AGEX THERAPEUTICS

Aging & Regenerative Medicine: An Emerging Synthesis

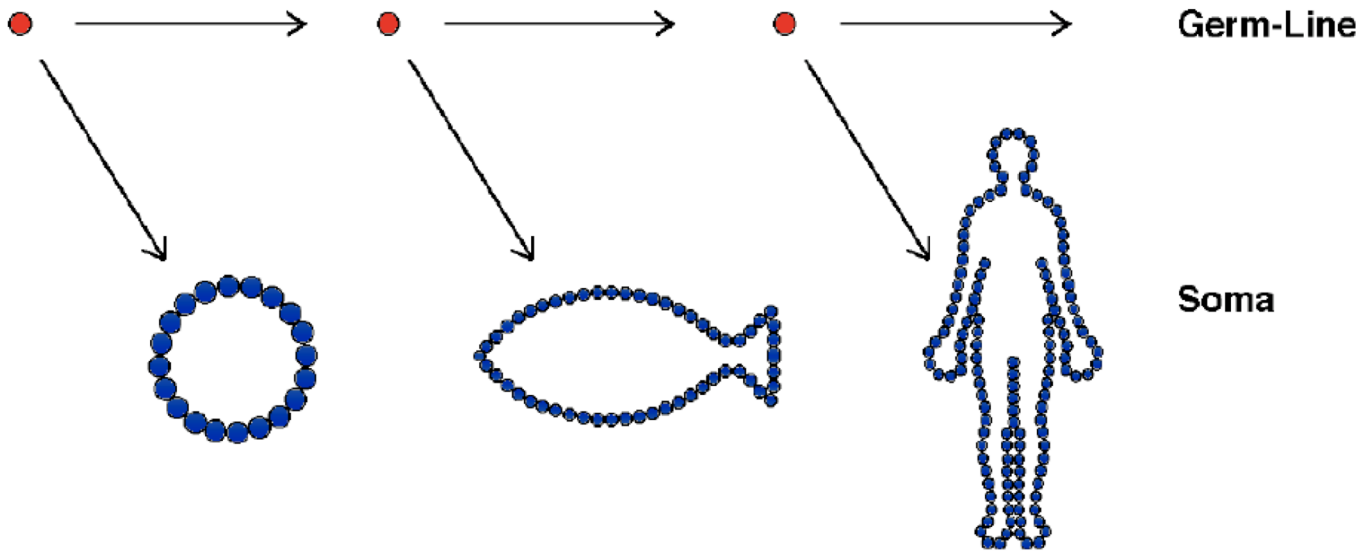
December 3, 2018

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 in developing new stem cell-based products and technologies; results of clinical trials of such products; the ability of AgeX 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; the ability of AgeX and its subsidiaries to maintain patent and other intellectual property rights; 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. 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 its other subsidiaries, particularly those mentioned in the cautionary statements found in AgeX's Securities and Exchange Commission filings. AgeX disclaims any intent or obligation to update these forward-looking statements.

AGEX THERAPEUTICS

Some Initial Observations



- The germ-line lineage of cells that produced our bodies has not aged for billions of years (otherwise reproduction itself would age and cease).
- Aging is a *somatic* phenomenon, turned on during cell differentiation in the body as opposed to the immortal germ-line.
- Aging in somatic cells must be completely reversible by reprogramming technology, otherwise cloning wouldn't make young animals.

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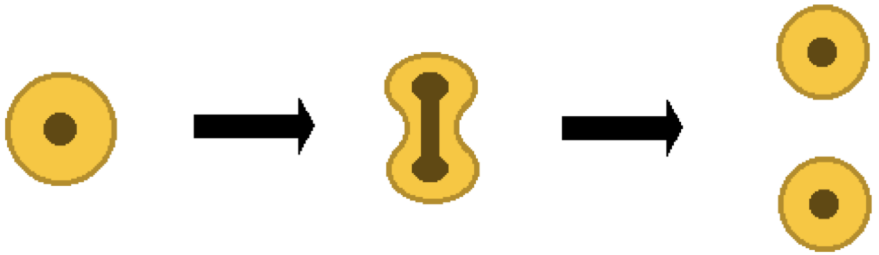
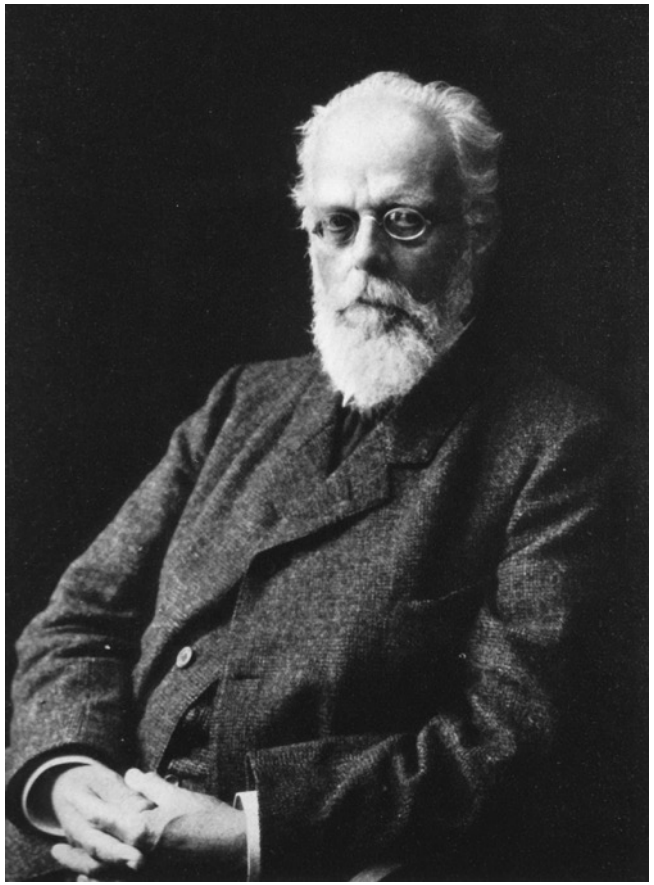


"Death takes place because a worn-out tissue cannot for ever renew itself, and because a capacity for increase by means of cell-division is not everlasting, but finite."

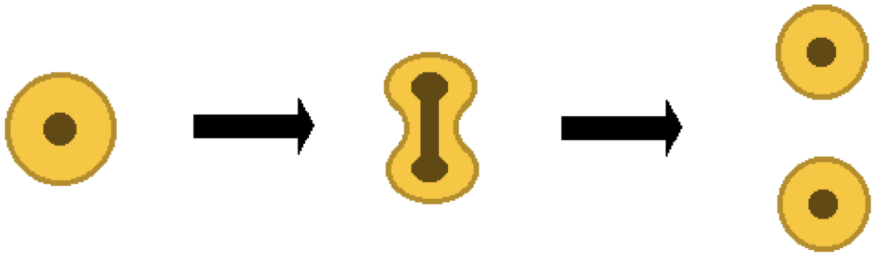
- A. Weismann, 1891



AGEX THERAPEUTICS

Some Initial Observations

Repression of Regeneration



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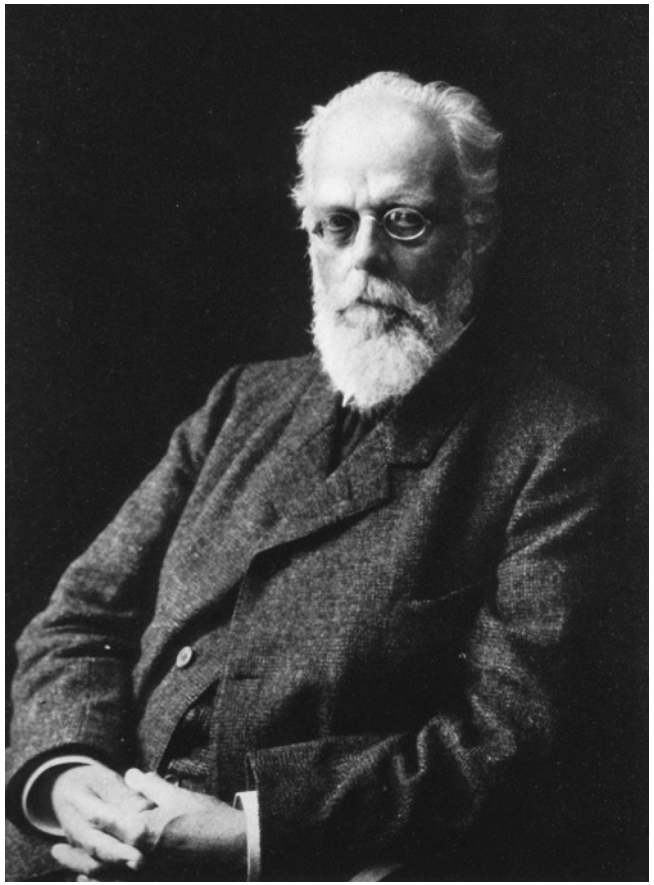
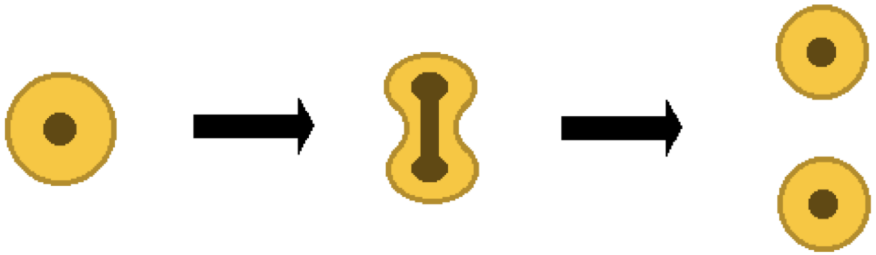


AGEX THERAPEUTICS

Some Initial Observations

Repression of Replicative Immortality



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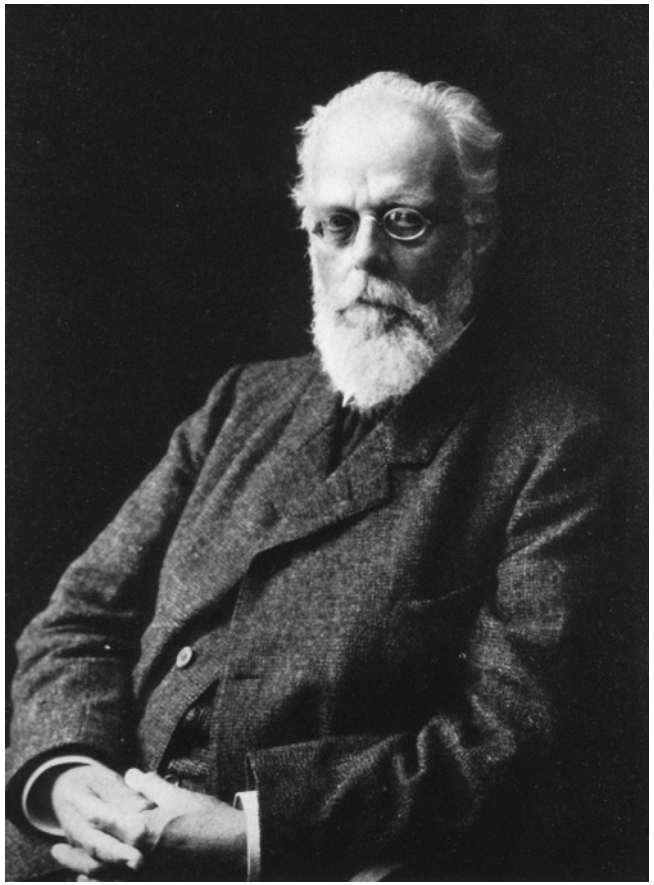
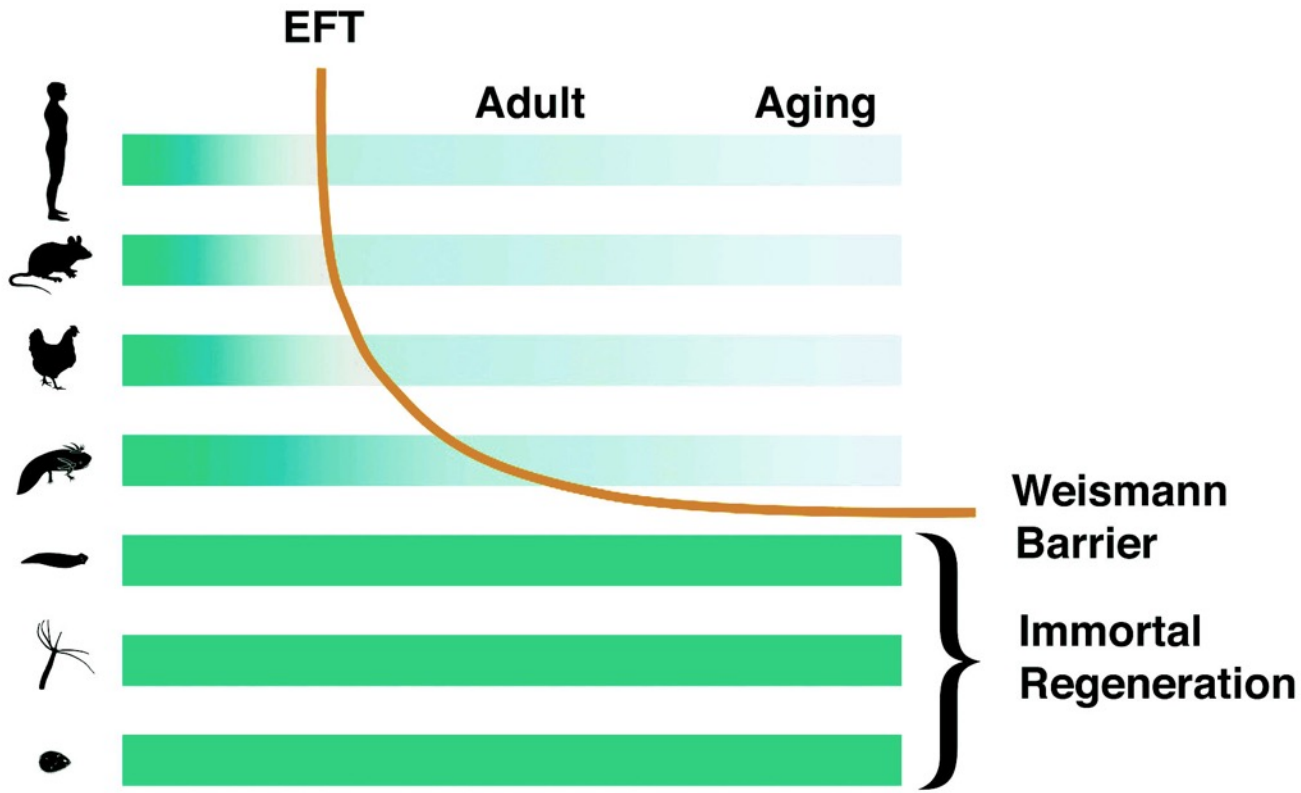


AGEX THERAPEUTICS

Some Initial Observations

Innate immortal regeneration is present throughout life in primitive animals, in humans it is restricted to early development (pre-EFT)



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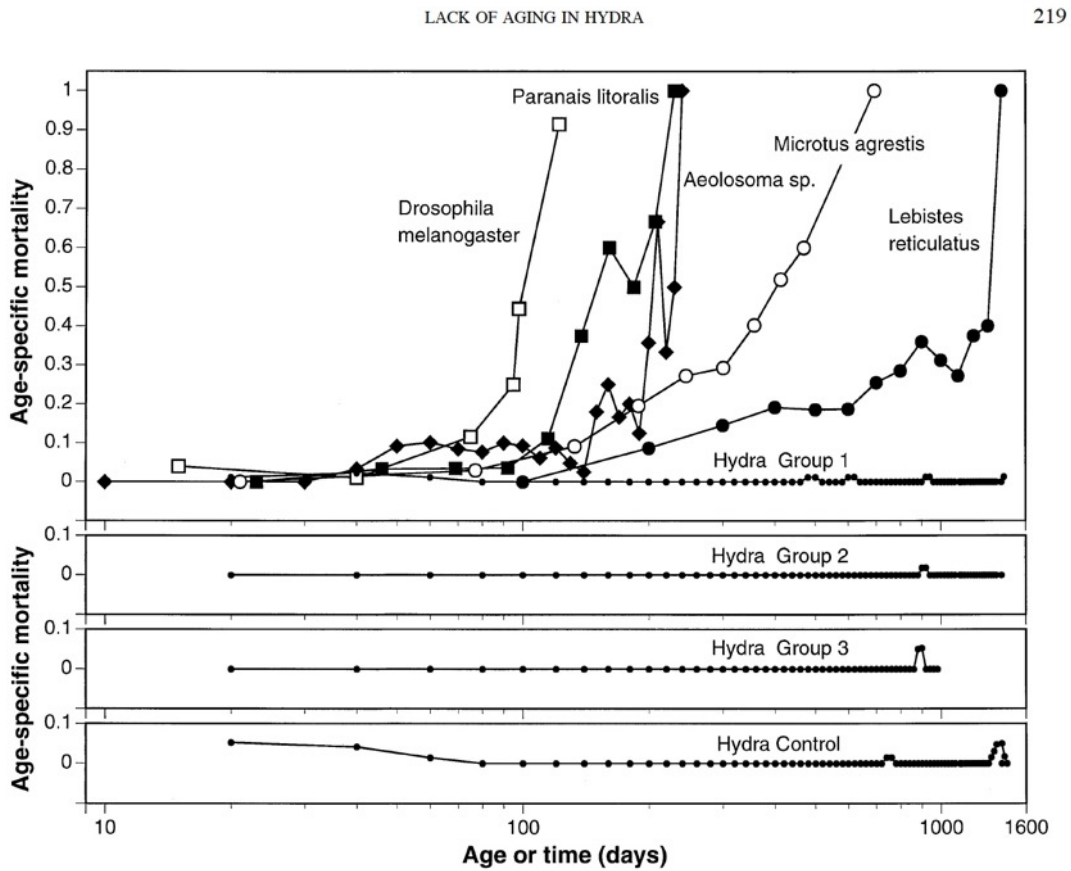
Some Initial Observations

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

Some Initial Observations

The concept of genetically-programmed aging through evolution was introduced by George Williams

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

GEORGE C. WILLIAMS

Michigan State University

Received February 26, 1957

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Some Initial Observations

How Williams' antagonistic pleiotropy works

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

AGEX THERAPEUTICS

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

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Some Initial Observations

How Williams' antagonistic pleiotropy works to repress telomerase in aging

Some Initial Observations

Antagonistic pleiotropy may similarly work to repress regeneration in aging

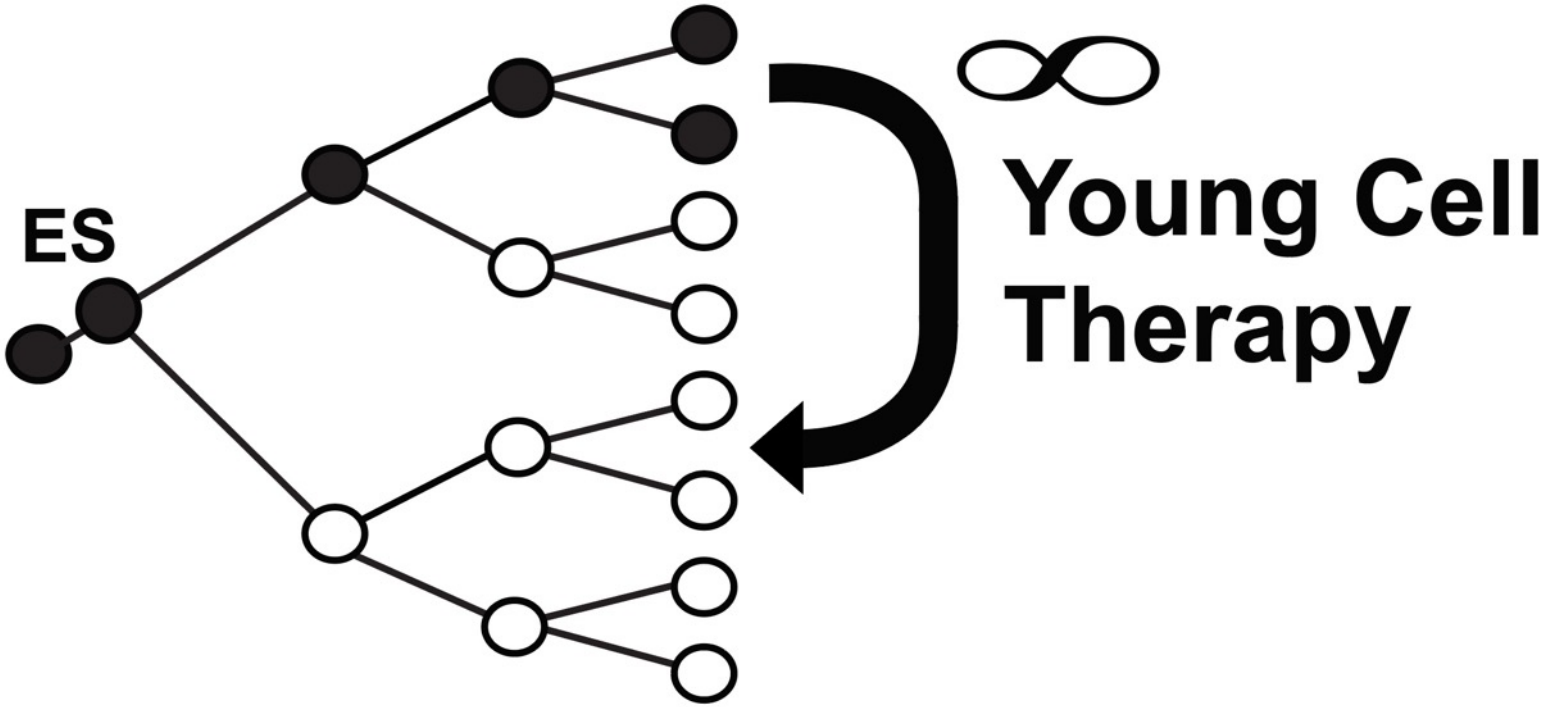
Regeneration OFF in somatic cells after EFT reduces cancer in young

Leads to disrepair/fibrosis in old

AGEX THERAPEUTICS

Pluripotency & Regenerative Medicine

AgeX's Regenerative Cell Therapies for Aging



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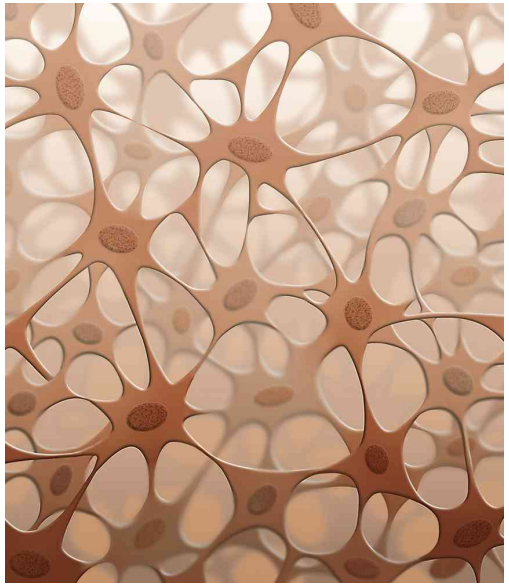
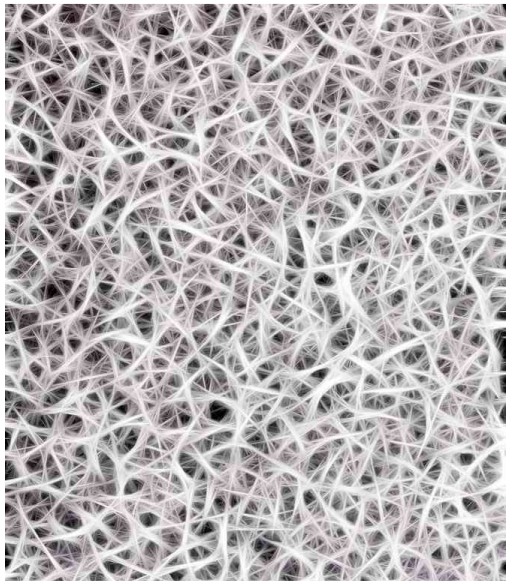
The Ideal Regenerative Technology Platform

- Young replacement cells of all kinds
- Cells capable of regeneration
- A path to an off-the-shelf product
- An injectable mix of cells/matrix to regenerate 3-D tissue



Young Cells

+



Matrix

= Regenerative Medicine For Age-Related Degenerative Disease

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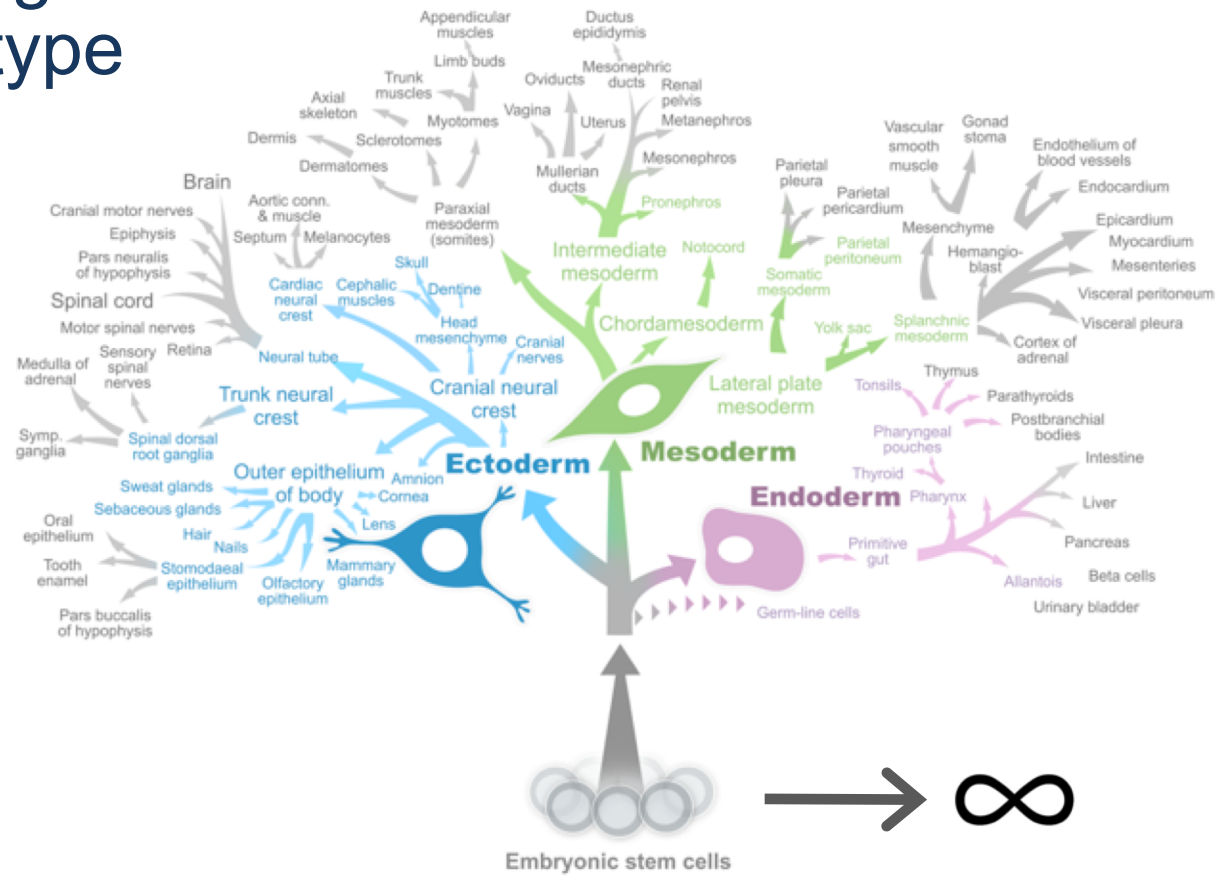
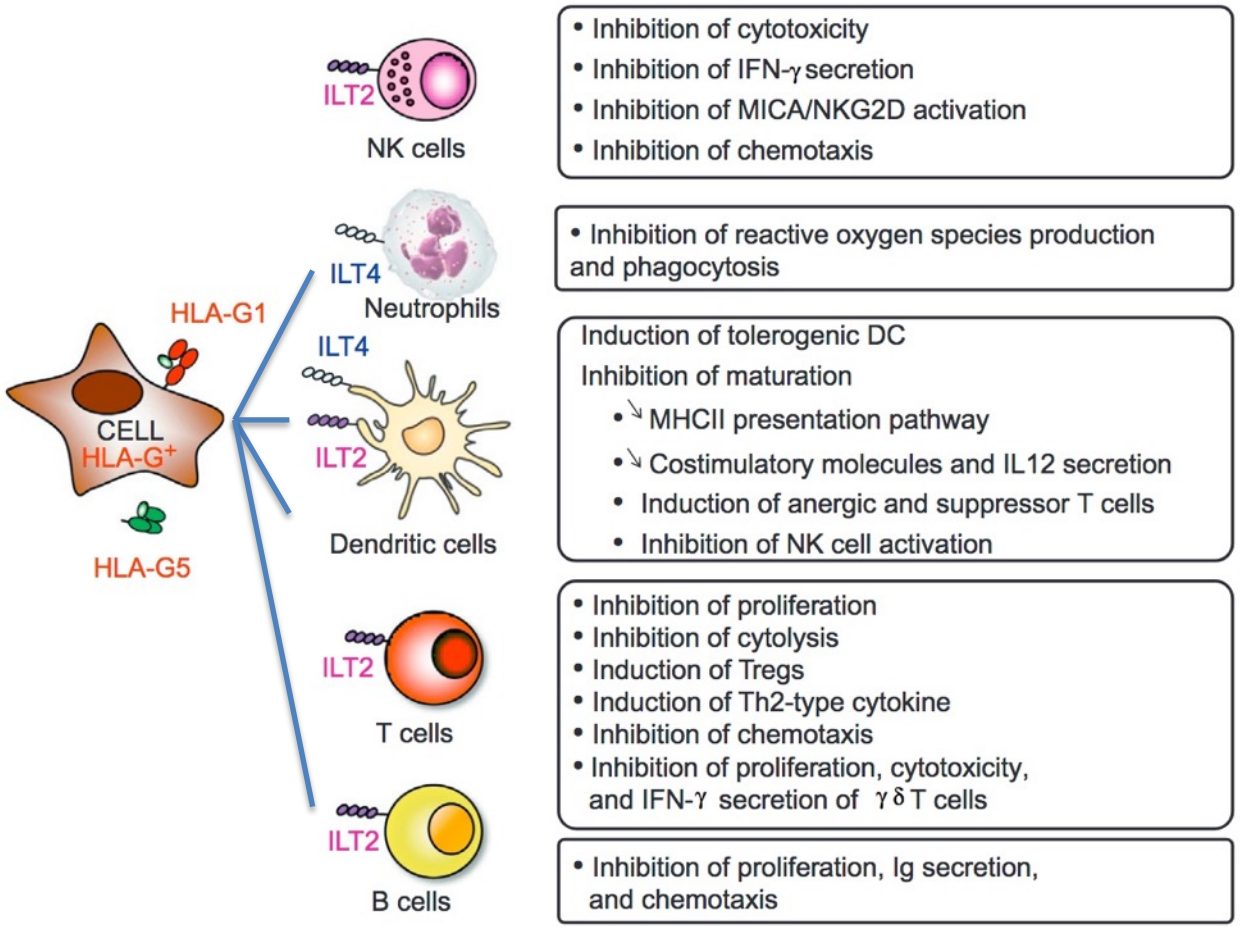
Pluripotency: An Immortal Source of Regenerative Cells

- Scalable source of all human cell types
- Cells are young
- Regen phenotype



UniverCyte™: HLA-G for Allogeneic Immunotolerance

- It appears that the primary role of HLA-G is to suppress maternal immune response to pregnancies.
- Appears to disarm multiple arms of immune system



Adv. Immunol. (2015) 127:33-144

AGEX THERAPEUTICS

Value of the UniverCyte Pluripotent Platform

AgeX will utilize the classical biologics off-the-shelf business model

Traditional Biologicals

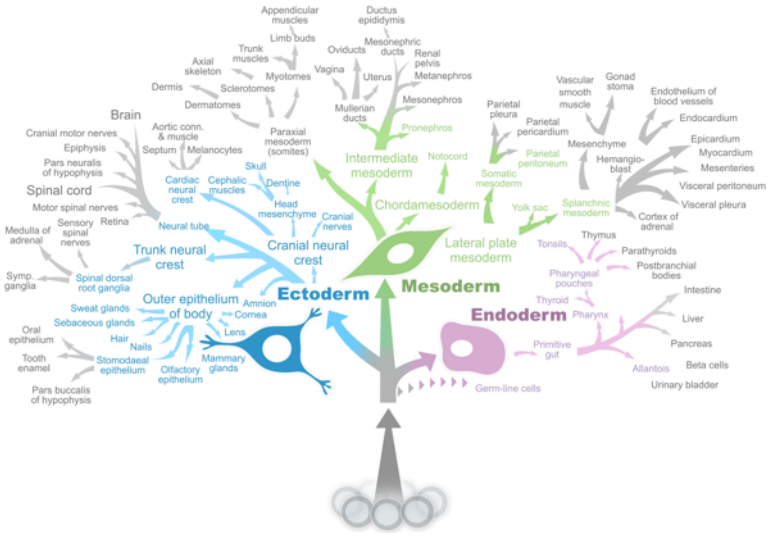
Centralized Production Facility → *Distributed Frozen Inventory* → *Point Of Care*

UniverCyte-Derived Cell Therapy Products

AGEX THERAPEUTICS

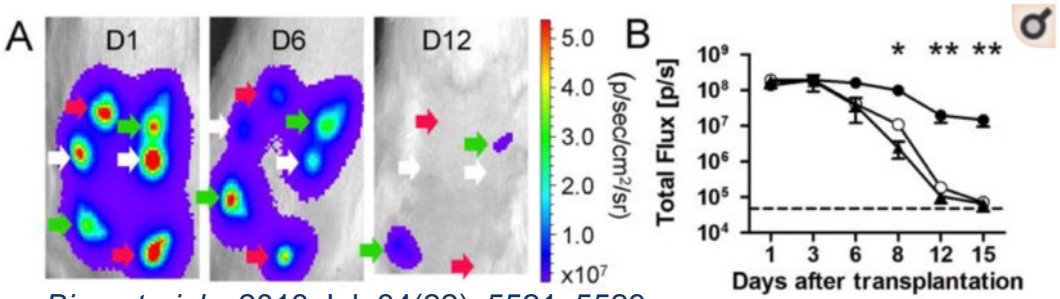
Twin Components: Cells & Matrix

Pluripotent Cell-Based Therapeutics



- Pluripotent Stem Cells (PSCs) allow the manufacture of all young human cell types on an industrial scale
- Engineered for allogeneic use
- Our cells are government (NIH) approved

HyStem® Matrix Delivery



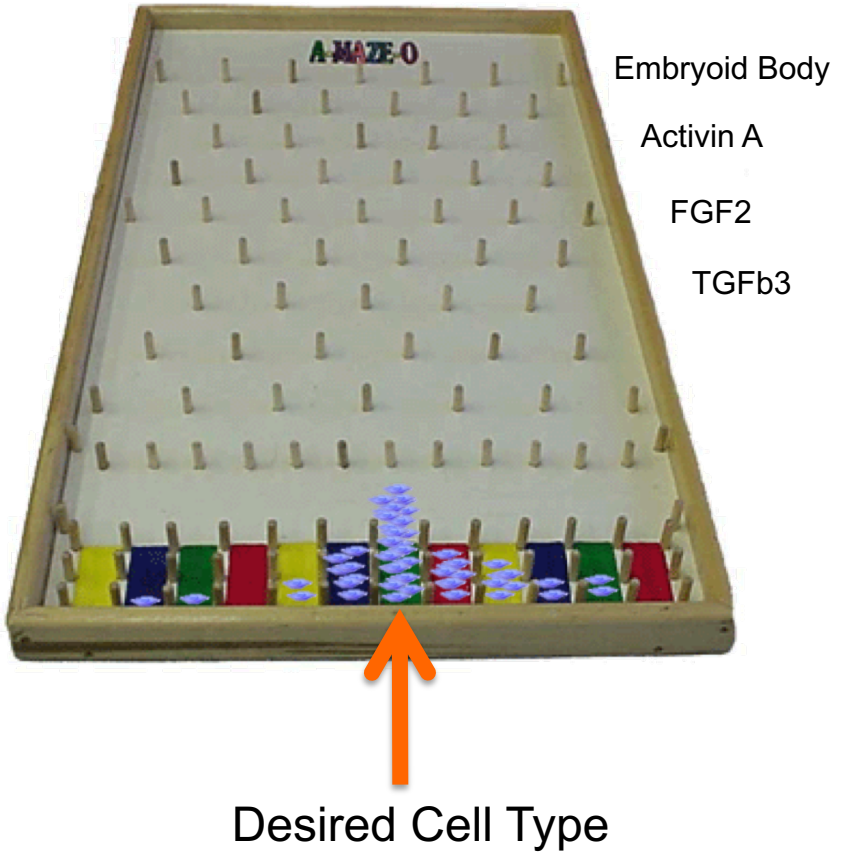
Biomaterials. 2013 Jul; 34(22): 5521–5529

AGEX THERAPEUTICS

Pluripotency – The Competitive Edge

The >1000-fold complexity of cell types derived from hPS cells leads to unique challenges:

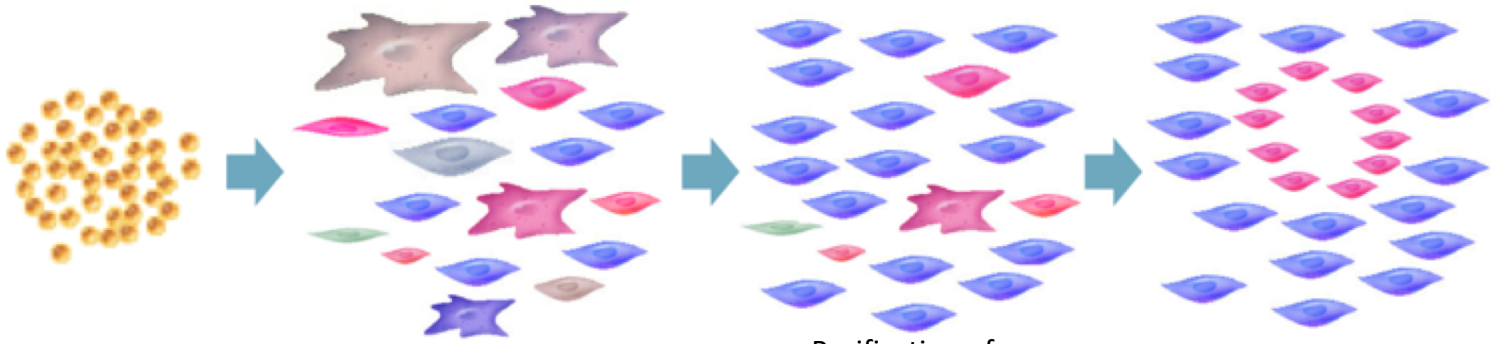
- How manufacture with cGMP?
- How produce allogeneic product?
- Identity - Lot-to-lot variability in composition
- Purity – Contamination with unknown cell types



AGEX THERAPEUTICS

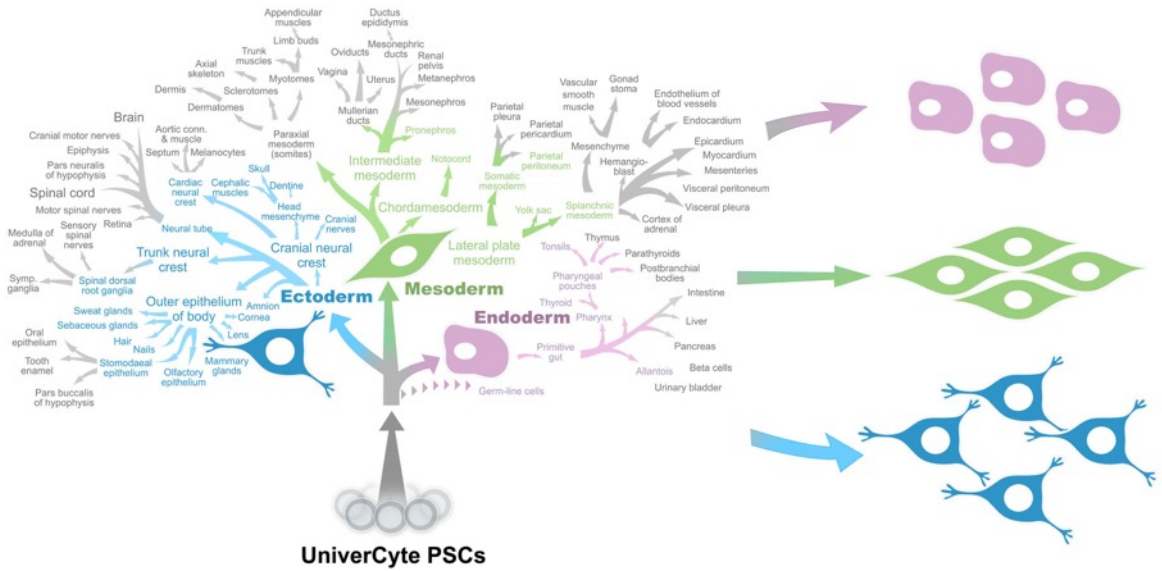
Universal *PureStem™* Technology

Traditional Manufacture



ES Cells | Differentiation | Purification of desired cell type | Problem of impurities

PureStem Technology

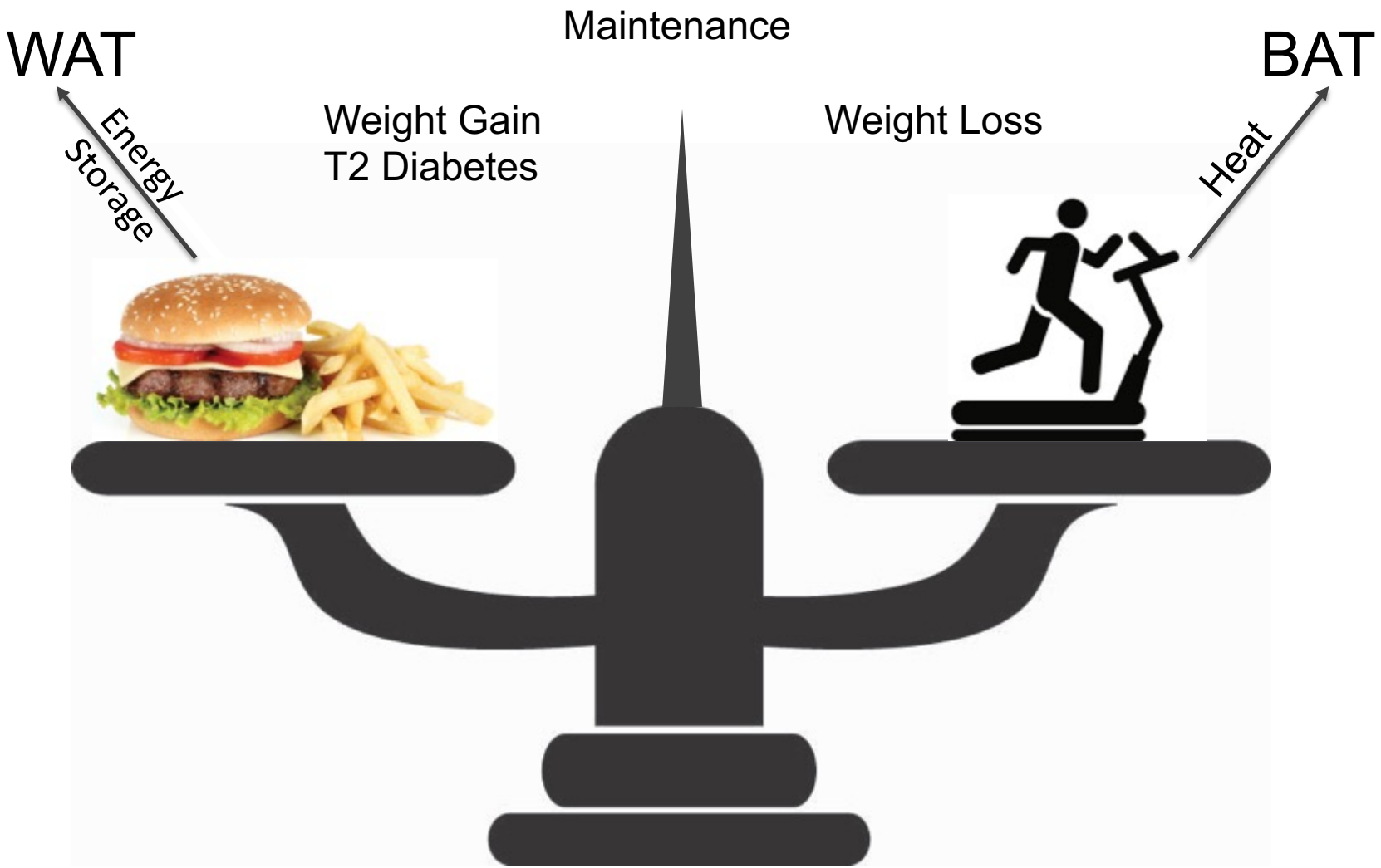


PureStem®

- >200-fold diversity
- Scalable, monoclonally-purified regenerative progenitor cell lines
- Off-the-shelf use

AGEX THERAPEUTICS

Brown Adipose Cells Regulate Metabolism



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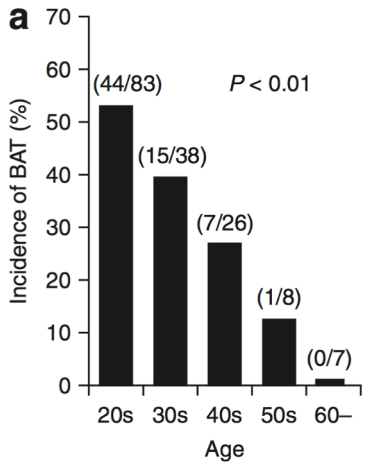
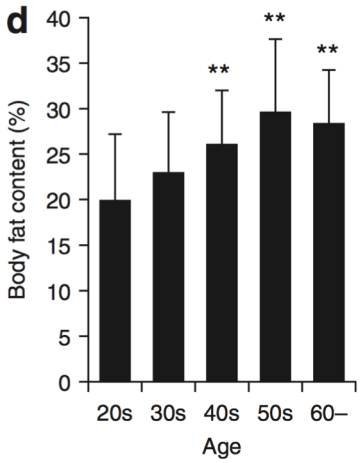


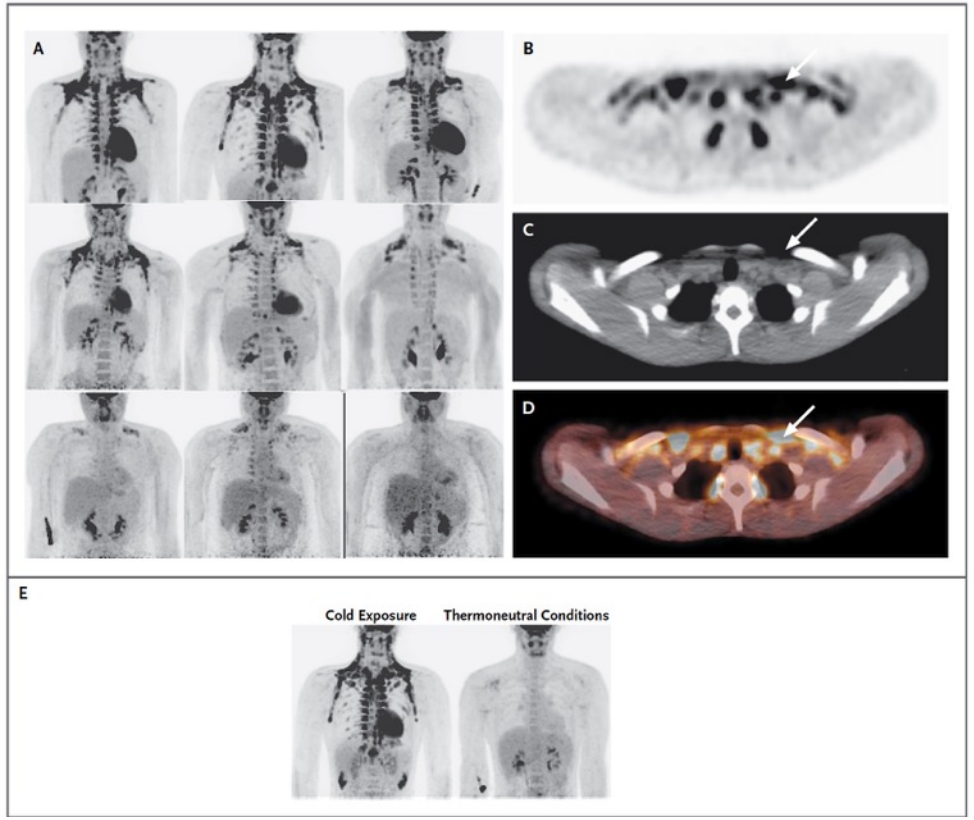


Obesity (2011) **19,** 1755–1760. doi:10.1038/oby.2011.125

Lean
High BAT
Activity

Lean
Low BAT
Activity

Obese
Lowest
BAT
Activity

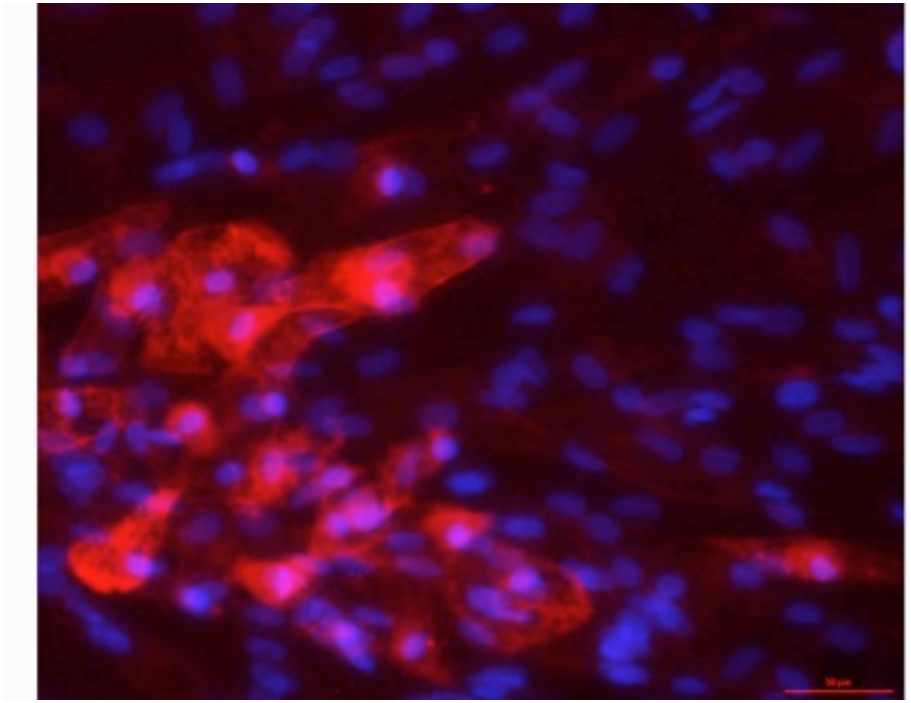


N Engl J Med 2009;360:1500-8

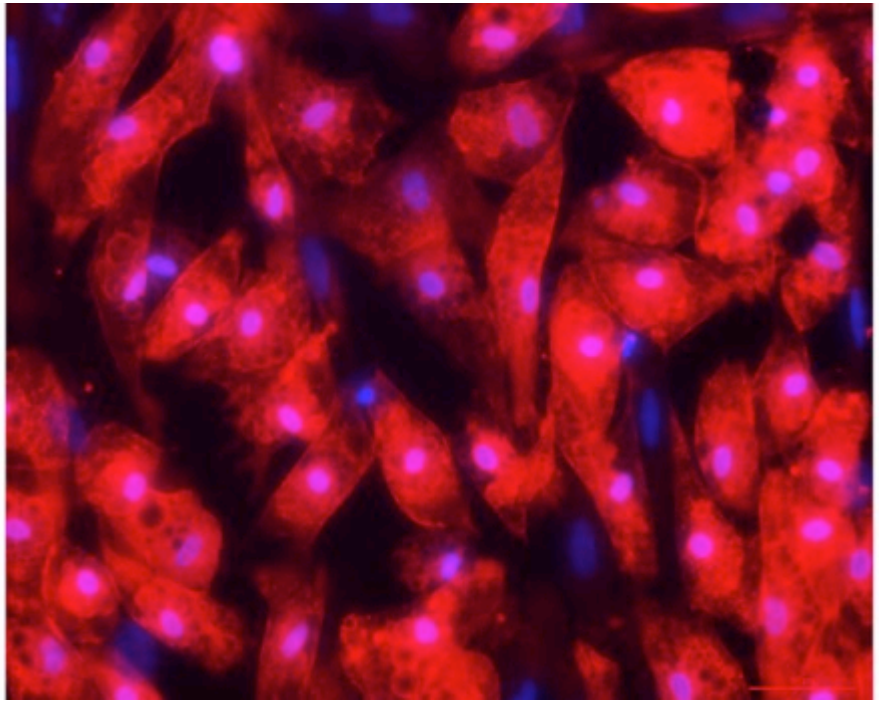
AGEX THERAPEUTICS

Industrially-Scalable *AgeX-BAT1*

Stained for Brown Adipocyte Marker UCP1



Tissue-Sourced Brown Adipocytes



PureStem Brown Adipocytes

Data from AgeX publication in press

AGEX THERAPEUTICS

Obesity/T2D Market/Competition

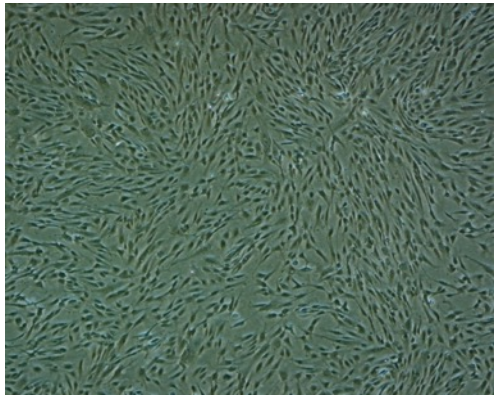
- 30M Americans have diabetes[1] 1:3 Americans will have diabetes by 2050
- The global market for diabetes mellitus and obesity is set to rise from $70.8 billion in 2015 to $163.2 billion by 2022, at a strong compound annual growth rate of 12.7%, according to business intelligence firm GBI Research.
- Invokana, which is marketed by Johnson & Johnson, is one of the key players in the disease cluster. It is expected to reach a huge $3.23 billion by 2022, and is set to be approved across T1DM, T2DM and obesity.
- Invokana belongs to a newer class of Type 2 diabetes treatments called sodium-glucose co-transporter 2 (SGLT2) inhibitors, a class of medication that works by stopping glucose from being reabsorbed into the blood. The FDA warned Invokana can also cause ketoacidosis, a condition that requires hospitalization and can cause fatal swelling of the brain, severe dehydration and coma.

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.

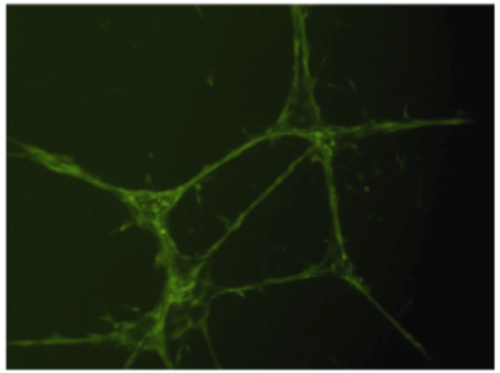
AGEX THERAPEUTICS

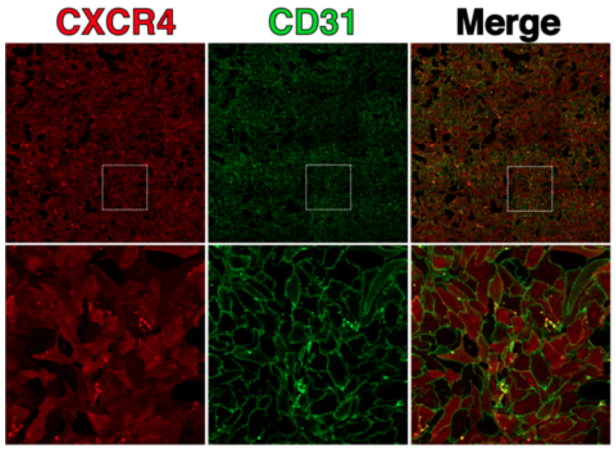
AgeX-VASC1 Purity

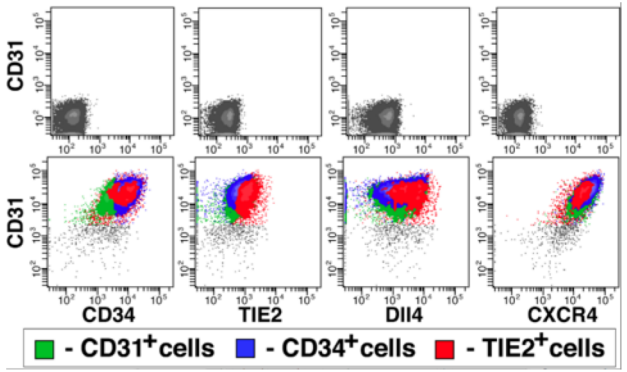
Monoclonal Endothelium

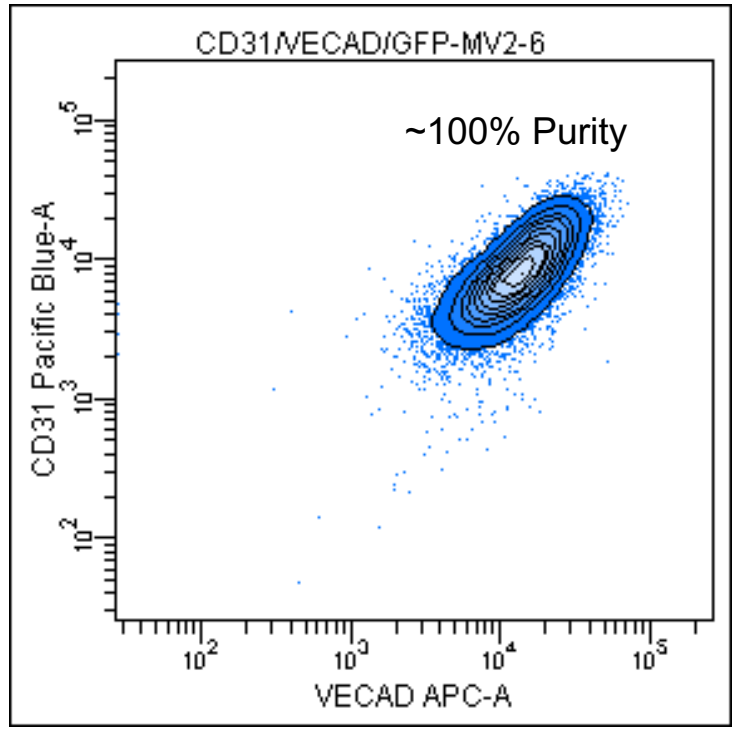


GFP Endothelium (168 hrs)





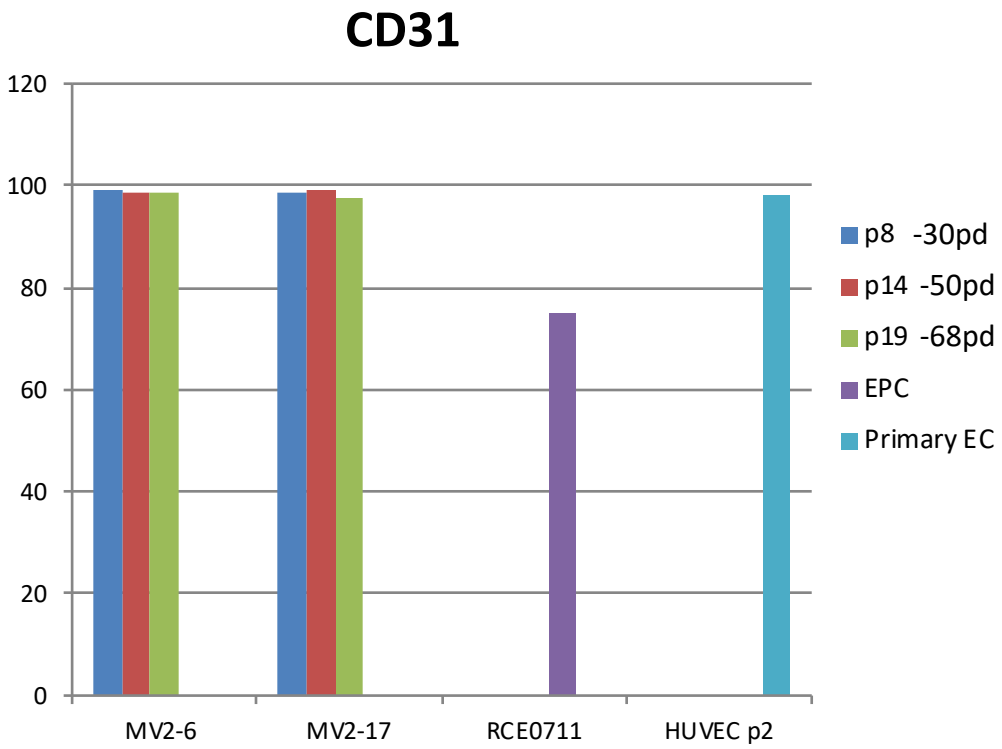




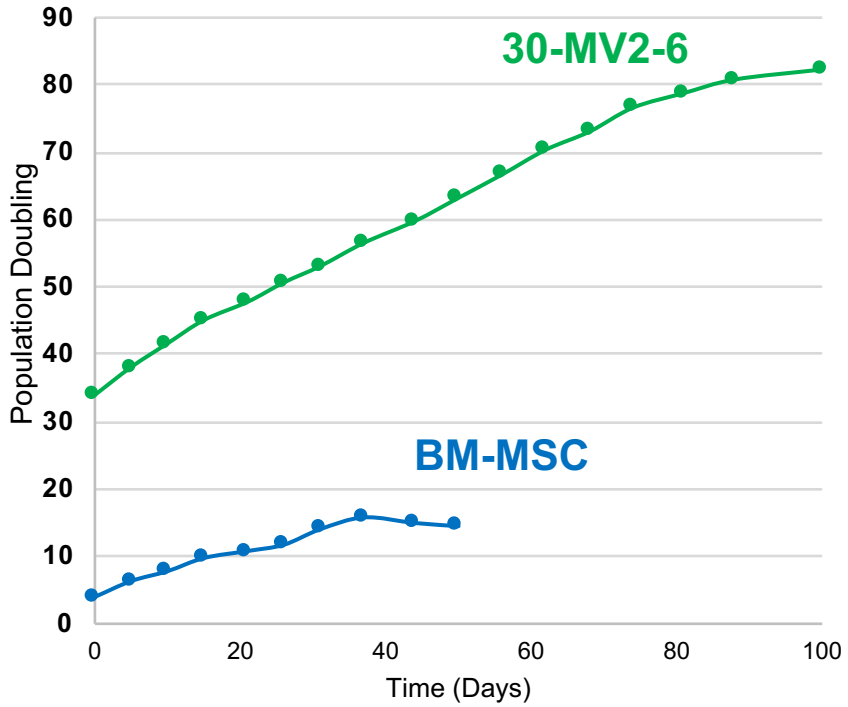
AGEX THERAPEUTICS

AgeX-VASC1 Scalability

Cell Identity is Stable



Production Capacity



AGEX THERAPEUTICS

Cardiovascular Market

> $Trillion Market Worldwide

American Heart Association | American Stroke Association

	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

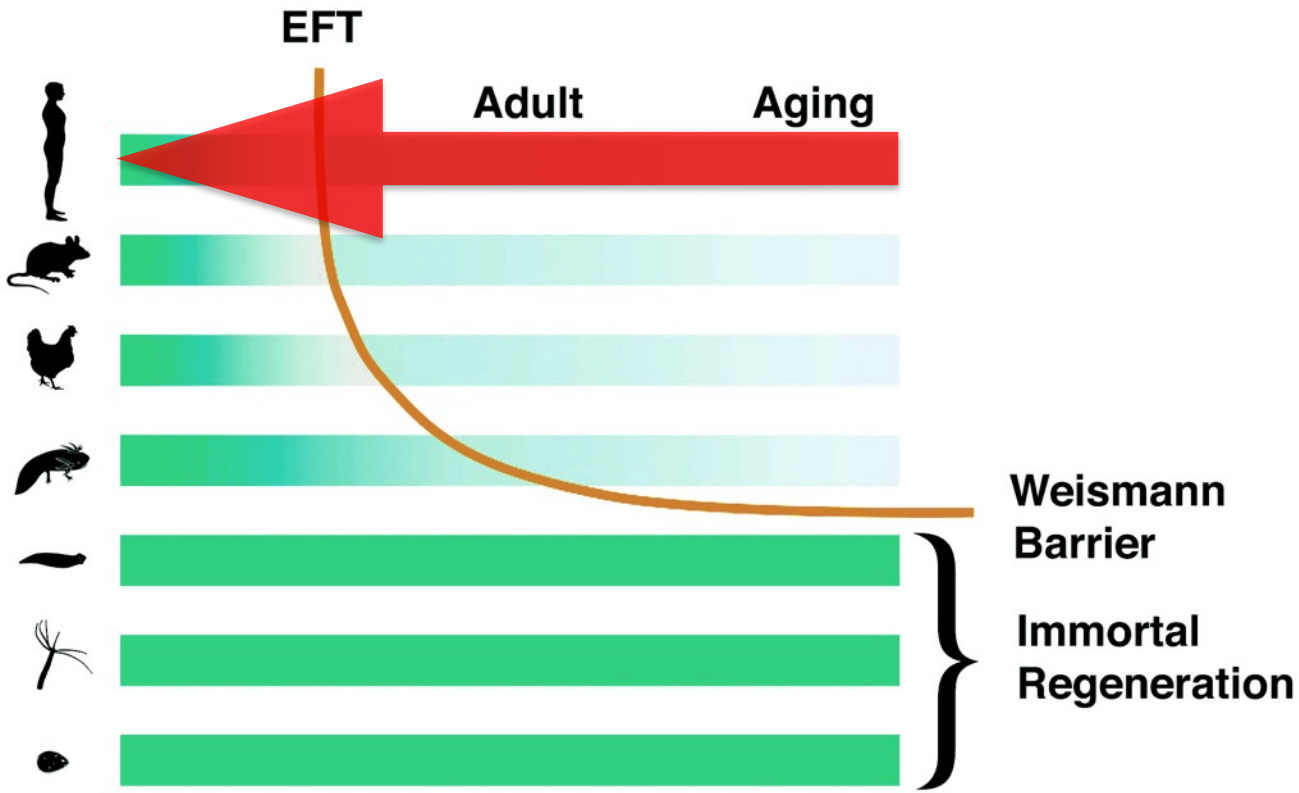
As Baby Boomers age, costs for CVD will shift from middle-aged Americans to individuals ages 65 and over. By 2035, Boomers who are 80 and older will be the source of the largest cost increases for CVD.

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

AGEX THERAPEUTICS

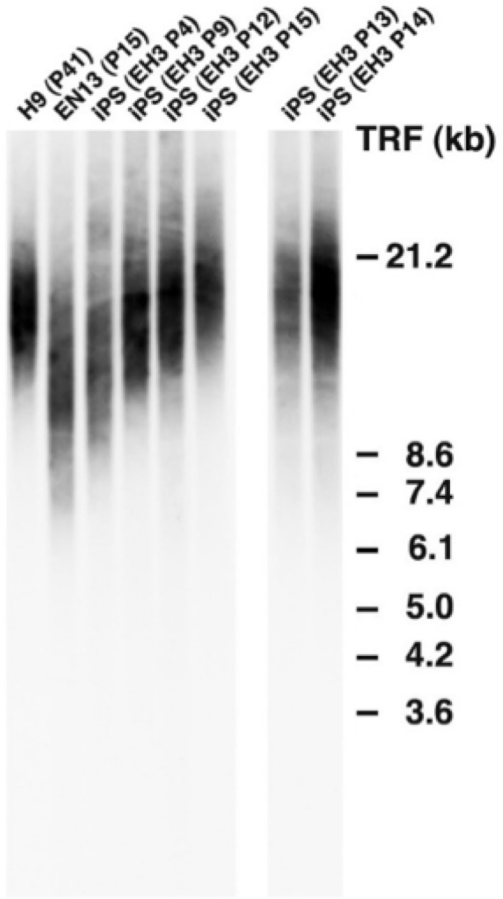
Some Initial Observations

The Weismann barrier has now been broken, allowing us to reprogram aged cells back to the first stages of pluripotency

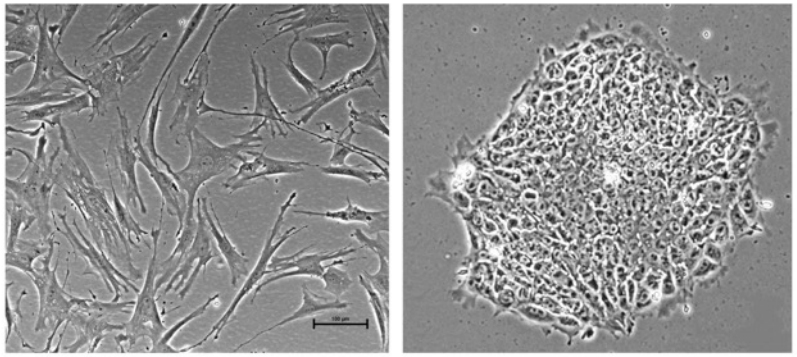


AGEX THERAPEUTICS

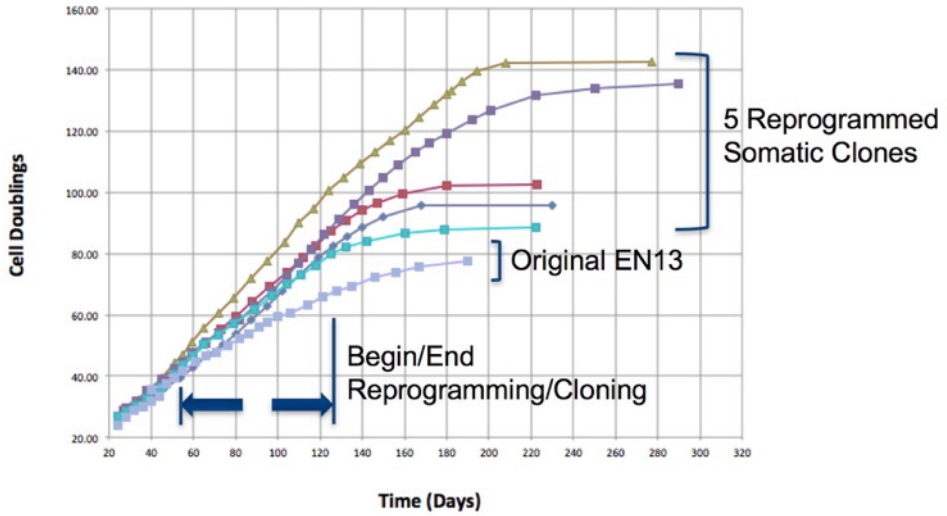
Reprogramming the Aging of Human Cells



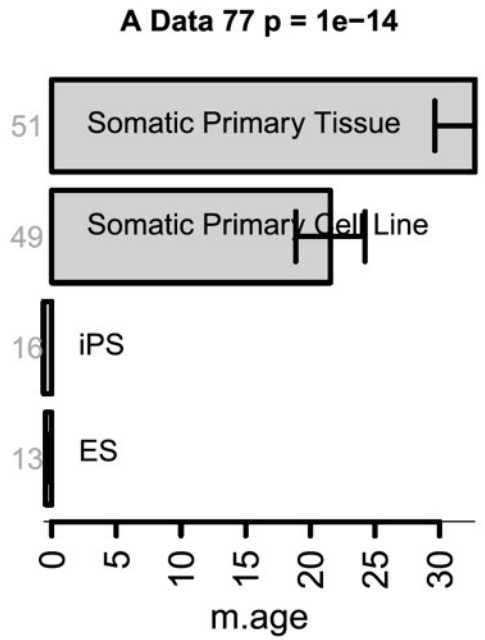
Regen Med 2010 May;5(3):345-63



Skin Fibroblasts iPS Cells



Reprogramming Methylation Age



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

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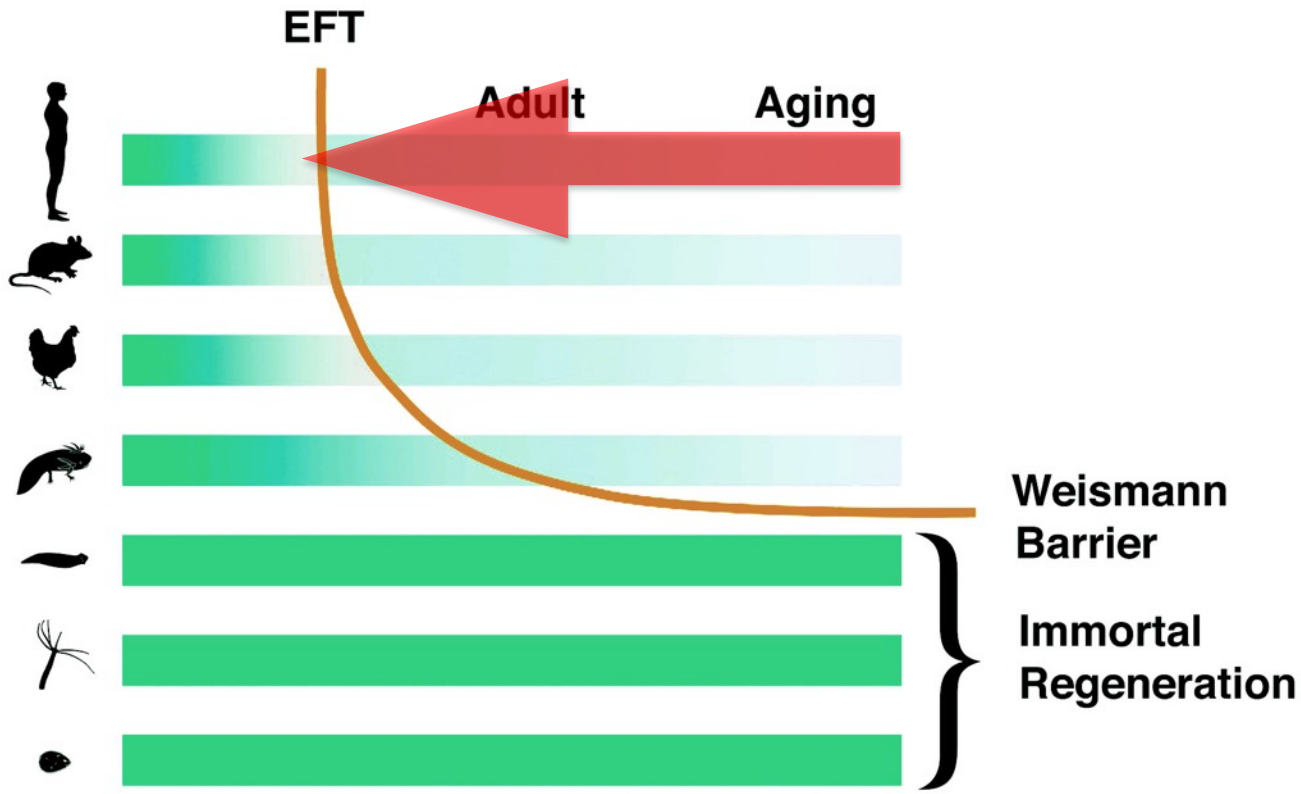
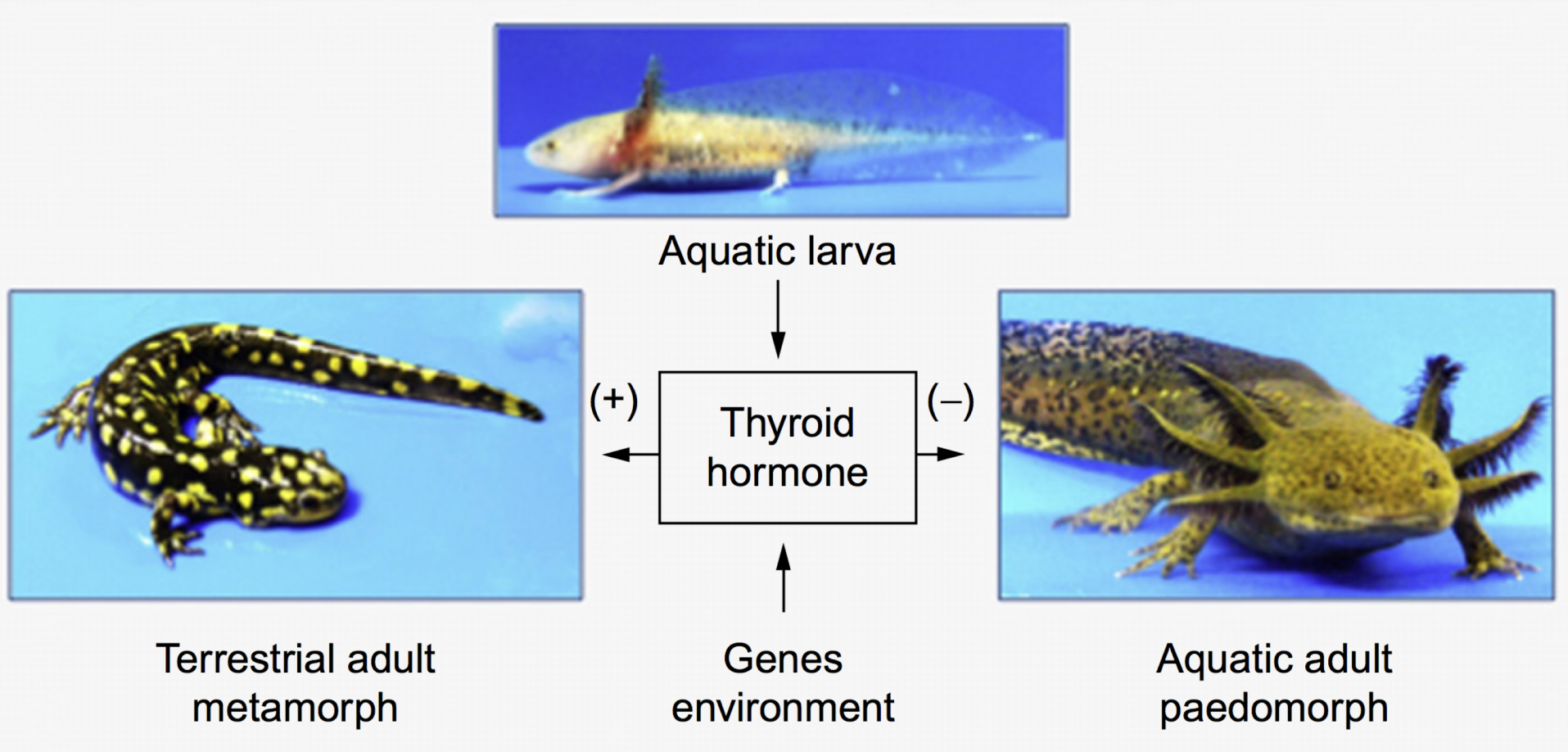


AGEX THERAPEUTICS

The Biology of Regeneration

Axolotls are abnormally stuck in an embryonic (larval) state throughout life, probably the basis of their profound 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

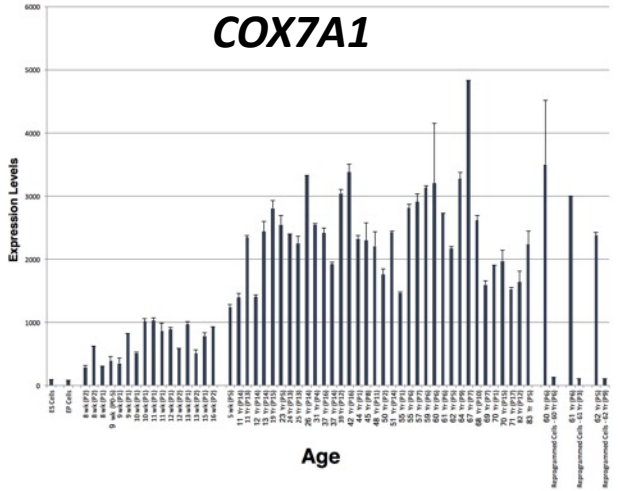
The Biology of Regeneration

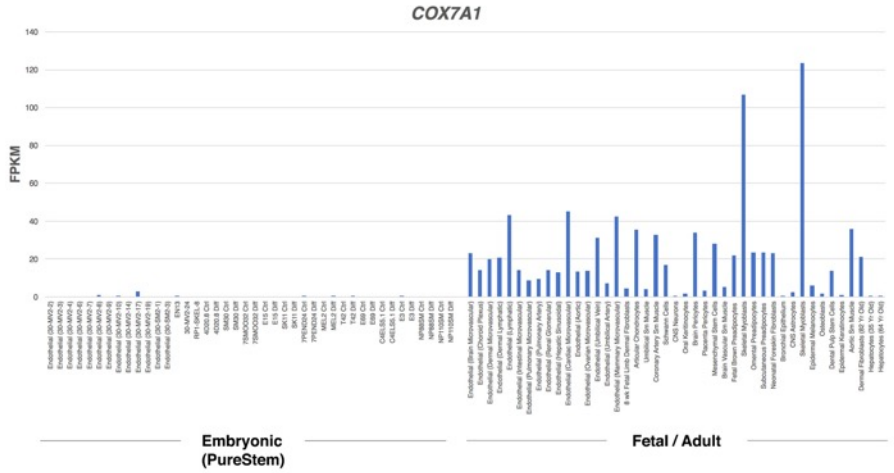
www.impactjournals.com/oncotarget/ Oncotarget, 2018, Vol. 9, (No. 8), pp: 7796-7811

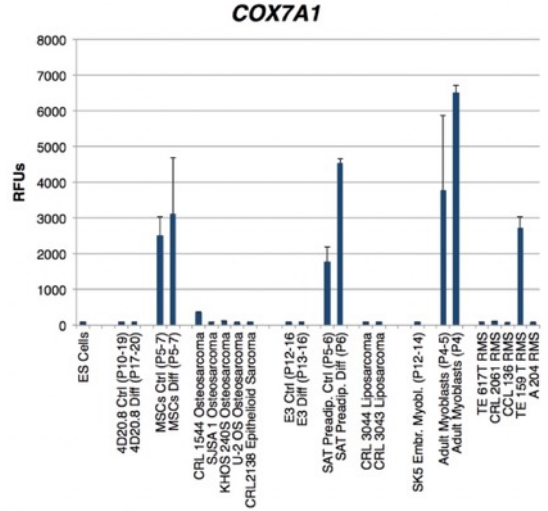
Research Paper

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]

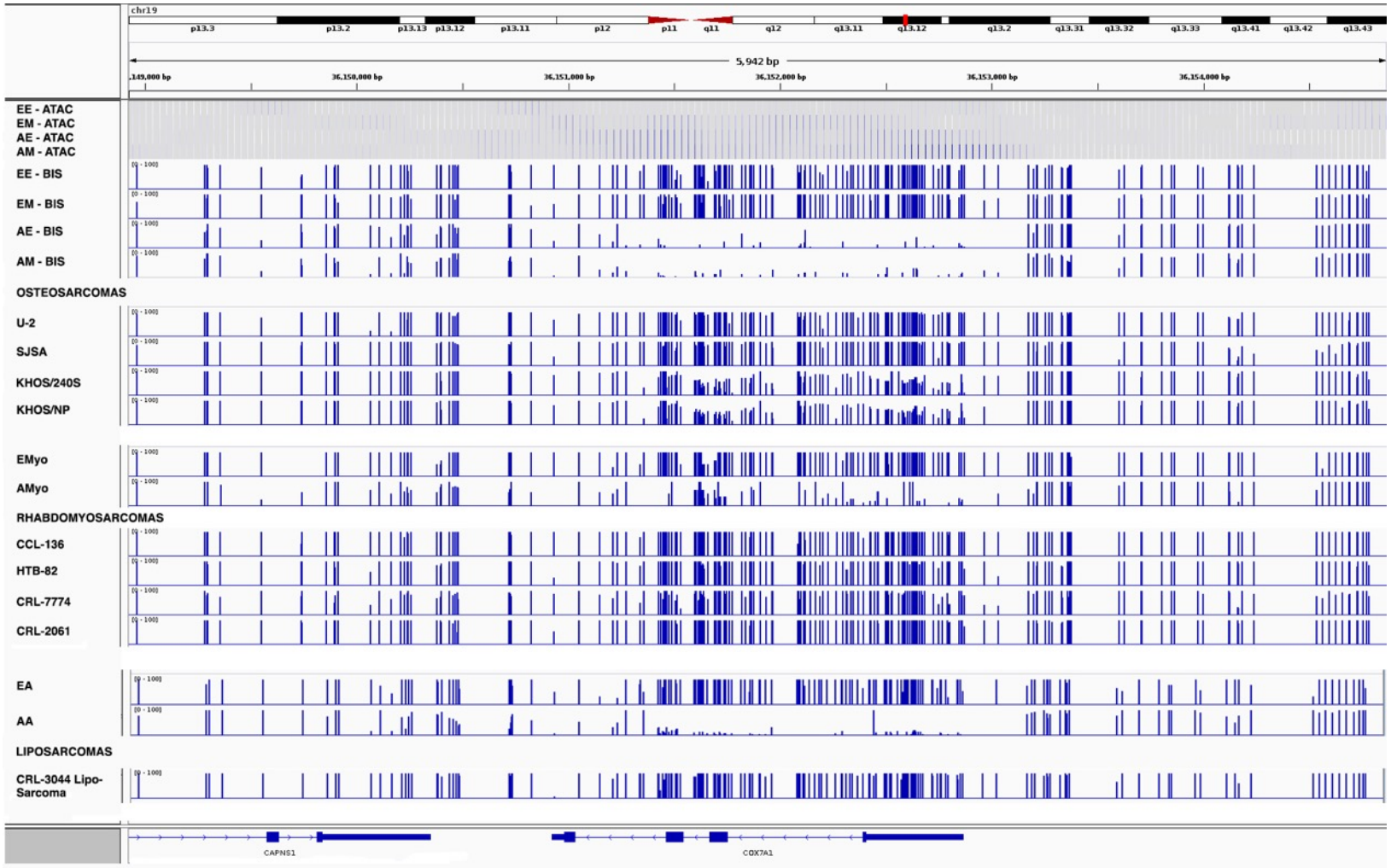




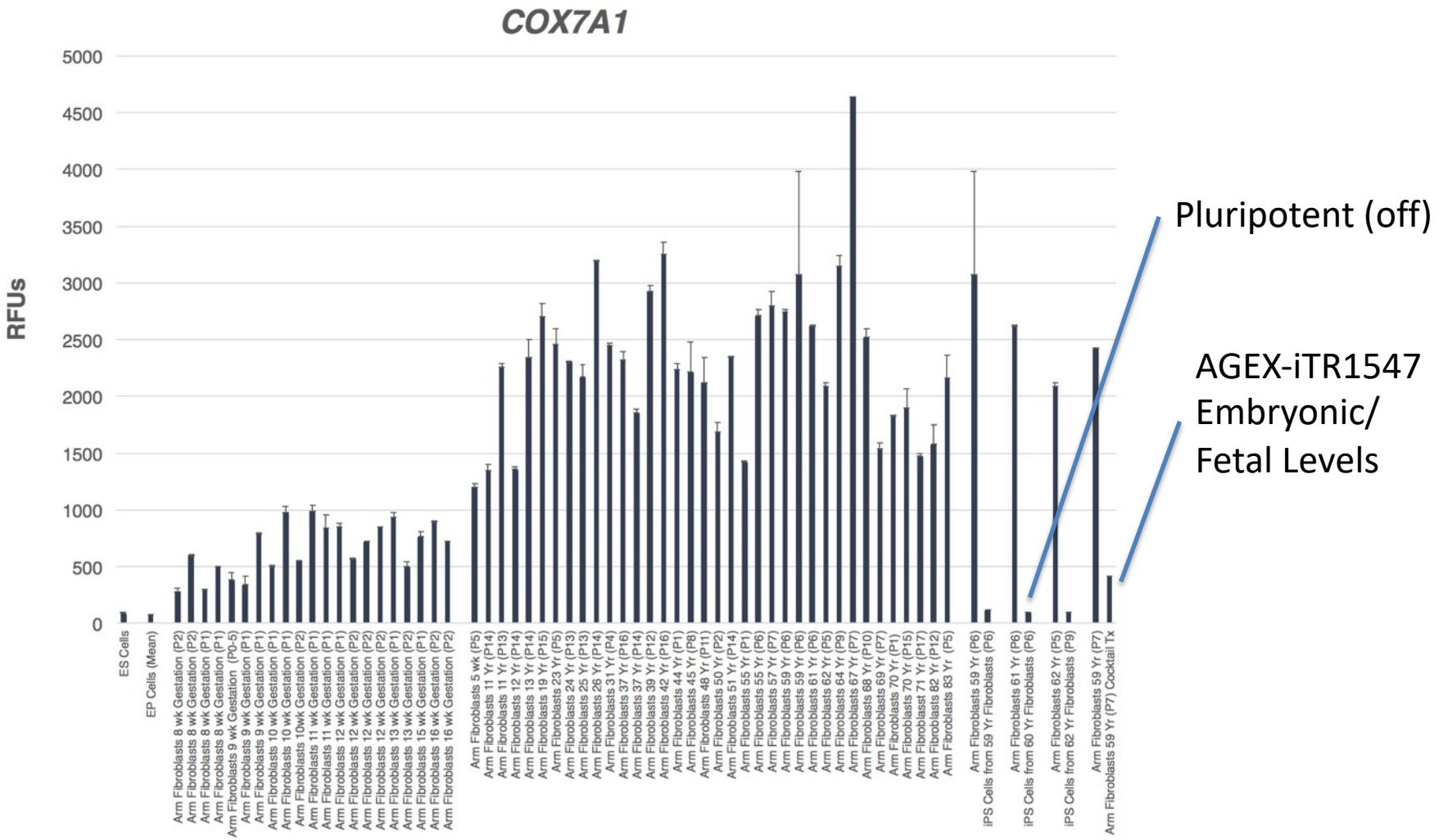


AGEX THERAPEUTICS

COX7A1 Chromatin Embryonic, Adult, Cancer



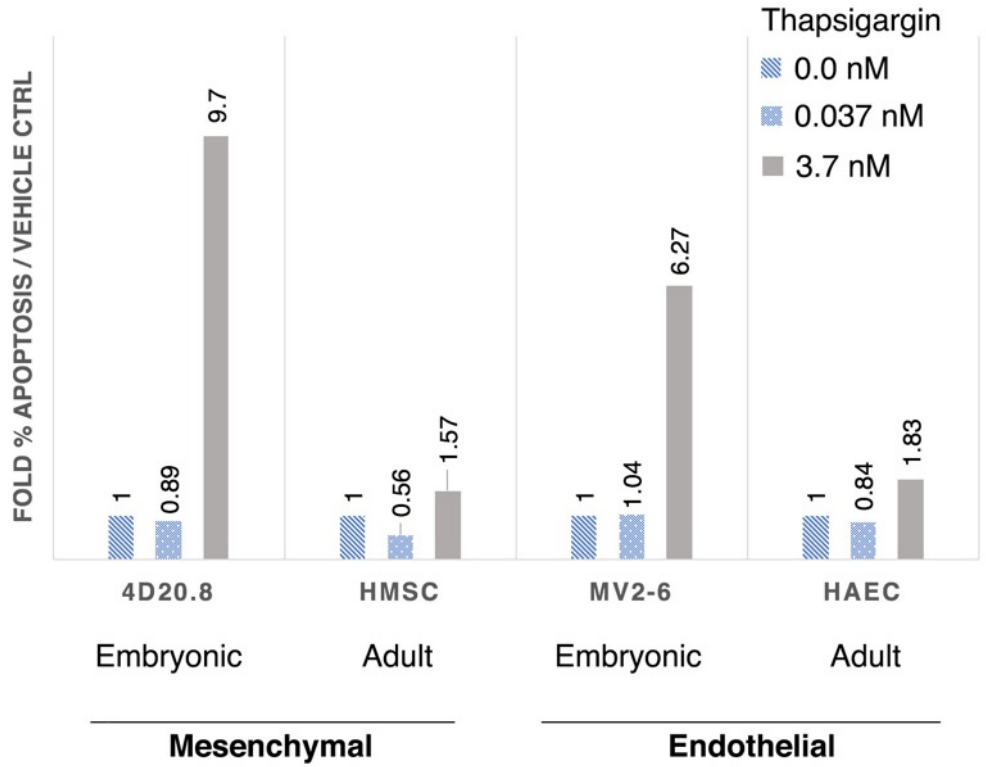
An Example of an iTR Formulation



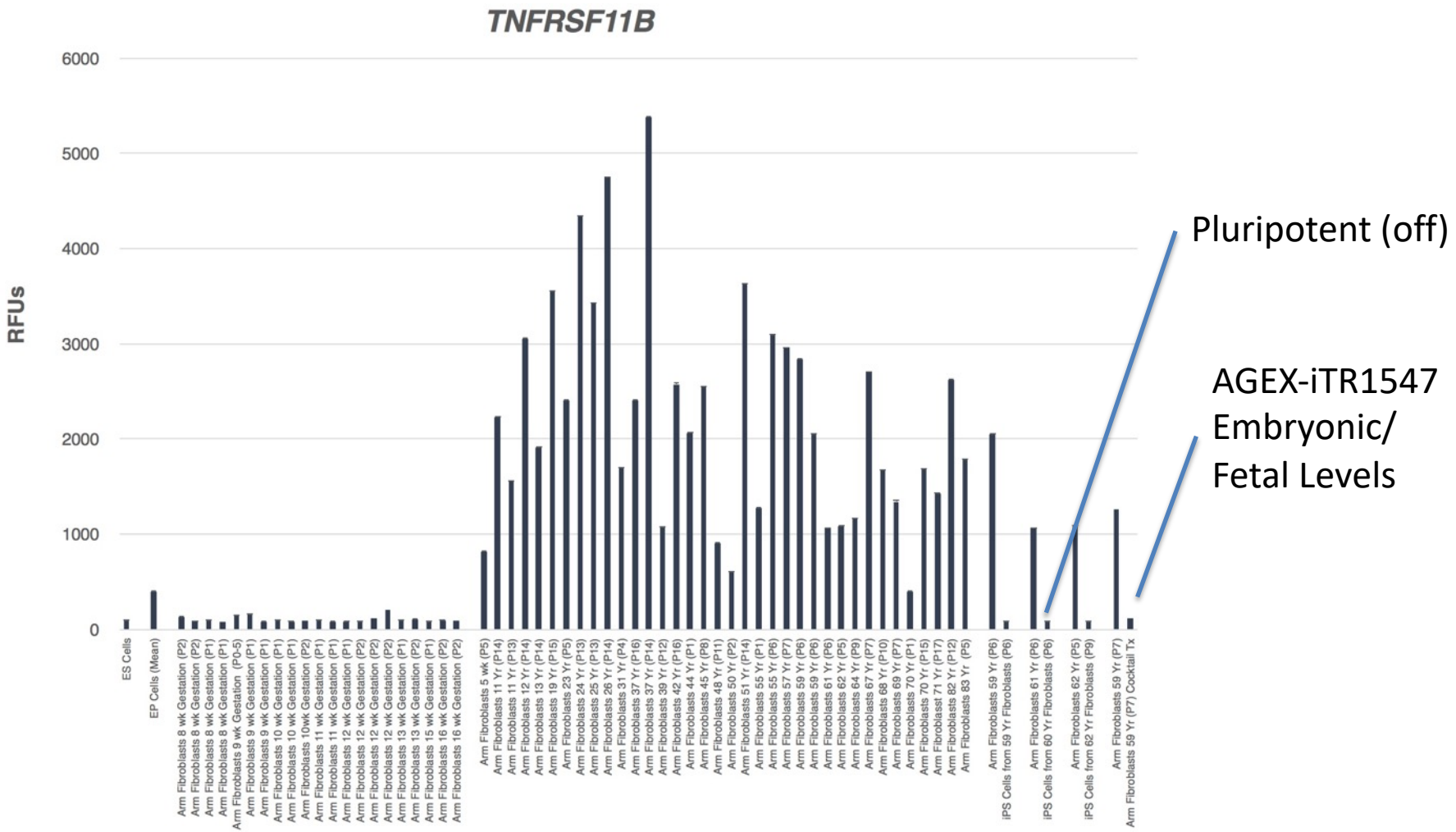
AGEX THERAPEUTICS

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:

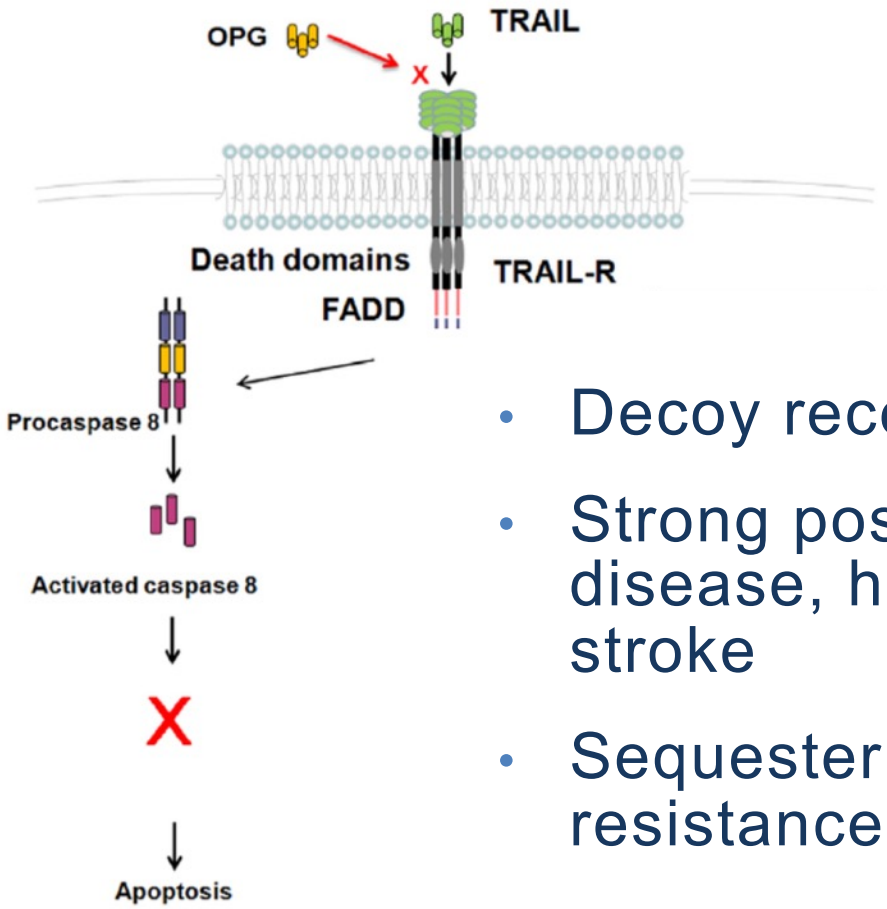


An Example of an iTR Formulation



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

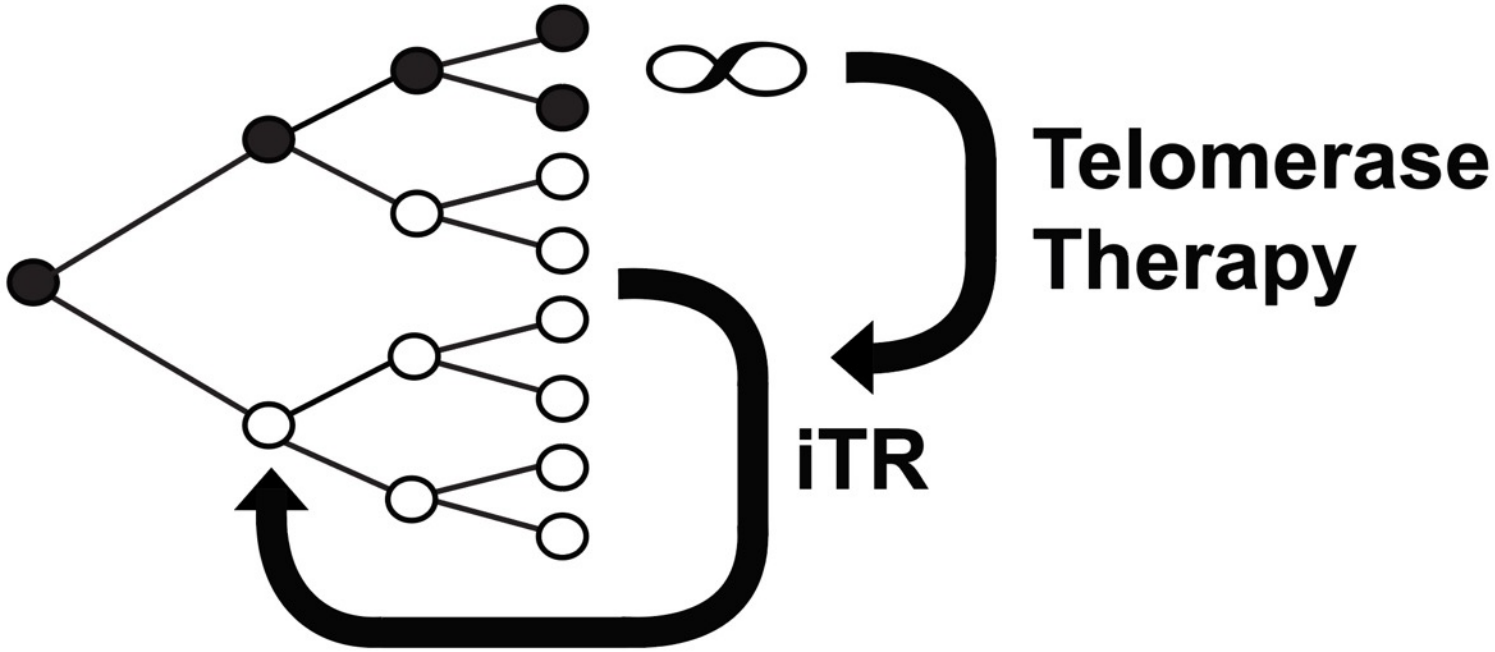
iTR: induced Tissue Regeneration

Senolysis a consequence?

AGEX THERAPEUTICS

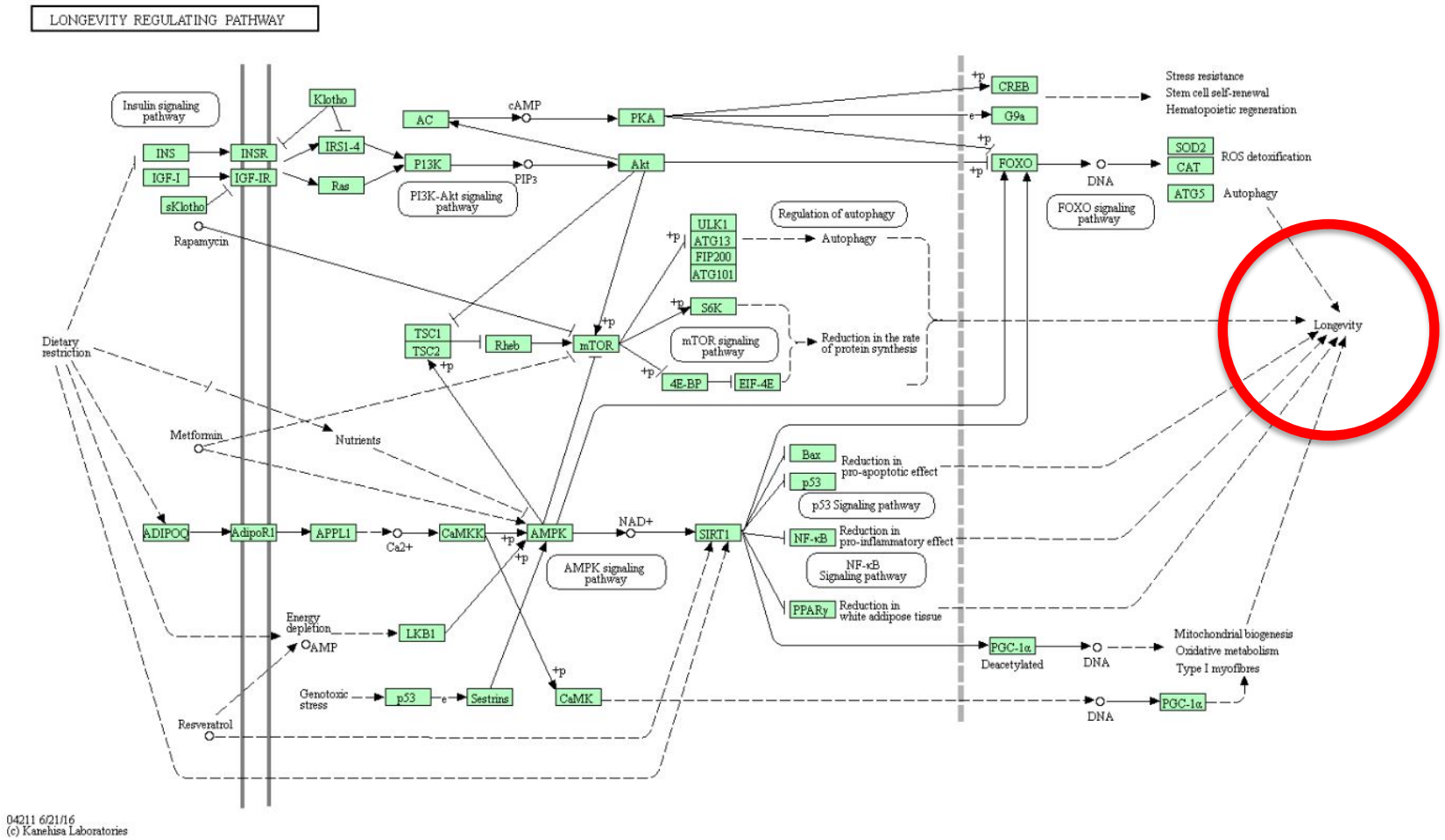
induced Tissue Regeneration (iTR)

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



A growing consensus that modulating these metabolic pathways effect aging, but how?

A complex analysis by AgeX scientists suggests that insights from regenerative biology will lead to a unified theory of aging.

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

Summary

- Aging: The demographic trend of our time
- Straightforward therapeutic strategy: Young cells for aged tissues
- Proprietary technology platform: PureStem, UniverCyte, and HyStem
- Three therapeutic programs
  - T2D/Obesity: Large & growing markets with *AGEX-BAT1* being highly novel
  - Cardiac Ischemia: The leading causes of mortality & disability in an aging population
  - iTR1547: Reversing cell aging back to a developmental regenerative state

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