AGEX THERAPEUTICS

Induction of Telomerase & Regeneration (iTR) for Age Reversal

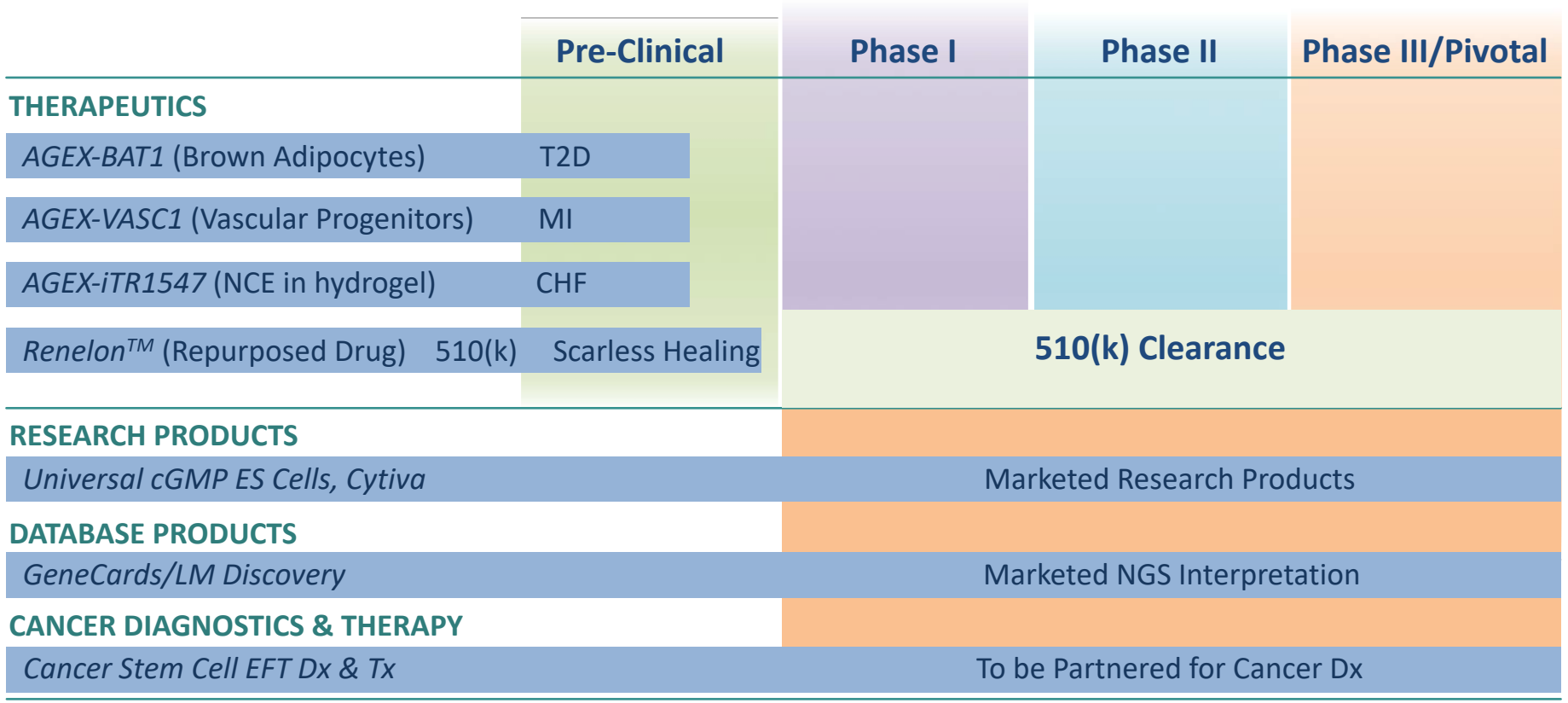
March 29, 2019

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

Product Pipeline



AGEX THERAPEUTICS

Product Pipeline

Focus of Today's Presentation

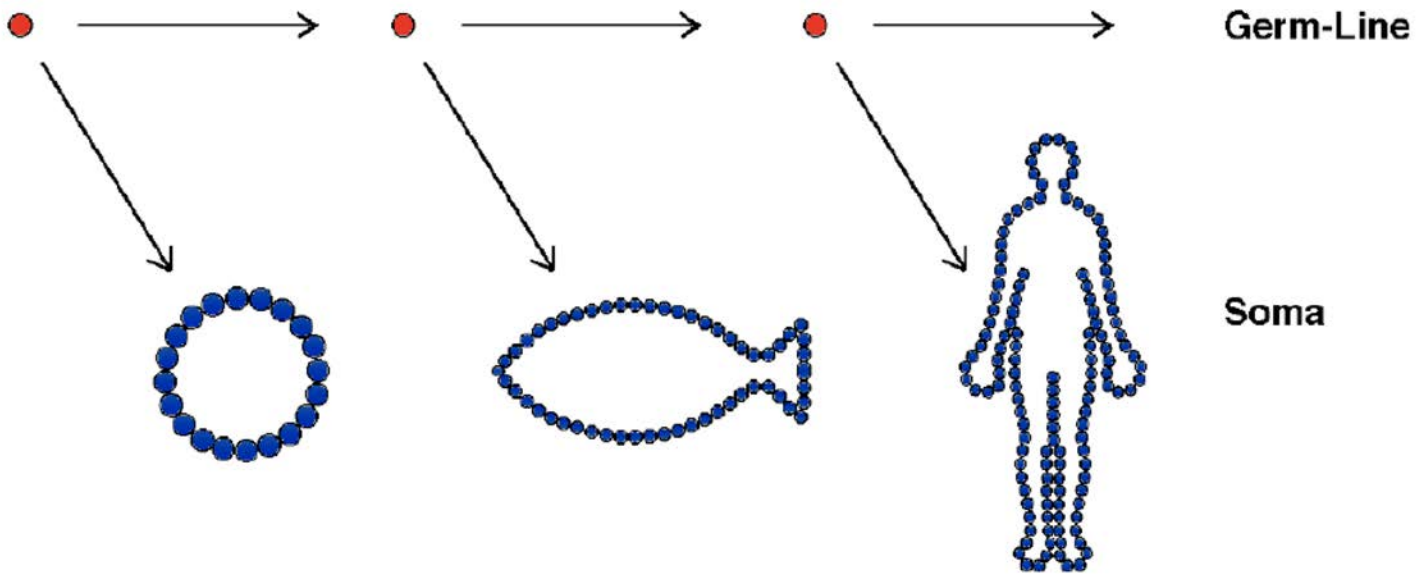
	Pre-Clinical	Phase I	Phase II	Phase III/Pivotal
THERAPEUTICS				
AGEX-BAT1 (Brown Adipocytes) T2D				
AGEX-VASC1 (Vascular Progenitors) MI				
AGEX-iTR1547 (NCE in hydrogel) CHF				
Renelon™ (Repurposed Drug) 510(k) Scarless Healing		**510(k) Clearance**		
RESEARCH PRODUCTS				
Universal cGMP ES Cells, Cytiva		Marketed Research Products		
DATABASE PRODUCTS				
GeneCards/LM Discovery		Marketed NGS Interpretation		
CANCER DIAGNOSTICS & THERAPY				
Cancer Stem Cell EFT Dx & Tx		To be Partnered for Cancer Dx		

AGEX THERAPEUTICS

Identification of Upstream Targets in Aging

AGEX THERAPEUTICS

Some Initial Observations

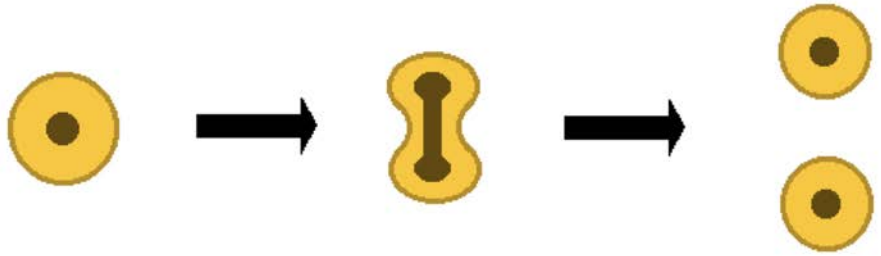


- The germ-line is a lineage of cells that created us. They have not aged for billions of years (otherwise we would not be here).
- Aging is a phenomenon unique to the soma, turned on during cell differentiation. It is also completely reversible by, say, SCNT, otherwise cloning wouldn't make animals born young.

AGEX THERAPEUTICS

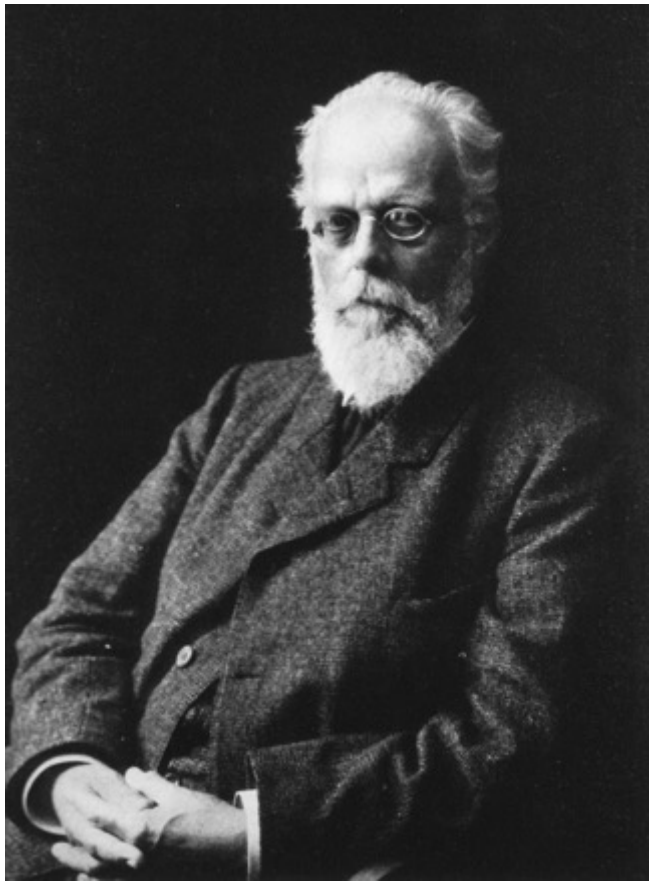
Some Initial Observations

August Weismann's prediction



"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

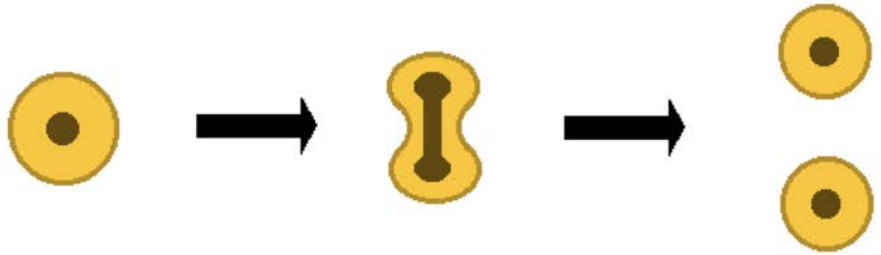


AGEX THERAPEUTICS

Some Initial Observations

August Weismann's prediction

Repression of Regeneration



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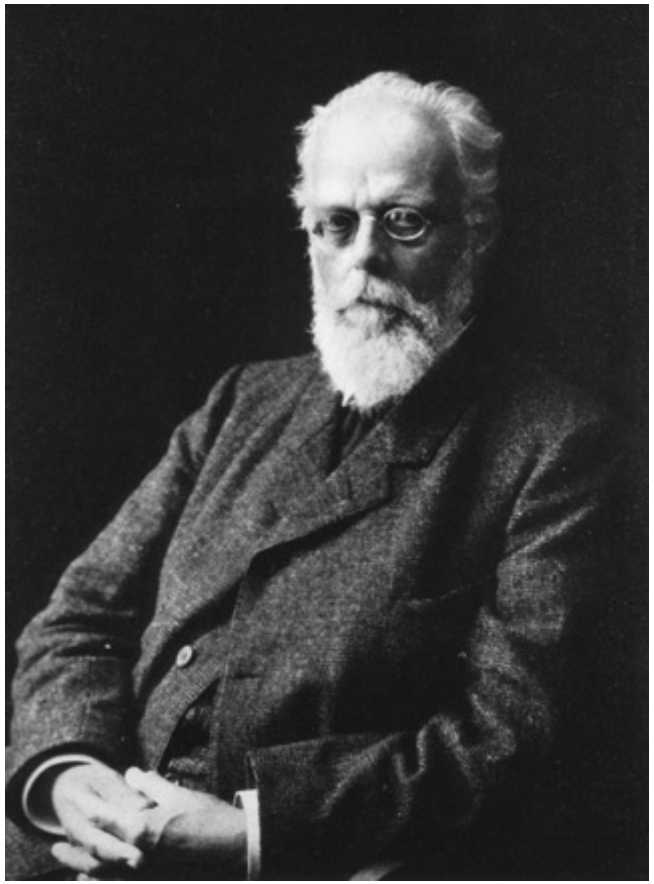
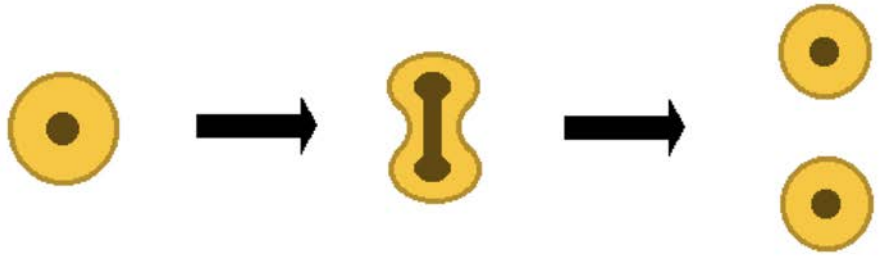


AGEX THERAPEUTICS

Some Initial Observations

August Weismann's prediction

Repression of Replicative Immortality



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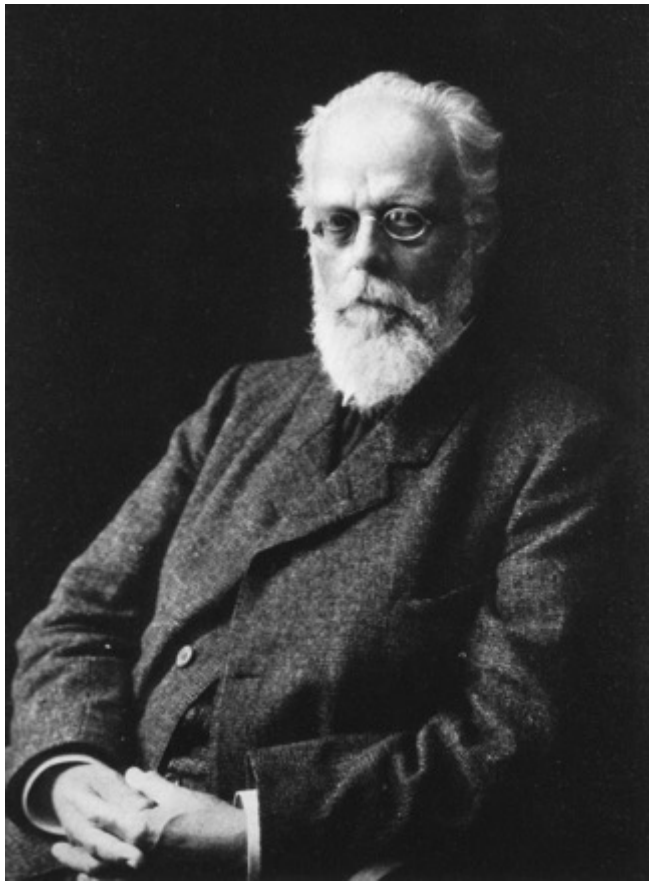
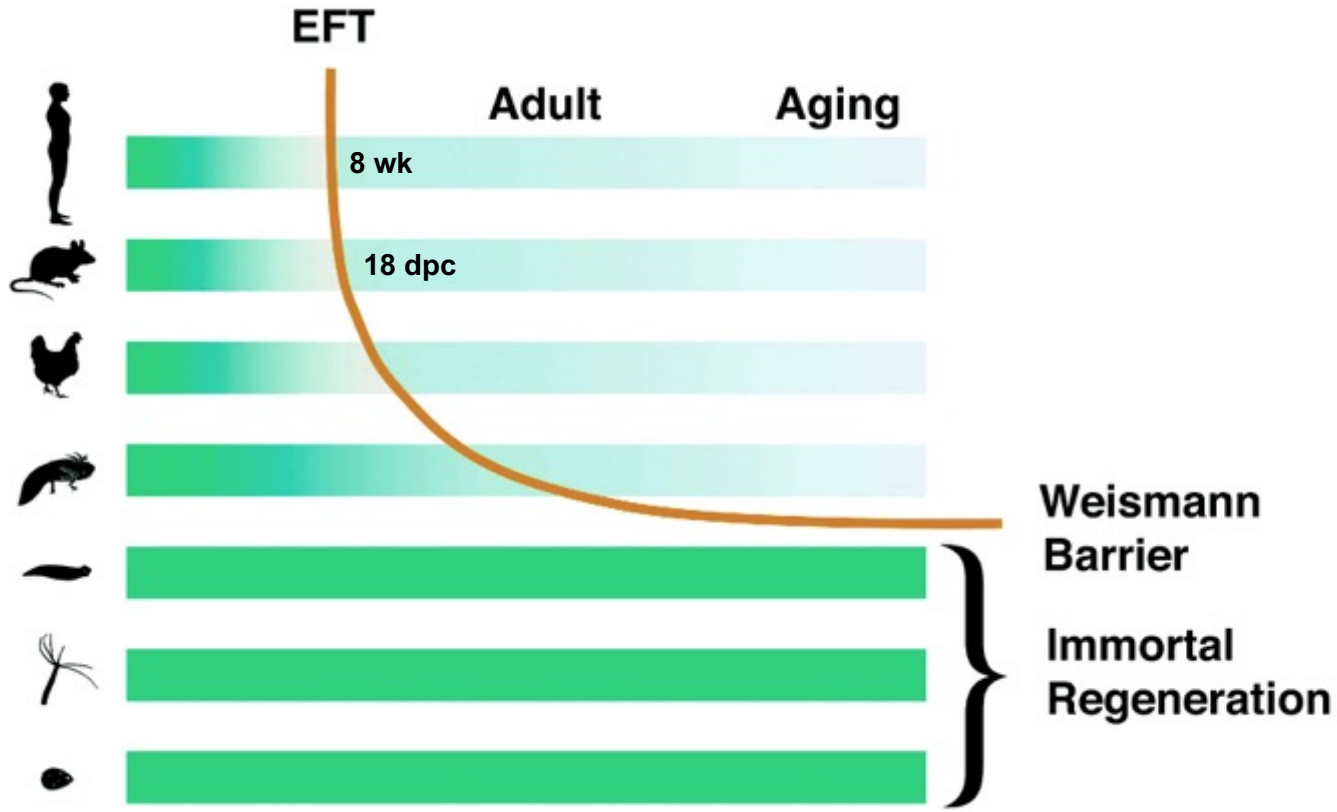
- A. Weismann, 1891



AGEX THERAPEUTICS

Some Initial Observations

Profound regeneration in humans is restricted to embryonic development



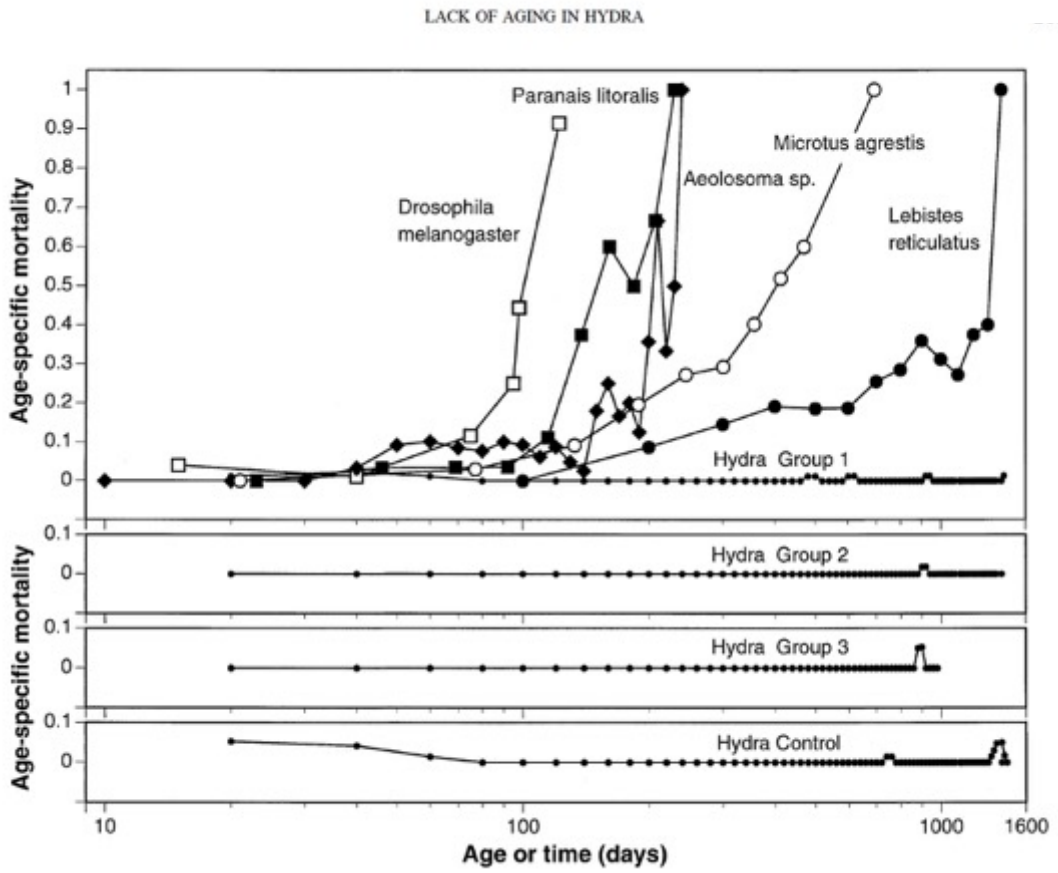
AGEX THERAPEUTICS

Some Initial Observations

Animals with somatic cells that have both replicative immortality and profound 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)

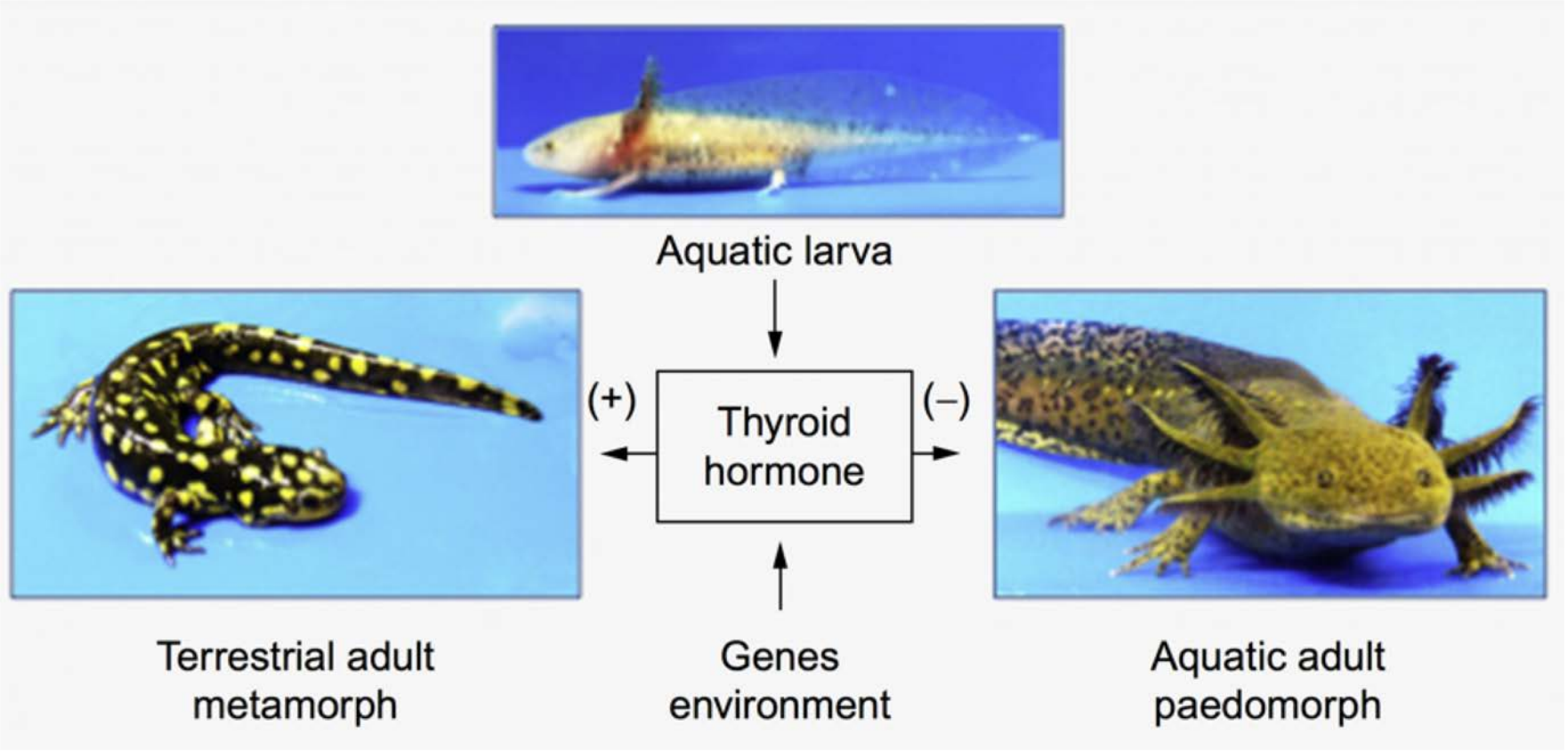


Experimental Gerontology, Vol. 33, No. 3, pp. 217–225, 1998

AGEX THERAPEUTICS

Some Initial Observations

Axolotls display a heterochronic arrest in an embryonic (larval) state throughout life, probably the basis of regenerative potential.



Current Topics in Developmental Biology, Volume 103:229

AGEX THERAPEUTICS

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

AGEX THERAPEUTICS

Research Strategy Utilized by AgeX

Weismann's theory of a developmental restriction of immortal traits in the mortal soma combined with Williams' theory of 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
- Those changes re-emerging in cancer are priority targets for investigation

AGEX THERAPEUTICS

AgeX Discovery Strategy

ES Embr Fetal Neonatal to Old Age Dev Mouse Sen Cancer Progeria iPSC

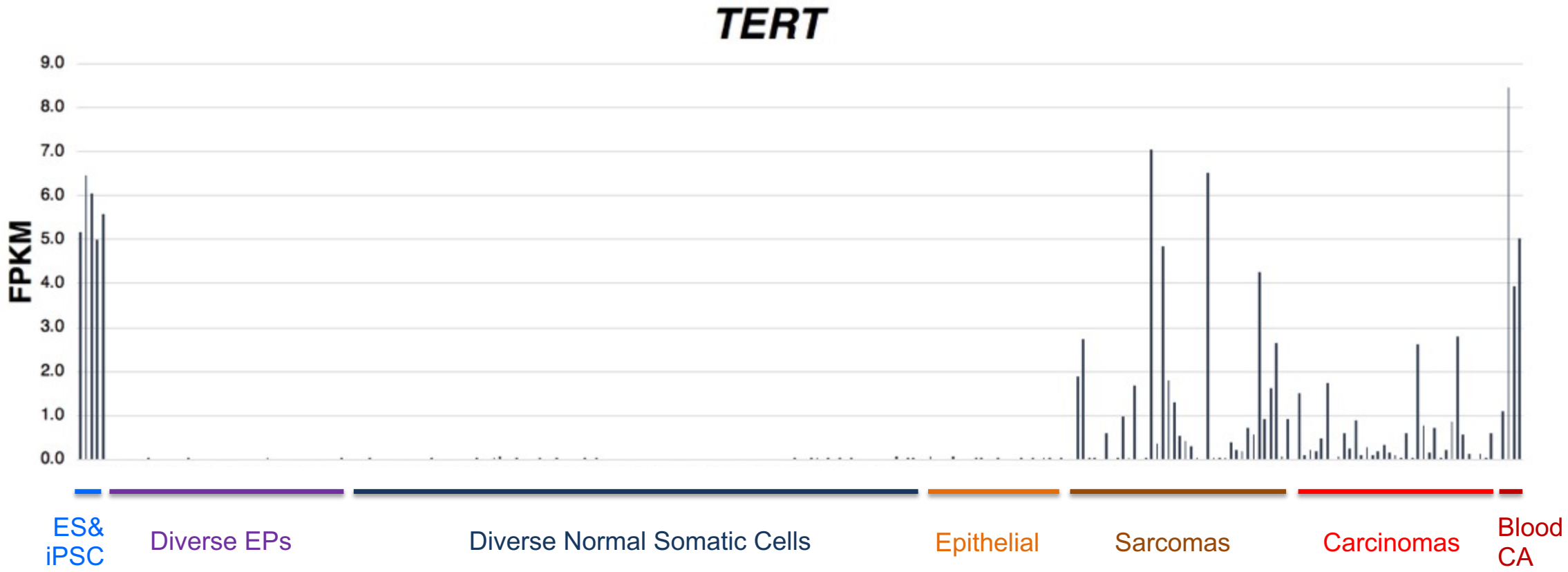
RNA PROTEIN DNA

Microarray RNA-seq Acomys Proteome Metabolome Seahorse BIS Methylome ChIP-seq Hi-C ATAC

SCREEN FOR PATTERN
OF ANTAGONISTIC PLEIOTROPY

AGEX THERAPEUTICS

Expression of the Immortalizing Gene Telomerase



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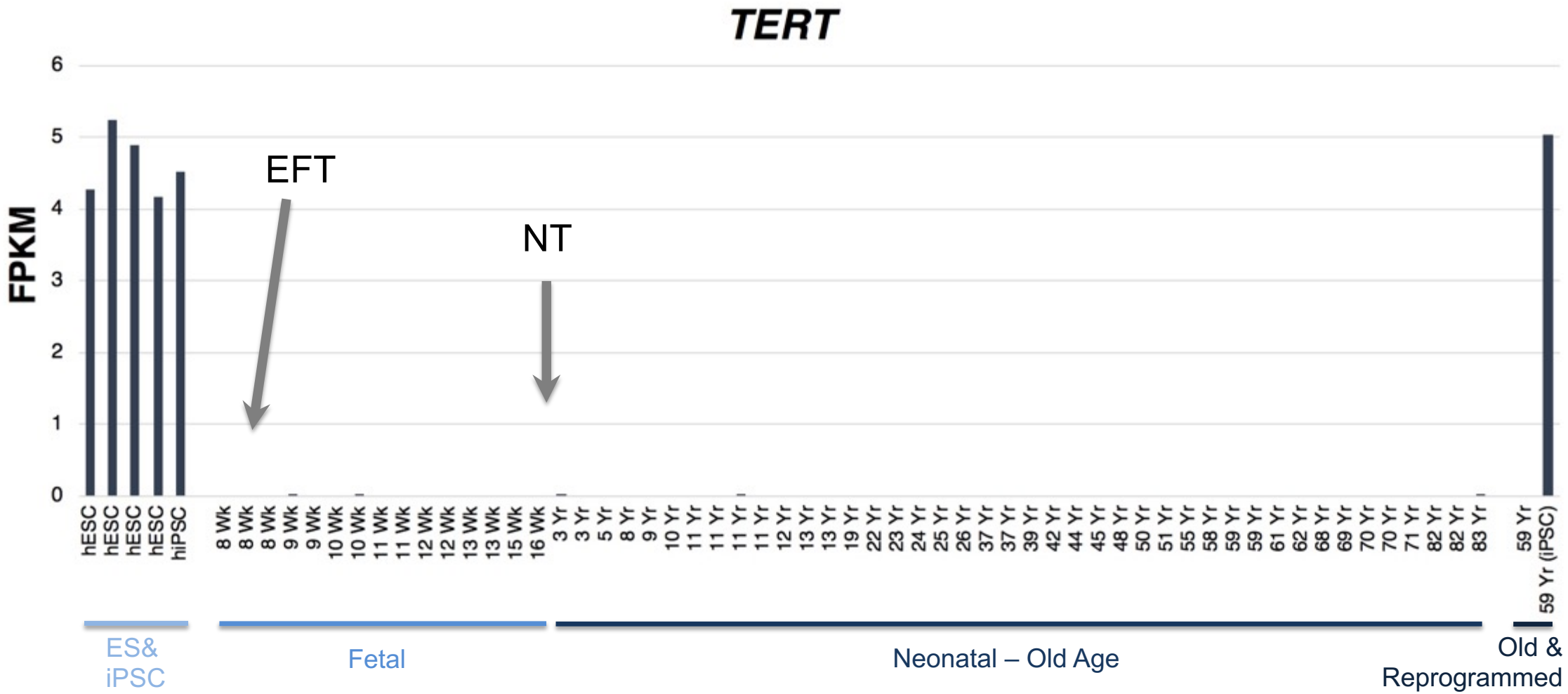
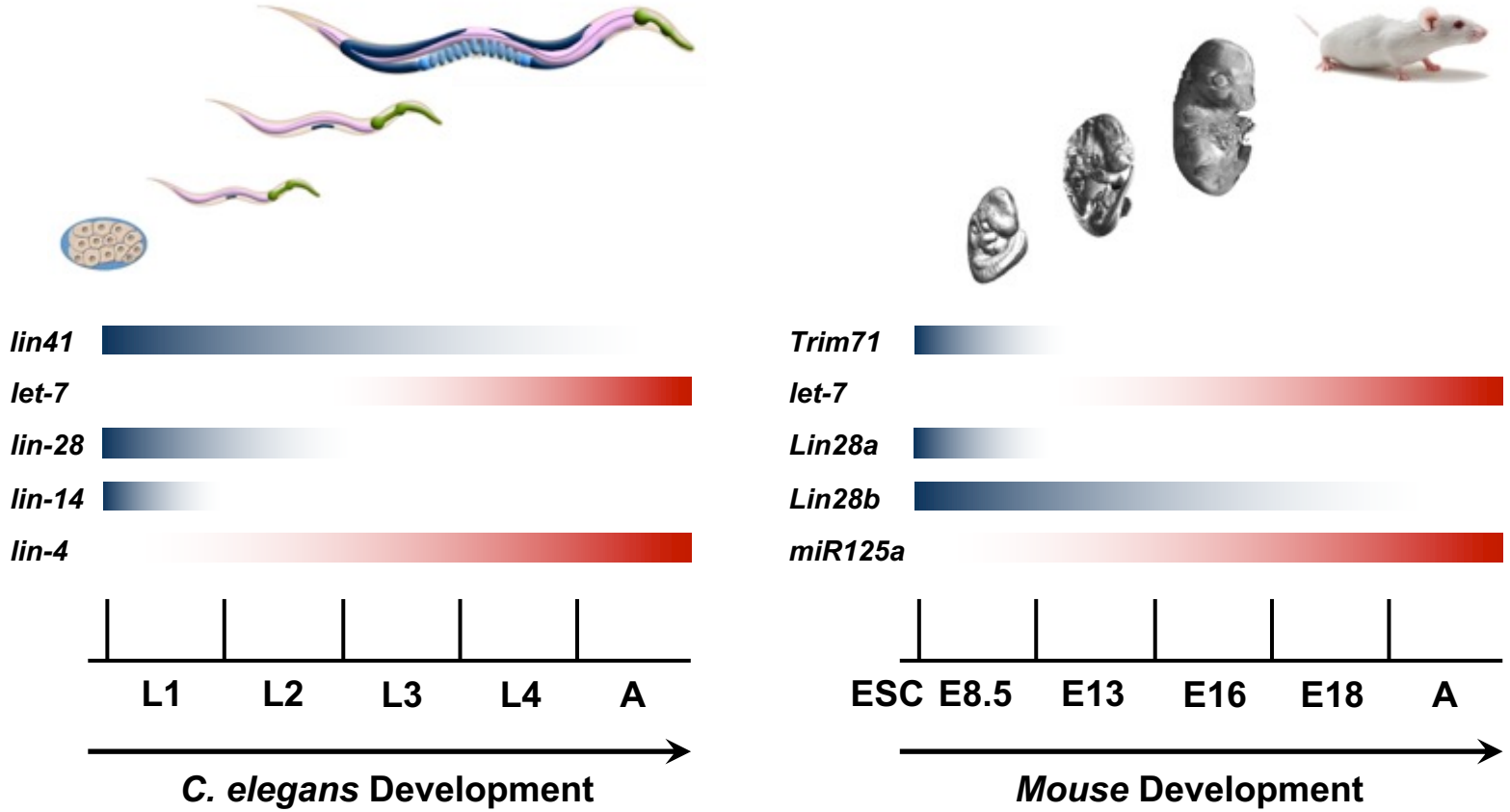
Expression of the Immortalizing Gene Telomerase



AGEX THERAPEUTICS

The Role of Small Temporal RNAs in Developmental Timing

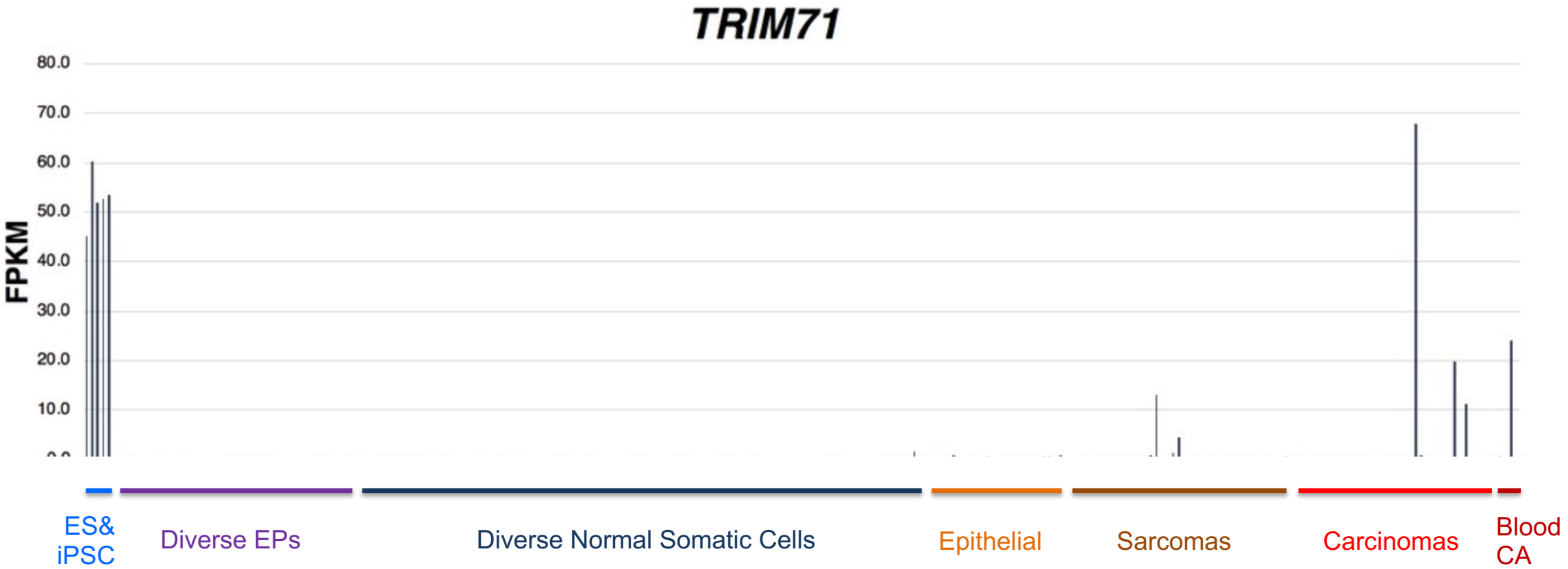


Human?

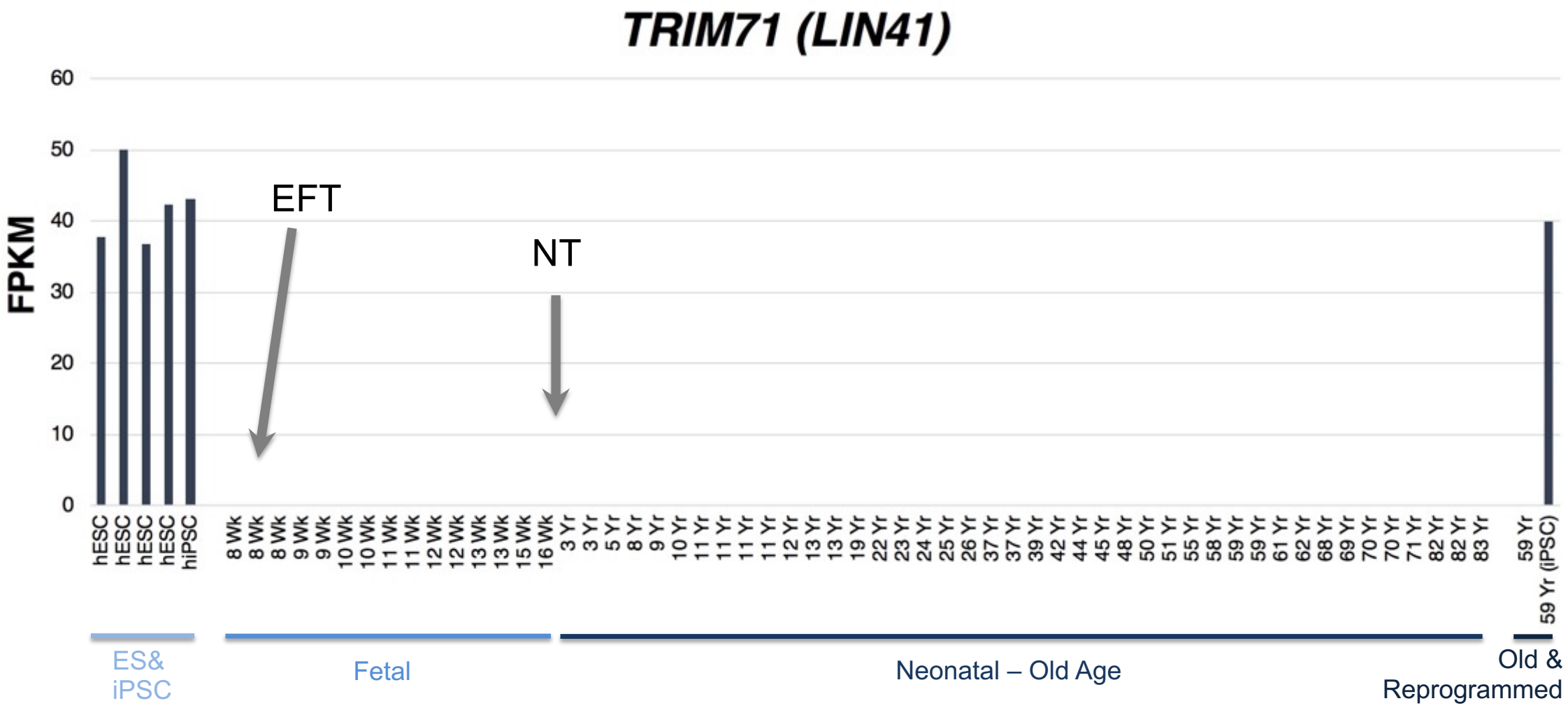
Adapted from Ouchi Y, Yamamoto J, Iwamoto T (2014) PLOS ONE 9(2): e88086.

AGEX THERAPEUTICS

TRIM71 (LIN41)



TERT



AGEX THERAPEUTICS

Developmental Restriction

Unrestricted
Immortal
Germ-Line

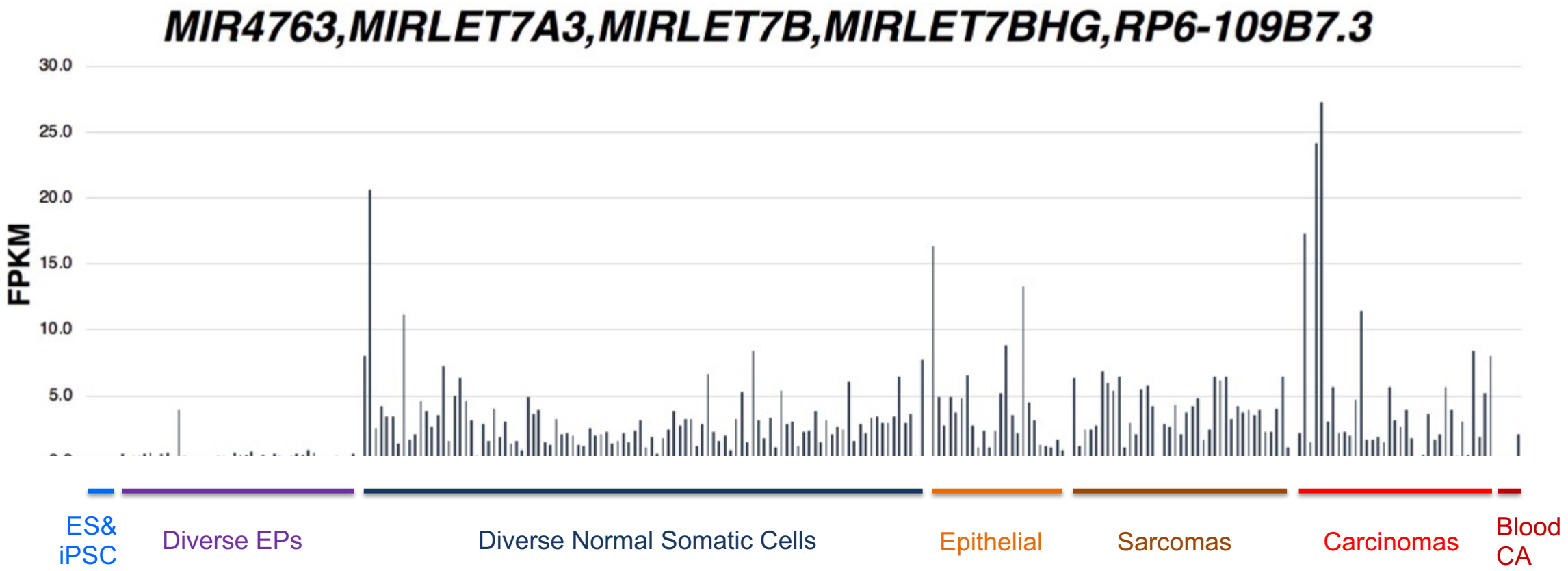
TERT
TRIM71
01

Cellular aging: Immunodeficiency, AMD, AAA

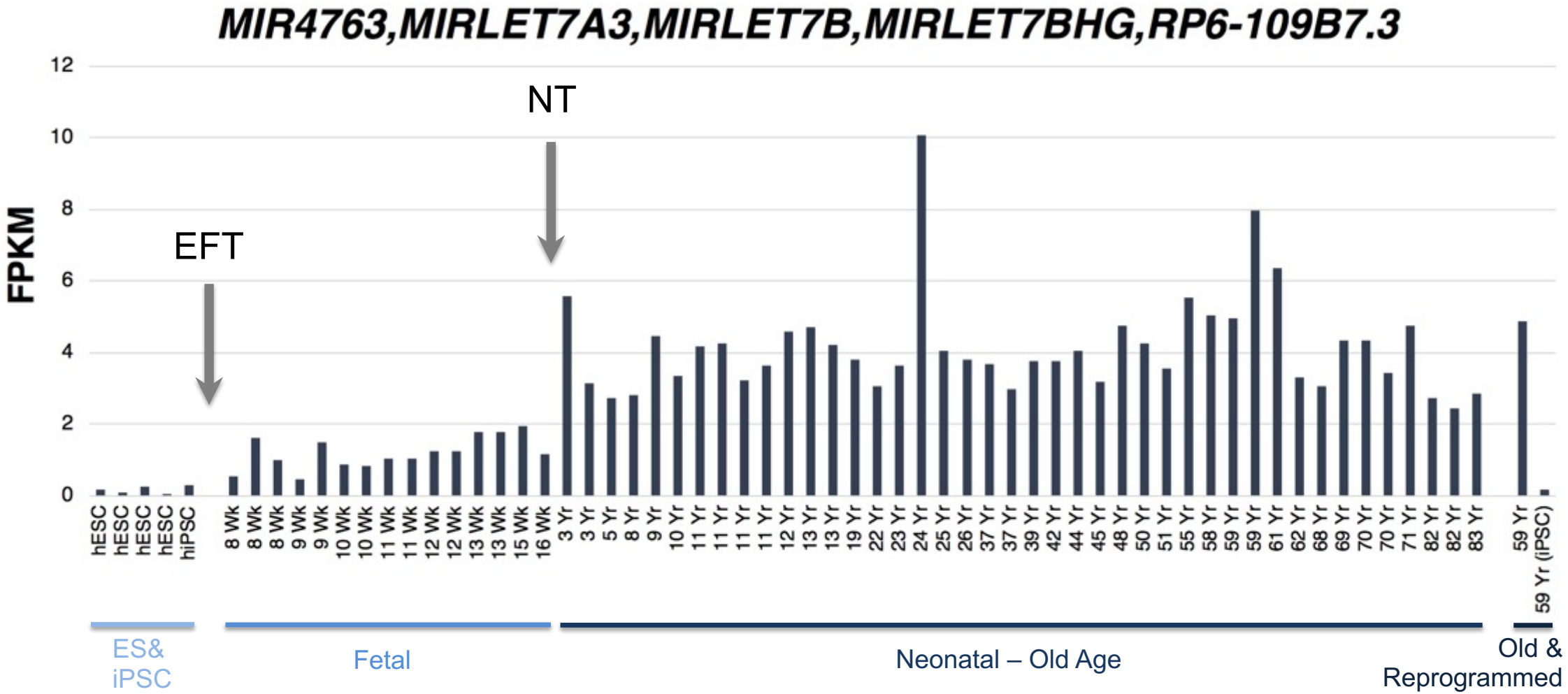
Somatic
Restriction

AGEX THERAPEUTICS

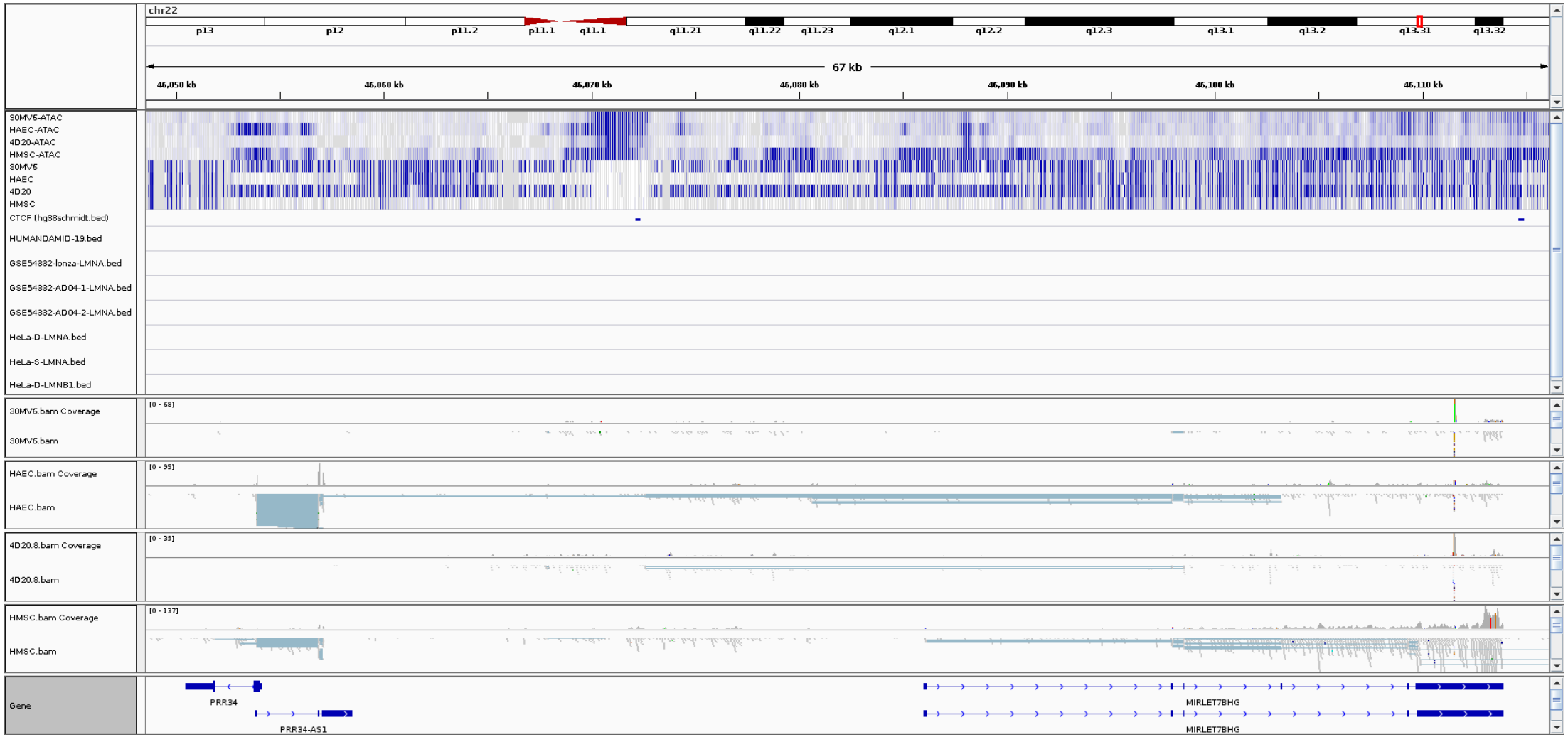
MIRLET7B Locus (chr22:46039839-46114113)



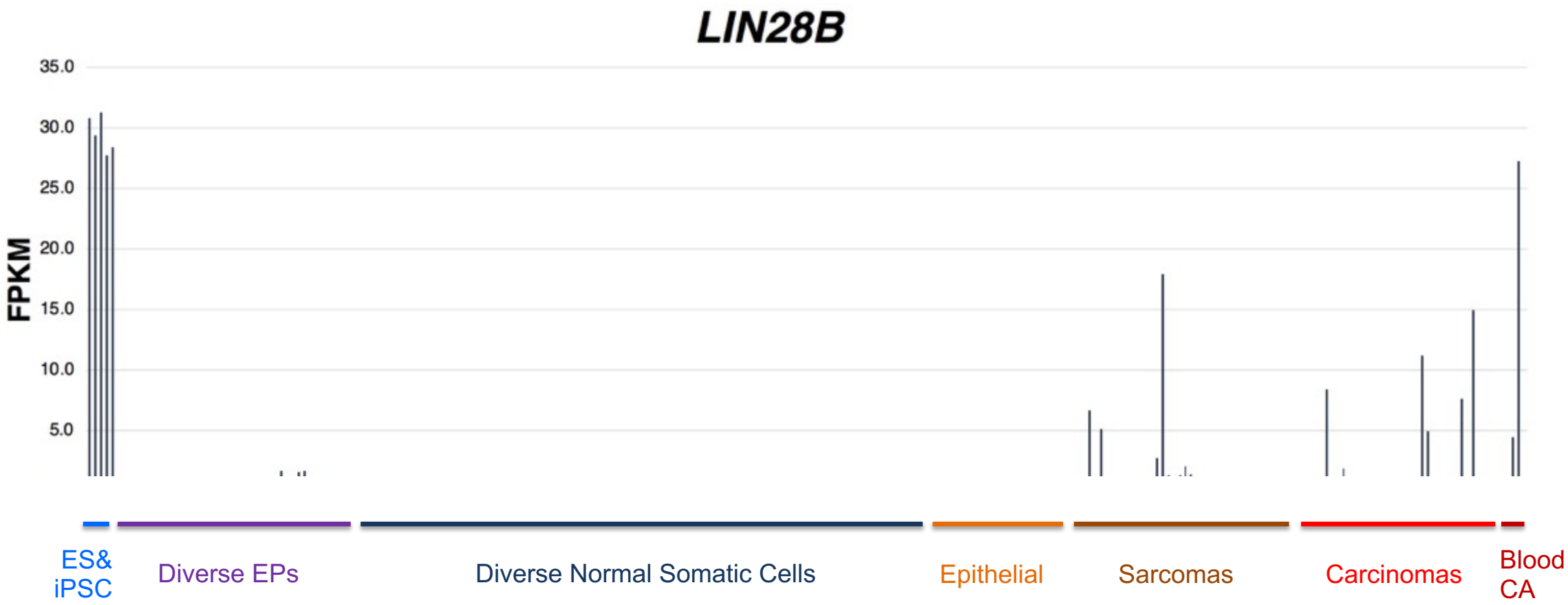
MIRLET7B Locus (chr22:46039839-46114113)



MIR4763,MIRLET7A3,MIRLET7B,MIRLET7BHG,RP6-109B7.3

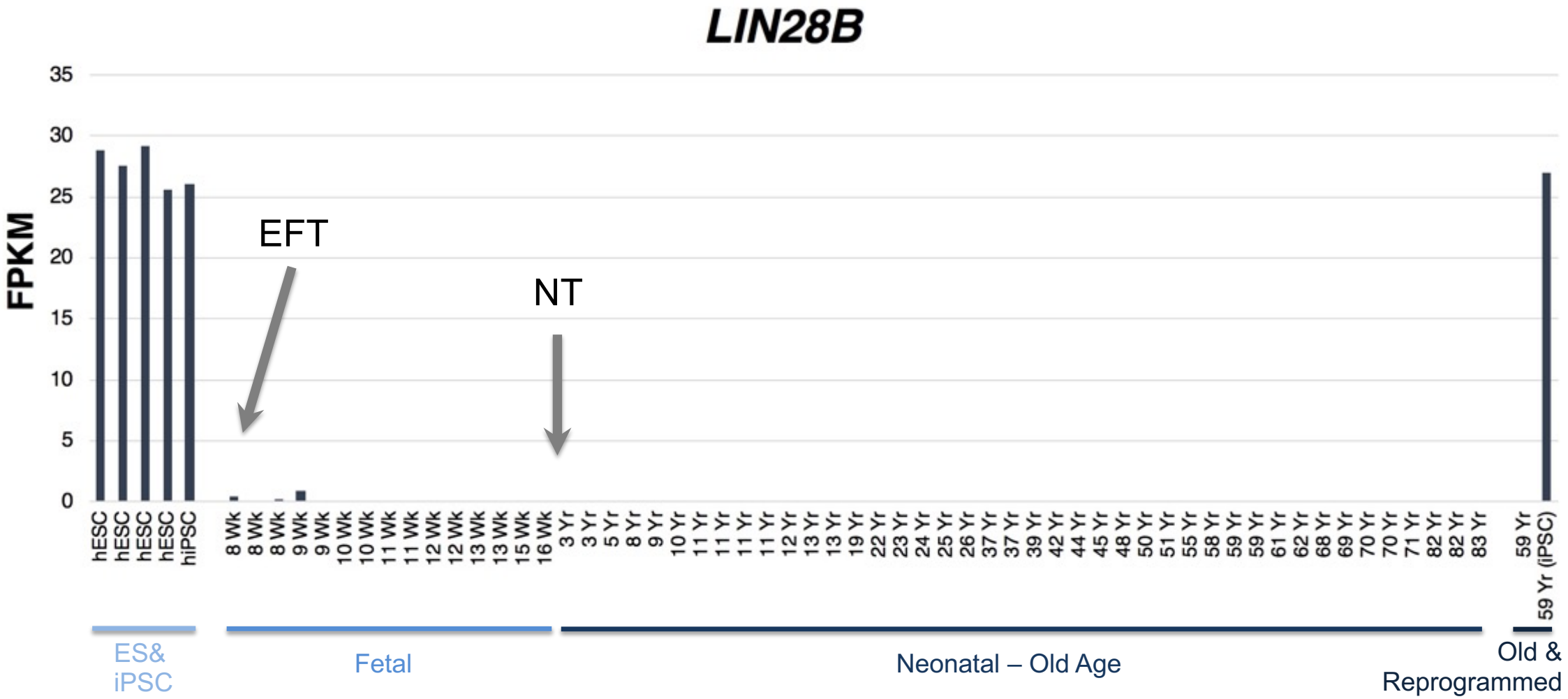


LIN28B



AGEX THERAPEUTICS

LIN28B


LIN28B
FPKM
35
30
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10
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0
EFT
NT
hESC
hESC
hESC
hESC
hiPSC
8 Wk
8 Wk
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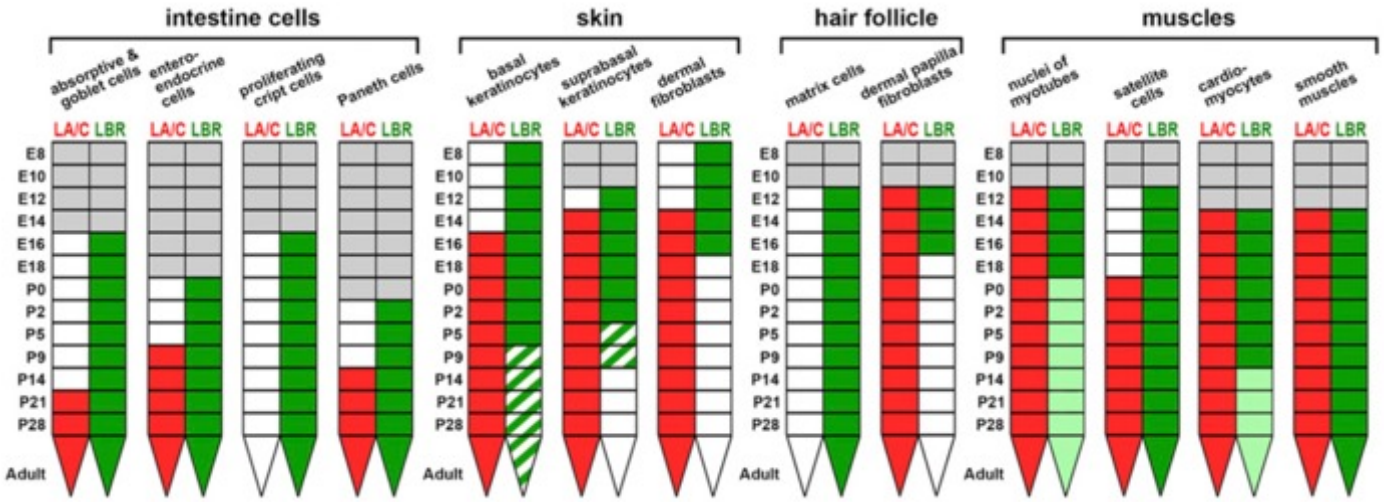
61 Yr
62 Yr
68 Yr
69 Yr
70 Yr
70 Yr
71 Yr
82 Yr
82 Yr
83 Yr
59 Yr
59 Yr (iPSC)
ES&
iPSC
Fetal
Neonatal – Old Age
Old &
Reprogrammed

Role of LMNA in Somatic Restriction

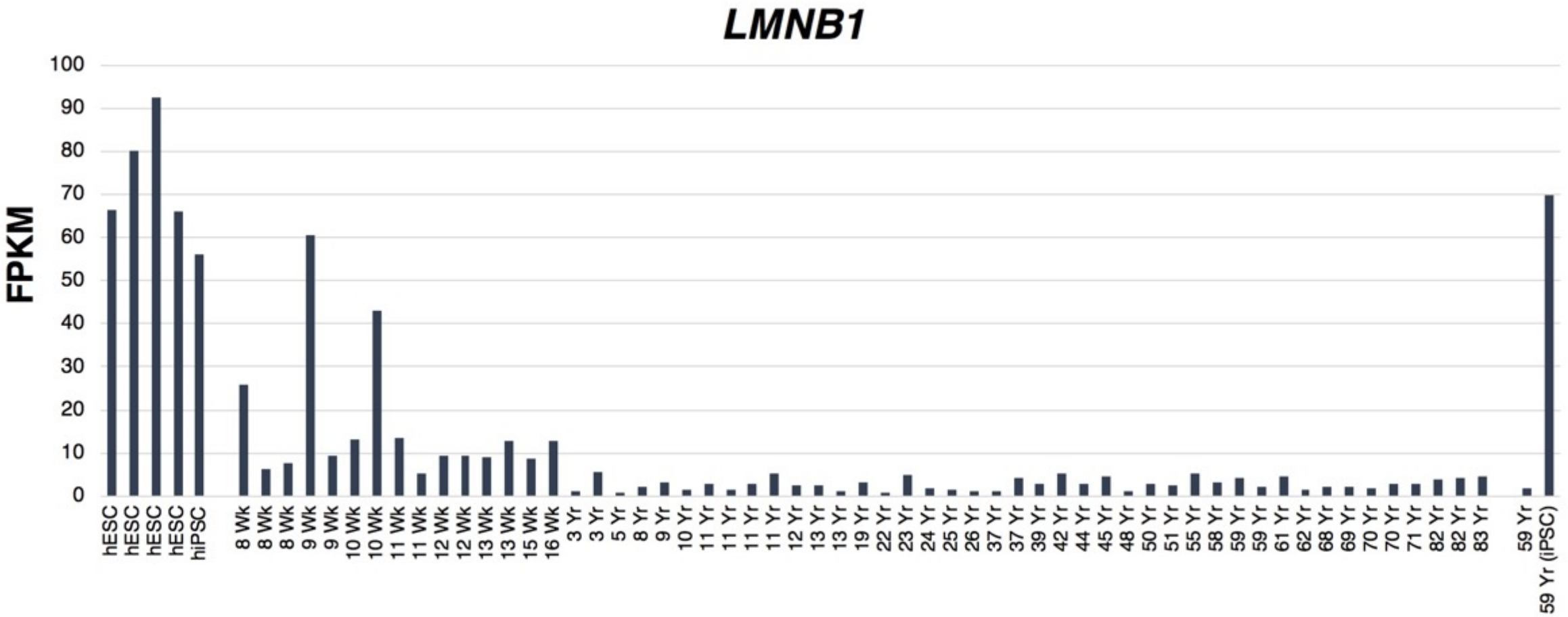
Timeline (Protein Levels):

LBR and Lamin A/C Sequentially Tether Peripheral Heterochromatin and Inversely Regulate Differentiation

Irina Solovei,[1] Audrey S. Wang,[2,3] Katharina Thanisch,[1] Christine S. Schmidt,[1] Stefan Krebs,[4] Monika Zwerger,[5] Tatiana V. Cohen,[6] Didier Devys,[7] Roland Foisner,[8] Leo Peichl,[9] Harald Herrmann,[5] Helmut Blum,[4] Dieter Engelkamp,[10] Colin L. Stewart,[2,3,*] Heinrich Leonhardt,[1,*] and Boris Joffe[1,*] *Cell* (2013) 152, 584–598



LMNB1


LMNB1
FPKM
100
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80
70
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50
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10
0
hESC
hESC
hESC
hESC
hiPSC
8 Wk
8 Wk
8 Wk
9 Wk
9 Wk
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11 Wk
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69 Yr
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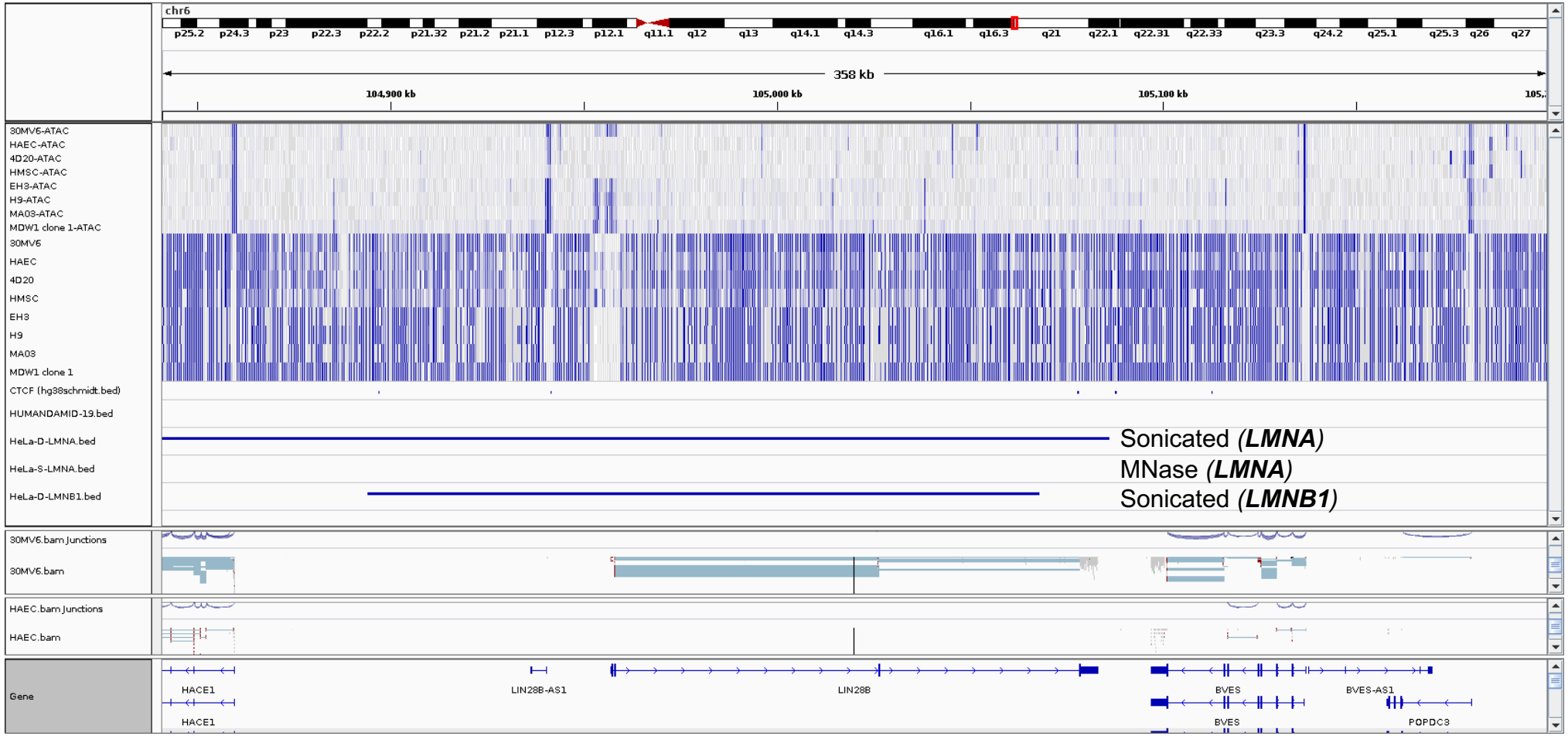
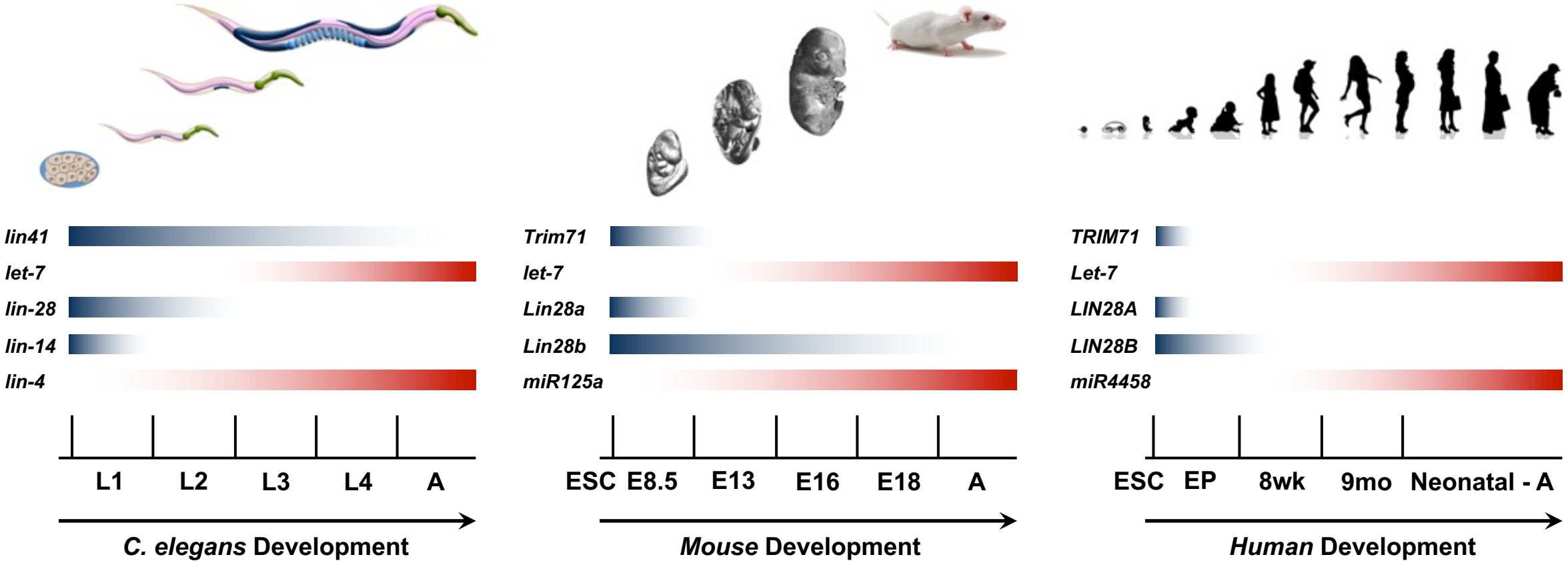
82 Yr
83 Yr
59 Yr
59 Yr (iPSC)

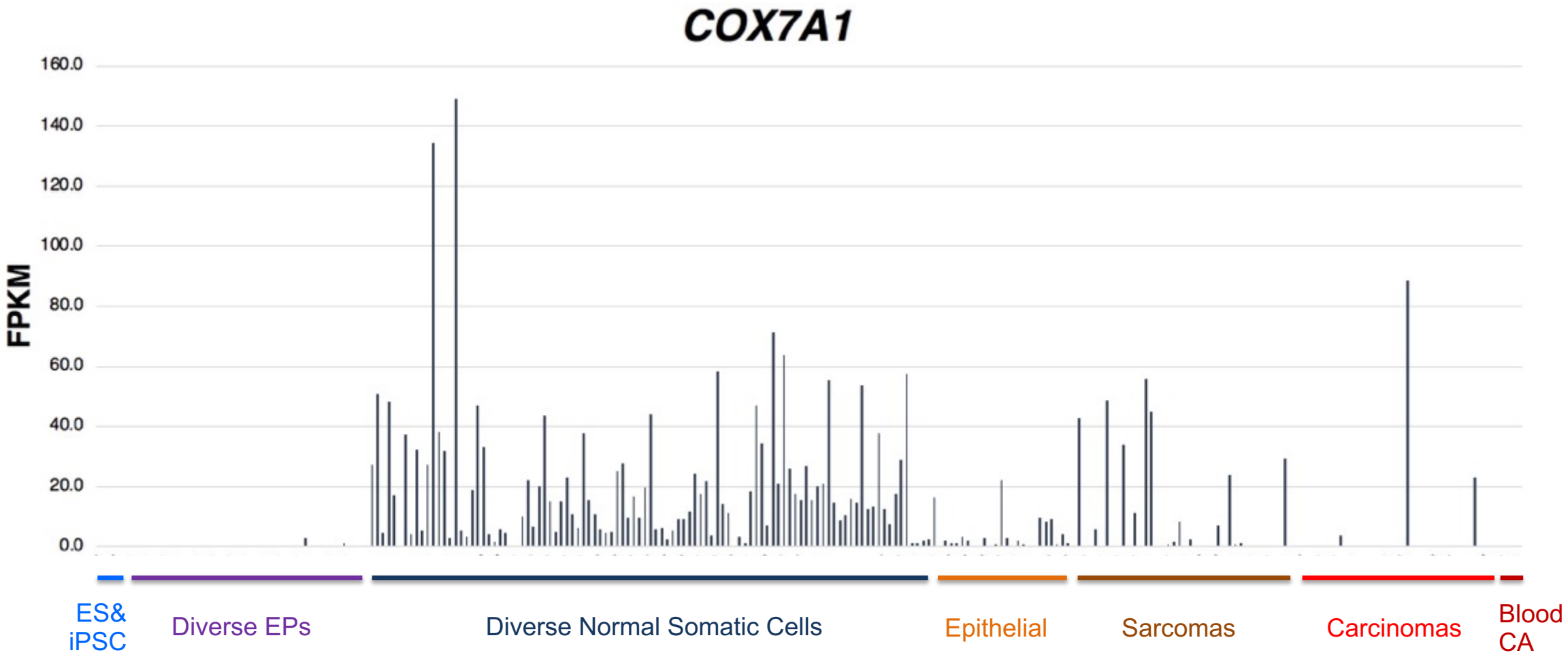
LIN28B ATAC, BIS, ChIP-Seq, & RNA-Seq



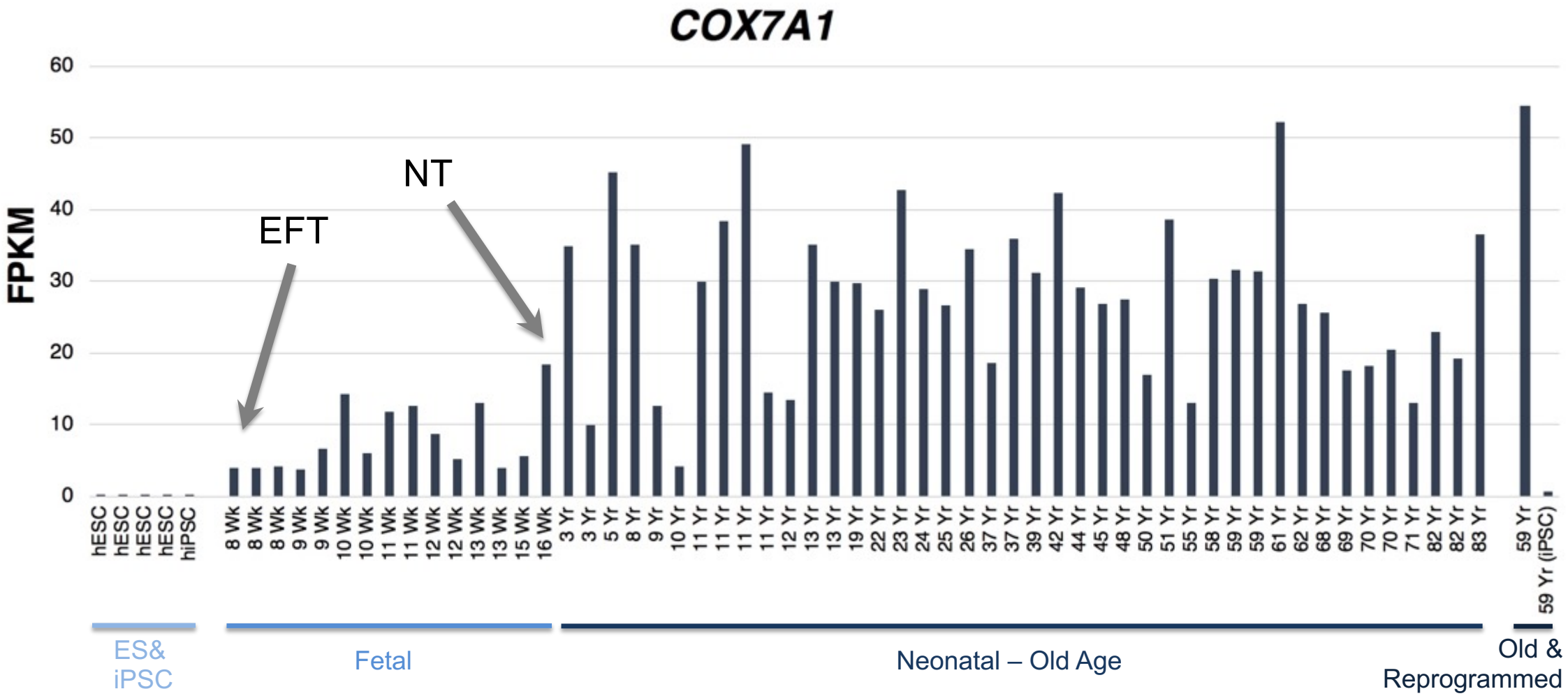
The Role of Small Temporal RNAs in Developmental Timing



COX7A1


COX7A1
FPKM
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
ES& iPSC
Diverse EPs
Diverse Normal Somatic Cells
Epithelial
Sarcomas
Carcinomas
Blood CA

COX7A1



AGEX THERAPEUTICS

Developmental Restriction

Unrestricted
Immortal
Germ-Line

TERT
TRIM71
01

Cellular aging: Immunodeficiency, AMD, AAA

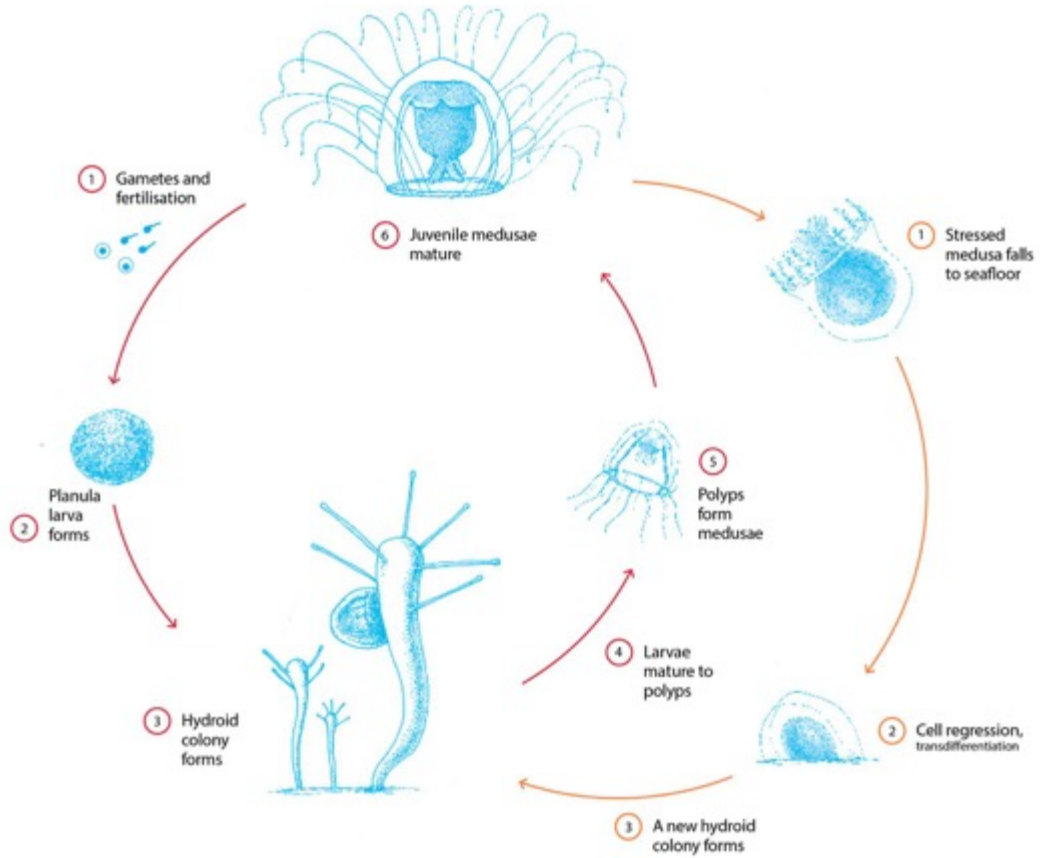
LET-7
COX7A1
LIN28B
PCDHA/B
02

EFT: Repression of regeneration

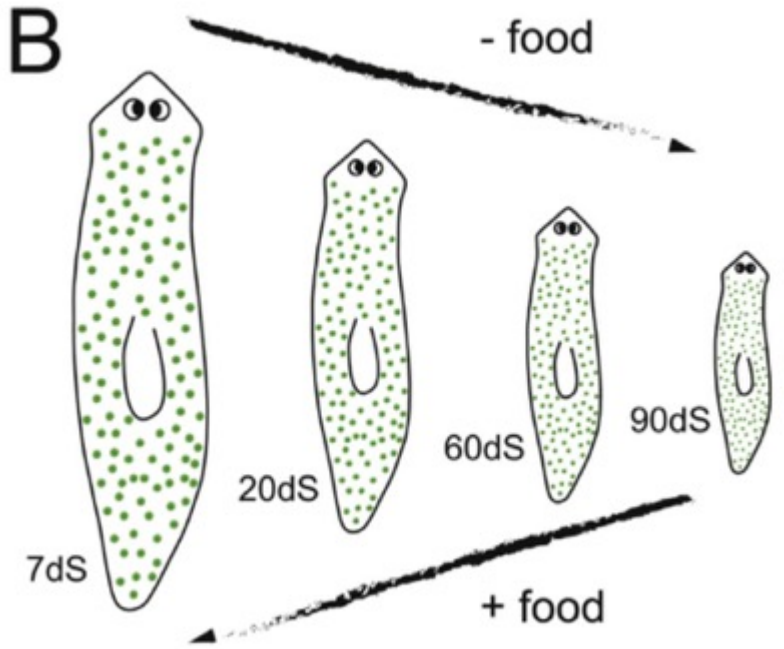
Somatic
Restriction

AGEX THERAPEUTICS

Feast/Famine & Regeneration



https://www.nzgeo.com/stories/the-jellyfish-that-wouldnt-die/



Felix, D.A. et al, *Semin in Cell & Dev Biol* 87 (2019) 169–181

AGEX THERAPEUTICS

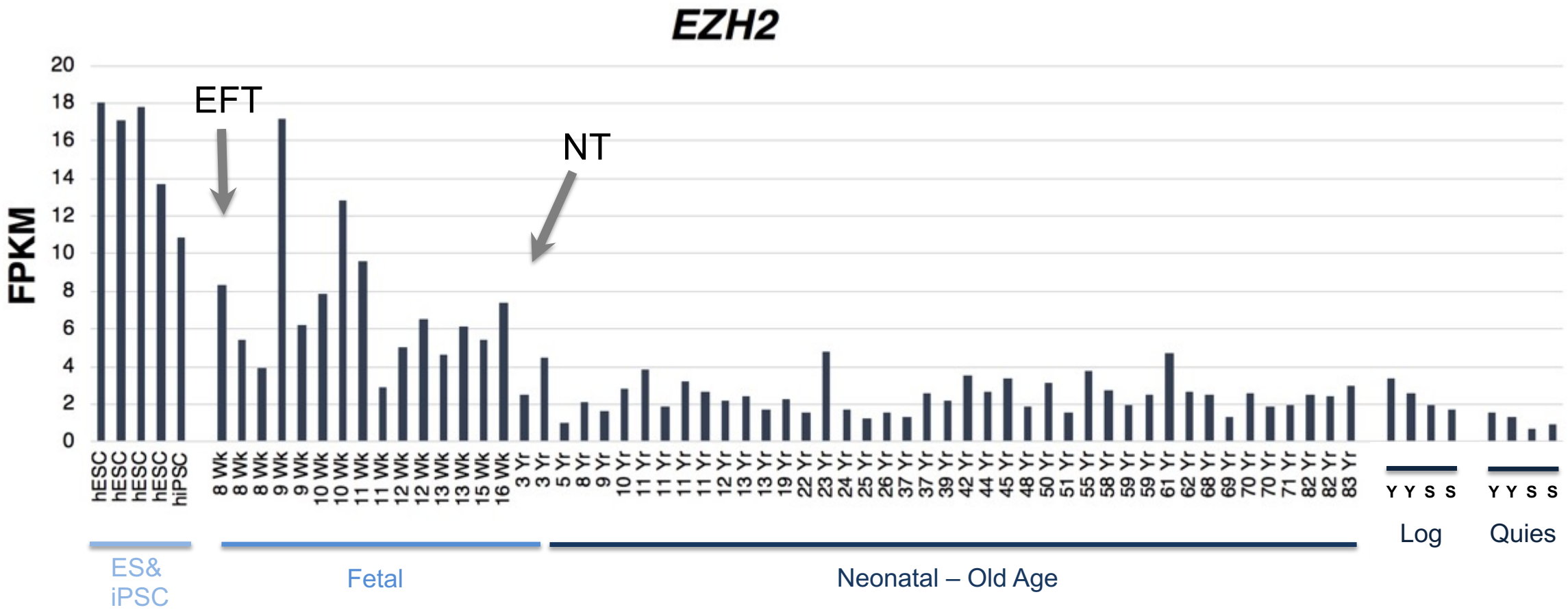
Feast/Famine & Regeneration

Thesis: Mammals retain limited facultative regeneration to survive feast/famine, can regress & regenerate primarily fat and muscle depending on availability of nutrition

- Dietary restriction (DR) de-represses regeneration and as a result, facilitates lifespan extension
- Mammalian DR-regeneration is regulated in part by changes in the H3K27Ac/H3K27me3 ratio that is in turn regulated by onco-metabolites/PRC
- This explains, at least in part, the observations relating to NAD, sirtuins, etc on lifespan in numerous model organisms

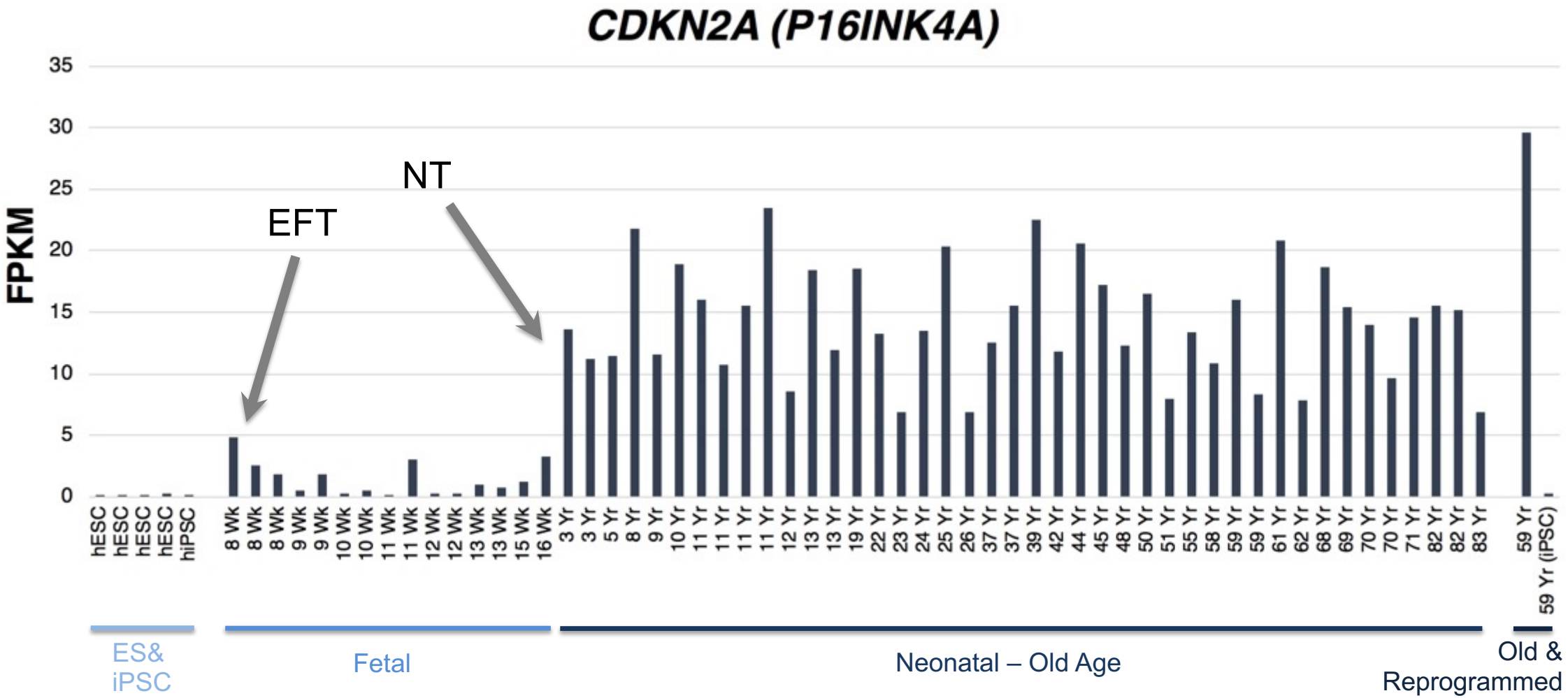
AGEX THERAPEUTICS

EZH2 - PcG Histone H3 lysine-27 methyltransferase



AGEX THERAPEUTICS

CDKN2A


CDKN2A (P16INK4A)
FPKM
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NT
hESC
hESC
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hESC
hiPSC
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68 Yr
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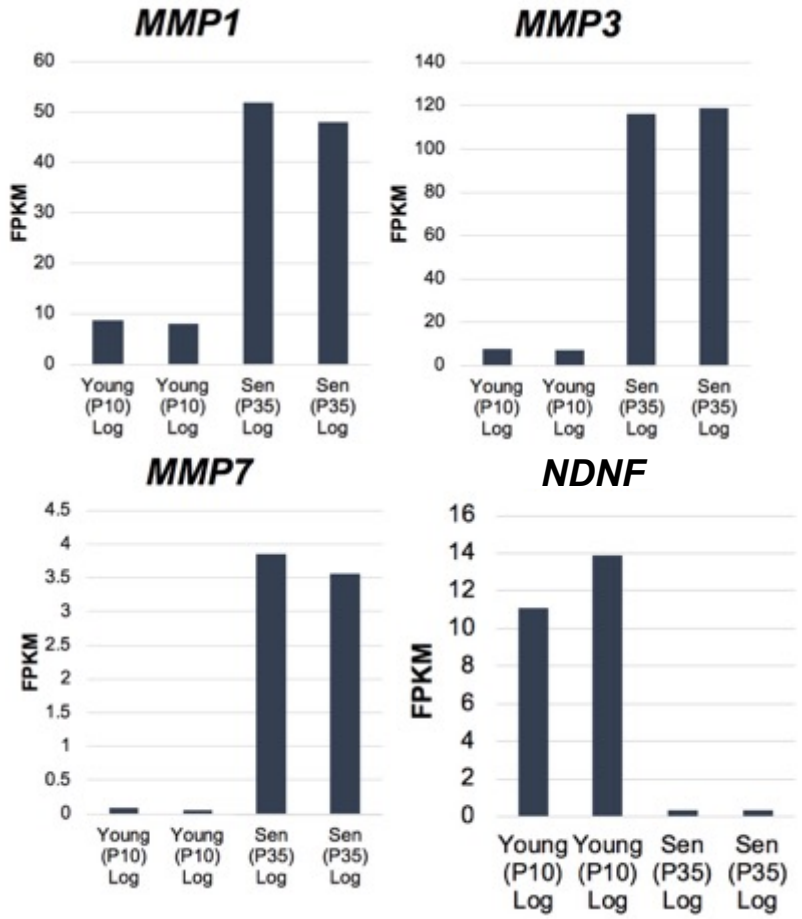
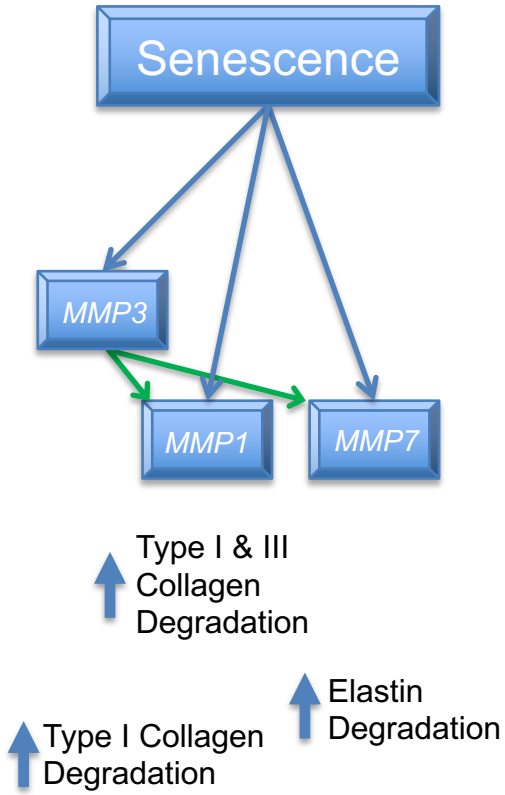
70 Yr
71 Yr
82 Yr
82 Yr
83 Yr
59 Yr
59 Yr (iPSC)
ES& iPSC
Fetal
Neonatal – Old Age
Old & Reprogrammed

The Hatchetmen – The Senescent Secretome

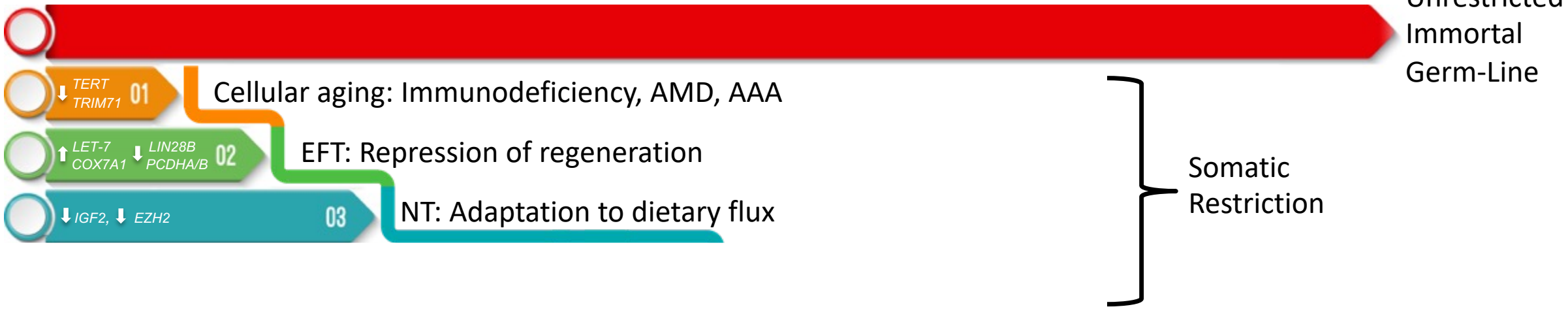
Senescent cells may induce tissue degeneration



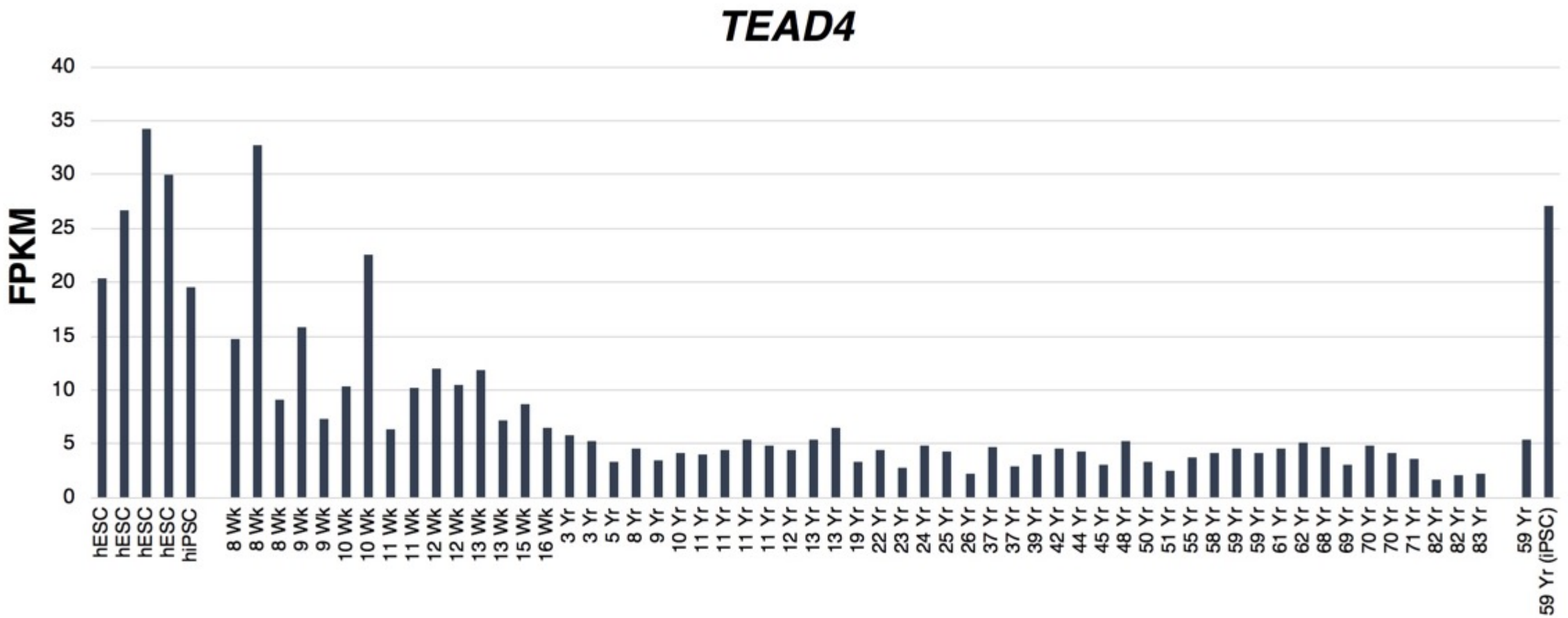


Cutis Laxa

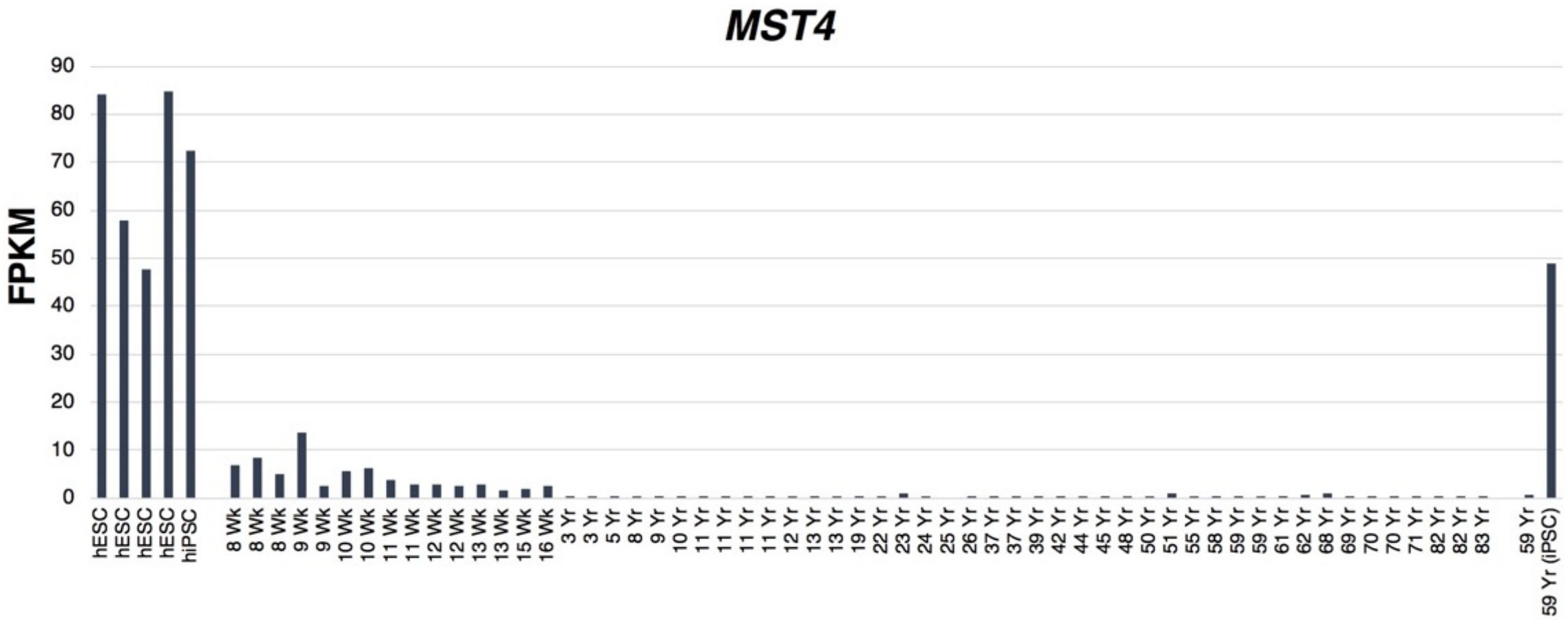
Developmental Restriction



Developmental Restriction - Hippo



Developmental Restriction - Hippo



AGEX THERAPEUTICS

Developmental Restriction

Unrestricted
Immortal
Germ-Line

⬇ *TERT* *TRIM71* 01 — Cellular aging: Immunodeficiency, AMD, AAA

⬆ *LET-7* *COX7A1* ⬇ *LIN28B* *PCDHA/B* 02 — EFT: Repression of regeneration

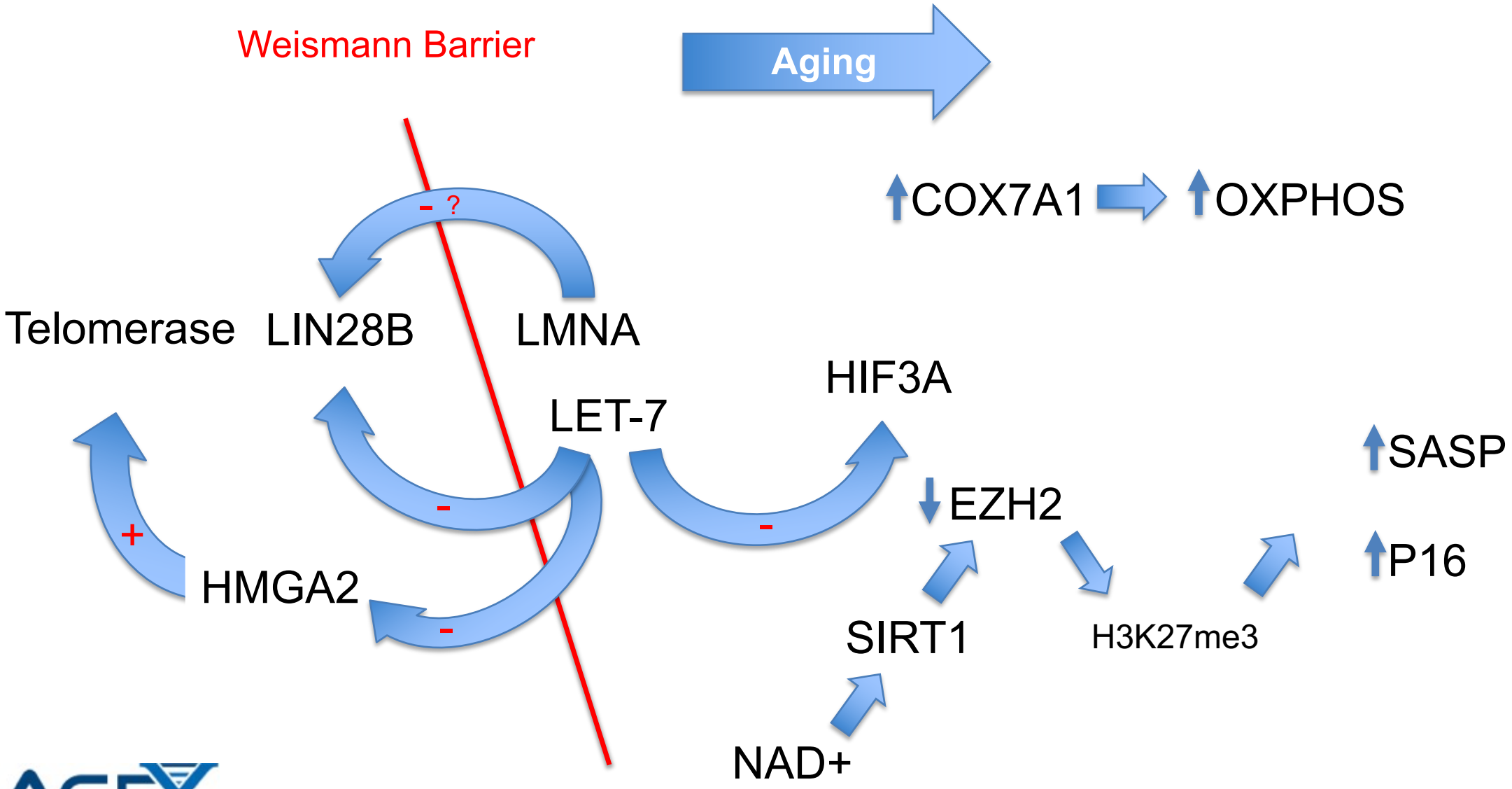
⬇ *IGF2*, ⬇ *EZH2* 03 — NT: Adaptation to dietary flux

⬇ *MST4*, *TEAD4* 04 — Repression of growth

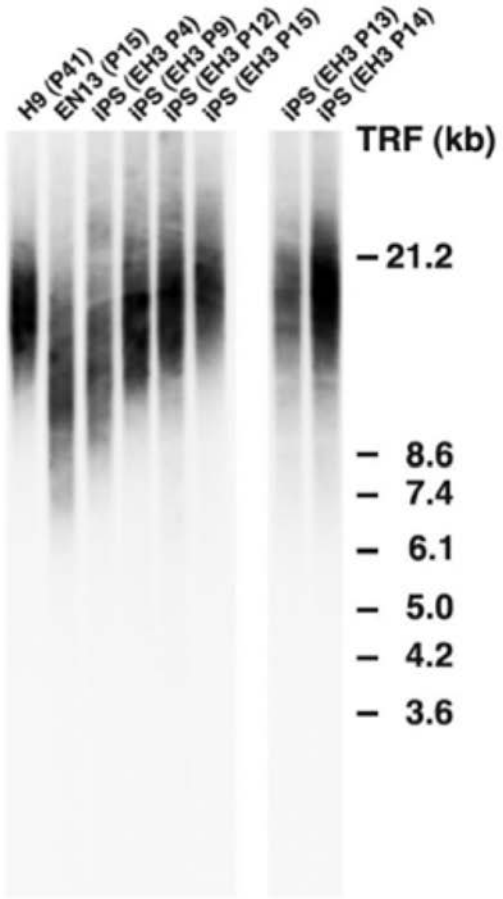
Somatic
Restriction

AGEX THERAPEUTICS

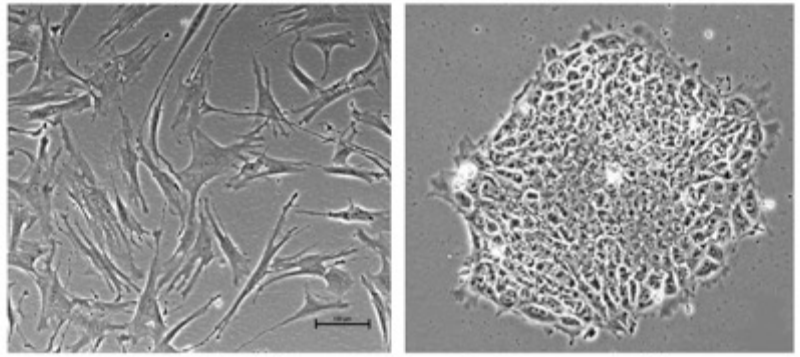
Summary of Pathways



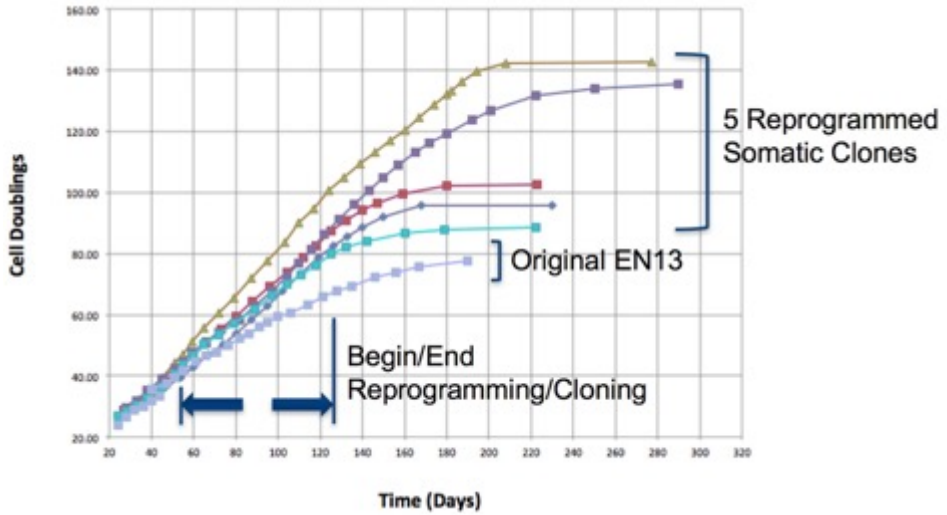
Reprogramming the Aging of Human Cells



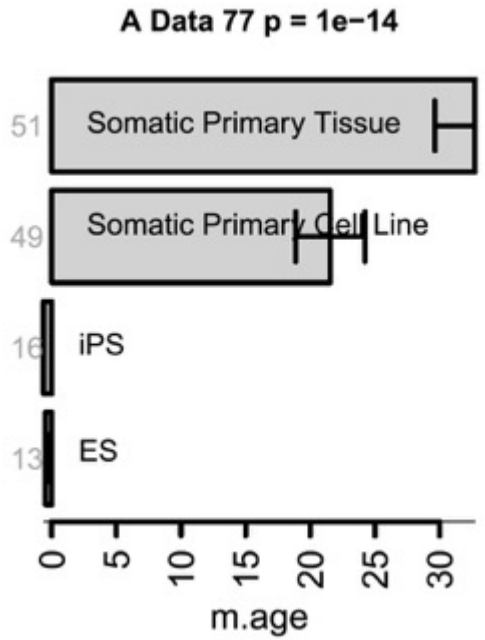
Regen Med 2010 May;5(3):345-63



Skin Fibroblasts iPS Cells



Reprogramming Methylation Age



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

AGEX THERAPEUTICS

Induced Telomerase & Regeneration (iTR™)

Embryonic → Fetal - Adult → Aging Adult

Highly Regenerative
Construction
↑ Senolysis

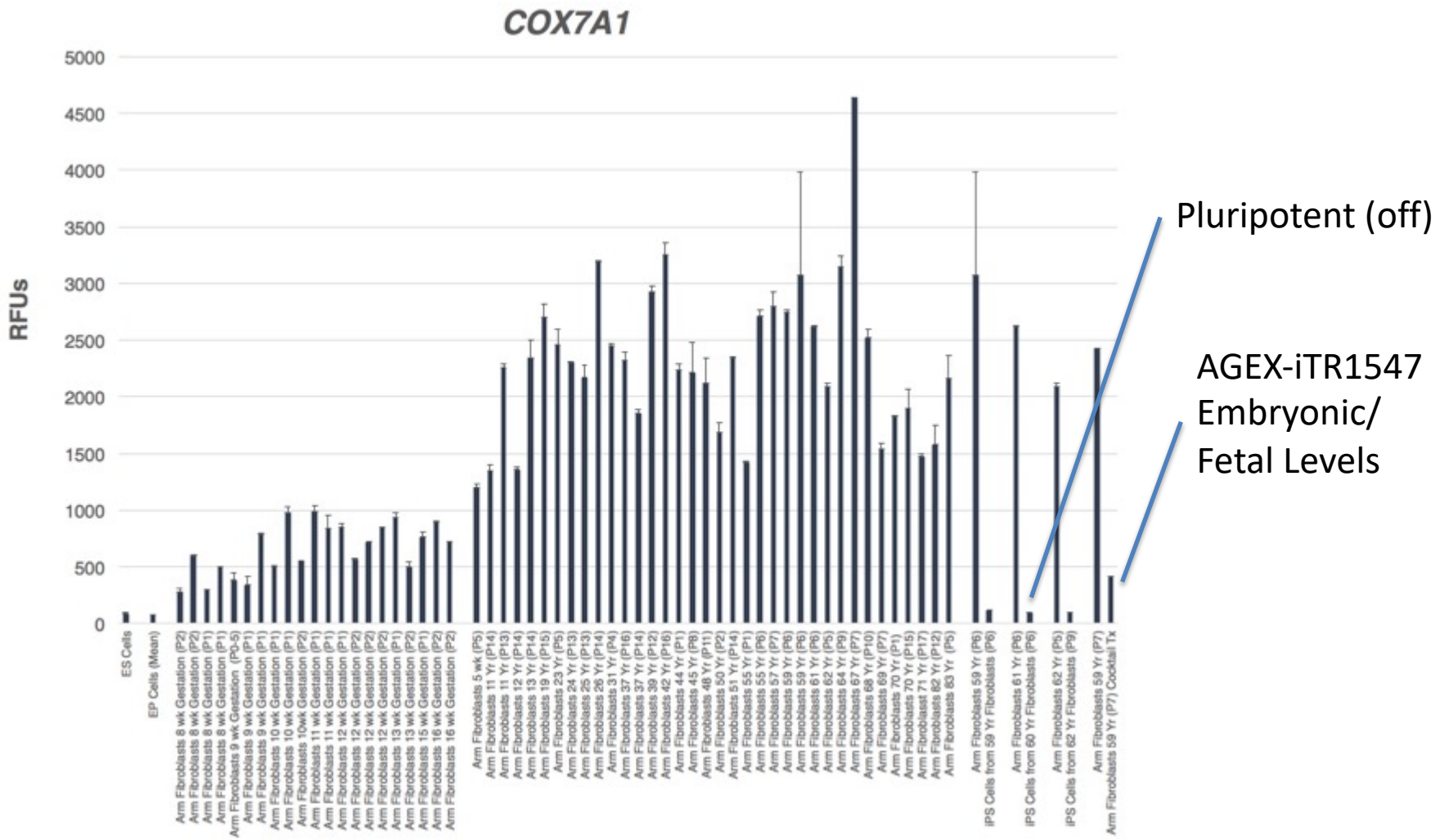
Declining Regeneration
Maintenance
↓ Senolysis

Non-Regenerative
Destruction
↓ Senolysis

Age Reversal through Telomerase
Activation & Induced Regeneration

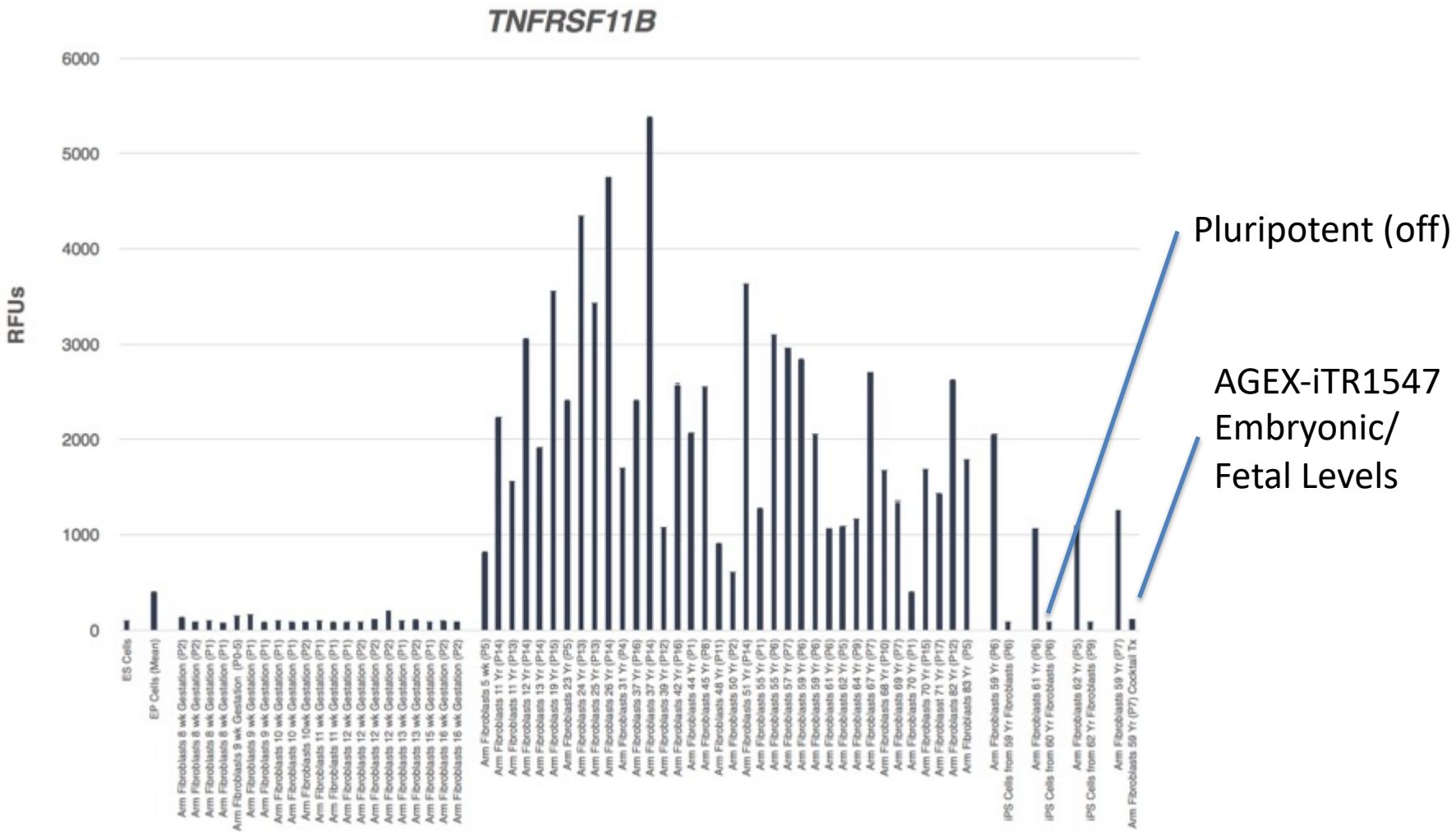
AGEX THERAPEUTICS

An Example of an iTR Formulation

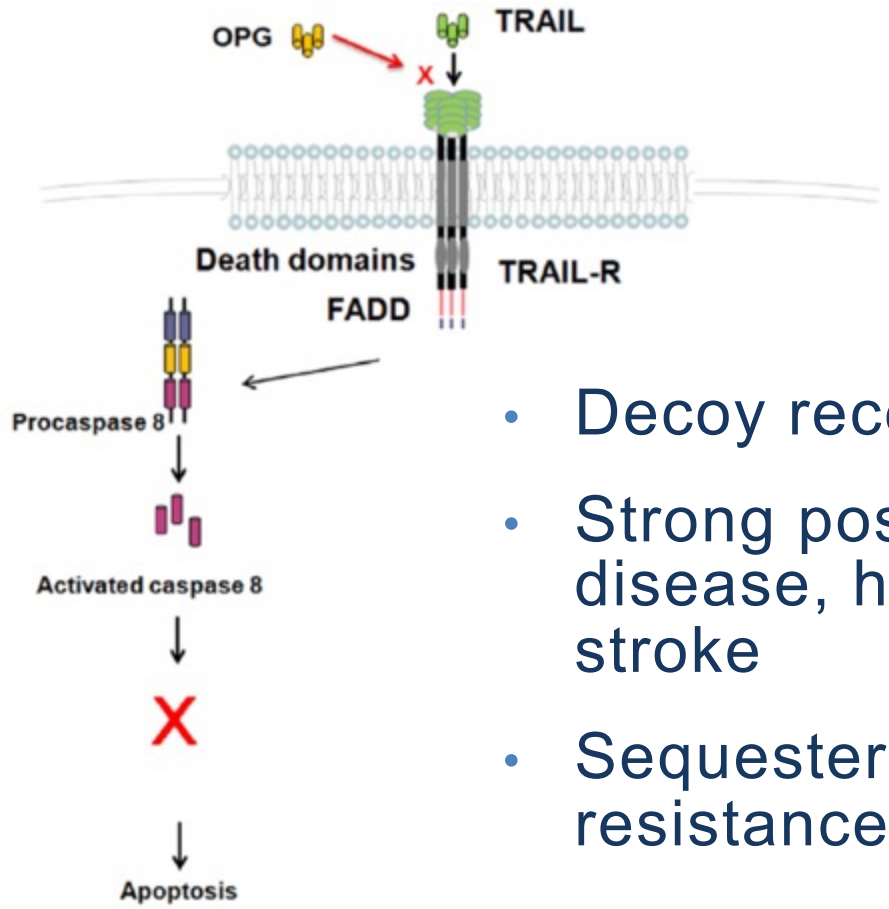


AGEX THERAPEUTICS

An Example of an iTR Formulation



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

Why is Senolysis Repressed?

- There is a probable natural apoptosis of senescent cells before crossing the Weismann Barrier
- If tissues can regenerate, then probable selective pressure to apoptose cells with genotoxic damage
- If restricted regeneration, then keep cells but arrest proliferation
- Result is accumulation of senescent cells with time

AGEX THERAPEUTICS

Summary

- Upstream triggers that lead to aging and senescence may begin as early as embryonic phases of development
- Small RNAs may be playing an important role in timing developmental and aging events
- Induced pluripotency appears to reverse the aging of cells by many known criteria
- The targeted induction of only telomerase and regeneration (iTR) as opposed to uncontrolled partial reprogramming may be achievable with potentially important applications in aging and regenerative medicine

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