

Systems Biology of Human Aging Network Model Wall Chart Network Node Box Notes and References

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This is a Work-in-Progress. I invite your collaborative suggestions of references and commentary regarding the numbered boxes, as well as pathways involving groups of boxes.

I also invite discussion regarding whether setting up an online Wiki, or database, or spreadsheet, or discussion thread might be more or less useful than a text document.

0xx Cytosolic or Intracellular Activities

1xx WHOLE CELL ACTIVITIES; populations of cells

2xx Extracellular spaces and ECM, blood, lymph

3xx Gene expression & repression. Intranuclear events

7xx External Intervention, Environmental Factors, Therapies, Drugs, Lifestyle, etc.

9xx TISSUE, ORGAN, & WHOLE BODY: PHYSIOLOGY & PATHOLOGY.

Downstream effects of aging.

001 Lysosomes digest Junk, until they become filled with LF

002 **ROS** oxidize proteins & lipids

005 Ana Maria Cuervo.

013 Spermidine. Madeo. Science 2018 Jan 26.

027 Iron-Sulfur cluster assembly depends on membrane potential.

<https://www.sciencedirect.com/science/article/pii/S0167488914004467>

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032 Clonal amplification of mutant mtDNA causes PM cell or skeletal muscle fiber segment to become anaerobic. Aubrey de Grey.

033 Spermidine. Madeo. Science 2018 Jan 26. Vitamin C & Fasting. Ana Maria Cuervo.

092, 093, 096, 923 With age, noradrenergic α_{2A} receptors in pre-frontal cortex neurons decline, allowing cytoplasmic cAMP levels to increase. This opens K⁺ channels, which inhibits neurons from firing, thus reducing working memory, executive function, and clarity of thinking. Wang M, Gamo NJ, Yang Y, Jin LE, Wang XJ, Laubach M, Mazer JA,

Systems Biology of Human Aging - Furber Network Model

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- 735==>131 **Senolytic** Drugs kill arrested cells to prevent spread of damage. Research includes quercetin, Dasatinib, and FOXO4-DRI (James Kirkland, Mayo Clinic)
- 153 Commanding neuroendocrine cell population in hypothalamus declines with age. Ulf Brunk.
- 726 ==> 157 van Praag, H., Shubert, T., Zhao, C. & Gage, F. H. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J. Neurosci*. 25, 8680–8685 (2005).
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Distinguishing and Quantifying Peptides and Proteins Containing d-Amino Acids by Tandem Mass Spectrometry. Christopher M. Adams and Roman A. Zubarev, Laboratory for Biological and Medical Mass Spectrometry, Uppsala University, Sweden *Anal. Chem.*, 2005, 77 (14), pp 4571–4580. June 21, 2005 PMID 16013875.
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- 338 Telomeres become oxidized and telomere length decreases in some cells.
- 339 Shawi M, Autexier C. Telomerase, senescence and ageing. *Mech Ageing Dev*. 2008;129(1–2):3–10.
- 342 <https://www.sciencedirect.com/science/article/pii/S0167488914004467>
- 359 Progerin and telomere dysfunction collaborate to trigger cellular senescence in normal human fibroblasts. Kan Cao, Cecilia D. Blair, Dina A. Faddah, Julia E. Kieckhaefer, Michelle Olive, Michael R. Erdos, Elizabeth G. Nabel, Francis S. Collins. *J Clin Invest*. 2011;121(7):2833–2844. doi:10.1172/JCI43578. "...progressive telomere damage during cellular senescence plays a causative role in activating progerin production. Progressive telomere damage was also found to lead to extensive changes in alternative splicing in multiple other genes. Interestingly, elevated progerin production was not seen during cellular senescence that does not entail telomere shortening."
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- 363 Without the action of telomerase or ALT, each cell's telomeres get shorter with each subsequent mitosis.
- 365 **Progerin shortens Telomeres.** [Nucleus](#). 2015;6(3):172-8. doi: 10.1080/19491034.2015.1048407. **A beginning of the end: new insights into the functional organization of telomeres.** [Wood AM](#), [Laster K](#), [Rice EL](#), [Kosak ST](#). Department of Cell and Molecular Biology; Feinberg School of Medicine; Northwestern University ; Chicago , IL , USA. PMID: 25961132
- 365 Gonzalez-Suarez *op.cit.* 2009.
- 366 Kan Cao *op.cit.* 2011.
- 367 Methylation of histones.
- 705 Agmatine is a precursor of Spermadine.
- 710 **Gene Editing, Genetic Engineering:**
Increase expression of beneficial genes: eg TFAM , Lamp2a, hTERT, Lon Protease, Proteasome.
- Make super-fibroblasts. Re-differentiate certain cells for improved performance. George Church. *The Next Big Future*. 16 Feb 2017
<http://www.nextbigfuture.com/2017/02/george-church-indicates-reversal-of.html>
Genetically engineer more TFAM into cells. This allows them to increase their own NAD⁺/NADH ratio, so there is no need to take NMN. This upregulates ATP production. TFAM is a key regulatory protein that is in this pathway of NMN and NAD⁺. It allows cells to manufacture the NMN precursor on their own, so you don't have to manufacture it outside the cell and then try to get it into the cell from outside. Ideally, you don't want to have to take NMN for the rest of your life, you want to fix the body's ability to make its own NMN and buy yourself rejuvenation for at least a few decades before you have to worry about NMN again. In order to accomplish this on a single cell level, they have used CRISPR to activate a TFAM activator, and they made it semi-permanent. With this technique, they were able to increase TFAM levels in the cell

Systems Biology of Human Aging - Furber Network Model

by 47-times. This resulted in restored ATP levels, increased NAD⁺, and an increased NAD⁺ / NADH ratio. It also increased total mitochondrial mass and reversed several other age-related changes.

714==>931 Tilly J.

722 TTR solubilizing drugs. Concept by JD Furber.

724 Stimulate or engineer super-fibroblasts or MSCs to be better and faster at repairing ECM, digesting bad ECM molecules; replacing them with good ones. Concept by John D. Furber. Chapter 19. *The Future of Aging*. (Springer 2010).

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731 => 338 Telomeres shorten in response to psychological stress, as well as to other factors. (Rita Effros, Elissa Epel)

732 => 238 => 218 Sleep enhances clearance of amyloid β . (Mendelsohn & Larrick book, ch 11)

735==>131 **Senolytic** Drugs kill arrested cells to prevent spread of damage. Research includes quercetin, Dasatinib, and FOXO4-DRI (James Kirkland, Mayo Clinic). Also <https://www.oisinbio.com/>

737 Nano-scavenger therapy. (Lou Hawthorne, US Patent)

739 Induce Exocytosis to remove lipofuscin. Concept by JD Furber.

740 Gamma frequency 40 Hz flashing light stimulates glia to remove amyloid β from brain. Li-Huei Tsai, Nature Dec 2016.

742 **J147** induces NGF & BDNF. *Alzheimers Res Ther.* 2013 May 14;5(3):25. doi: [10.1186/alzrt179](https://doi.org/10.1186/alzrt179). eCollection 2013. "The neurotrophic compound J147 reverses cognitive impairment in aged Alzheimer's disease mice". Prior M(1), Dargusch R(1), Ehren JL(1), Chiruta C(1), Schubert D(1). Author information: (1)The Salk Institute for Biological Studies, Cellular Neurobiology Laboratory, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA.

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PMID:

29316249

743 **SM04554** stimulates hair growth in androgenic alopecia. Sansumed drug candidate SMO4554 in clinical trials. <https://clinicaltrials.gov/ct2/show/NCT02503137>

745 Minor surgery can remove bone depositions blocking the channels in the cribiform plate. A **shunt** is installed to allow natural circulation of cerebrospinal fluid. (Prof. Doug Ethell, UC Riverside and Leucadia Therapeutics)

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748 **Macrophages** digest LF - filled Exosomes

749 *Science Advances.*

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923, 092, 093, 096, With age, noradrenergic α_{2A} receptors in pre-frontal cortex neurons decline, allowing cytoplasmic cAMP levels to increase. This opens K^+ channels, which inhibits neurons from firing, thus reducing working memory, executive function, and clarity of thinking. Wang M, Gamo NJ, Yang Y, Jin LE, Wang XJ, Laubach M, Mazer JA, Lee D, Arnsten AF. Neuronal basis of age-related working memory decline. *Nature.* 2011 Jul 27;476(7359):210-3. doi: 10.1038/nature10243. PubMed PMID: 21796118; PubMed Central PMCID: PMC3193794.

935, 163, 164, 332 Inflammation of Hypothalamus & skin. Zhang. *Nature.* 2 May 2013.

936 **GnRH** improves Cognition, muscle strength, skin, bone, neurogenesis, memory

937 **CardiacHypertrophy**

938 **Body Plan Dysregulation**

939 Failure to **Regenerate**

940 Prostate Hyperplasia