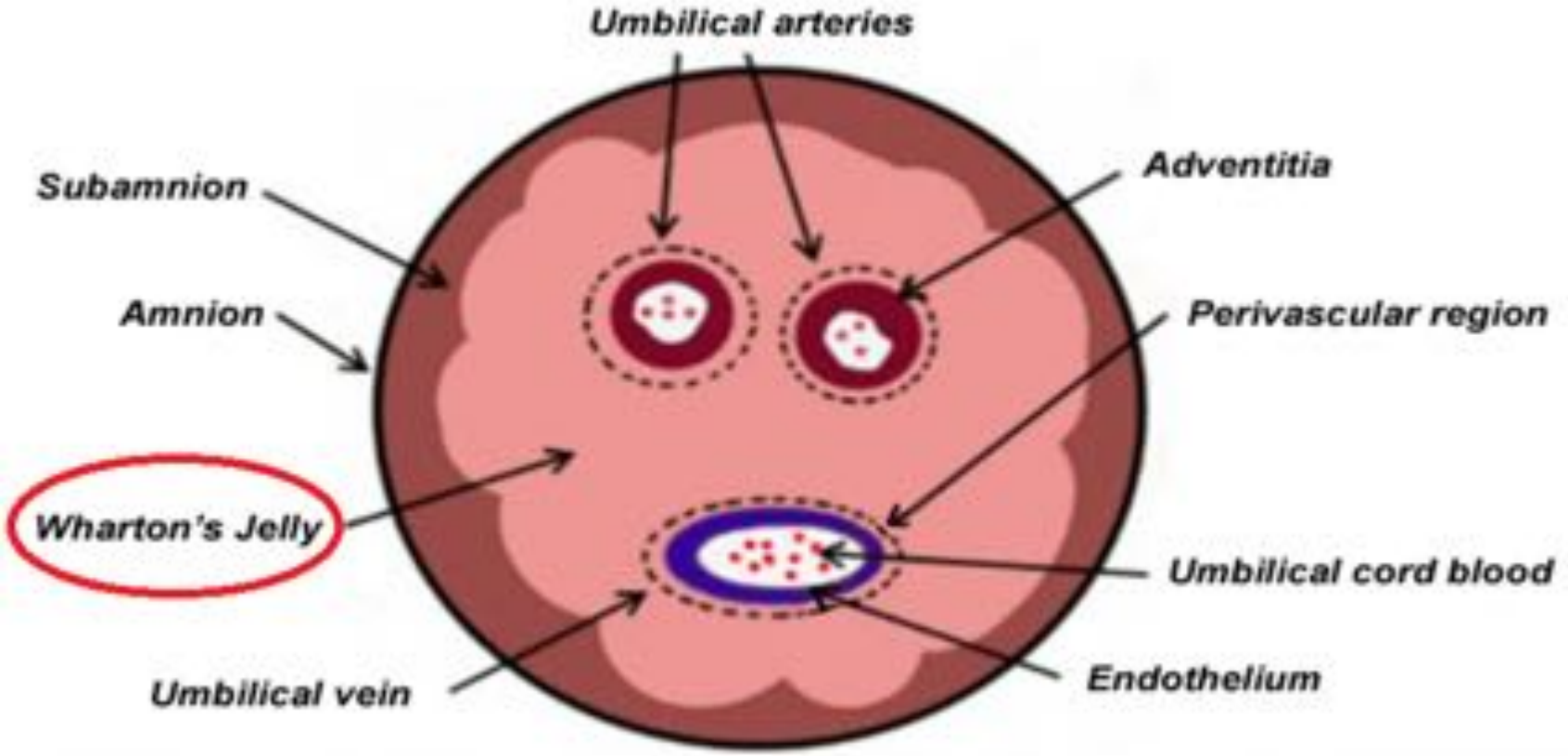
Signaling molecules: Individual factors coming soon

- VEGF – stimulates formation of blood vessels
- BDNF – supports survival of neurons and encourage growth
- *particular* miRNAs[1]

[1] miR-133b, for example, which has been shown to help with stroke recovery, neurite outgrowth, and so on.

Medicinal signaling cells (MSCs) from young sources

Birth associated tissue–derived cells



http://cellsafegroup.com/cellsafegroup/services/whartons-jelly-msc

Status of the evidence for MSCs stem cells: *Fairly weak*

- Many studies in rodents with good results.
- Many case reports in humans for non-aging-related conditions.
- But: almost no (human) clinical trials for aging-related conditions.

Why aren't the hundreds – thousands? – of clinics offering stem cells for age reversal purposes conducting studies?

- Regulations make it very difficult.
- Physicians, by definition, practice personalized medicine. Isolating one independent variable difficult.

Questions to ask a provider

- What's your success rate, and am I a good fit?
- What kind of data do you collect and report?
- Is there independent oversight of the treatment plan by an ethics committee?
- Is there any independent oversight or accreditation of the clinic where the treatment will be done and the facility where the cells are processed?
- Is there approval from a national or regional regulatory agency, such as the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA) or Japan's Pharmaceuticals and Medical Devices Agency (PMDA), for this treatment of this specific disease?
- What sort of follow-up is there?

LONGEVERON CLINICAL TRIALS - ROBUST PIPELINE

	PHASE 1	PHASE 2	PHASE 3	APPROVAL
US Trials				
Aging Frailty				
Immune Response to Influenza Vaccine in Aging Frailty				
Hypoplastic Left Heart Syndrome (ultra rare pediatric condition)				
Alzheimer's Disease				
Metabolic Syndrome				
JAPAN Trials				
Aging Frailty				
BAHAMAS Trials				
Open Label Treatment Registry for Aging Frailty				

Enrolling patients`

Enrollment pending

Expanded access program approved by Ministry of Health

AllogeneiC Human Mesenchymal Stem Cells (hMSC) in Patients With Aging FRAilTy Via IntravenoUS Delivery. (CRATUS)

- Physical performance improvements.
- Female sexual quality of life improvement.
- Serum TNF-α levels decrease.

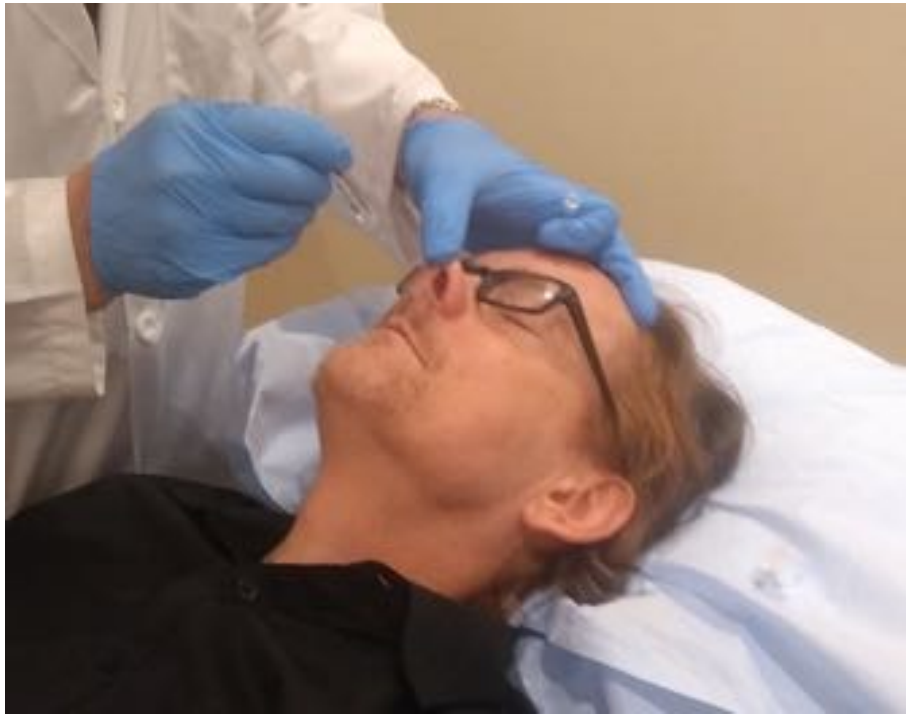
(100m cells proved *better* than 200m cells.)

J Gerontol A Biol Sci Med Sci. 2017 Oct 12;72(11):1513-1522. Allogeneic Mesenchymal Stem Cells Ameliorate Aging Frailty: A Phase II Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Hare JM, et al.

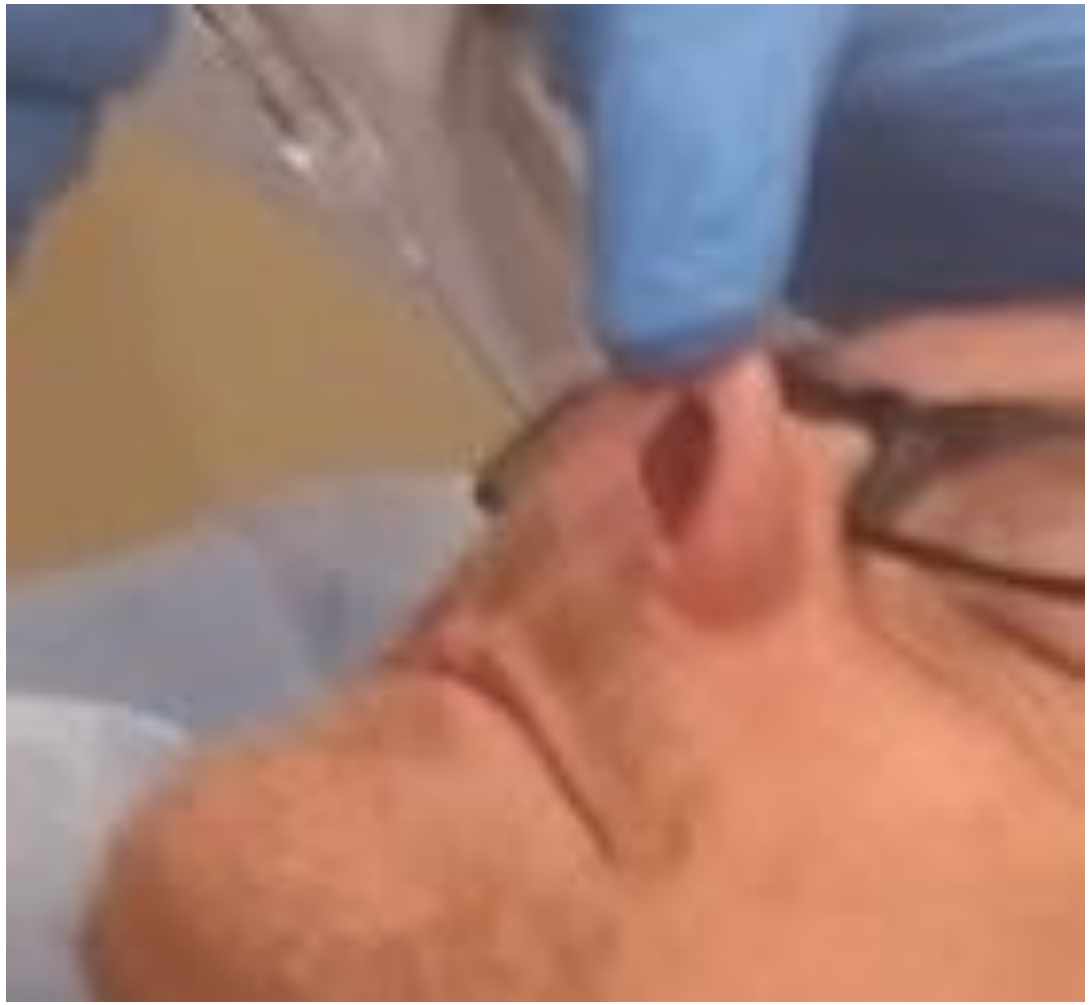
Where else can you get stem cells?

- Almost everywhere!

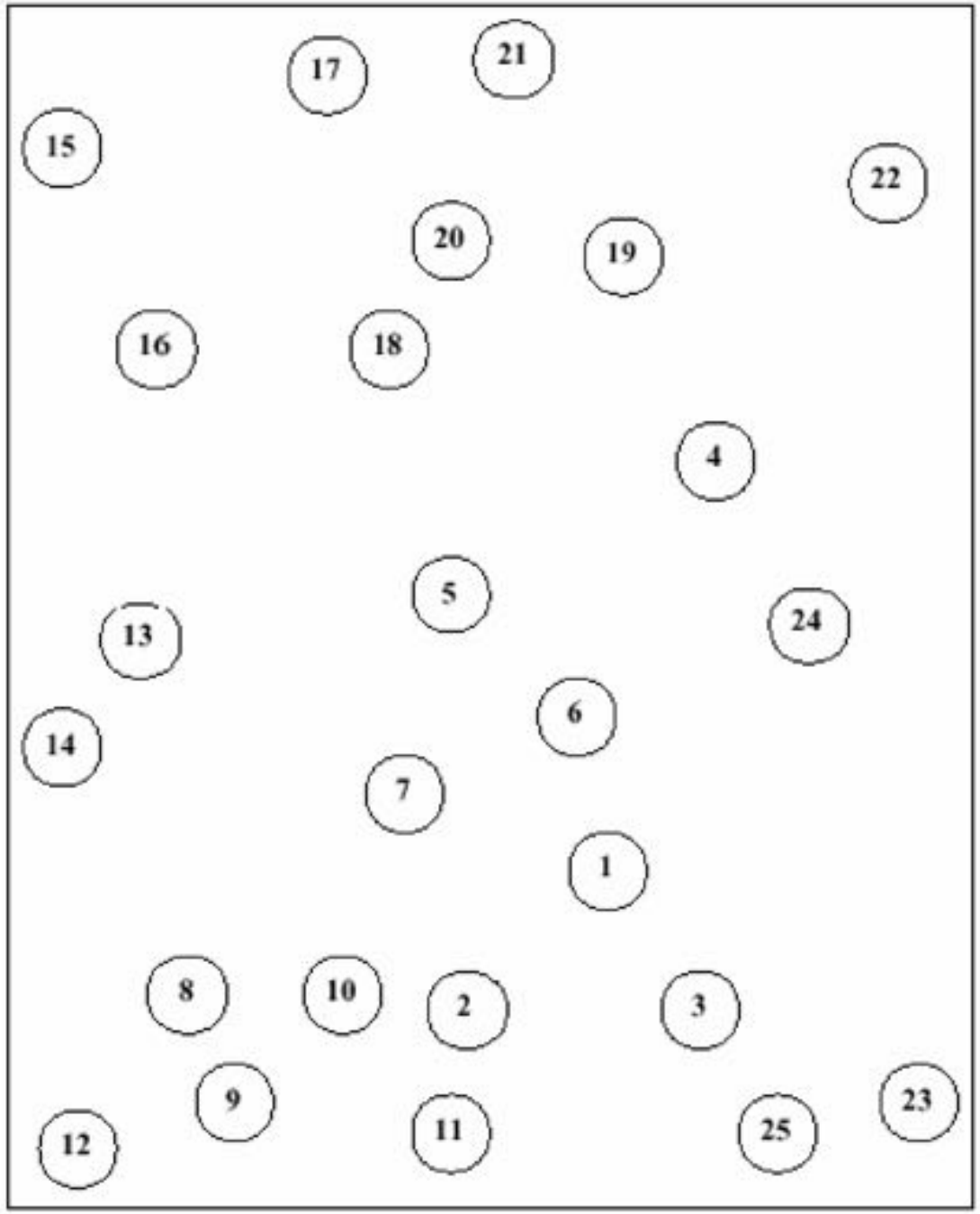
Preparing for intranasal stem cell injection.
Dr. Farshchian of the Center for Regenerative Medicine



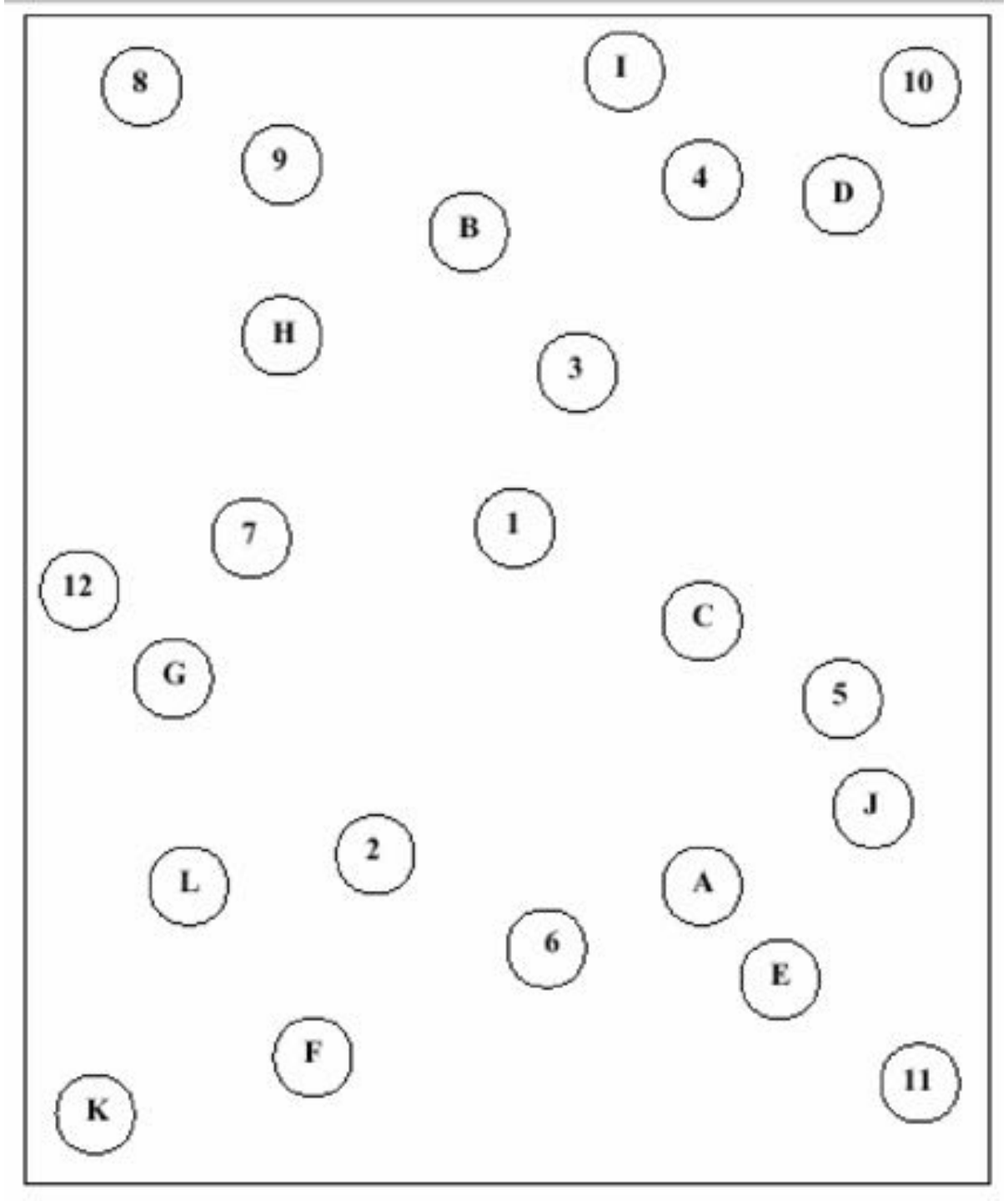
No pain, no . . . immortality



Trail Making Test A



Trail Making Test B



TMT results, before and after

2018-Oct-10: baseline tests.

2018-Oct-10; 21:00.
Trail-making A: 13 seconds
Trail-making B: 33 seconds

2018-Oct-12; 14:00: stem cell injections.

2018-Nov-03; 21:00.
Trail-making A: 13 seconds
Trail-making B: 37 seconds

Gene-editing/-therapy has arrived

- Several treatments approved by FDA (for non-aging related conditions)
- BioViva Science

  Telomerase lengthening (TERT)[1]

  Myostatin inhibitor
- Numerous clinical trials starting or soon to start.

  Example: *APOE*-ε4 → *APOE*-ε2

  (*Lots* of promising pre-clinical work.)

[1] EMBO Mol Med. 2012 Aug; 4(8): 691–704. Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer. Blasco, MA et al.

https://clinicaltrials.gov/ct2/show/NCT03634007?term=APOE+gene+therapy

Gene Therapy for APOE-ε4 Homozygote of Alzheimer's Disease

Condition or disease	Intervention/treatment	Phase
Alzheimer Disease Early Onset Alzheimer Disease	Biological: AAVrh.10hPOE2 vector	Phase 1

Putting all this together
Case study:
Brian