AGEX THERAPEUTICS

Hayflick Rewound:
Somatic Restriction, Epigenetics, and the Reversibility of Human Aging

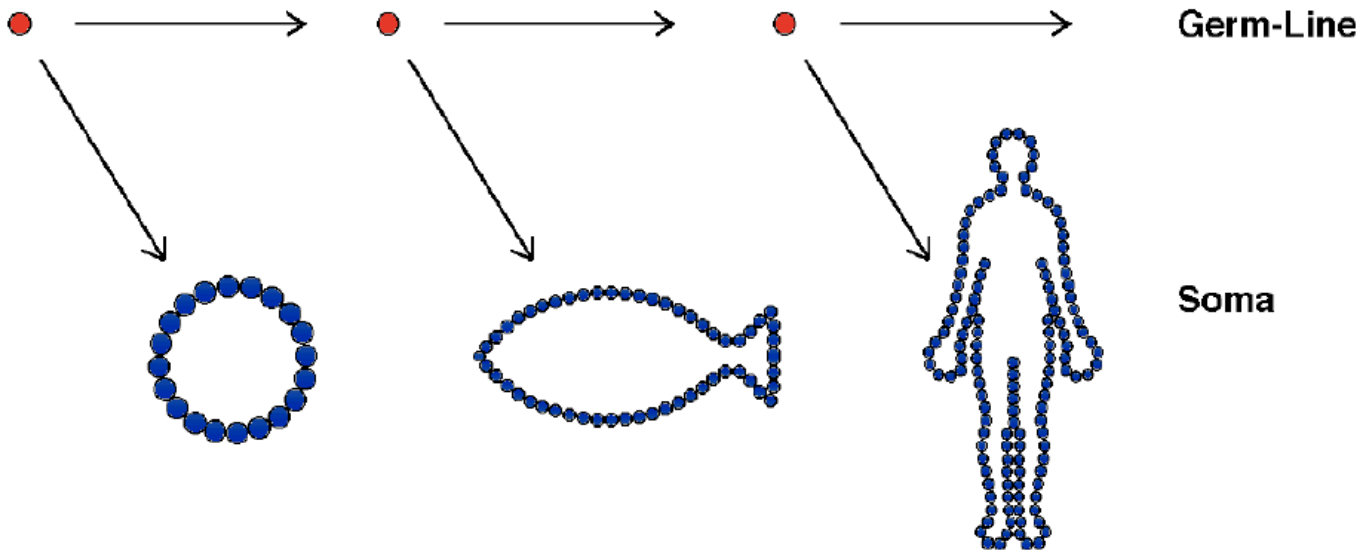
July 12, 2018

Forward Looking Statements

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 including its parent company BioTime, Inc. 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 disclaims 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 by, say, SCNT, otherwise cloning wouldn't make young animals.

AGEX THERAPEUTICS

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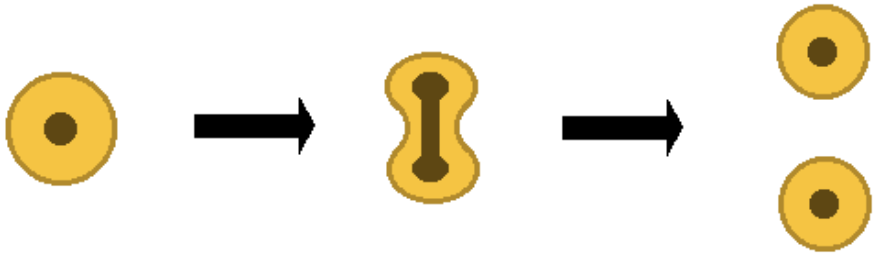
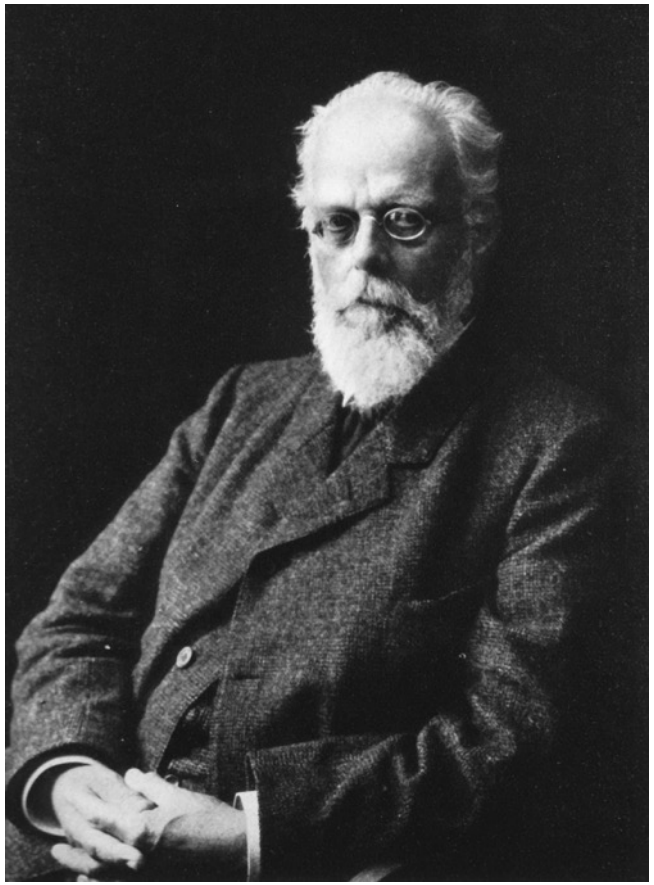


"Death takes place because a worn-out tissue cannot for ever renew itself, and because a capacity for increase by means of cell-division is not everlasting, but finite."

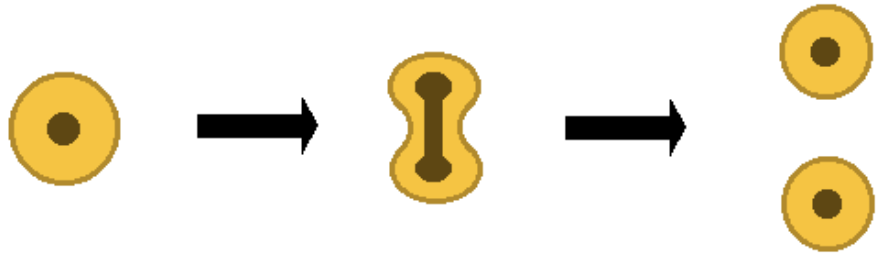
- A. Weismann, 1891



AGEX THERAPEUTICS

Some Initial Observations

Repression of Regeneration



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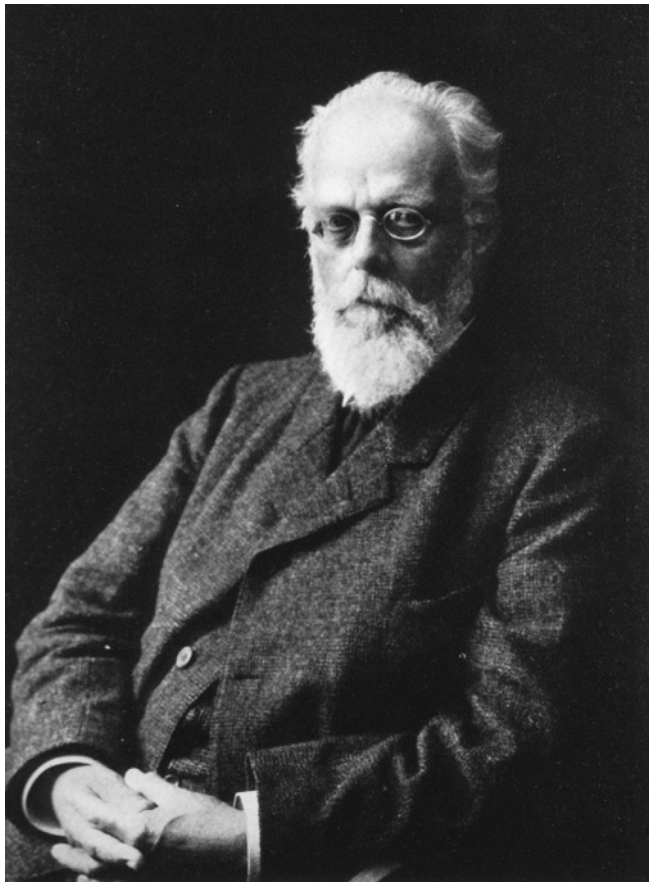
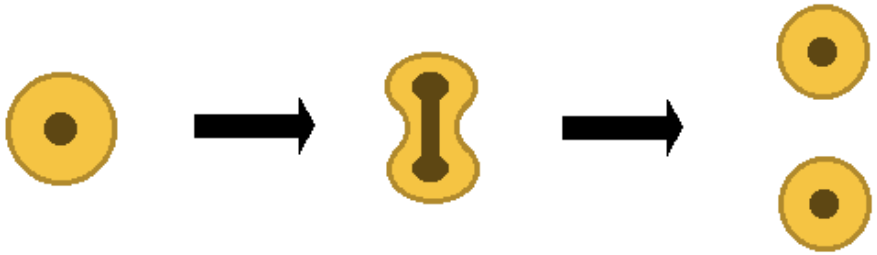


AGEX THERAPEUTICS

Some Initial Observations

Repression of Replicative Immortality



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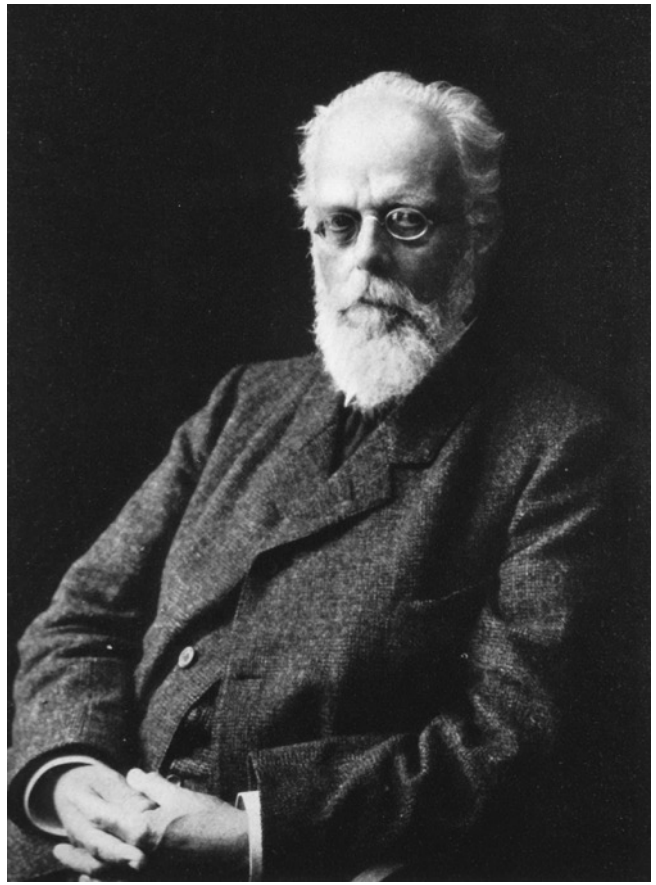
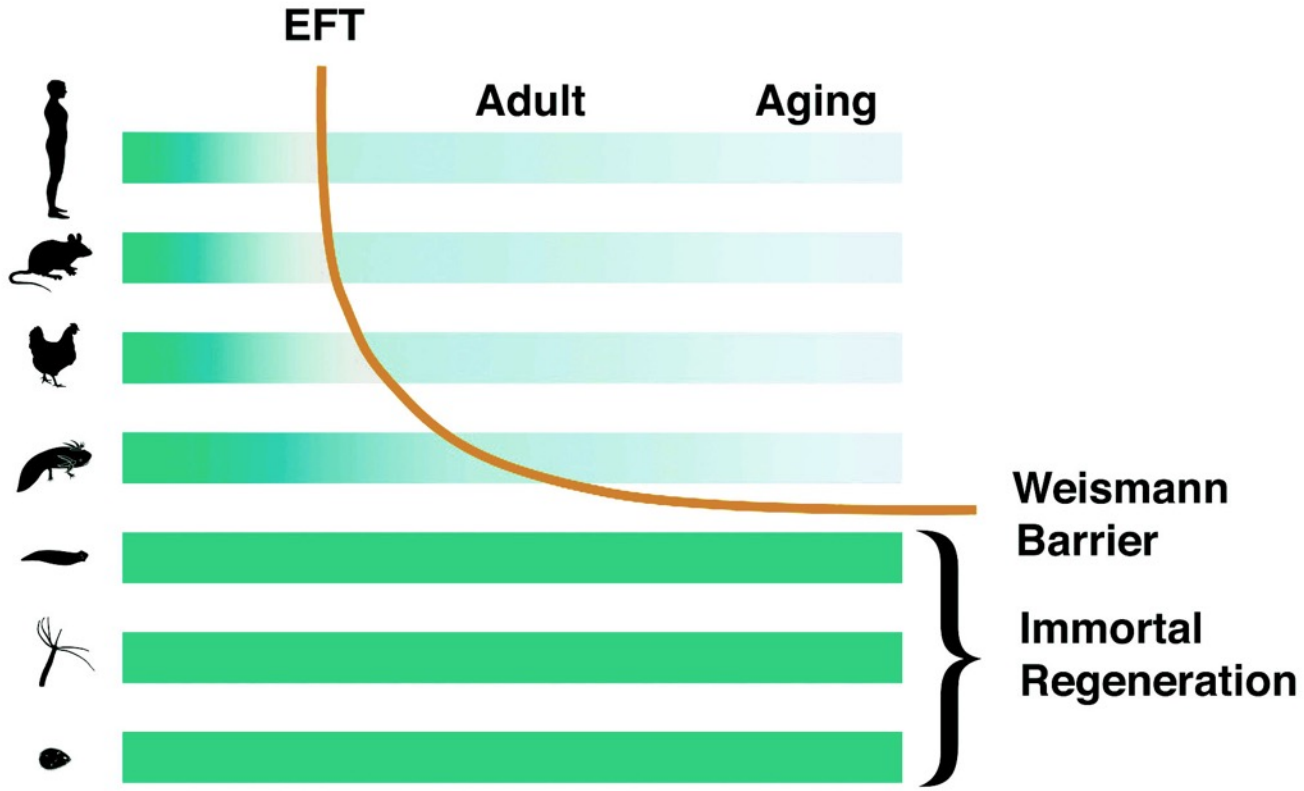


AGEX THERAPEUTICS

Some Initial Observations

Innate Regeneration in Humans Restricted to Embryonic Development

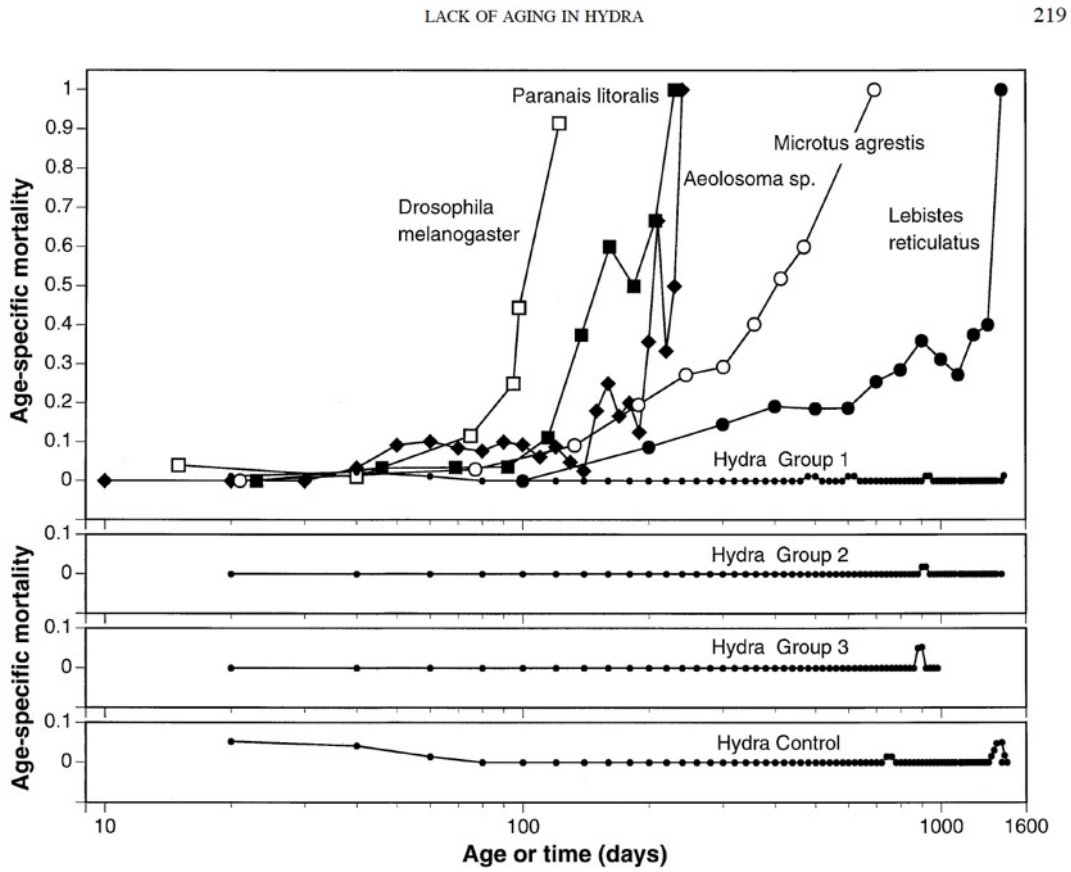


Some Initial Observations

Animals with somatic cells that have both replicative immortality and regenerative potential often don't age:

Some examples are:

- Hydra (data right)
  (*Exp Geront* 1998 33 (3) 217–225)
- Planaria
  (*Ageing Res Rev* 201416:66-82)
- Lobsters
  (*FEBS Lett* 1998 13;439(1-2):143-6)



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

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Some Initial Observations

The Concept of Genetically-Programmed Aging

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

GEORGE C. WILLIAMS

Michigan State University

Received February 26, 1957

AGEX THERAPEUTICS

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

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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 immortal regenerative to mortal non-regenerative somatic cells

- Whether or not genes/pathways function in tumor suppression may be a means of qualifying candidates

AGEX THERAPEUTICS

Antagonistic Pleiotropy & Telomerase

Telomerase OFF in somatic cells reduces cancer in young

Leads to senescence in old

Antagonistic Pleiotropy & Regeneration

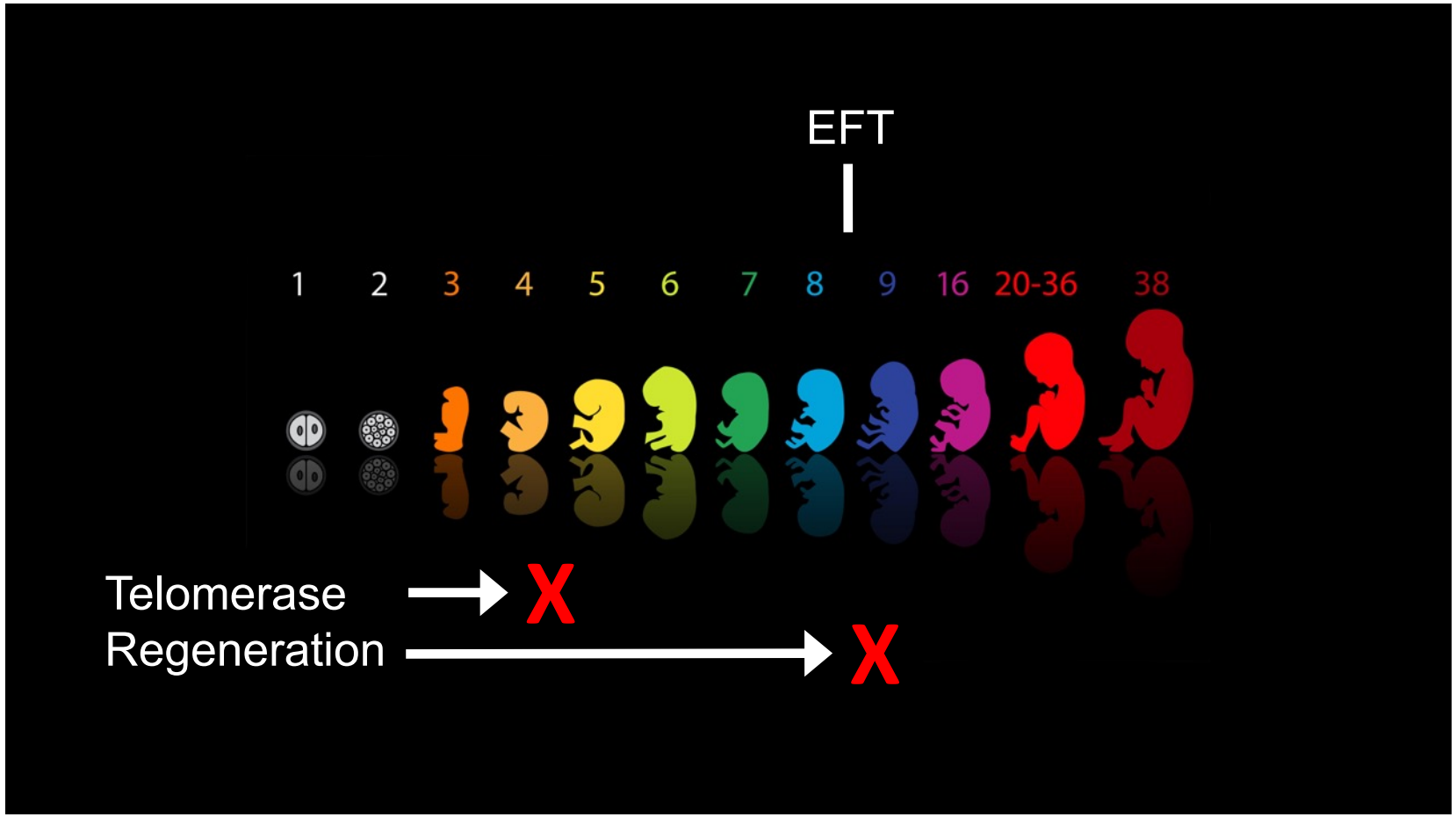
Regeneration OFF in somatic cells after EFT reduces cancer in young

Leads to disrepair/fibrosis in old

AGEX THERAPEUTICS

Some Initial Observations

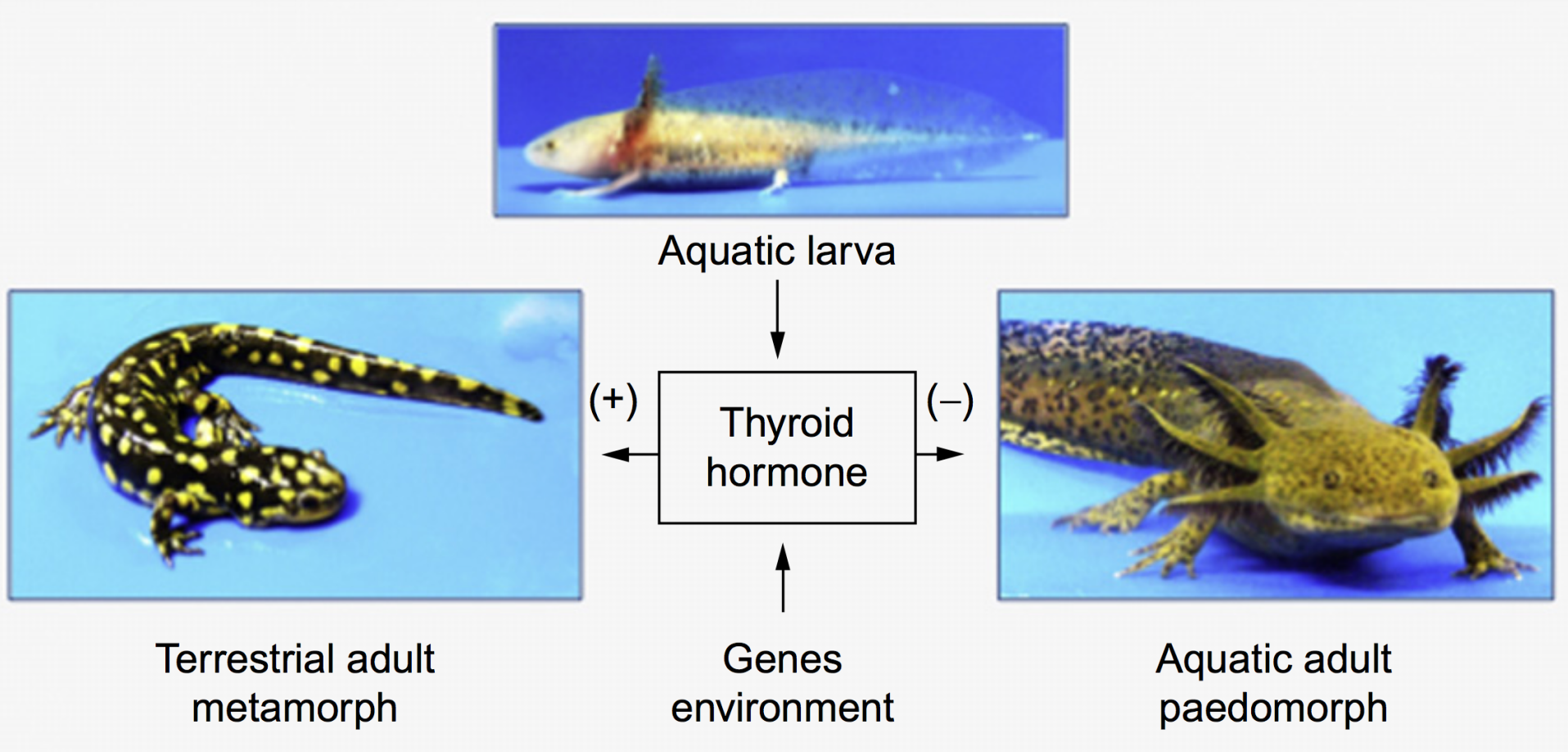
Timing of the Weismann Barrier Allows for Selection of a Program



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

iTR – Pathway Analysis

Embryonic → Fetal - Adult → Aging Adult

Highly Regenerative
Construction

Limited Regeneration
Maintenance

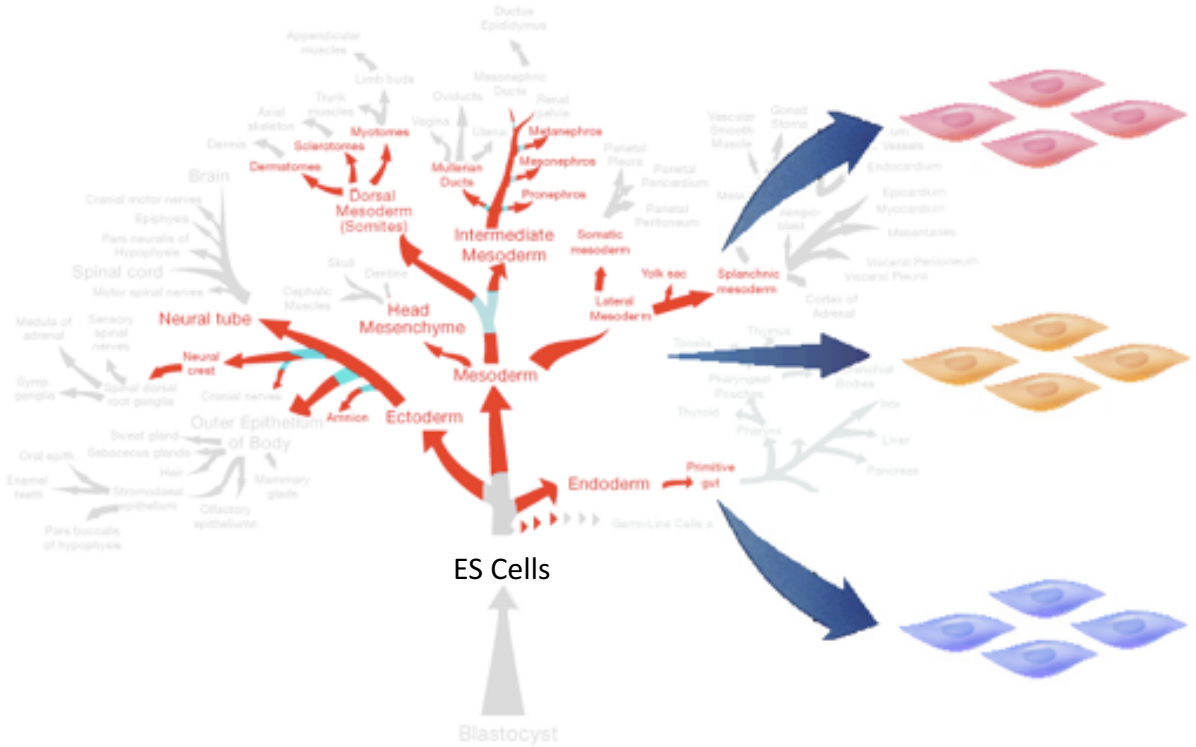
Non-Regenerative
Destruction

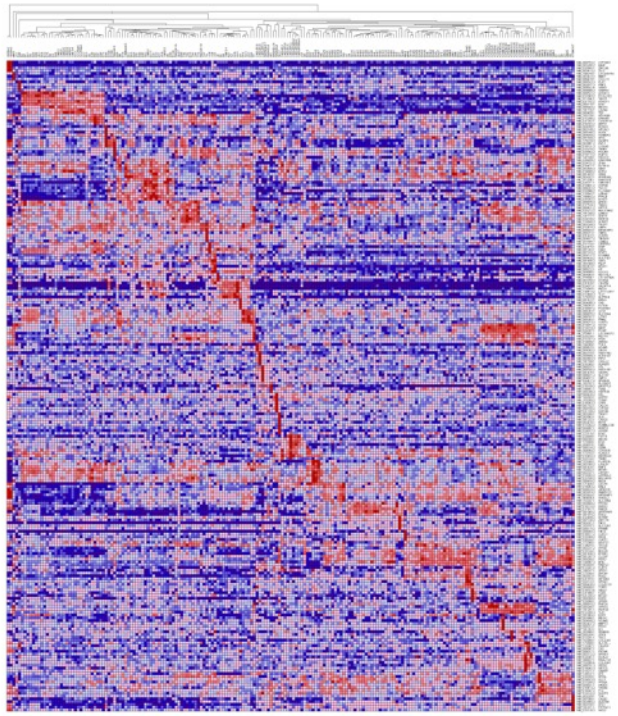
iTR: induced Tissue Regeneration

AGEX THERAPEUTICS

Use of Diverse Clonal Embryonic Progenitors

>200 Diverse Human Clonal Embryonic Progenitor Lines can be Compared with Adult Cell Counterparts





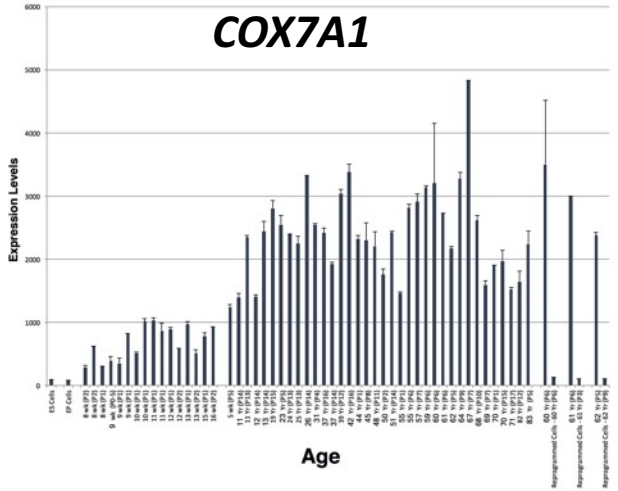
The Biology of Regeneration

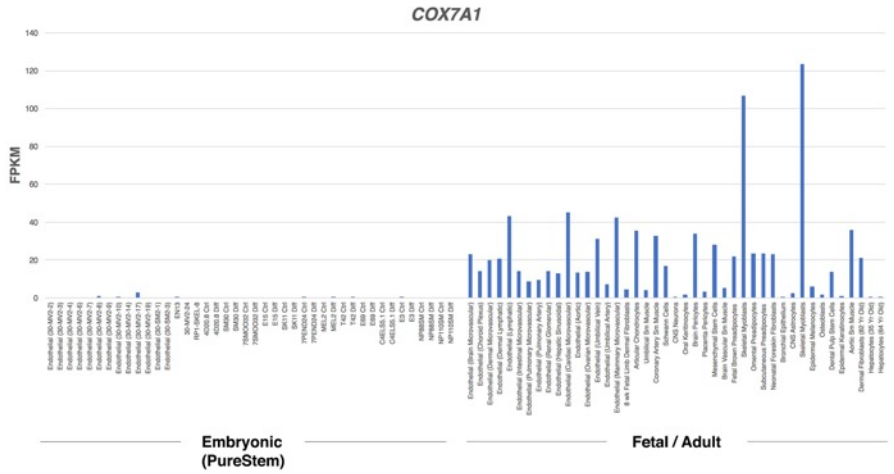
www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 8), pp: 7796-7811

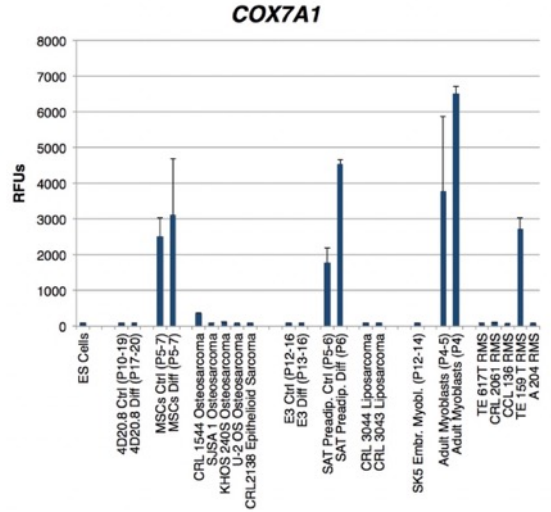
Research Paper

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]

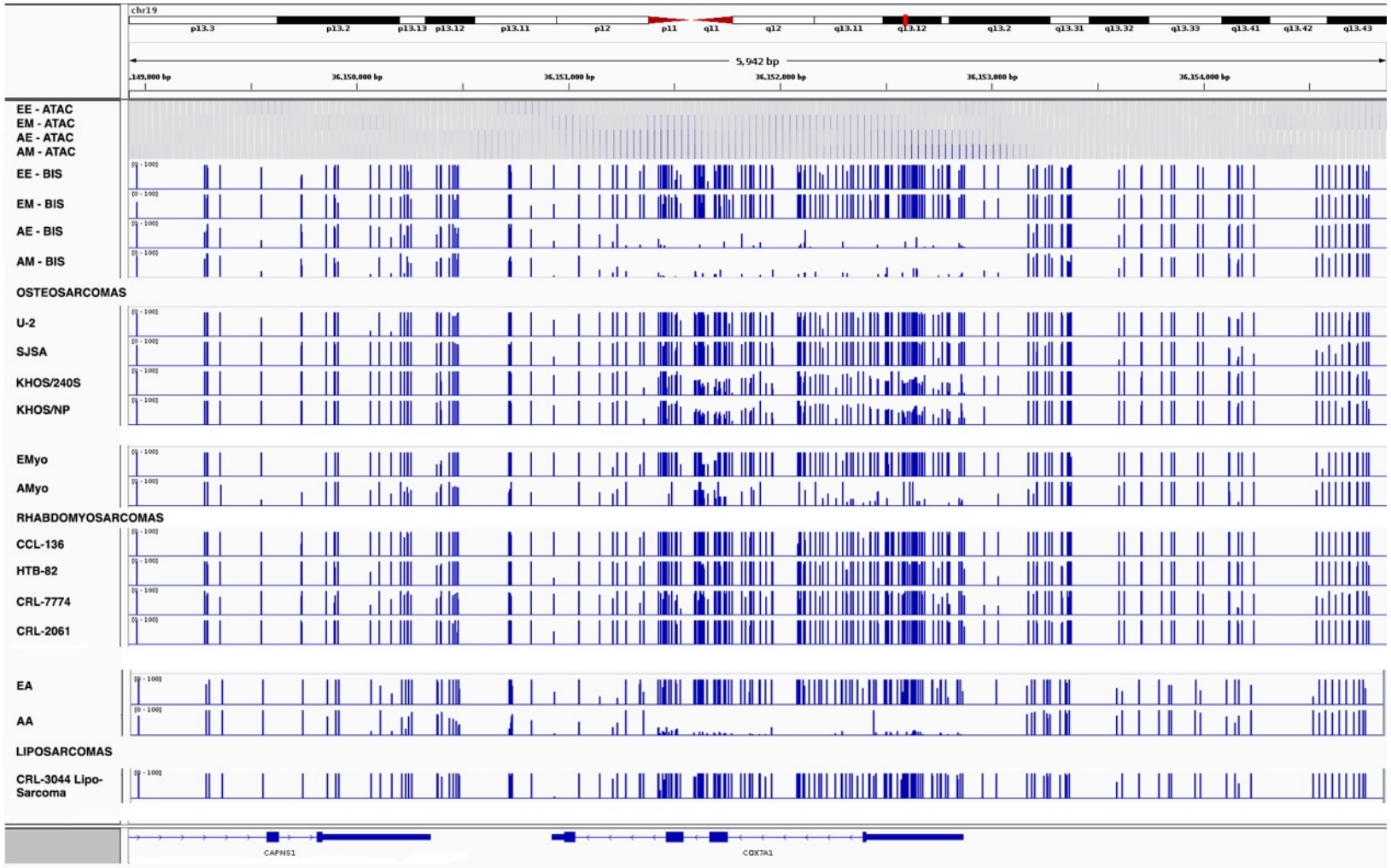






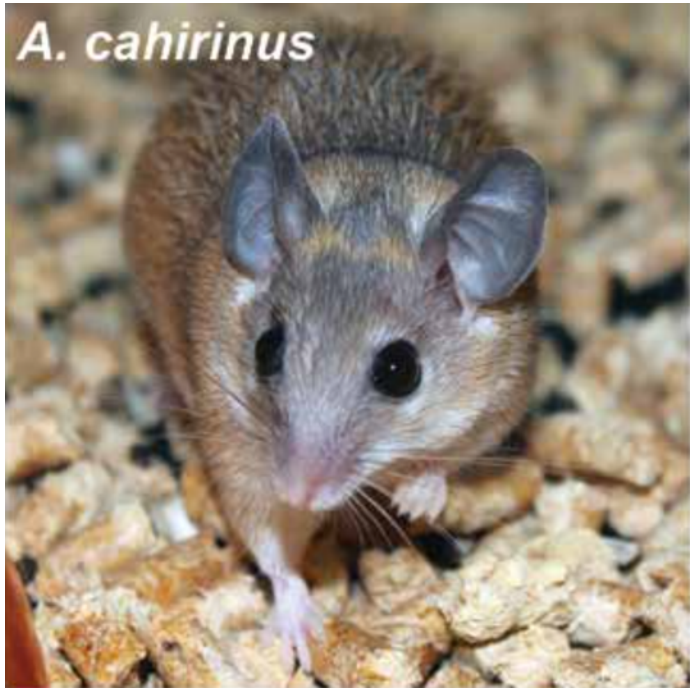
AGEX THERAPEUTICS

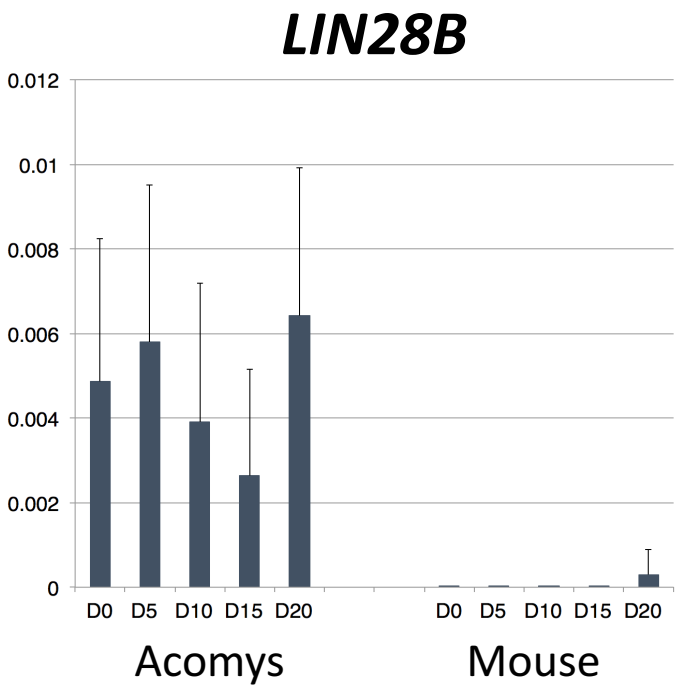
COX7A1 Chromatin Embryonic, Adult, Cancer

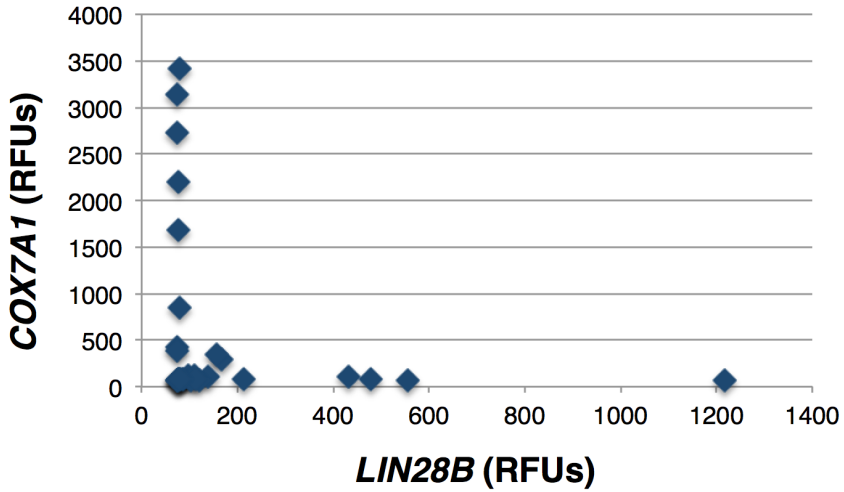


iTR – Pathway Analysis – *LIN28B*

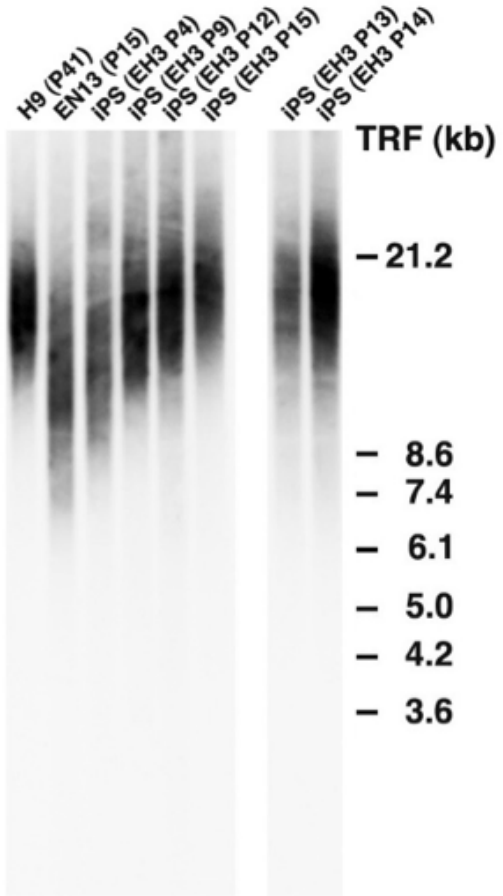
Acomys is a long-lived mouse with profound regenerative potential:



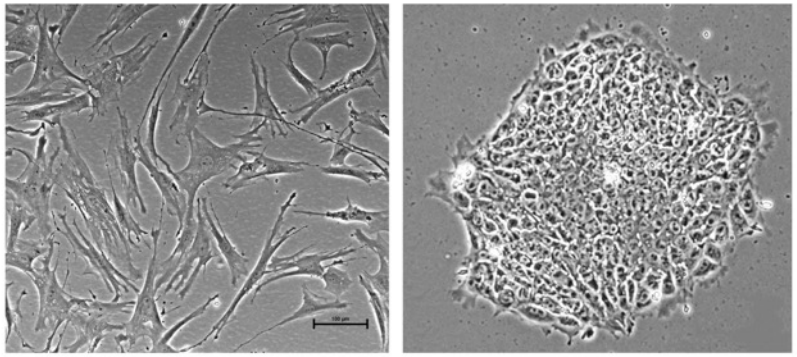




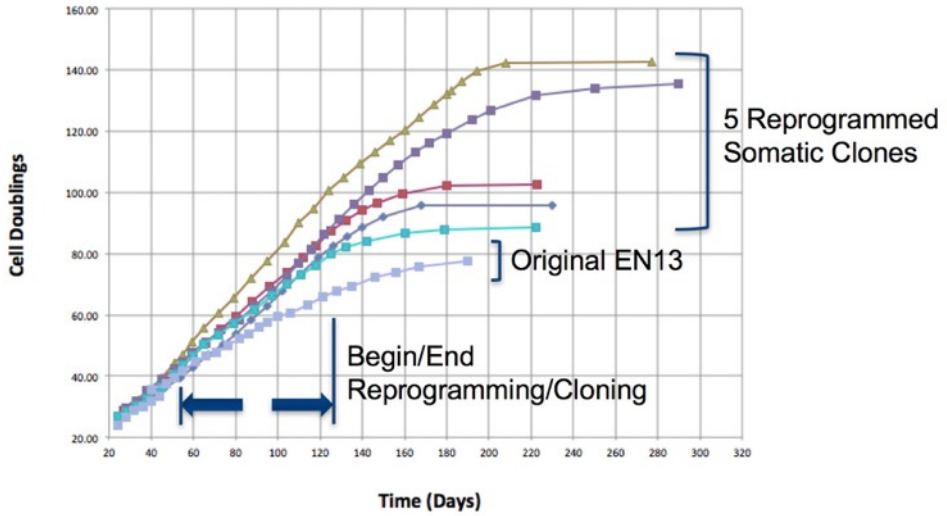
Reprogramming the Aging of Human Cells



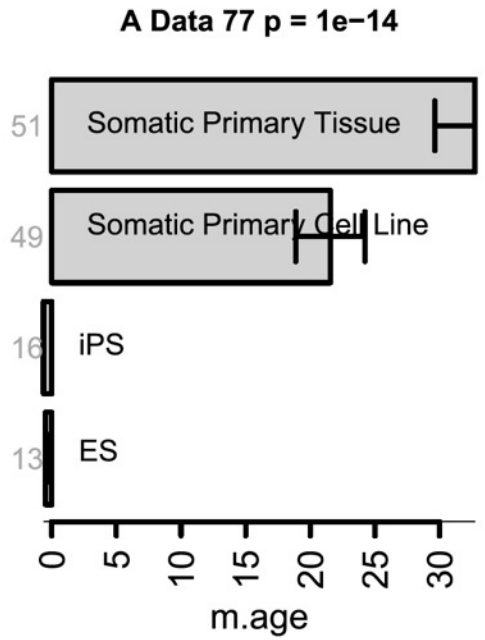
Regen Med 2010 May;5(3):345-63



Skin Fibroblasts iPS Cells



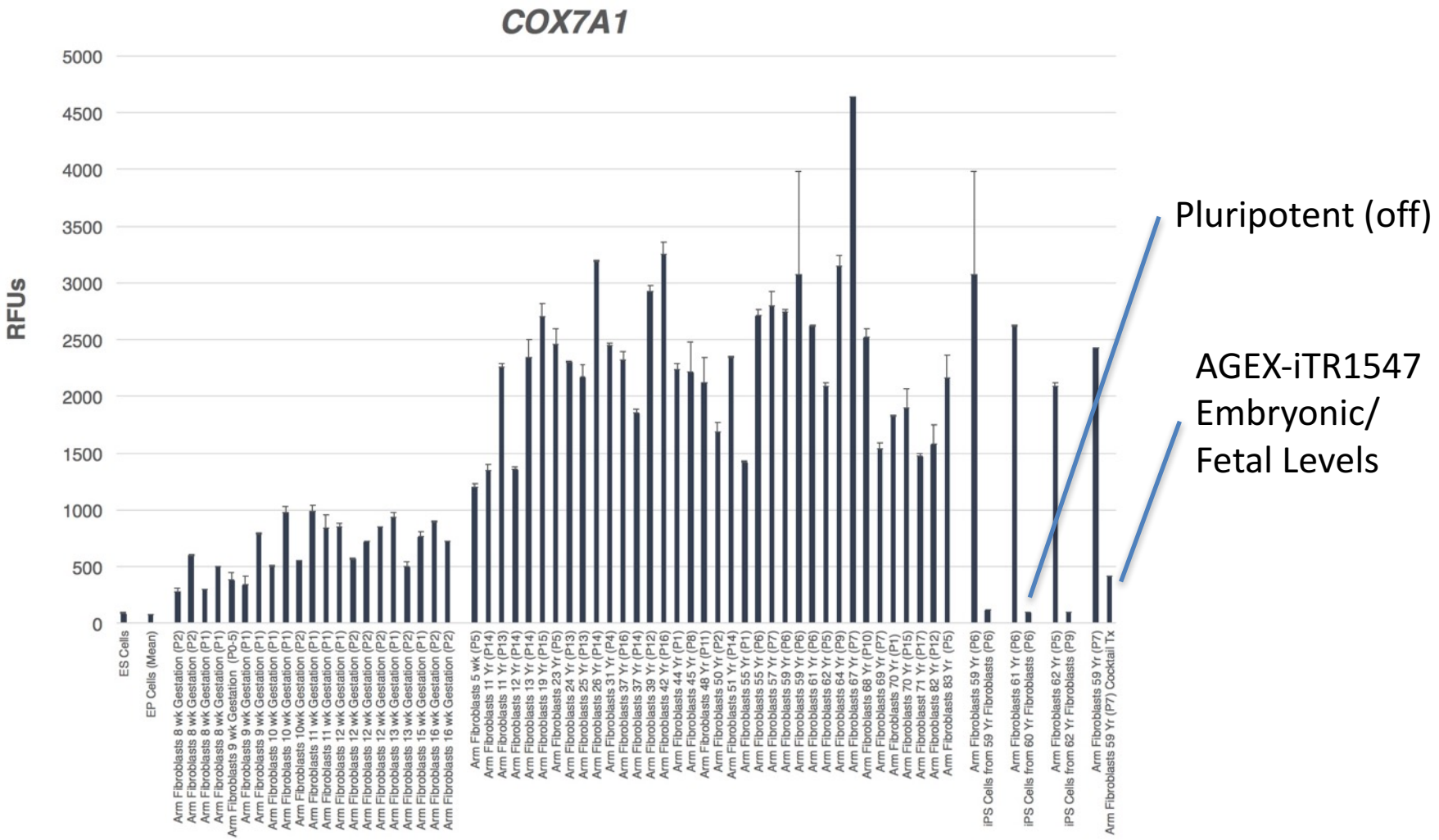
Reprogramming Methylation Age



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

AGEX THERAPEUTICS

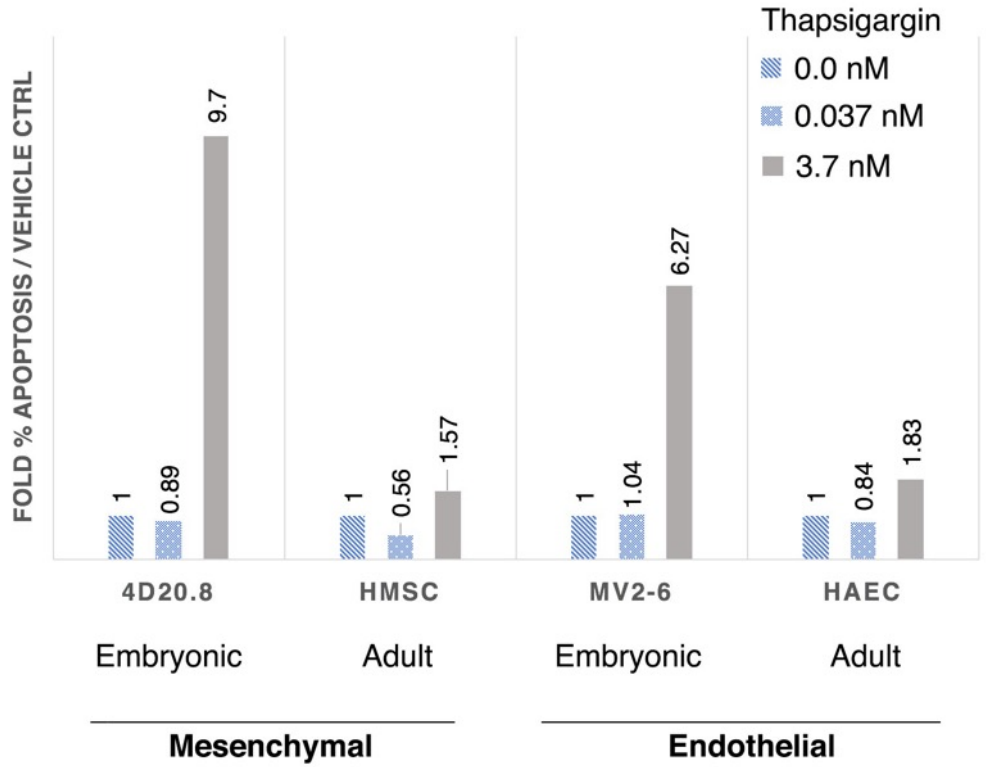
An Example of an iTR Formulation



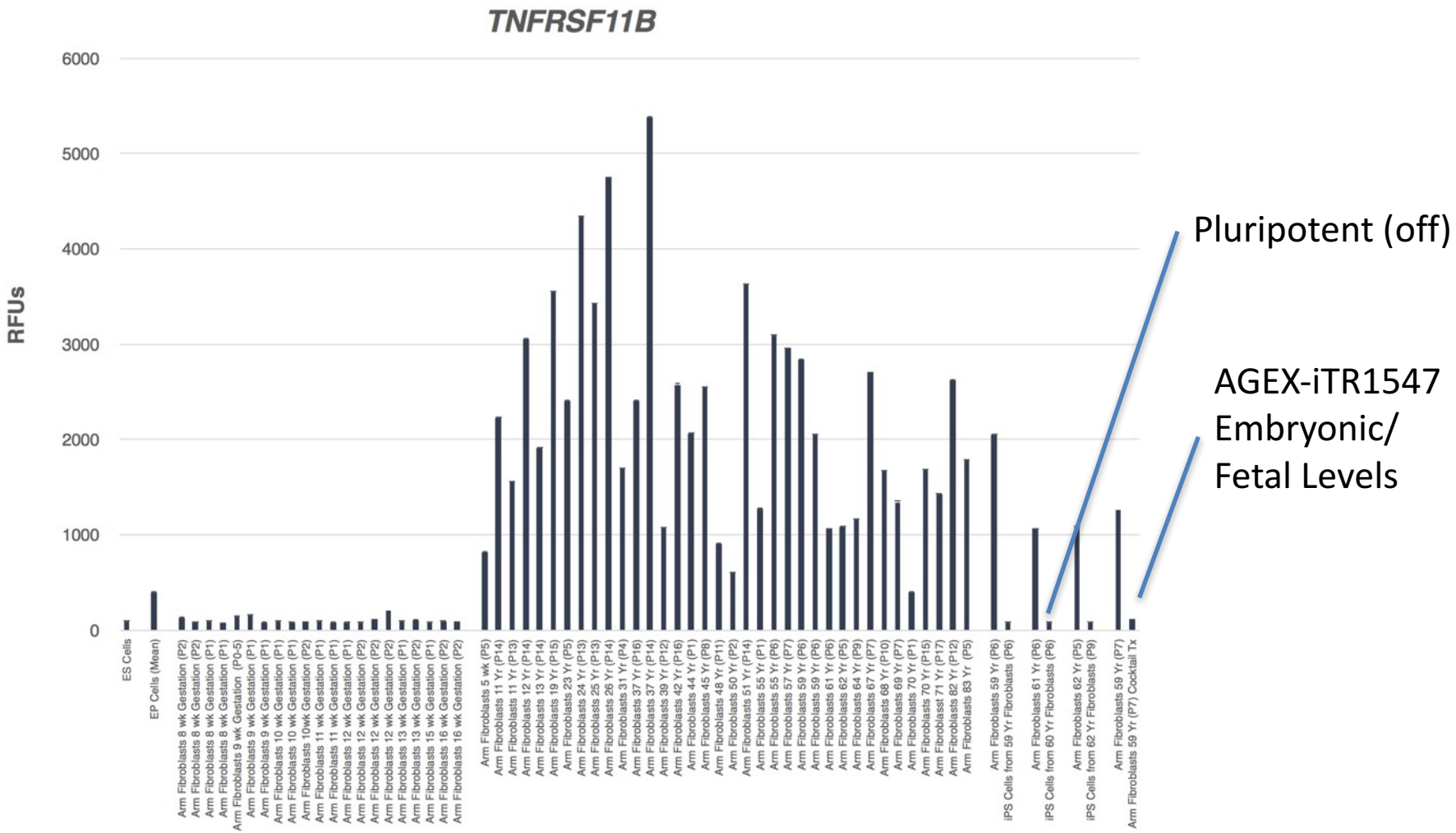
AGEX THERAPEUTICS

Apoptosis/Senolysis

Cells with regenerative potential may allow cells with genotoxic damage to apoptose which makes sense since they are easily replaced while post-regenerative tissues tend to resist apoptosis since they cannot be replaced:

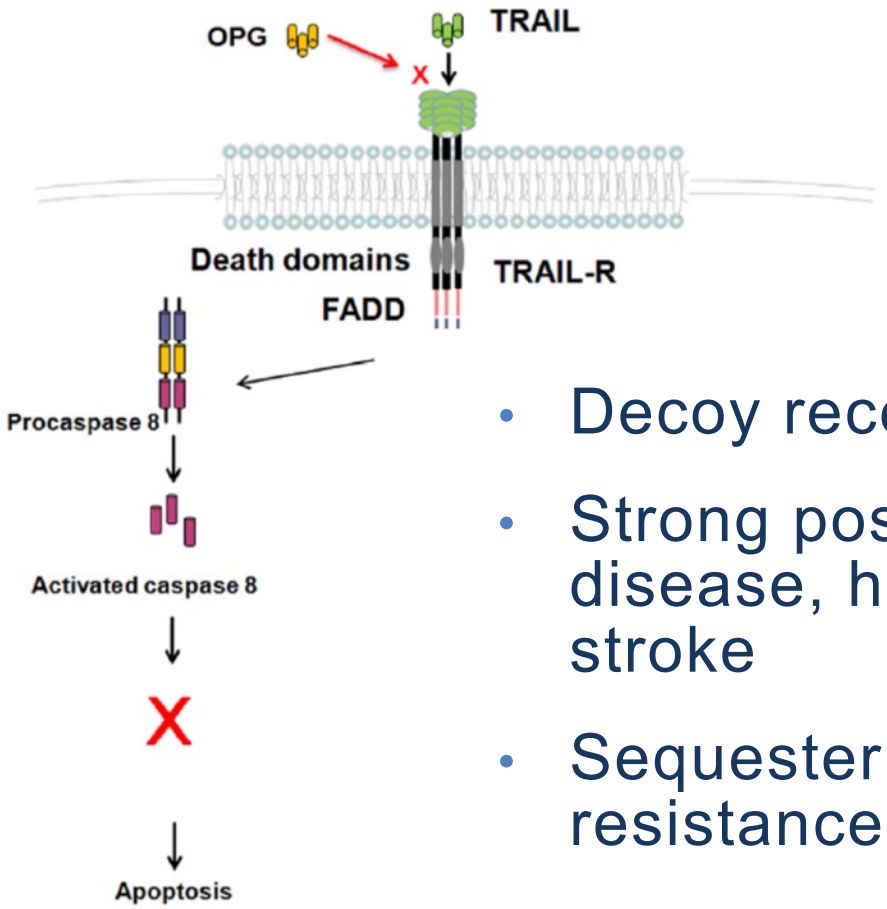


An Example of an iTR Formulation



AGEX THERAPEUTICS

TNFRSF11B (Osteoprotegerin (OPG))



- Decoy receptor for TRAIL
- Strong positive correlation with coronary disease, heart failure, peripheral artery disease, stroke
- Sequestering TRAIL may play a role in resistance to apoptosis/senolysis

AGEX THERAPEUTICS

iTR vs Senolysis

Embryonic → Fetal - Adult → Aging Adult

Highly Regenerative
Construction
↑ Apoptosis

Limited Regeneration
Maintenance
↓ Apoptosis

Non-Regenerative
Destruction
↓ Apoptosis

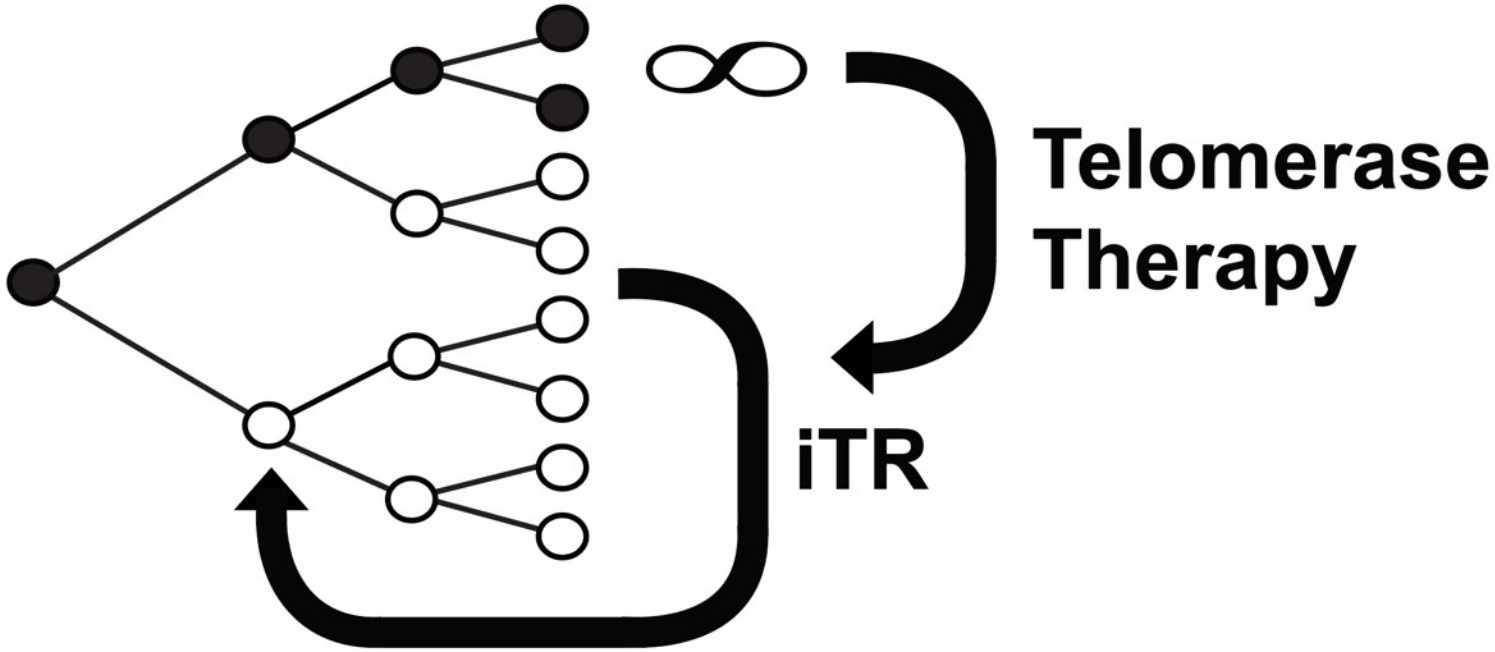
iTR: induced Tissue Regeneration

Senolysis a consequence?

AGEX THERAPEUTICS

induced Tissue Regeneration (iTR)

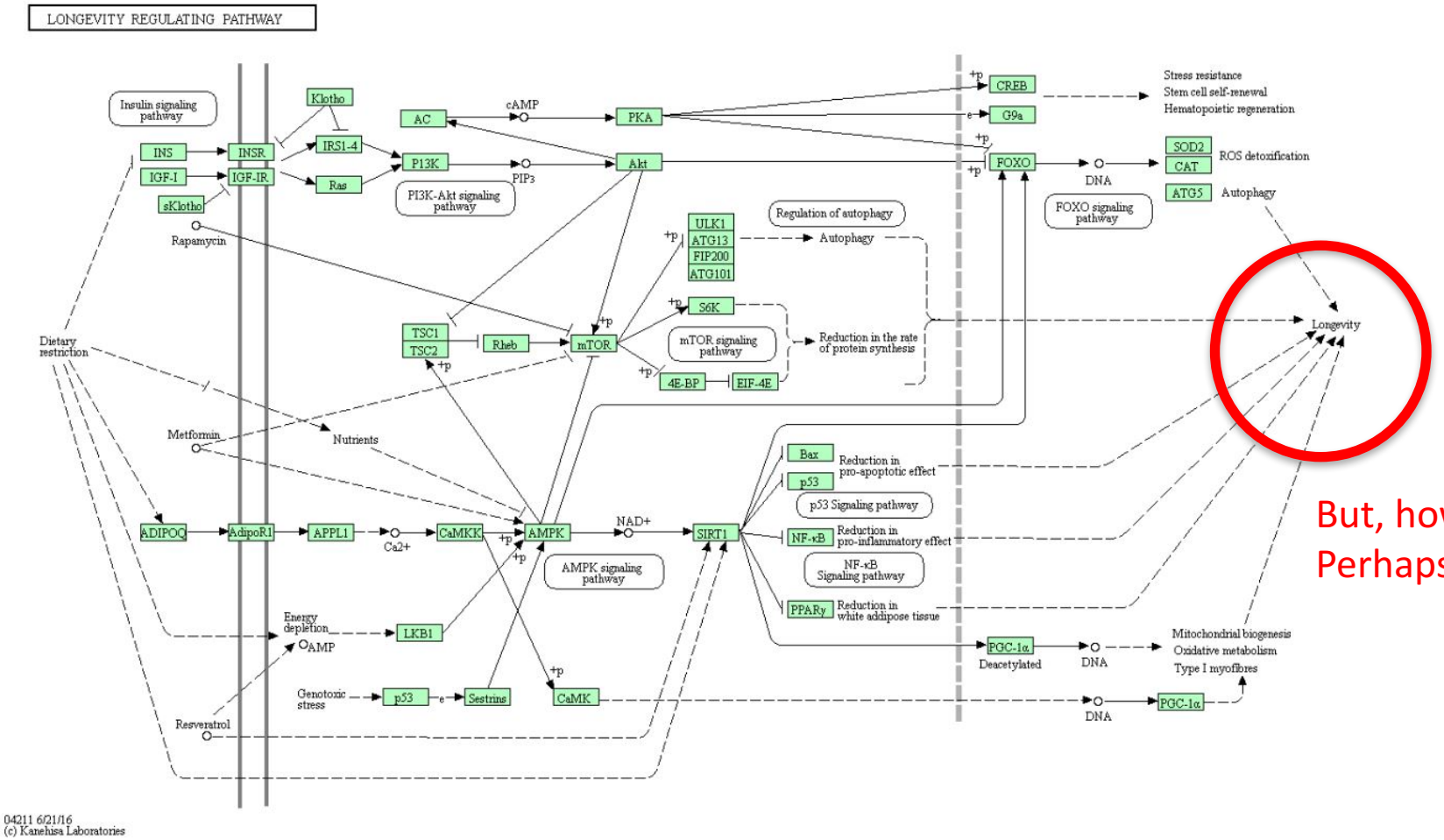
Since animals that have both telomerase and full regenerative potential may escape senescence, combining iTR with telomerase therapy may make sense.



AGEX THERAPEUTICS

Toward a Unified Theory of Aging

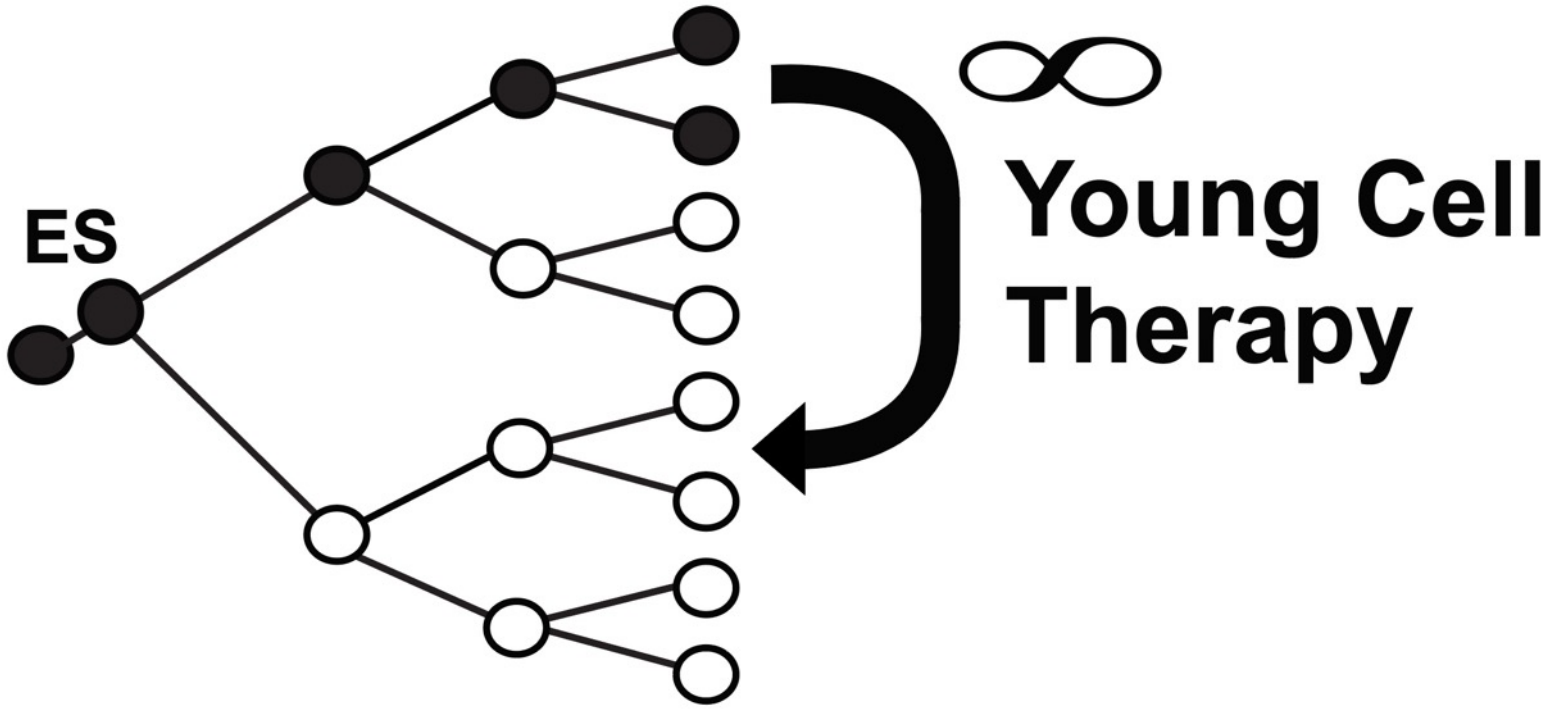
Is Somatic Restriction of Regeneration the Target?



But, how?
Perhaps Regeneration

AGEX THERAPEUTICS

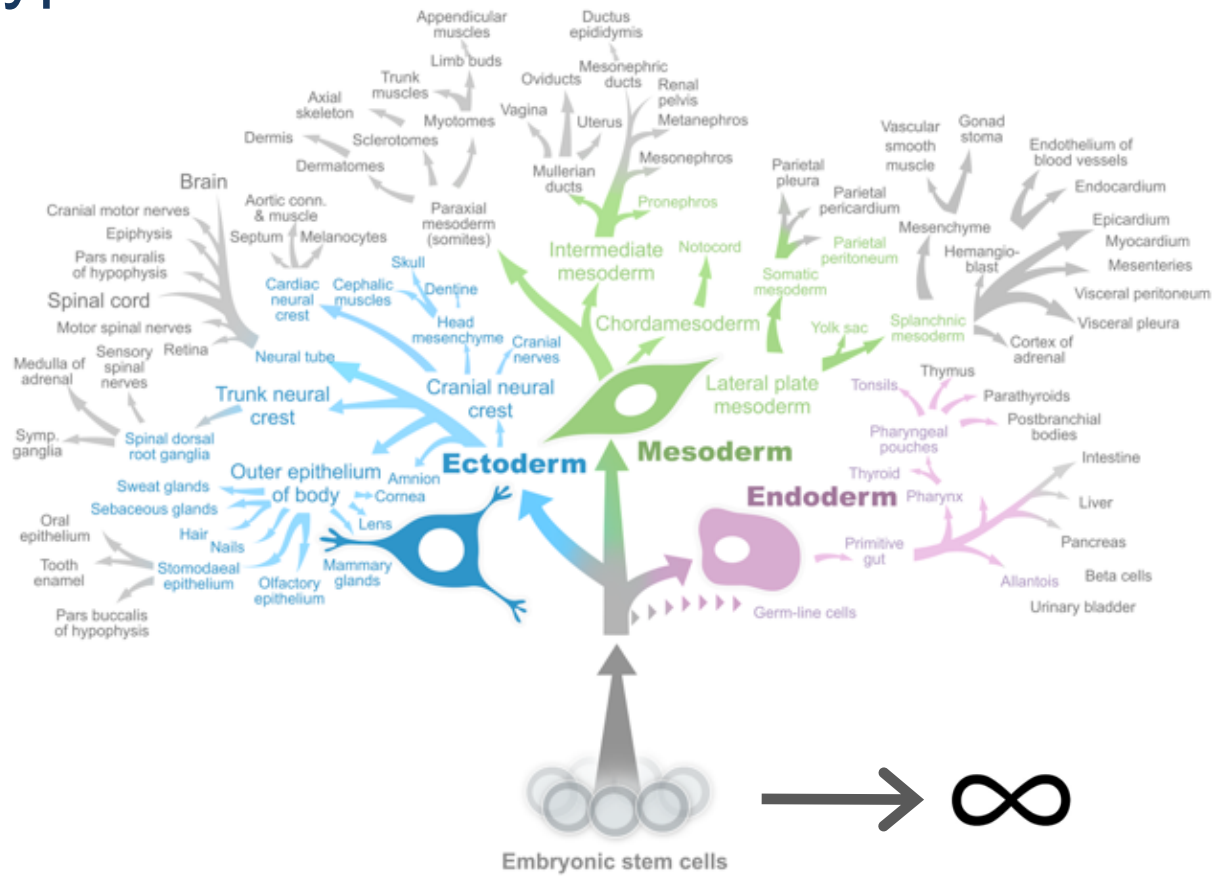
Pluripotency & Regenerative Medicine



AGEX THERAPEUTICS

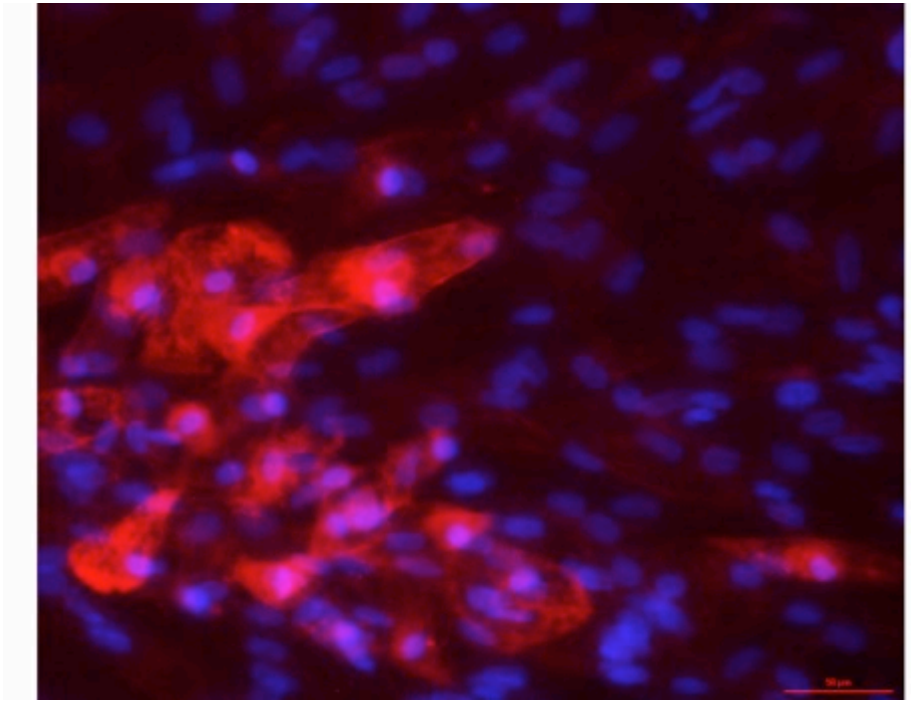
Pluripotency

- Scalable source of all human cell types
- Regen phenotype

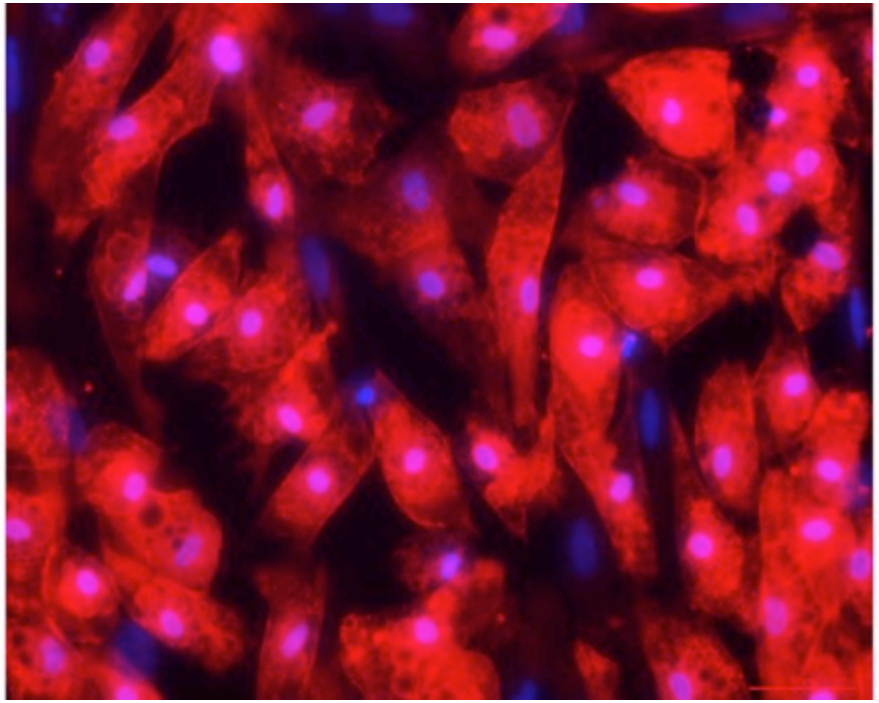


Industrially-Scalable *AgeX-BAT1*

Stained for Brown Adipocyte Marker UCP1



Tissue-Sourced Brown Adipocytes



PureStem Brown Adipocytes

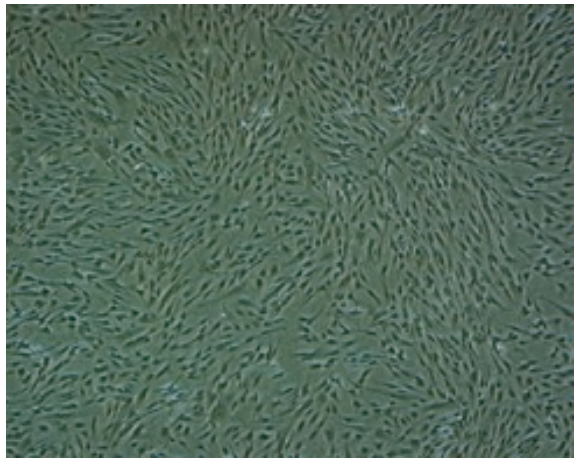
Data from AgeX publication in preparation

AGEX THERAPEUTICS

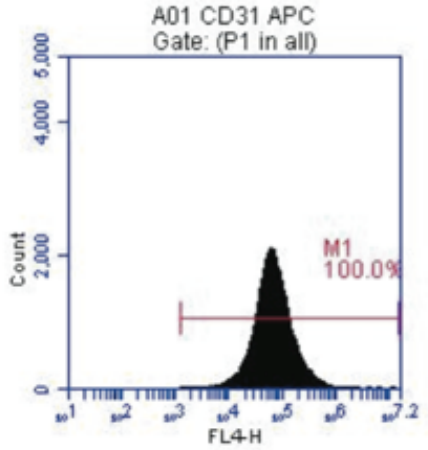
Cardiac Program: *AGEX-VASC1*

Regenerative Vascular Progenitors

Monoclonal Endothelial Cells



100% Purity



- Highly scalable with high purity & potency
- Extensive IP estate
- Formulated in a proprietary matrix with good safety profile for human lipotransfer

AGEX THERAPEUTICS

Potential of iTR

So, iTR may impart multiple benefits:

- A natural senolytic capacity (with regeneration)
- Imparting scarless tissue regeneration in multiple tissues
- Potentially impacting the downstream biology of aging, e.g. sirtuins, NAD, mTOR, etc

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

“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)

AGEX THERAPEUTICS