AGEX THERAPEUTICS

The Reprogramability of Aging

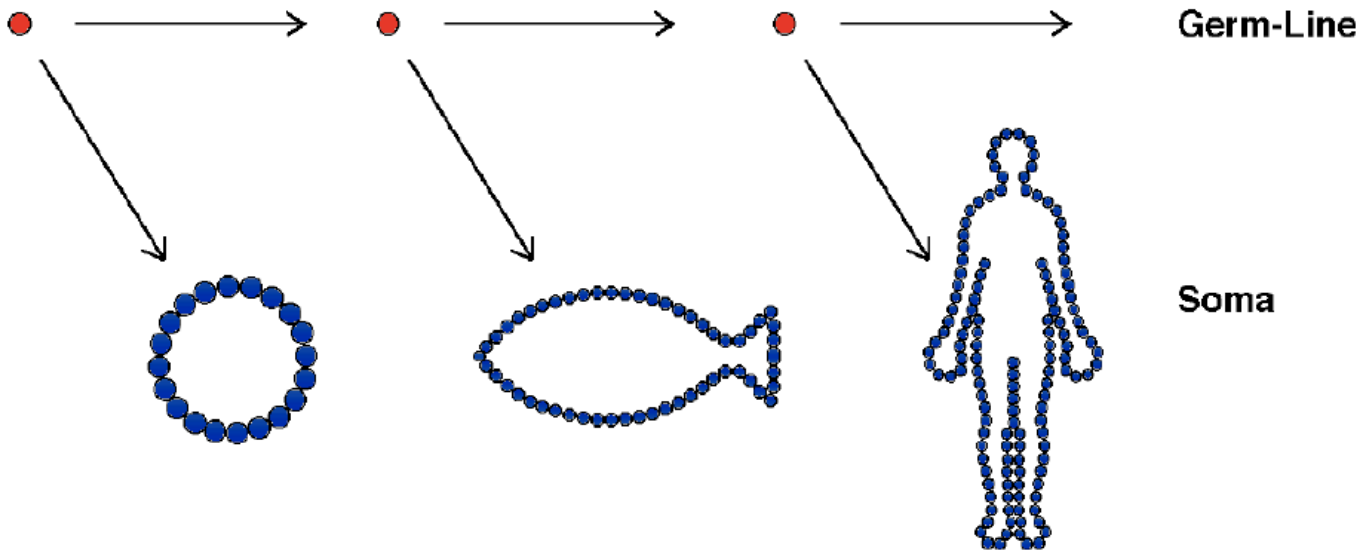
March 16, 2018

Safe Harbor Statement

The matters discussed in this presentation include forward looking statements which are subject to various risks, uncertainties, and other factors that could cause actual results to differ materially from the results anticipated. Such risks and uncertainties include but are not limited to the success of AgeX Therapeutics and its affiliates in developing new stem cell products and technologies; results of clinical trials of such products; the ability of Agex and BioTime and its licensees to obtain additional FDA and foreign regulatory approval to market products; competition from products manufactured and sold or being developed by other companies; the price of and demand for such products; and the ability of Agex to raise the capital needed to finance its current and planned operations. Any statements that are not historical fact (including, but not limited to statements that contain words such as "will," "believes," "plans," "anticipates," "expects," "estimates") should also be considered to be forward-looking statements. Forward-looking statements involve risks and uncertainties, including, without limitation, risks inherent in the development and/or commercialization of potential products, uncertainty in the results of clinical trials or regulatory approvals, need and ability to obtain future capital, and maintenance of intellectual property rights. As actual results may differ materially from the results anticipated in these forward-looking statements they should be evaluated together with the many uncertainties that affect the business of Agex and BioTime and its other subsidiaries, particularly those mentioned in the cautionary statements found in BioTime's Securities and Exchange Commission filings. BioTime and AgeX disclaim any intent or obligation to update these forward-looking statements.

AGEX THERAPEUTICS

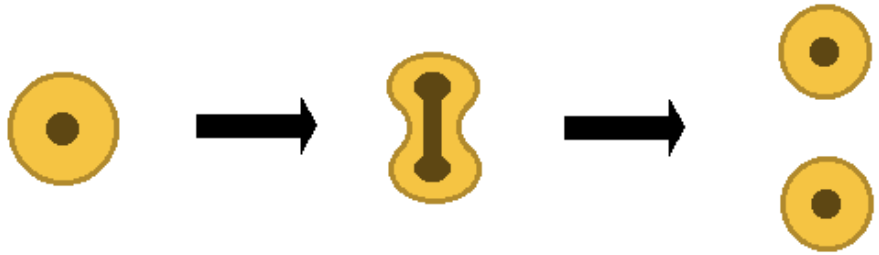
Some Initial Observations



- The germ-line lineage of cells that created us have not aged for billions of years (otherwise we would not be here).
- Aging is a somatic phenomenon, turned on during somatic cell differentiation. It is also completely reversible on a cellular level otherwise SCNT wouldn't make young animals.

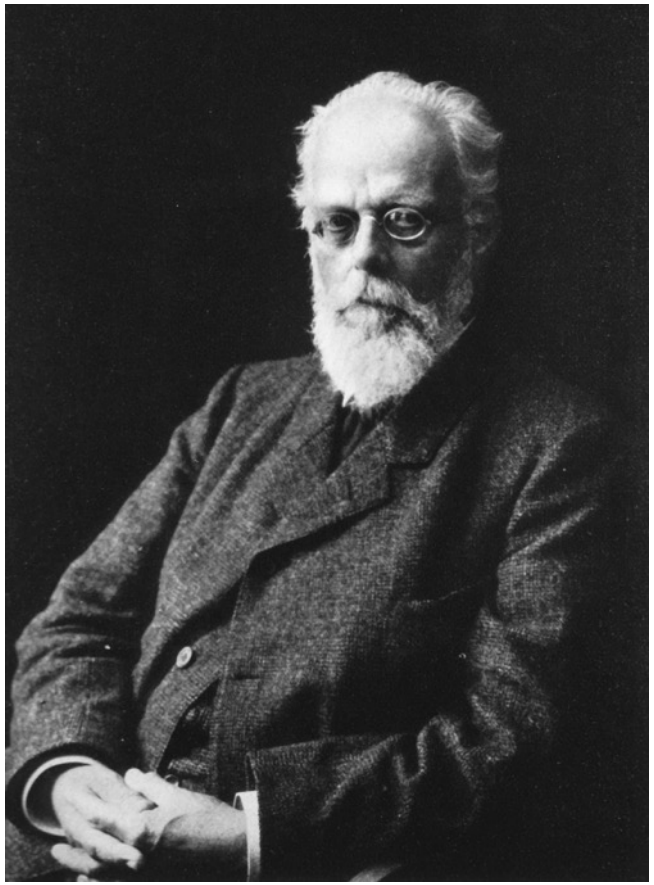
AGE X THERAPEUTICS

Some Initial Observations



"Death takes place because a worn-out tissue cannot for ever renew itself, and because a capacity for increase by means of cell-division is not everlasting, but finite."

- A. Weismann, 1891



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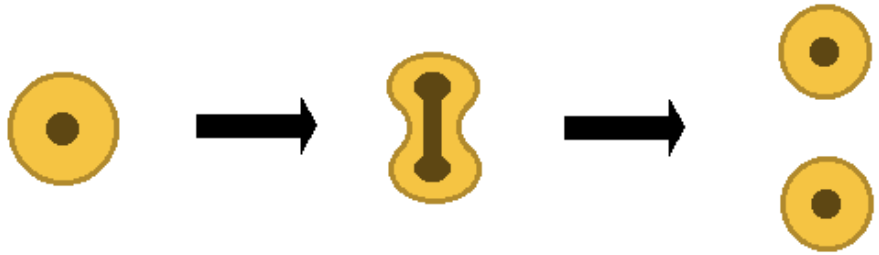

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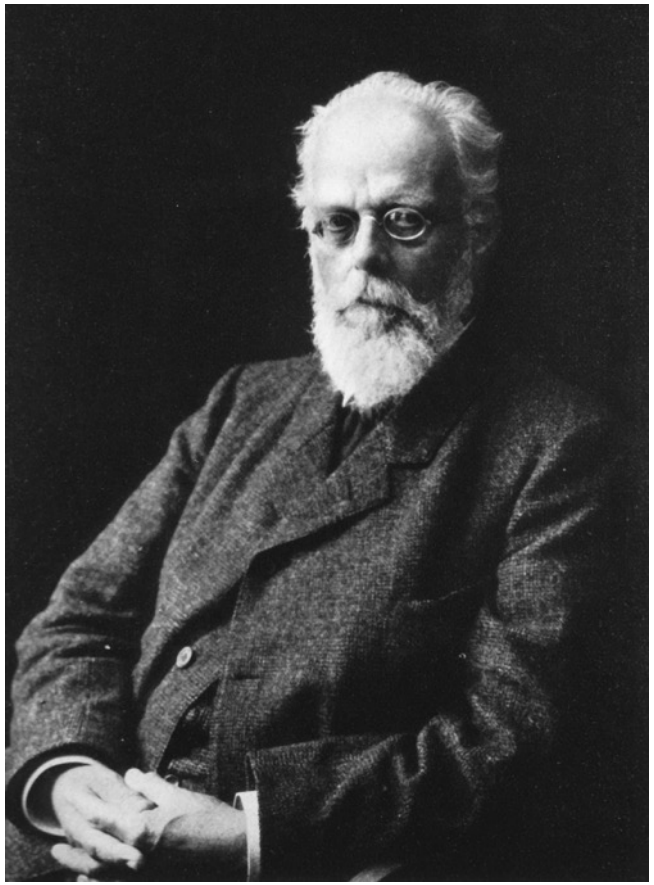

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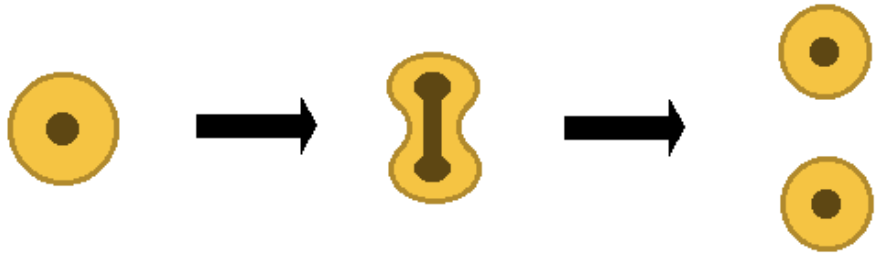

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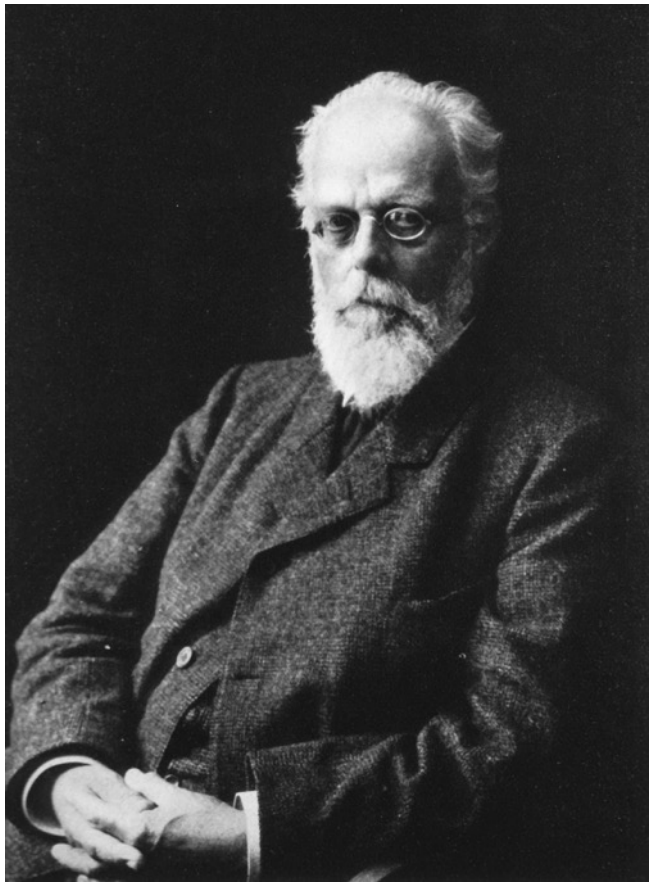


AGEX THERAPEUTICS

Some Initial Observations

To “reprogram” aging implies there was a program in the first place…

There has been resistance to this idea because it was thought to be unlikely that evolution would select for a program that played out only after reproduction.

AGEX THERAPEUTICS

Some Initial Observations

PLEIOTROPY, NATURAL SELECTION, AND THE EVOLUTION OF SENESCENCE [1]

GEORGE C. WILLIAMS

Michigan State University

Received February 26, 1957

Some Initial Observations

The Nature of the Antagonistic Pleiotropy

Genes whose expression/lack of expression early in life confers a survival benefit, but late in life results in aging and mortality of the soma

Some Initial Observations

Taken together, Weismann's barrier between mortality and immortality through antagonistic pleiotropy suggests the following:

- We are looking for molecular changes that occur during the shift from the germ-line to somatic cells
- The late-life antagonism is likely tumor suppression
- So, prediction would be that when cancer cells do emerge, they will re-express the immortal/ regenerative phenotype

AGEX THERAPEUTICS

Antagonistic Pleiotropy & Telomerase

Telomerase OFF in somatic cells reduces cancer in young

Leads to senescence in old

Antagonistic Pleiotropy & Regeneration

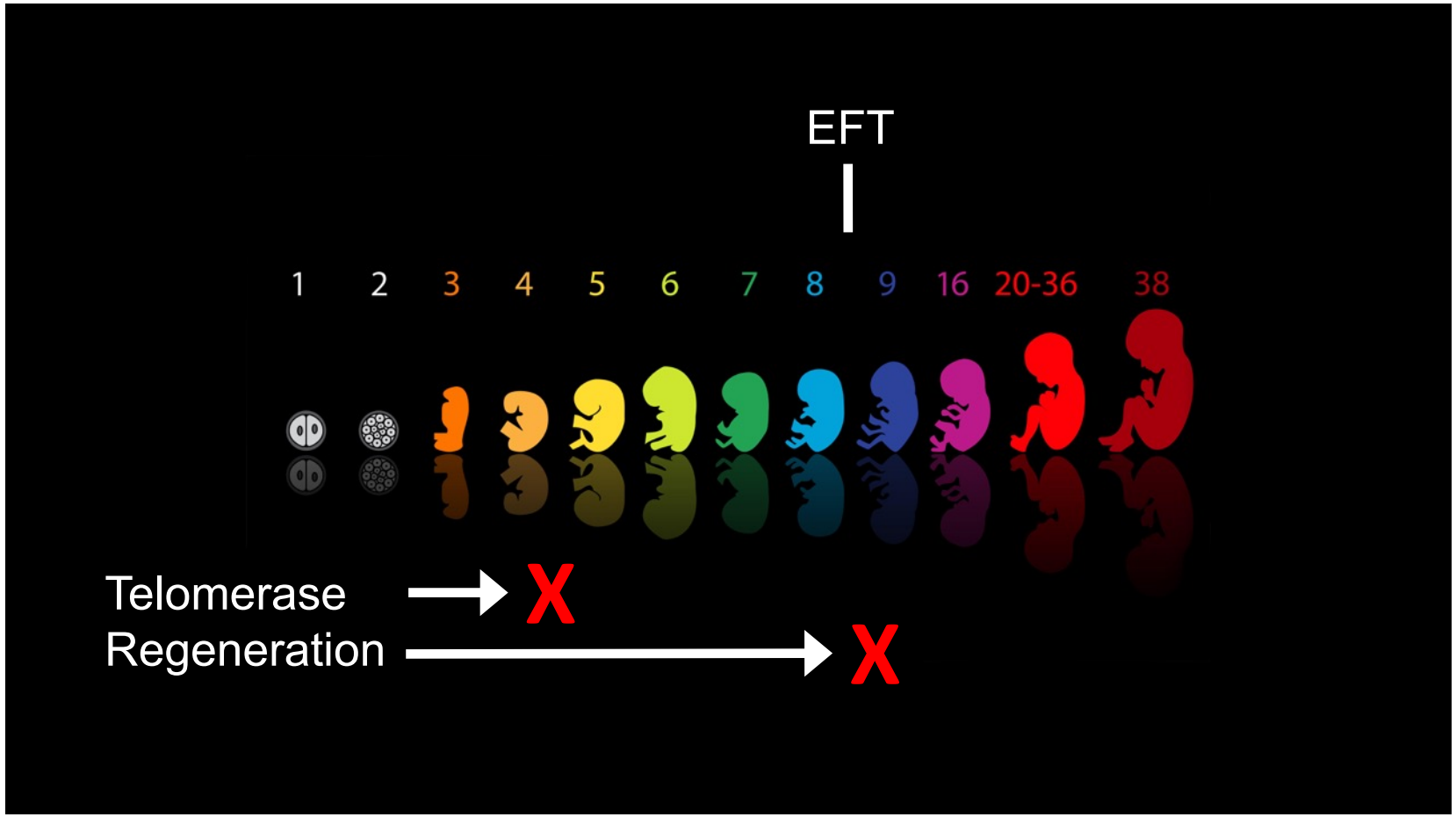
Regeneration OFF in somatic cells
after EFT reduces cancer in young

Leads to disrepair/fibrosis
in old

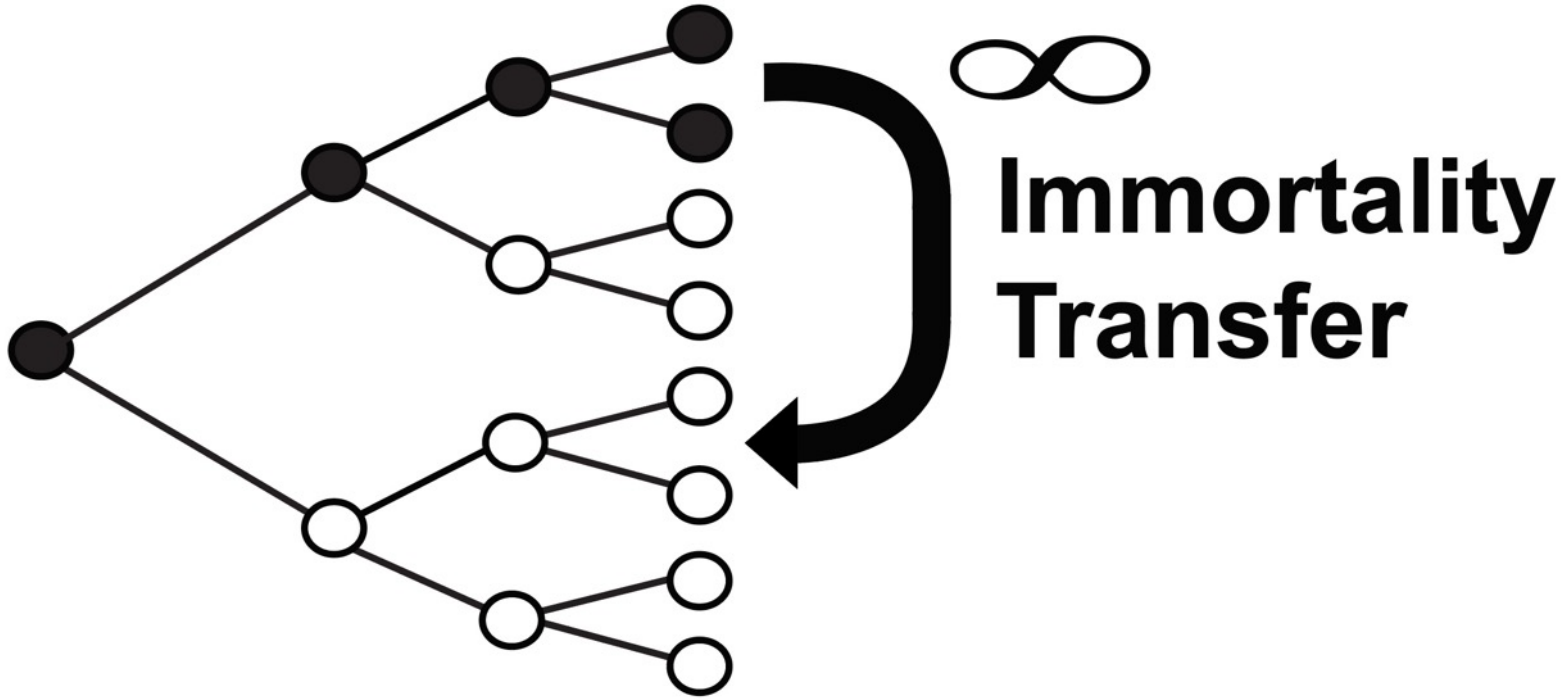
AGEX THERAPEUTICS

Some Initial Observations

Timing of the Weismann Barrier Allows for Selection of a Program

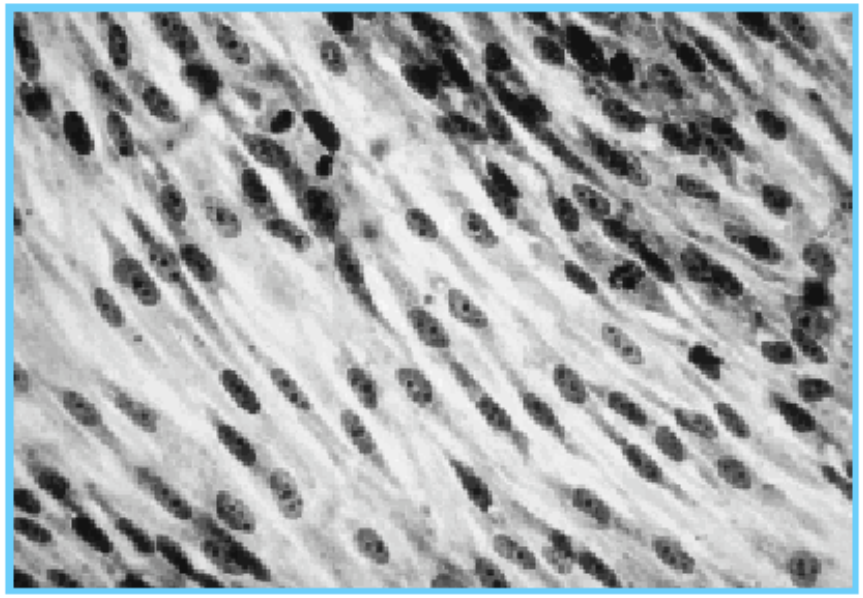


Somatic Cell Mortality & Immortality

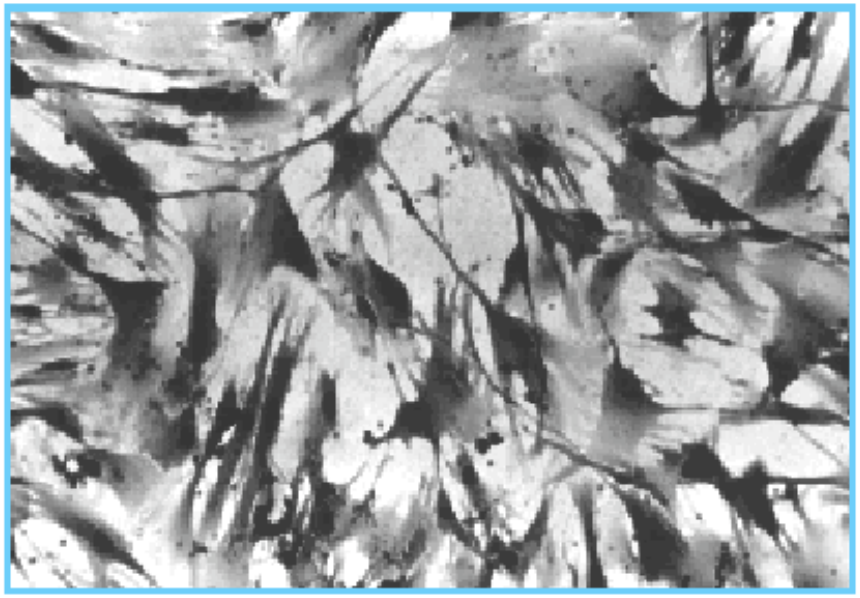


Somatic Cell Mortality & Immortality

Somatic Cells Have a Finite Lifespan



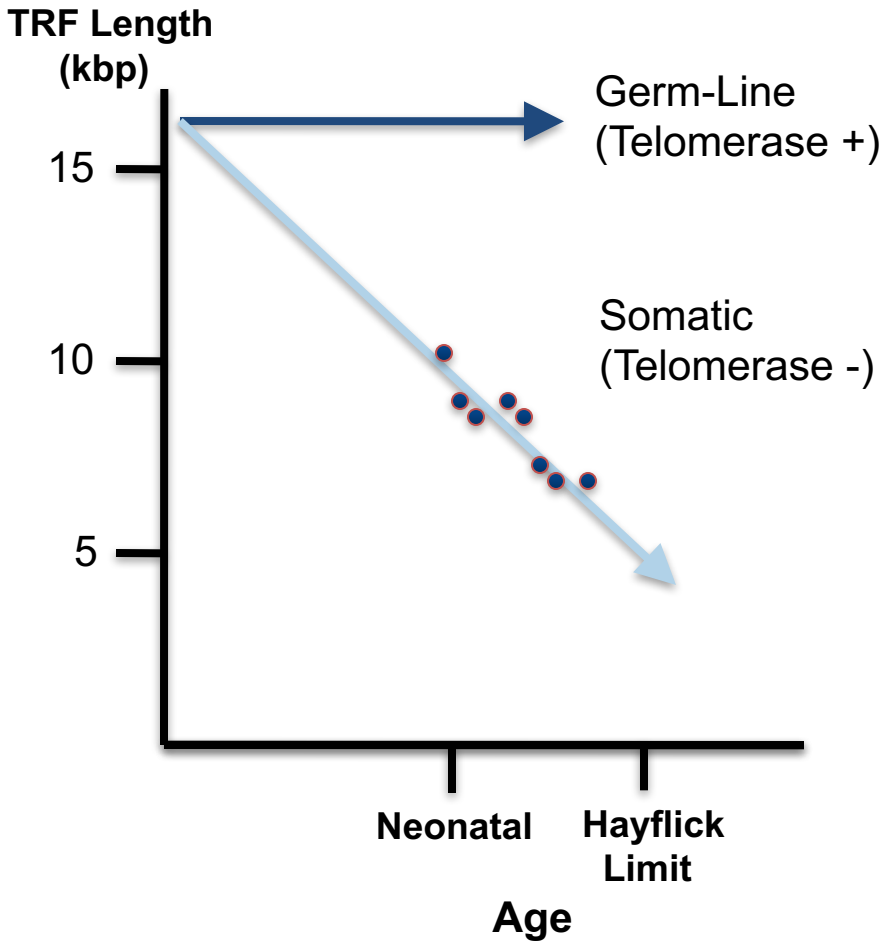
Young
Fibroblasts

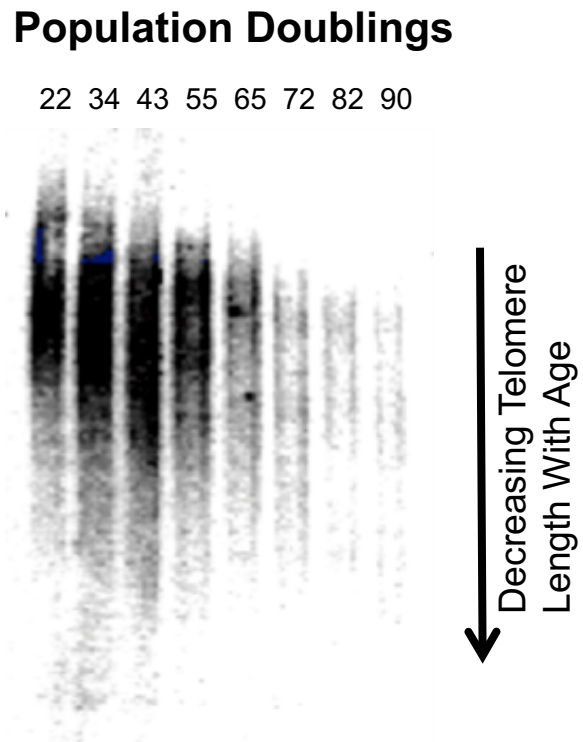


Senescent
Fibroblasts

AGEX THERAPEUTICS

Somatic Cell Mortality & Immortality





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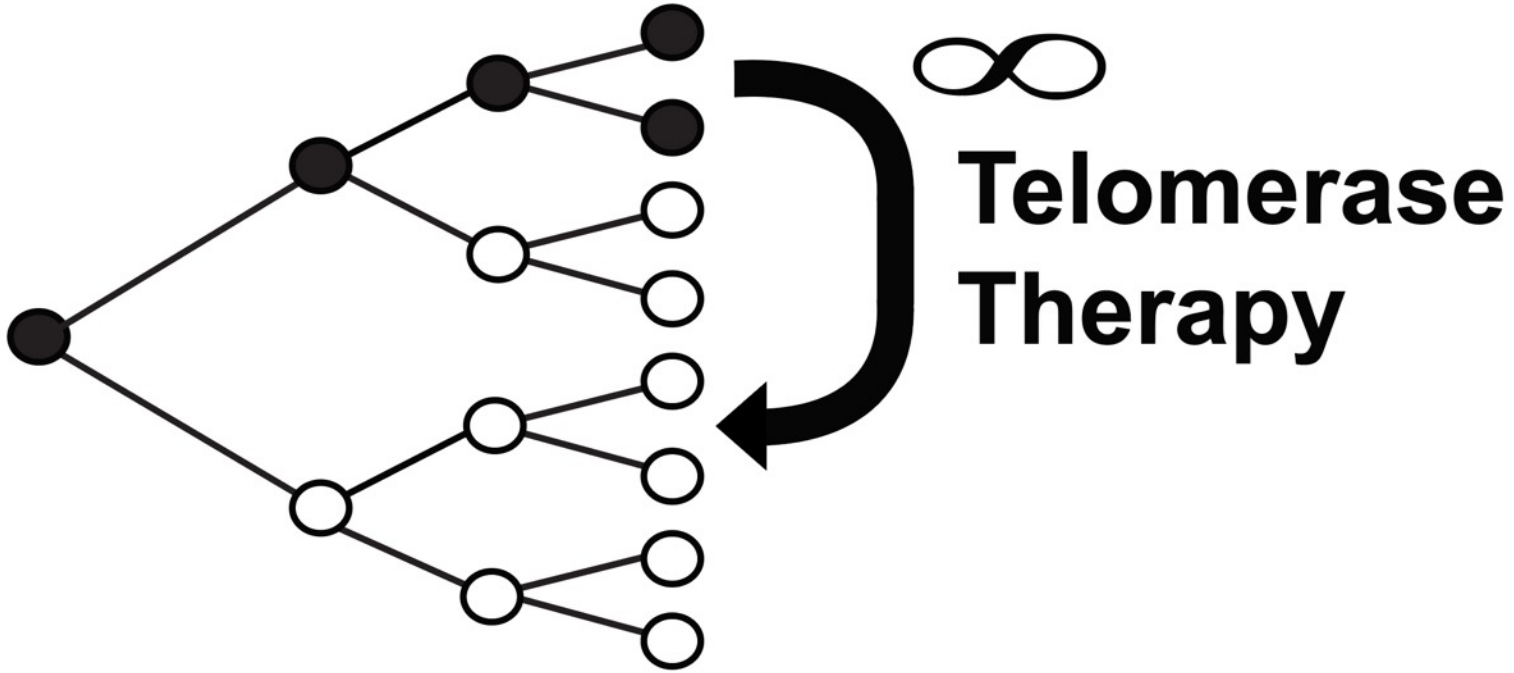
Somatic Cell Mortality & Immortality



Antagonistic Pleiotropy & Telomerase

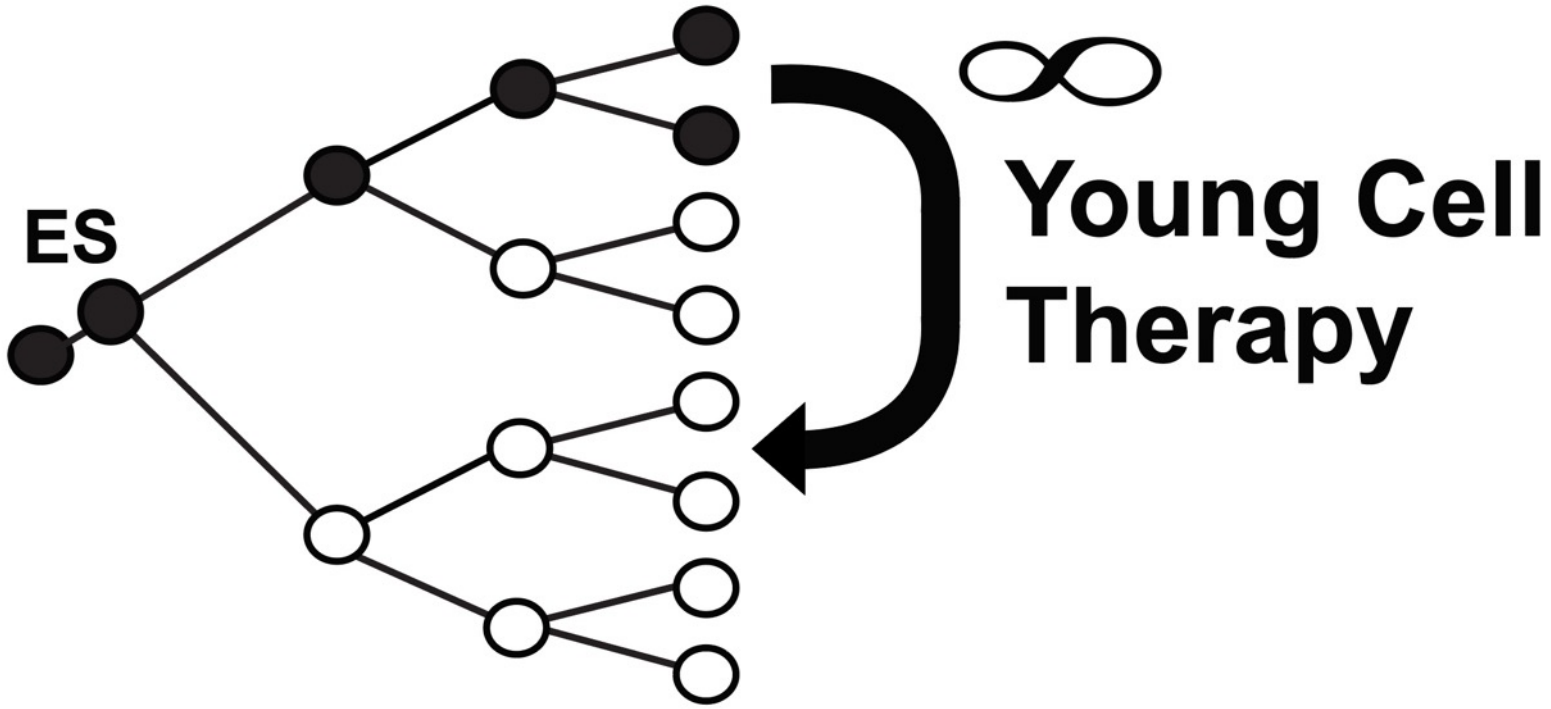
Specific Association of Human Telomerase Activity with Immortal Cells and Cancer

Nam W. Kim,* Mieczyslaw A. Piatyszek,* Karen R. Prowse,
Calvin B. Harley, Michael D. West, Peter L. C. Ho,
Gina M. Coviello, Woodring E. Wright, Scott L. Weinrich,*†
Jerry W. Shay*†

Synthesis of DNA at chromosome ends by telomerase may be necessary for indefinite proliferation of human cells. A highly sensitive assay for measuring telomerase activity was developed. In cultured cells representing 18 different human tissues, 98 of 100 immortal and none of 22 mortal populations were positive for telomerase. Similarly, 90 of 101 biopsies representing 12 human tumor types and none of 50 normal somatic tissues were positive. Normal ovaries and testes were positive, but benign tumors such as fibroids were negative. Thus, telomerase appears to be stringently repressed in normal human somatic tissues but reactivated in cancer, where immortal cells are likely required to maintain tumor growth.

AGEX THERAPEUTICS

Pluripotency & Regenerative Medicine



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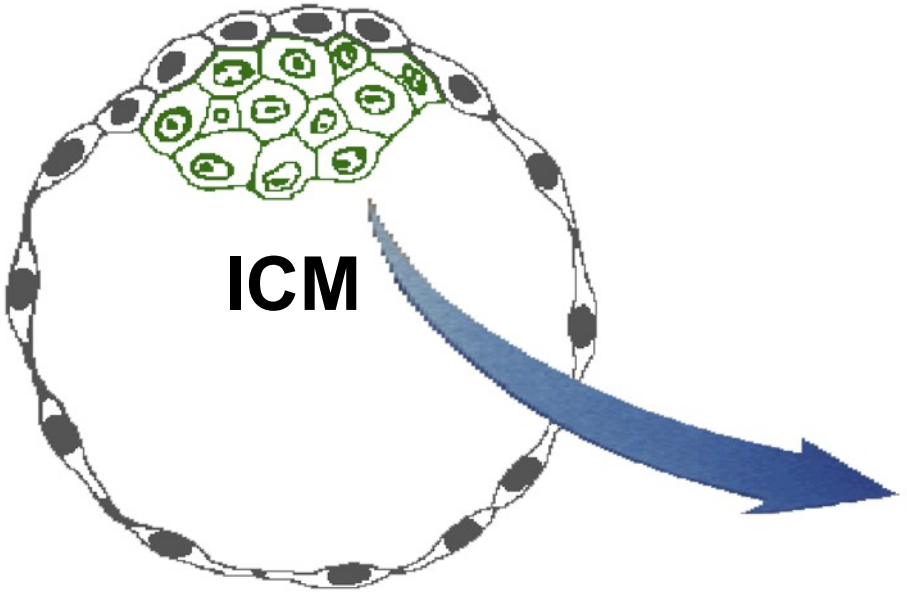
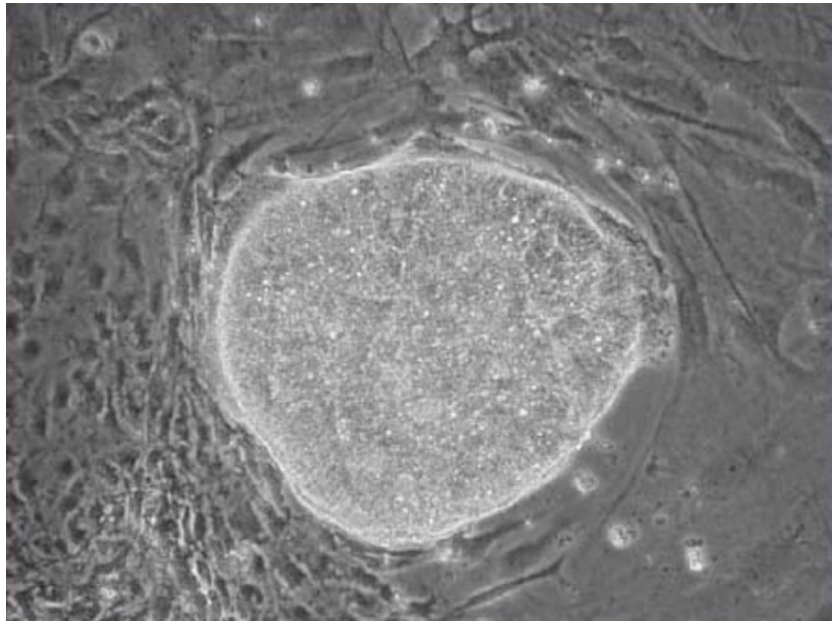


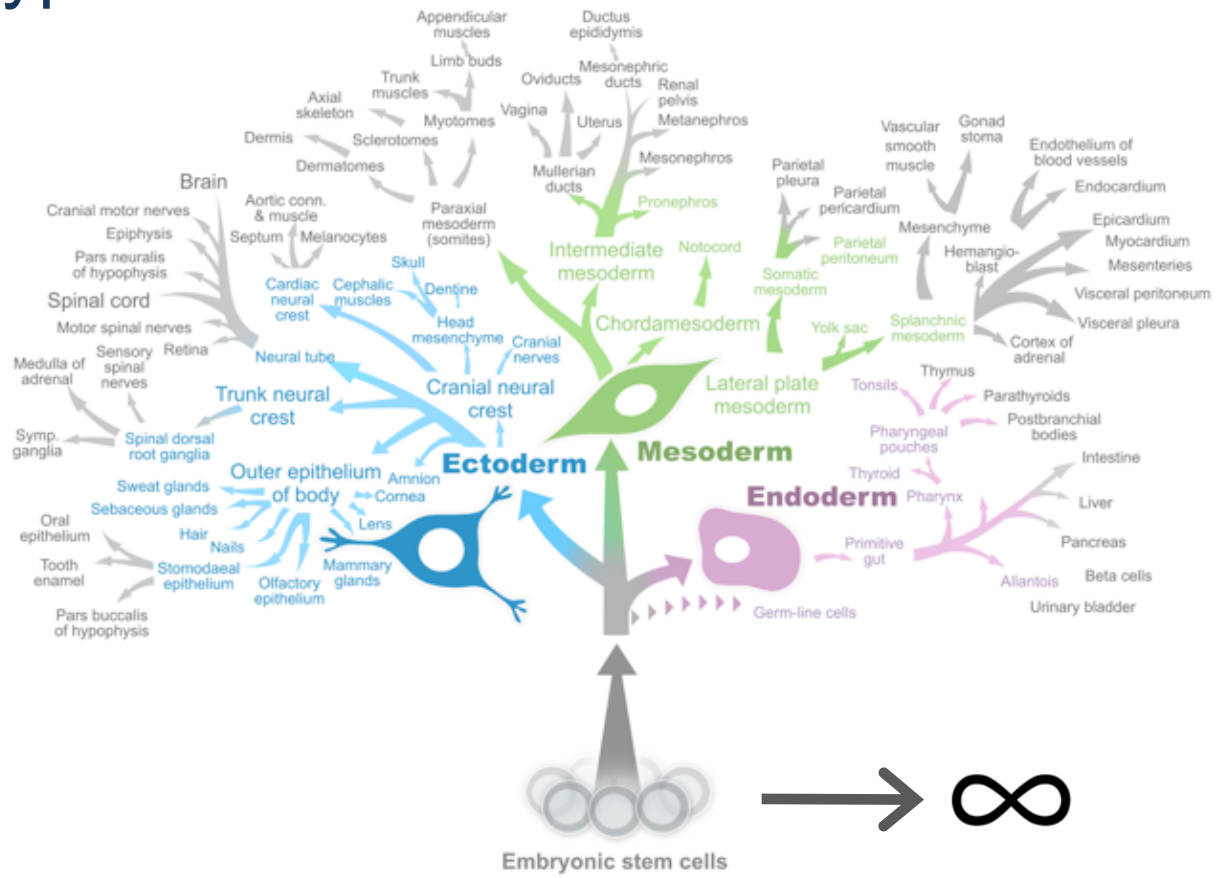


Human ES Cells

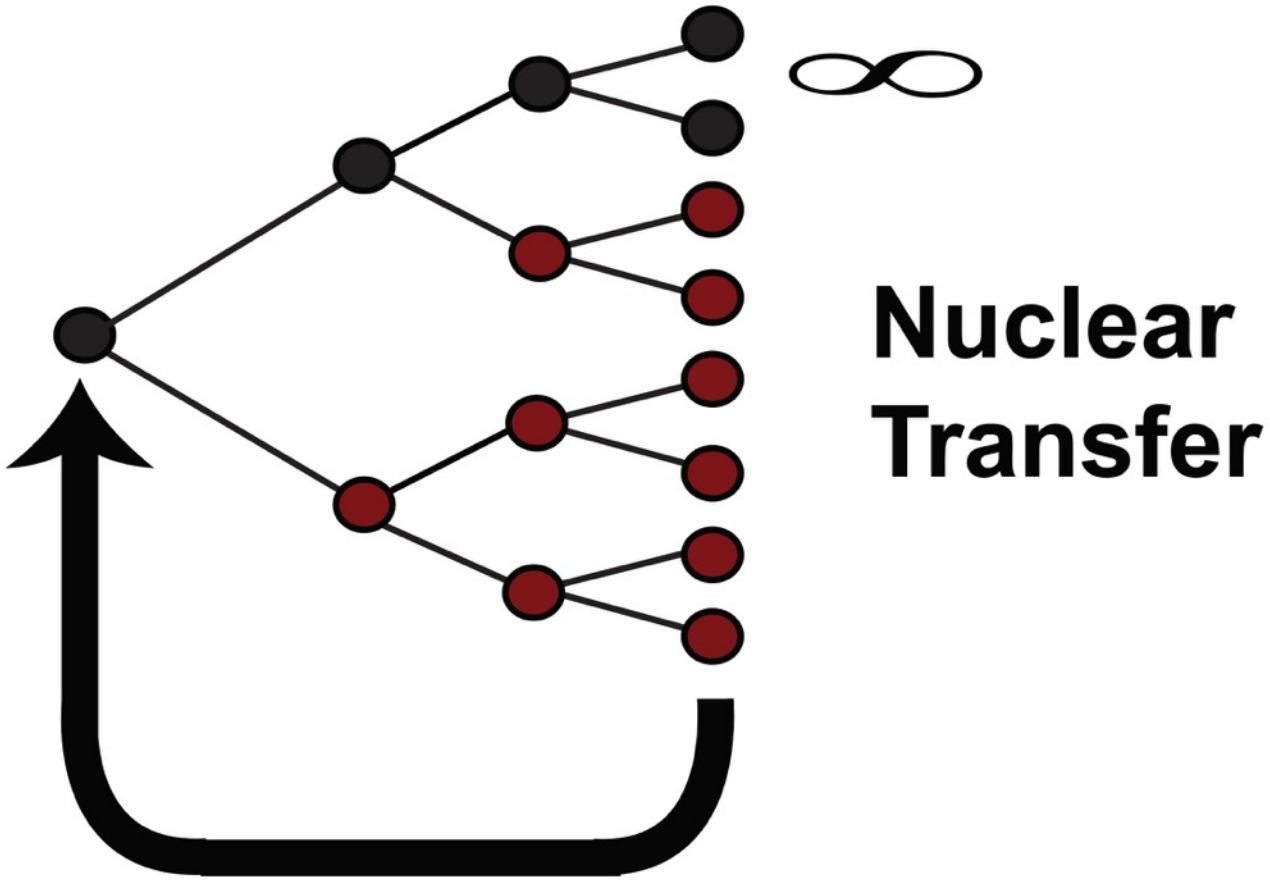
AGE X THERAPEUTICS

Pluripotency

- Scalable source of all human cell types
- Regen phenotype



Reprogramming the Aging of Somatic Cells



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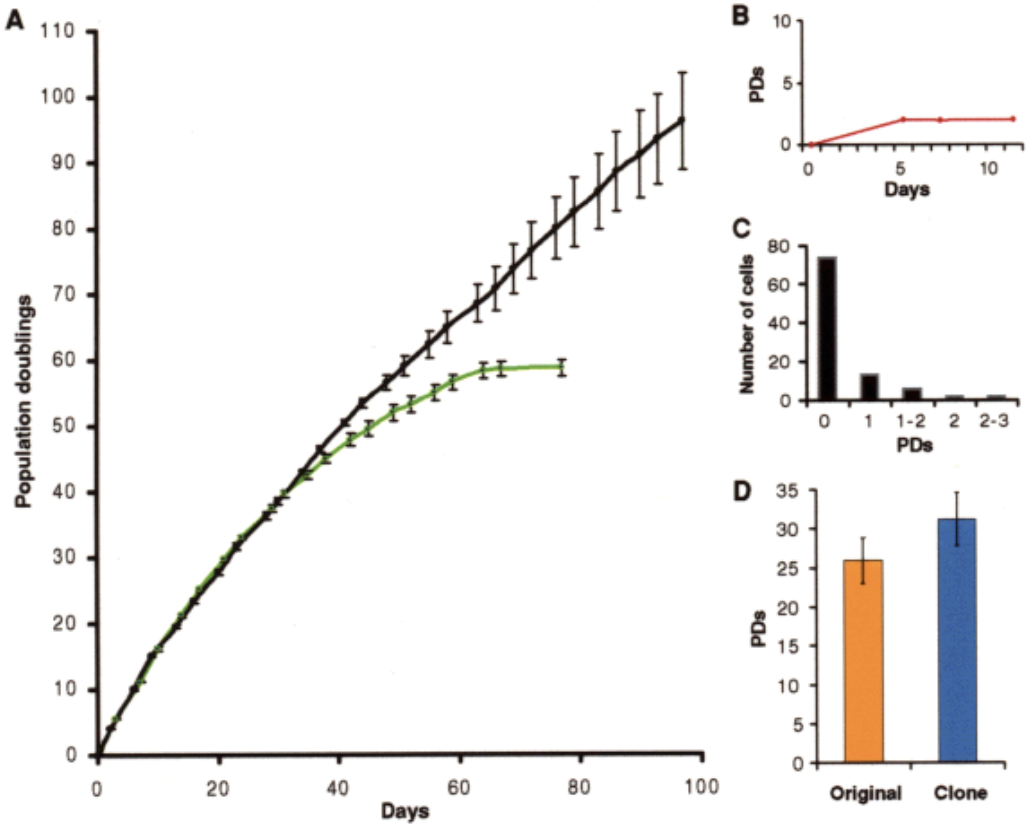
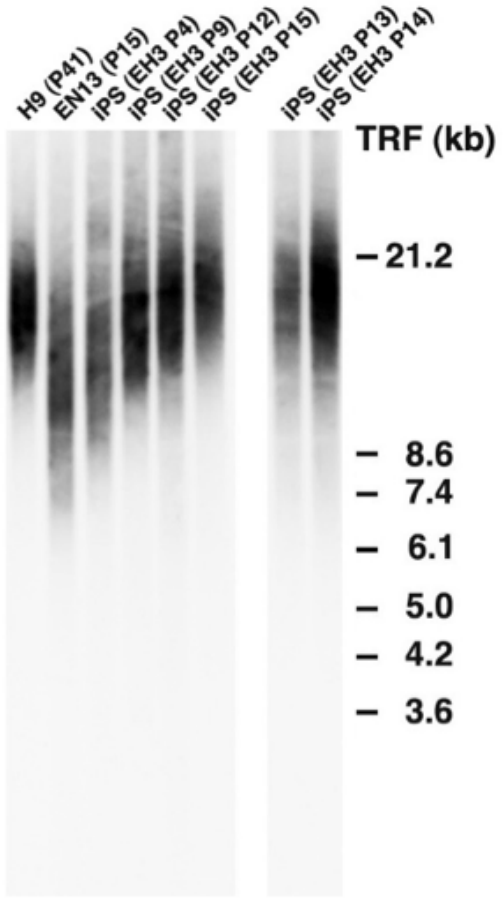
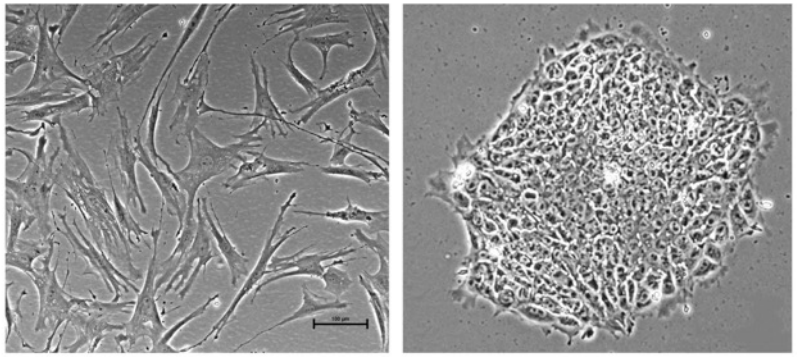


Science 288: 665 (2000)

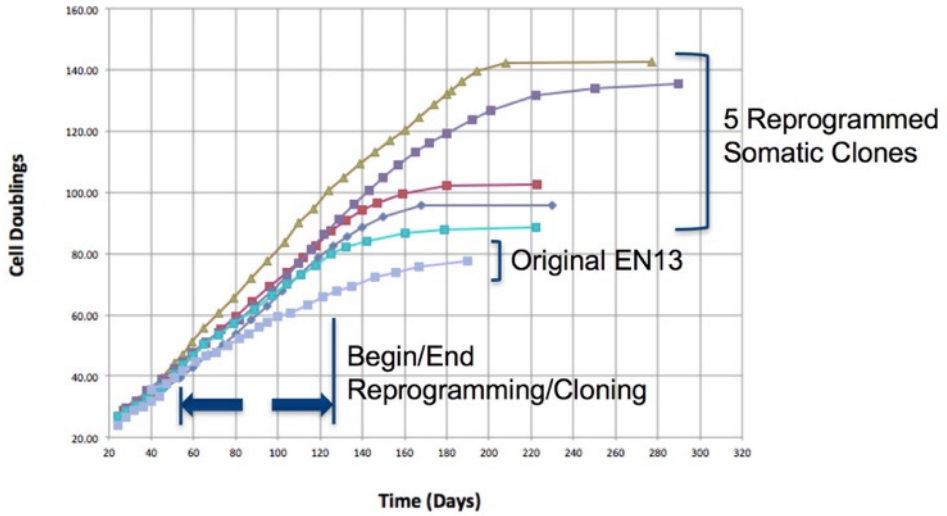
Reprogramming the Aging of Human Cells



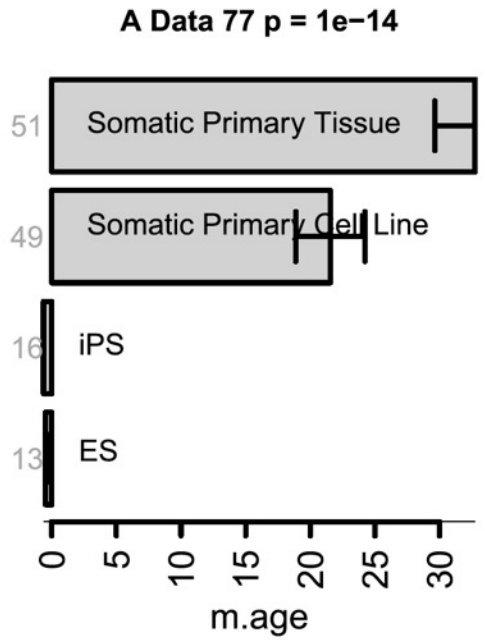
Regen Med 2010 May;5(3):345-63



Skin Fibroblasts iPS Cells



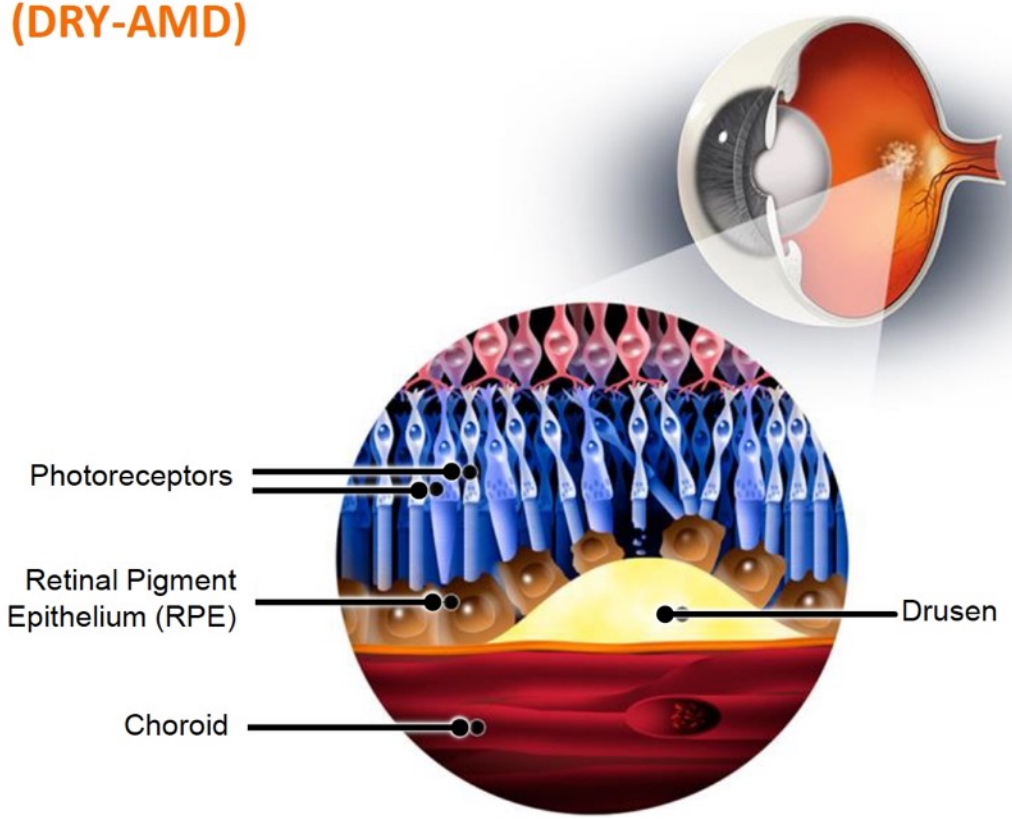
Reprogramming Methylation Age



Horvath
Genome Biol. 2013;14(10):R115

Age-Related Macular Degeneration

CELL REPLACEMENT IN DRY AGE-RELATED MACULAR DEGENERATION (DRY-AMD)



Loss of RPE cells in the eye may cause both dry or wet AMD

The leading cause of blindness in people over age 60

OpRegen®: off-the-shelf injection

OpRegen® cells integrate into subretinal space to replace missing RPE cells

FDA Fast-Track designation

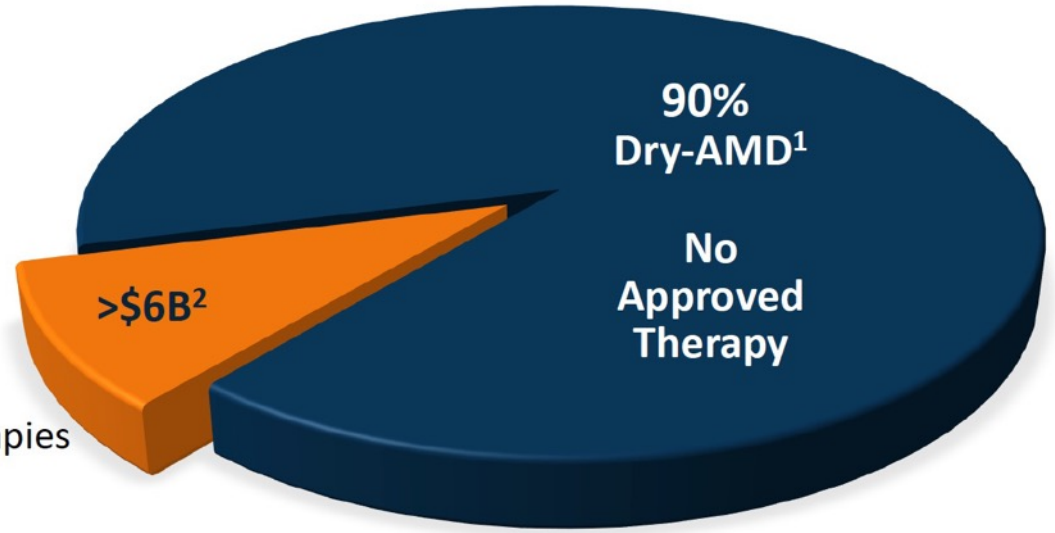
*No serious adverse events reported

BIOTIME

AGE X THERAPEUTICS

Age-Related Macular Degeneration

- AMD afflicts 30+ million people worldwide[1]
- Currently, no approved therapies available for Dry-AMD
- Dry-AMD represents ~90% of all AMD[1]
- ~$6B in approved Wet-AMD therapies[2]: Lucentis and Eylea

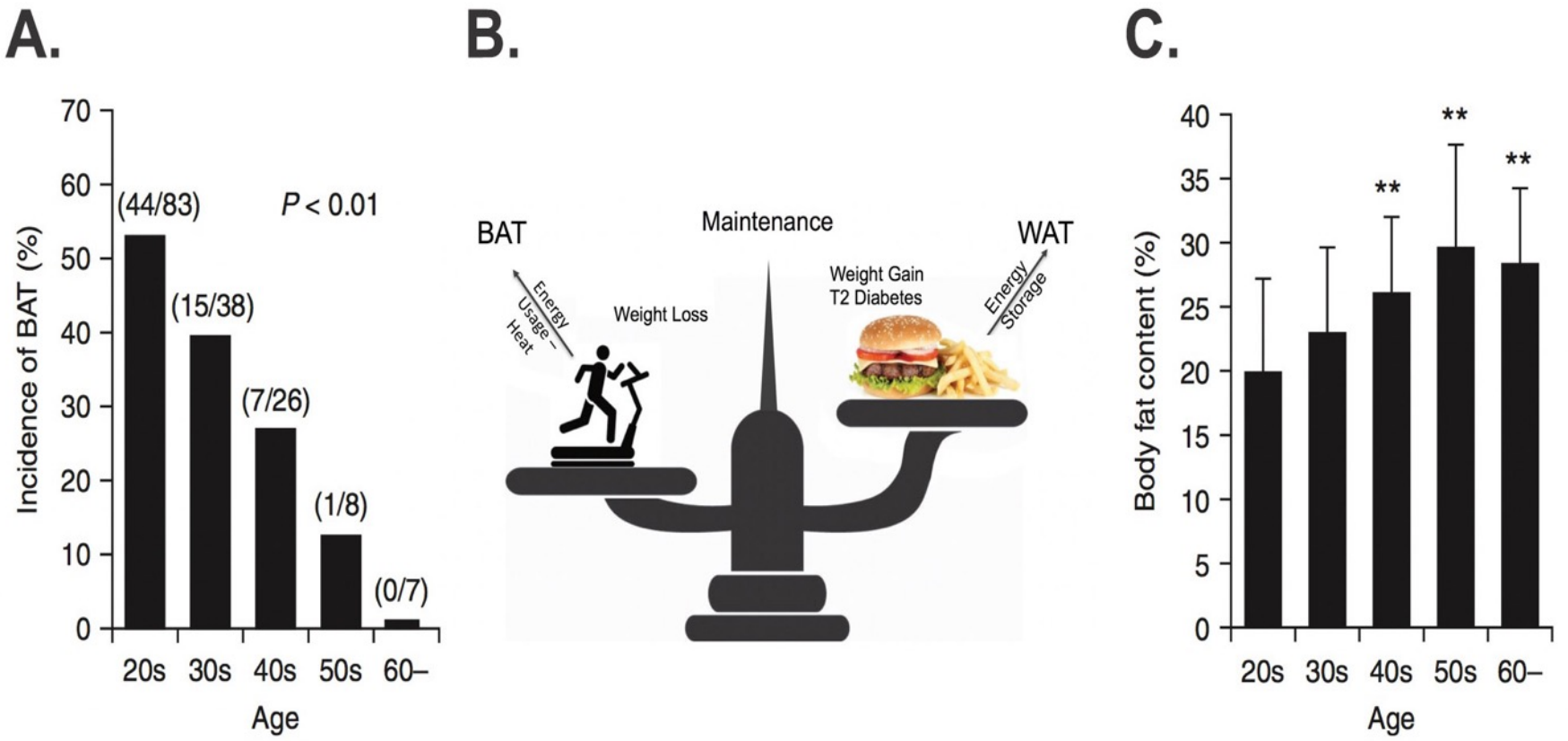


Sources: (1) Company compilation of published information (articles, news releases, SEC filings), analyst reports; and (2) 2016 product sales summary based on publicly reported revenue figures for Lucentis and Eylea

BIOTIME

AGE X THERAPEUTICS

Brown Adipose Cells Regulate Metabolism

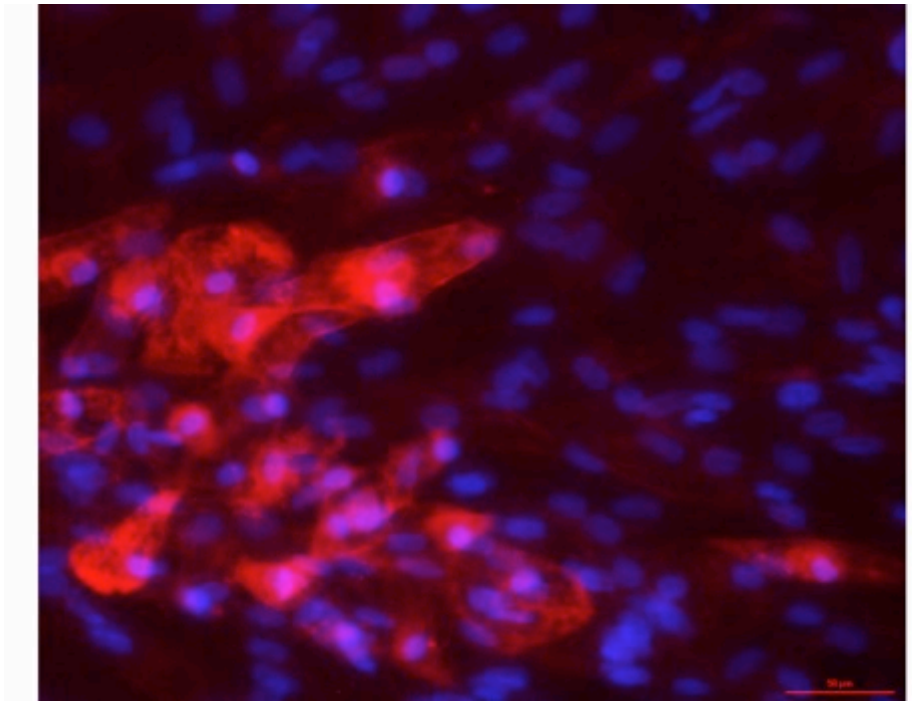


Obesity (2011) **19,** 1755–1760. doi:10.1038/oby.2011.125

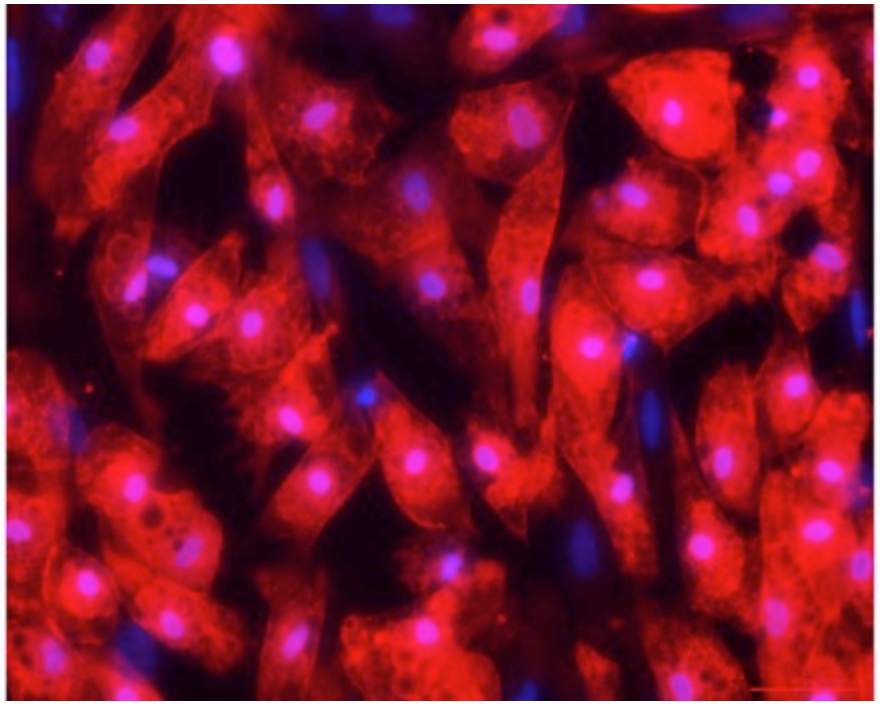
AGE X THERAPEUTICS

Industrially-Scalable *AgeX-BAT1*

Stained for Brown Adipocyte Marker ***UCP1***



Tissue-Sourced Brown Adipocytes



PureStem Brown Adipocytes

AGEX THERAPEUTICS

Obesity/T2D Market

- 30M Americans have diabetes[1] 1:3 Americans will have diabetes by 2050

- The global market for diabetes mellitus and obesity is set to rise from $70.8 billion in 2015 to $163.2 billion by 2022, at a strong compound annual growth rate of 12.7%, according to business intelligence firm GBI Research.

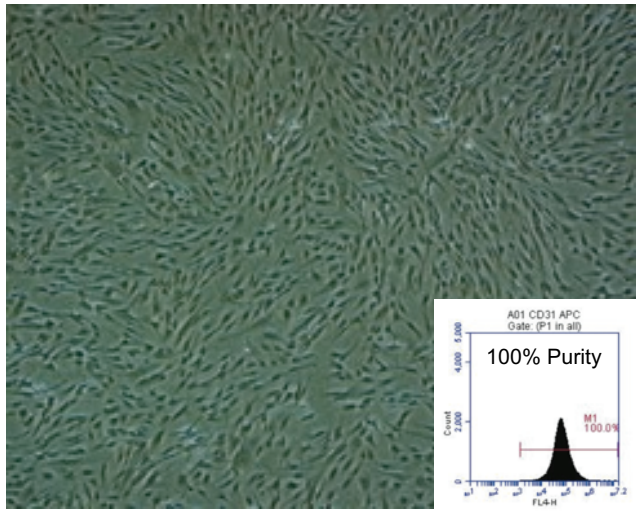
1) Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States. US Department of Health and Human Services; Atlanta, GA: 2014.

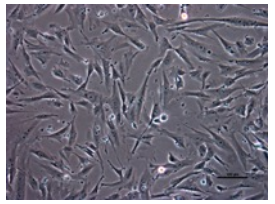
AGE X THERAPEUTICS

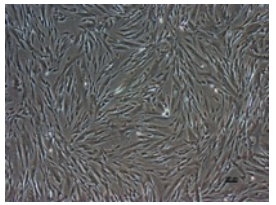
AGEX-VASC1

Regenerative Vascular Progenitors

Monoclonal Endothelial Cells

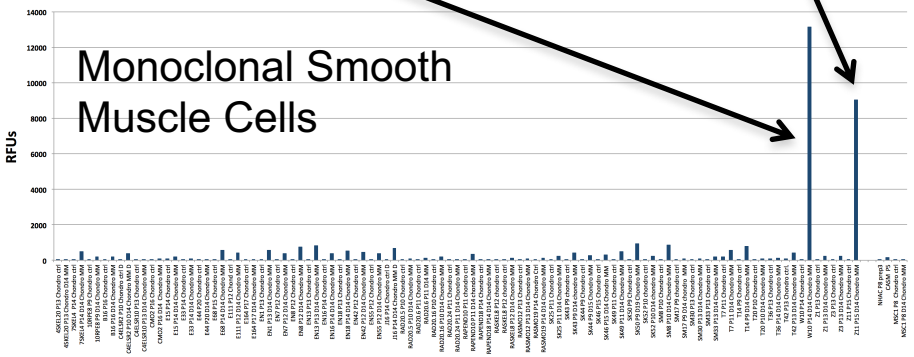






W10

Z11



- Highly scalable with high purity & potency
- Extensive IP estate
- Formulated in HyStem

AGEX THERAPEUTICS

Cardiovascular Market

> *$Trillion Market Worldwide*

American Heart Association | American Stroke Association

life is why

	Current	2035
Medical costs up 135 percent	$318 billion	$749 billion
Indirect costs up 55 percent (Lost productivity)	$237 billion	$368 billion
TOTAL COSTS	**$555 billion**	**$1.1 trillion**

The Cost Generators: Aging Baby Boomers

As Baby Boomers age, costs for CVD will shift from middle-aged Americans to individuals ages 65 and over. By 2035, Boomers who are 80 and older will be the source of the largest cost increases for CVD.

http://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_491543.pdf

AGEX THERAPEUTICS

The Biology of Regeneration

PLEIOTROPY, NATURAL SELECTION, AND THE EVOLUTION OF SENESCENCE[1]

GEORGE C. WILLIAMS

Michigan State University

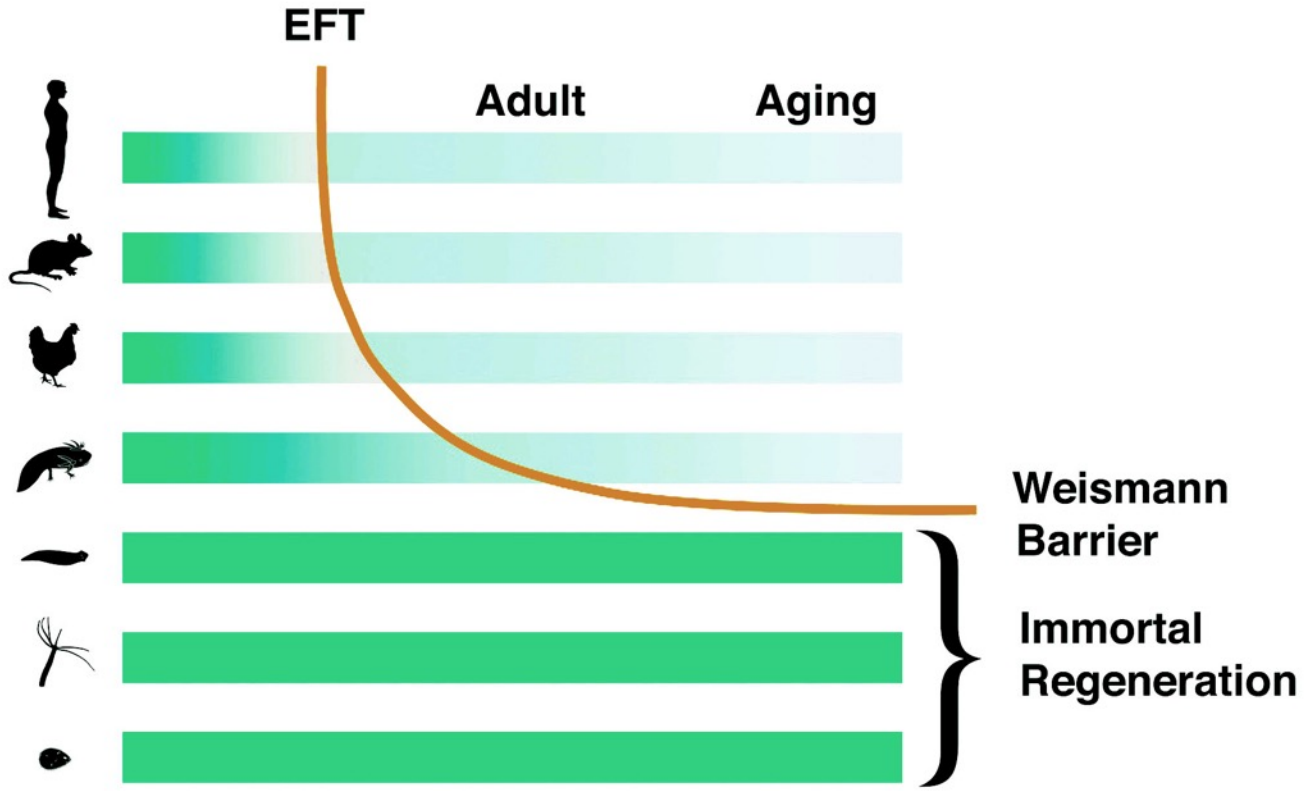
Received February 26, 1957

"It is indeed remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed."

AGEX THERAPEUTICS

The Biology of Regeneration

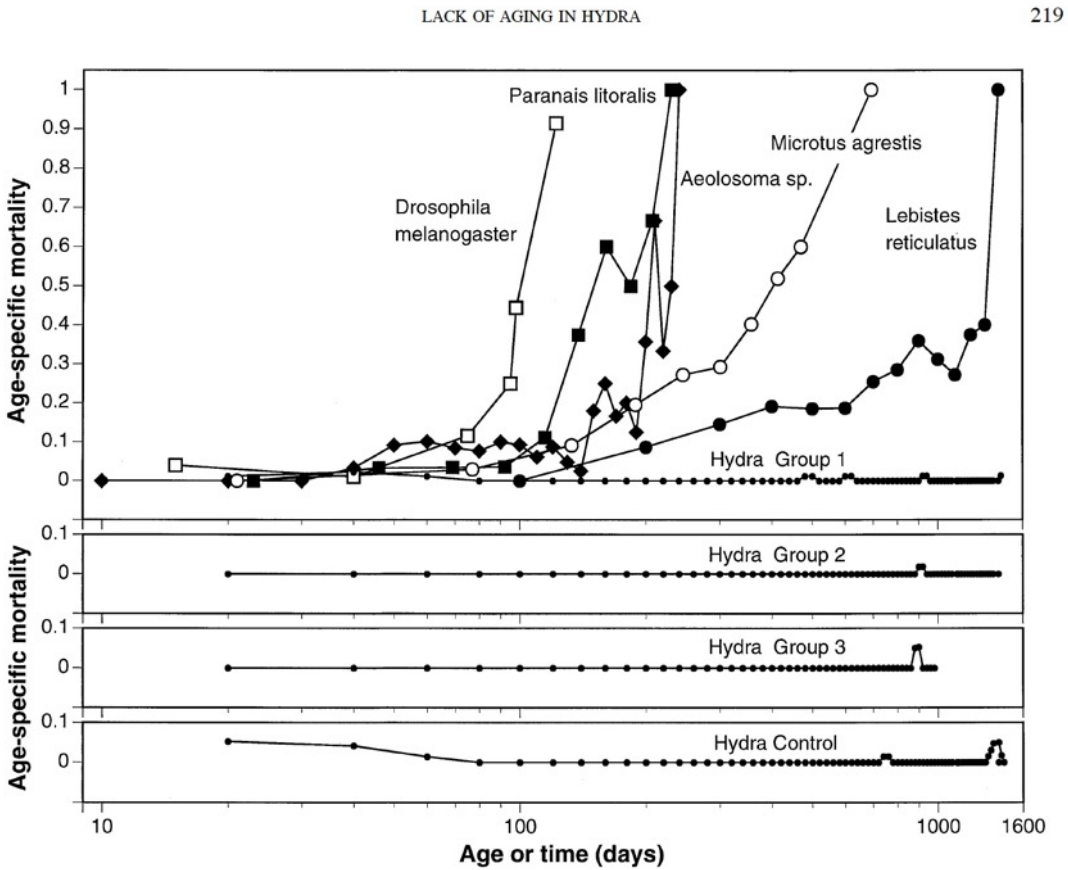
Innate Regeneration in Humans Restricted to Embryonic Development



AGEX THERAPEUTICS

The Biology of Regeneration

Hydra don’t age



Experimental Gerontology, Vol. 33, No. 3, pp. 217–225, 1998

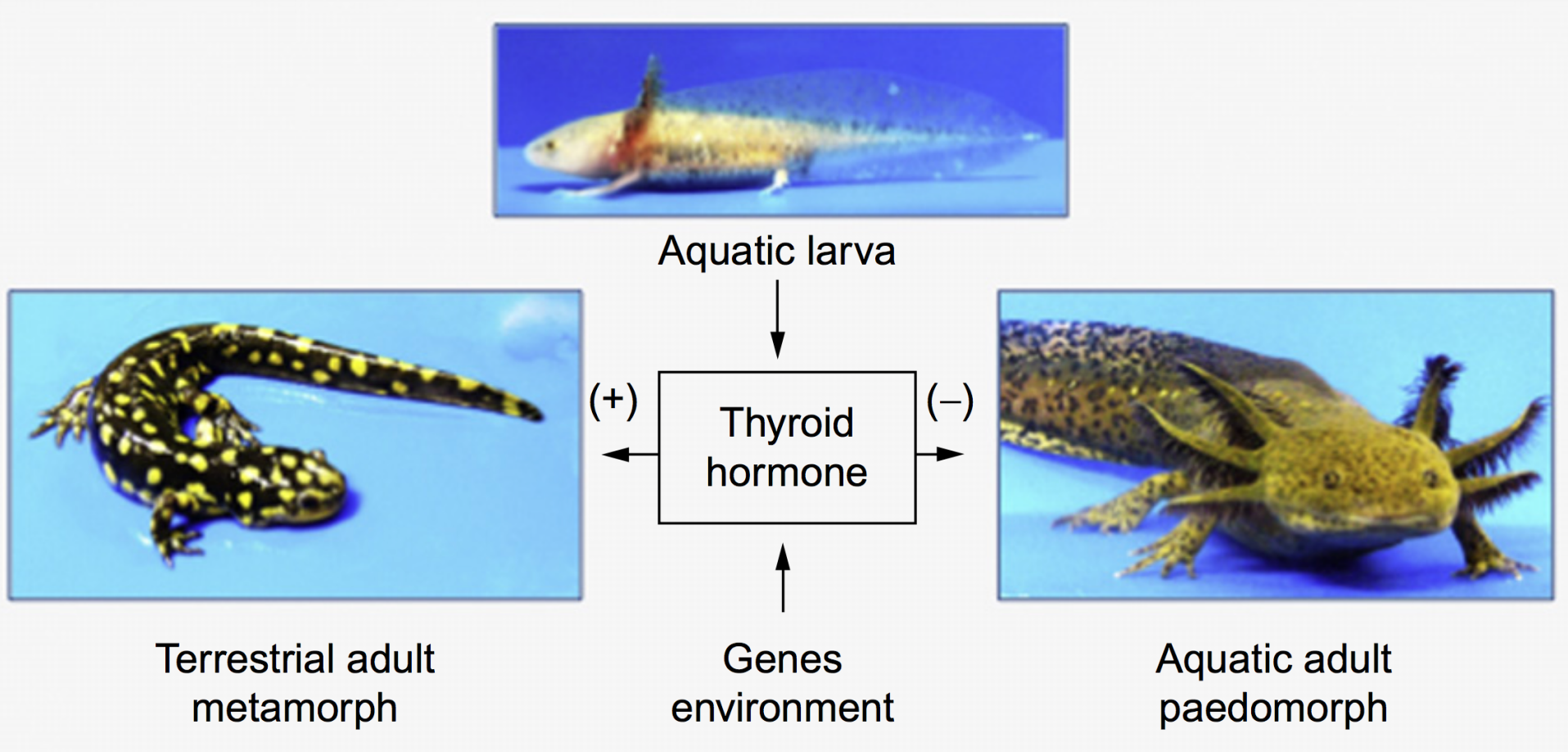
The Biology of Regeneration

Planaria: Immortal Regeneration

AGEX THERAPEUTICS

The Biology of Regeneration

Axolotls are abnormally stuck in an embryonic (larval) state throughout life, probably the basis of regenerative potential.



Current Topics in Developmental Biology, Volume 103:229

AGEX THERAPEUTICS

The Biology of Regeneration

The Biology of Regeneration

Mammalian and human skin regenerates scarlessly in the embryonic period, begins scarring in fetal and beyond.

THE ROYAL SOCIETY

Published online 20 April 2004

Scar-free healing: from embryonic mechanisms to adult therapeutic intervention

Mark W. J. Ferguson[1,2*] and Sharon O'Kane[2]

[1]*UK Centre for Tissue Engineering, School of Biological Sciences, University of Manchester, 3.239 Stopford Building, Oxford Road, Manchester M13 9PT, UK*

[2]*Renovo Limited, Manchester Incubator Building, 48 Grafton Street, Manchester M13 9XX, UK*

In man and domestic animals, scarring in the skin after trauma, surgery, burn or sports injury is a major medical problem, often resulting in adverse aesthetics, loss of function, restriction of tissue movement and/or growth and adverse psychological effects. Current treatments are empirical, unreliable and unpredictable: there are no prescription drugs for the prevention or treatment of dermal scarring. Skin wounds on early mammalian embryos heal perfectly with no scars whereas wounds to adult mammals scar. We investigated

AGE X THERAPEUTICS

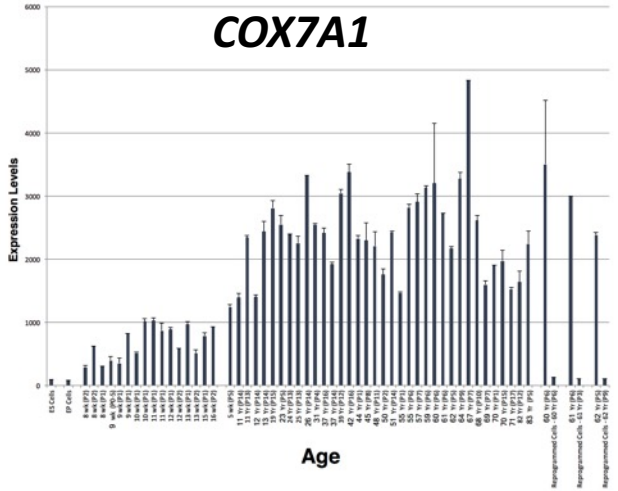
The Biology of Regeneration

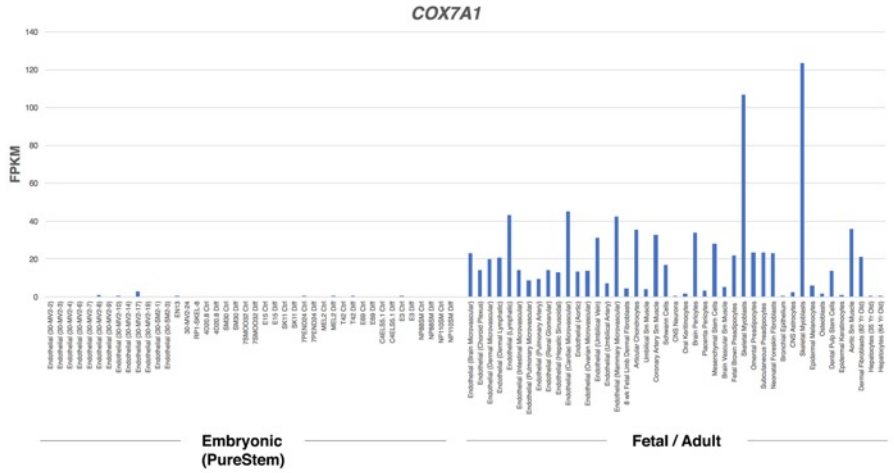
www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 8), pp: 7796-7811

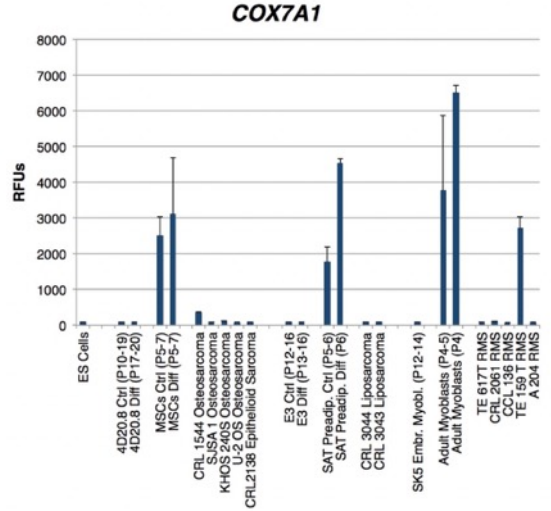
Research Paper

Use of deep neural network ensembles to identify embryonic-fetal transition markers: repression of *COX7A1* in embryonic and cancer cells

Michael D. West[1], Ivan Labat[1], Hal Sternberg[1], Dana Larocca[1], Igor Nasonkin[2], Karen B. Chapman[3], Ratnesh Singh[2], Eugene Makarev[4], Alex Aliper[4], Andrey Kazennov[4,5], Andrey Alekseenko[4,10], Nikolai Shuvalov[4,5], Evgenia Cheskidova[4,5], Aleksandr Alekseev[4,5], Artem Artemov[4], Evgeny Putin[4,6], Polina Mamoshina[4], Nikita Pryanichnikov[4], Jacob Larocca[1], Karen Copeland[7], Evgeny Izumchenko[8], Mikhail Korzinkin[4] and Alex Zhavoronkov[4,9]

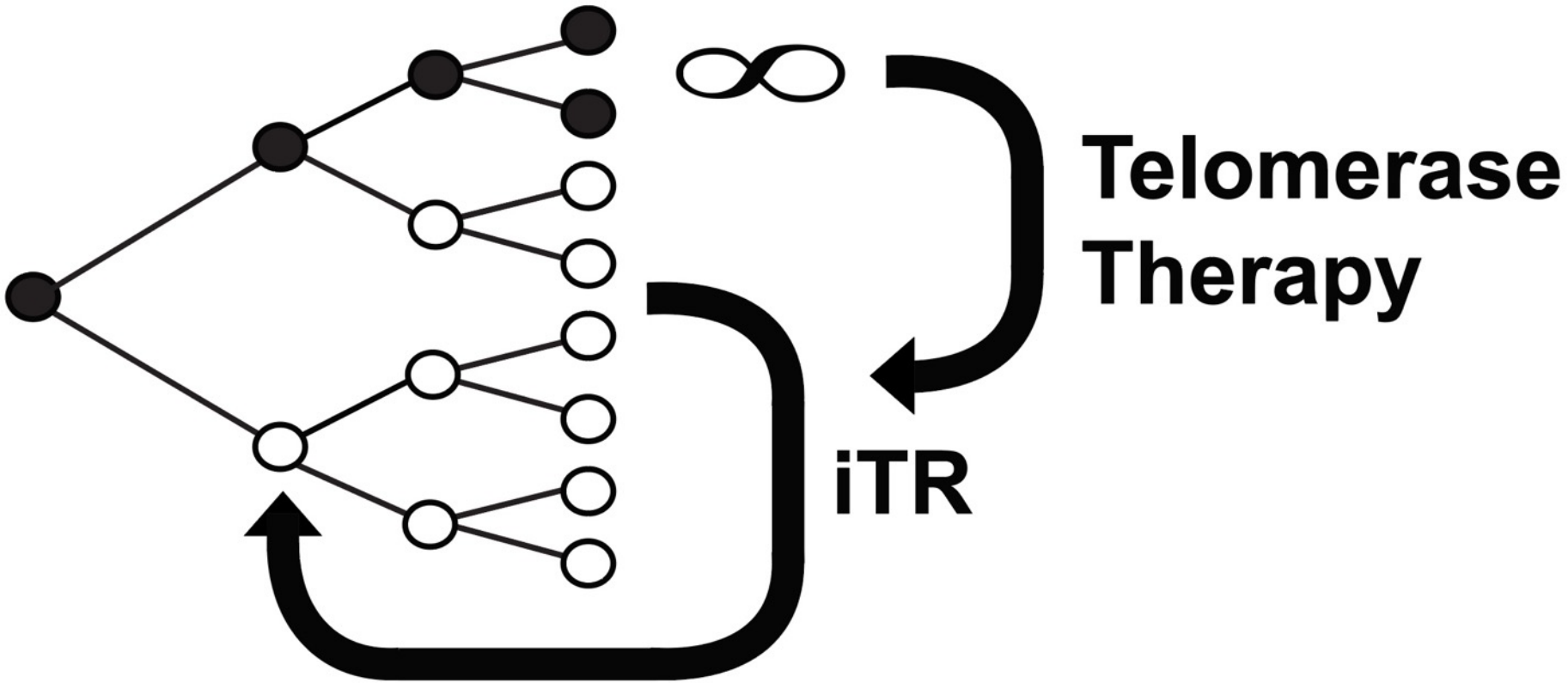






AGE X THERAPEUTICS

induced Tissue Regeneration (iTR)



Toward a Unified Theory of Aging

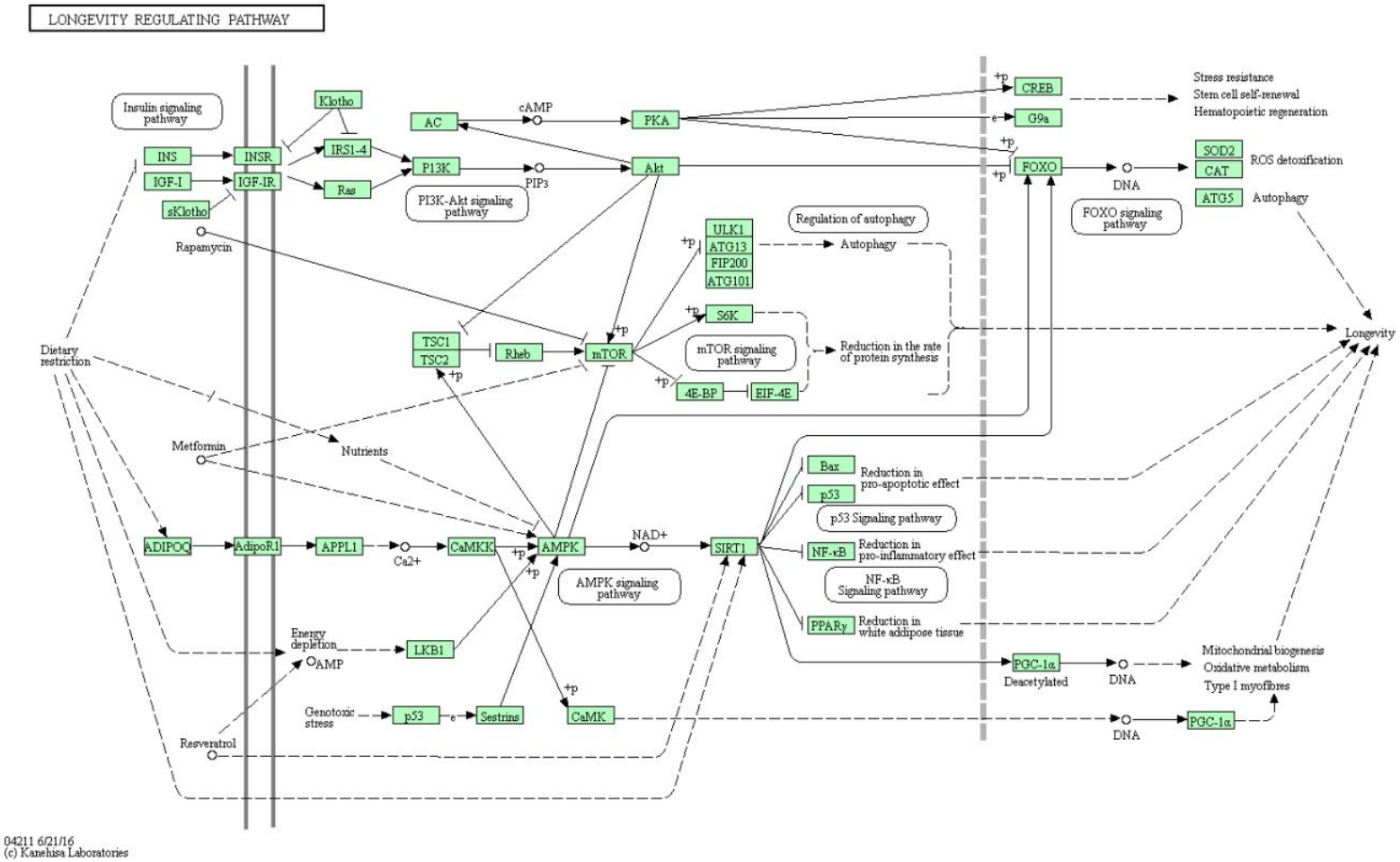
Can Telomerase/Regeneration Inhibition Explain All These?

- Lipofuscin (altered autophagy and mitophagy)
- Dietary restriction
- Growth hormone axis (INS, GH, mTOR)
- Hydrogen sulfide effect
- Sirtuins
- NAD
- Mitochondrial DNA damage
- NMR Longevity
- APOE
- Accumulation of p16/Effects of senolysis

AGE X THERAPEUTICS

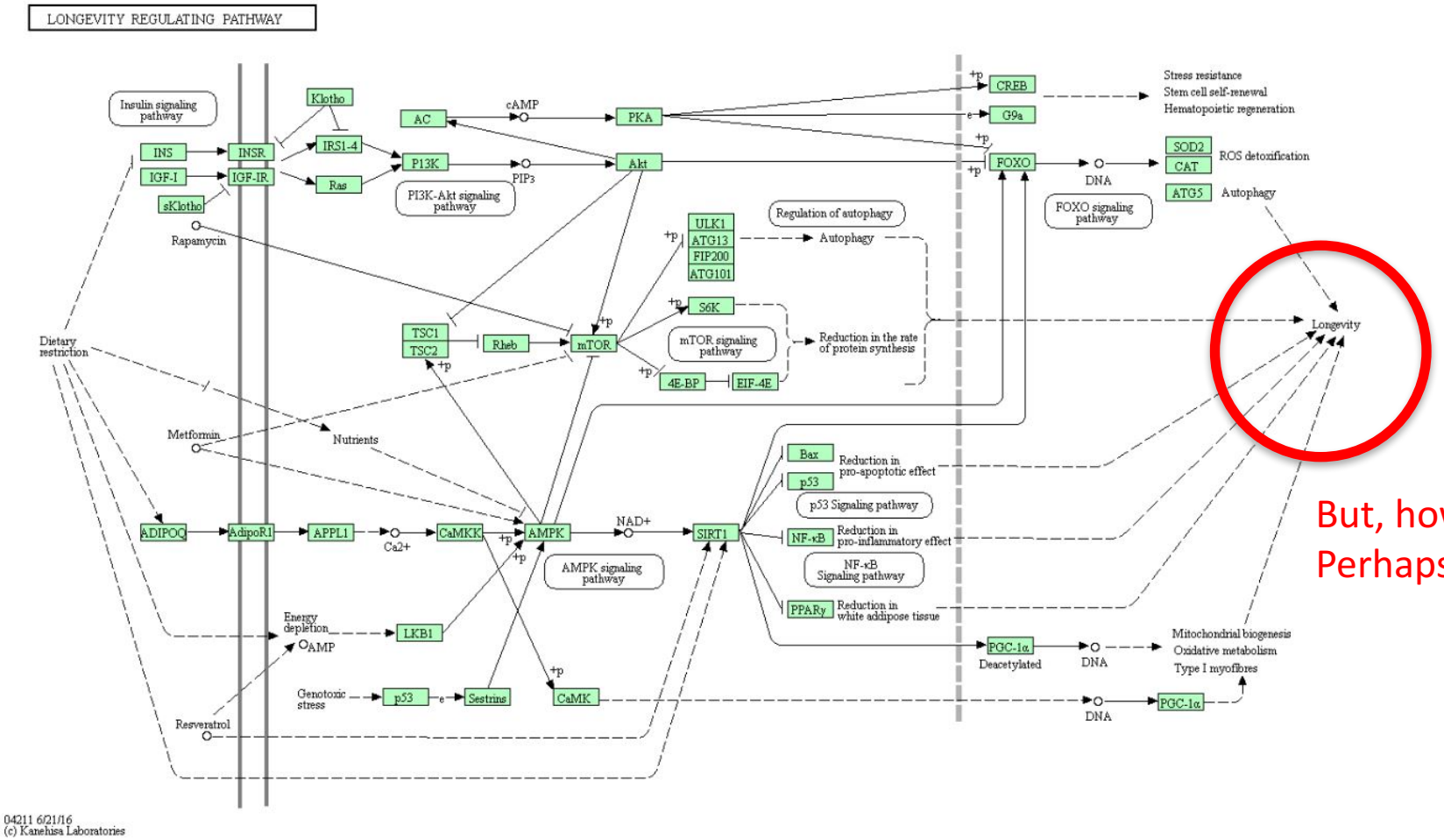
Toward a Unified Theory of Aging

More specifically, these pathways?



Toward a Unified Theory of Aging

More specifically, these pathways?



But, how?
Perhaps Regeneration

Toward a Unified Theory of Aging

It is tempting to speculate that tissues with regenerative potential apoptose cells with genotoxic damage since they are easily replaced while post-regenerative tissues tend to resist apoptosis:

Embryonic → Fetal - Adult → Aging Adult

Highly Regenerative
Construction
↑ Apoptosis

Limited Regeneration
Maintenance
↓ Apoptosis

Non-Regenerative
Destruction
↓ Apoptosis

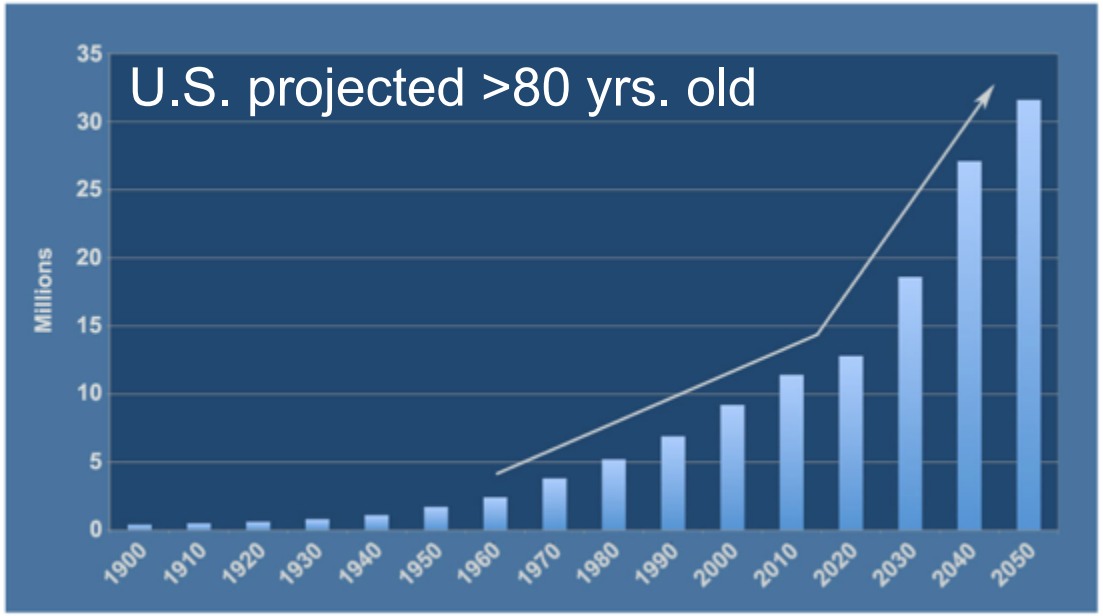
iTR: induced Tissue Regeneration

Senolysis a consequence?

AGEX THERAPEUTICS

The Market

Aging: The demographic trend of our time



- 80% of $2.5T health care costs associated with chronic disease.
- Age-related chronic degenerative diseases typically have few effective drug targets.

AGE X THERAPEUTICS

Summary

"If there were no regeneration there would be no life.
If everything regenerated there would be no death."

Richard J. Goss
- Principles of Regeneration (1969)

Summary

- Pluripotency offers a means of manufacturing diverse regenerative progenitors to address degenerative diseases of aging: The demographic trend of our time
- AgeX focused on three therapeutic programs with potential to address large causes of mortality in U.S.
  - T2D/Obesity
  - Ischemic Disease: The leading causes of mortality & disability in an aging population
  - iTR: Systemic therapy to induce scarless tissue regeneration
- Planned distribution to BTX shareholders and public listing in 2018

AGEX THERAPEUTICS