Conserved Modulators of Ageing: Will They Work In Humans?

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HEALTHY LIFE EXPECTANCY - SINGAPORE

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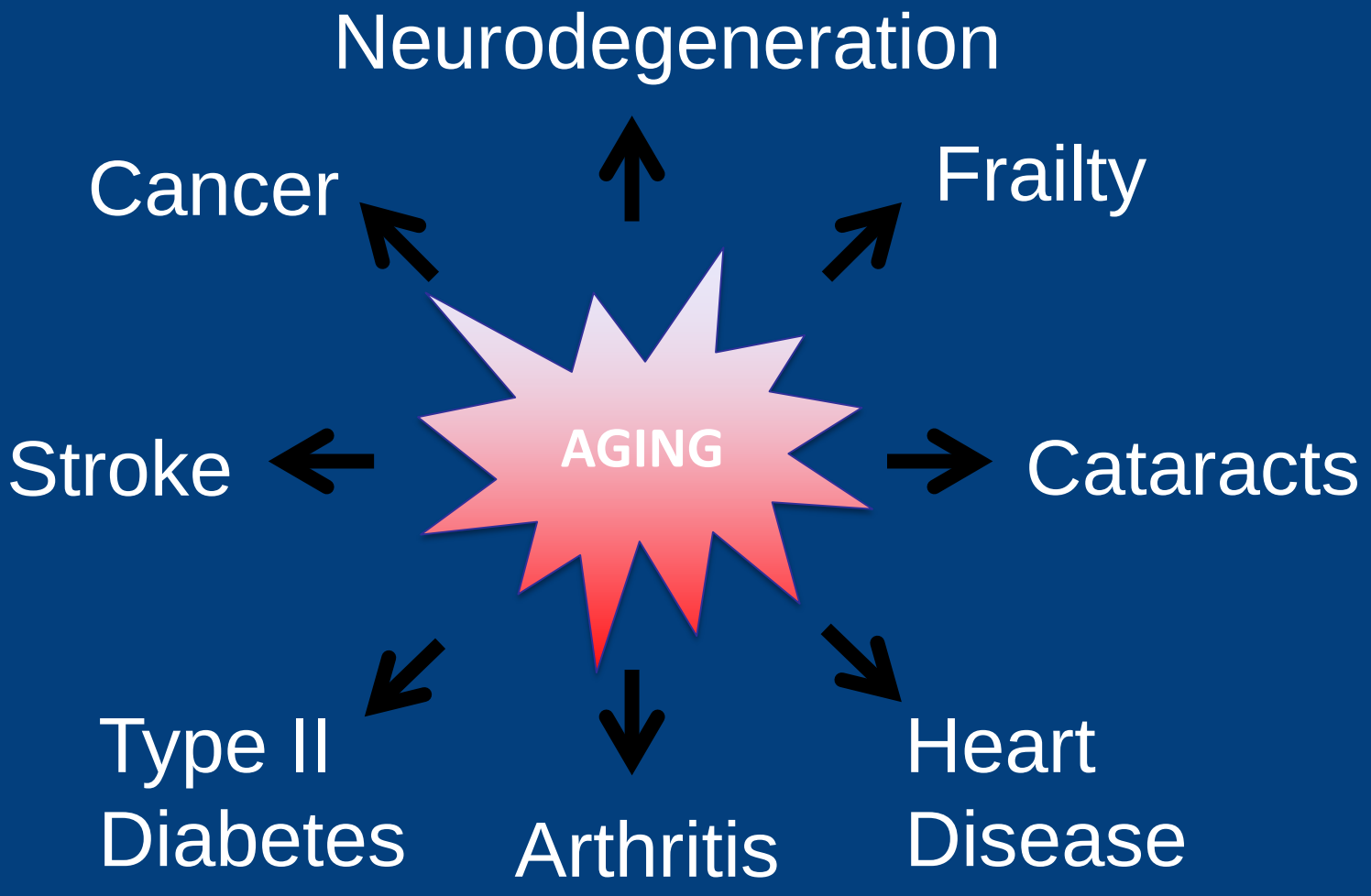
1990 - 2010	MALES	FEMALES
Change in Life Expectancy	+ 6.0	+ 5.4
Change in Healthy Life Expectancy	+ 4.1	+ 3.4

Lancet 2012; 380: 2144–62

AGING IS A DRIVER OF CHRONIC DISEASE



LIFESPAN EXTENSION AGENTS

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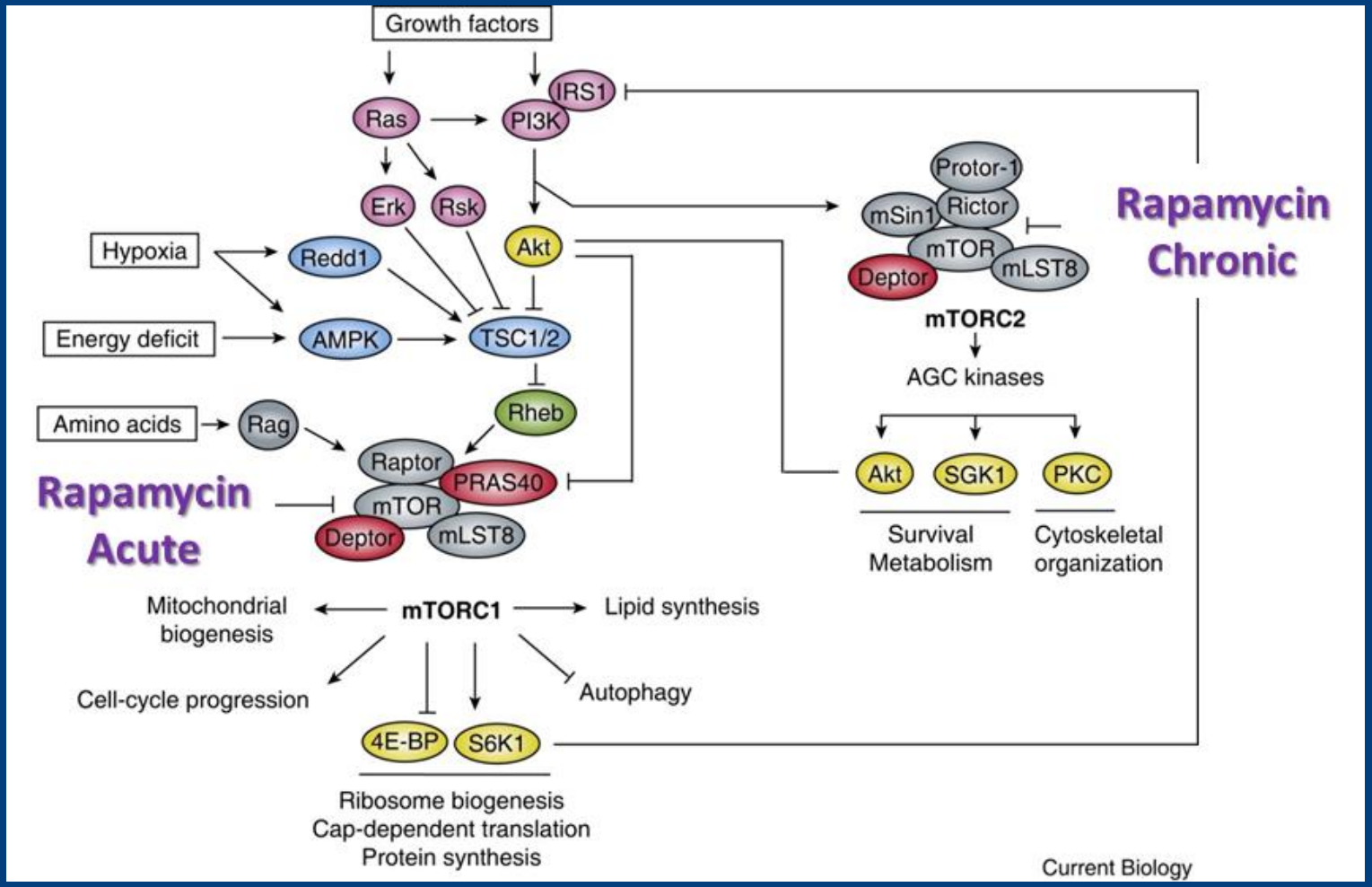
BEHAVIORAL

1. Calorie Restriction
2. Exercise
3. Intermittent Fasting
4. Alcohol??????

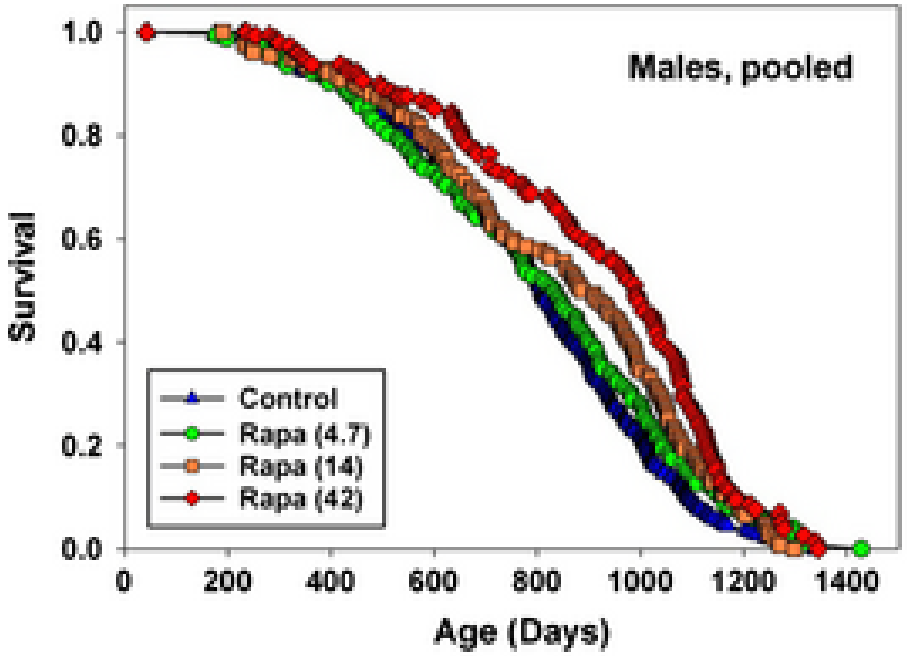
SMALL MOLECULES

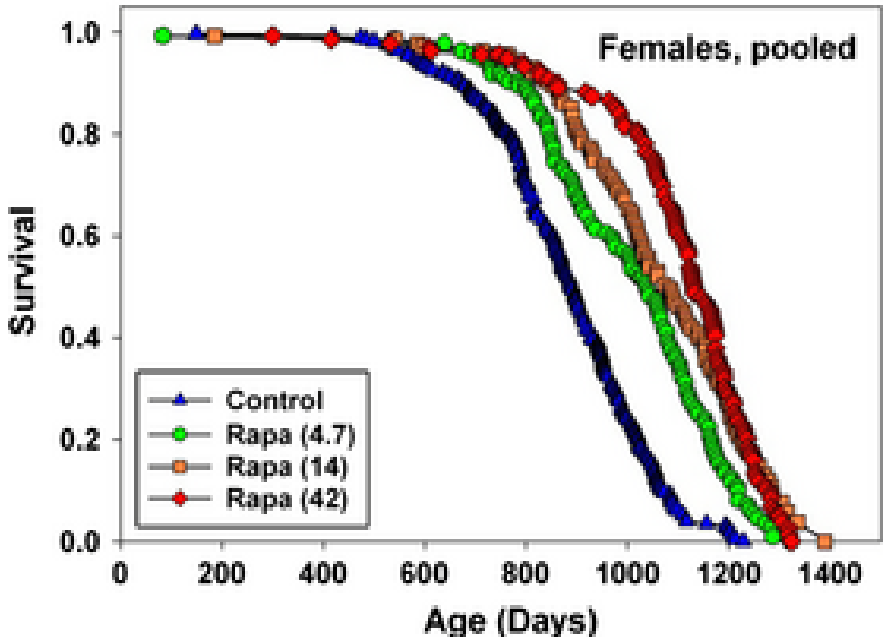
1. Rapamycin
2. Metformin
3. NSAIDs
4. Acarbose
5. STACs (Resveratrol)
6. NAD Precursors
7. Factors in young blood
8. Senolytics

RAPAMYCIN


Growth factors
IRS1
Ras
PI3K
Erk
Rsk
Akt
Hypoxia
Redd1
Energy deficit
AMPK
TSC1/2
Amino acids
Rag
Rheb
Raptor
PRAS40
mTOR
Deptor
mLST8
Rapamycin
Acute
Protor-1
mSin1
Rictor
mTOR
Deptor
mLST8
mTORC2
AGC kinases
Akt
SGK1
PKC
Survival
Metabolism
Cytoskeletal
organization
Rapamycin
Chronic
Mitochondrial
biogenesis
mTORC1
Lipid synthesis
Cell-cycle progression
Autophagy
4E-BP
S6K1
Ribosome biogenesis
Cap-dependent translation
Protein synthesis
Current Biology

RAPAMYCIN IS DOSE DEPENDENT

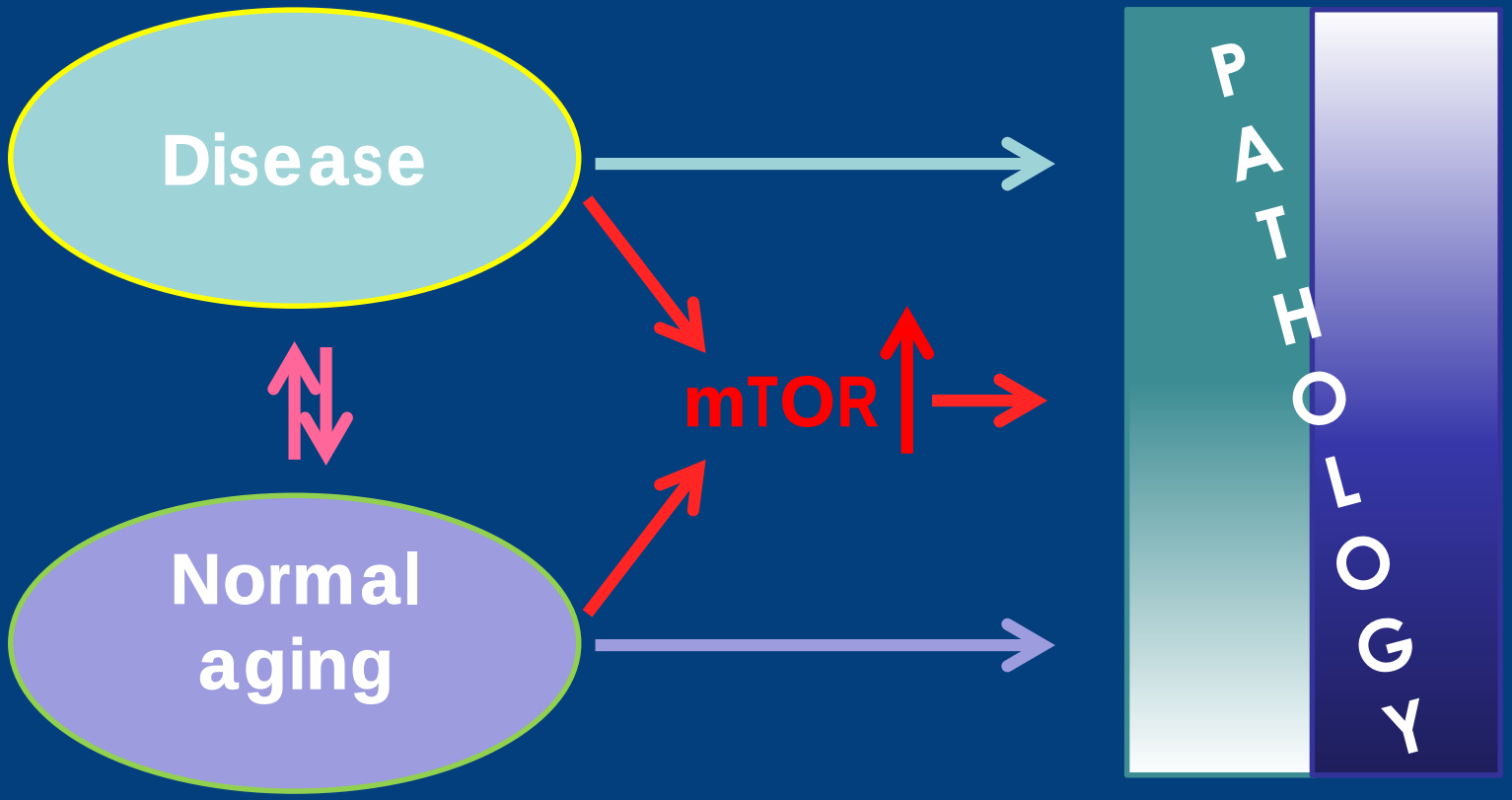




Aging Cell (2013) pp1–10 Doi: 10.1111/acel.12194

Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction

ABERRANT mTOR ACTIVATION



DEPLETION OF ADULT STEM CELL POPULATIONS AND mTOR SIGNALING

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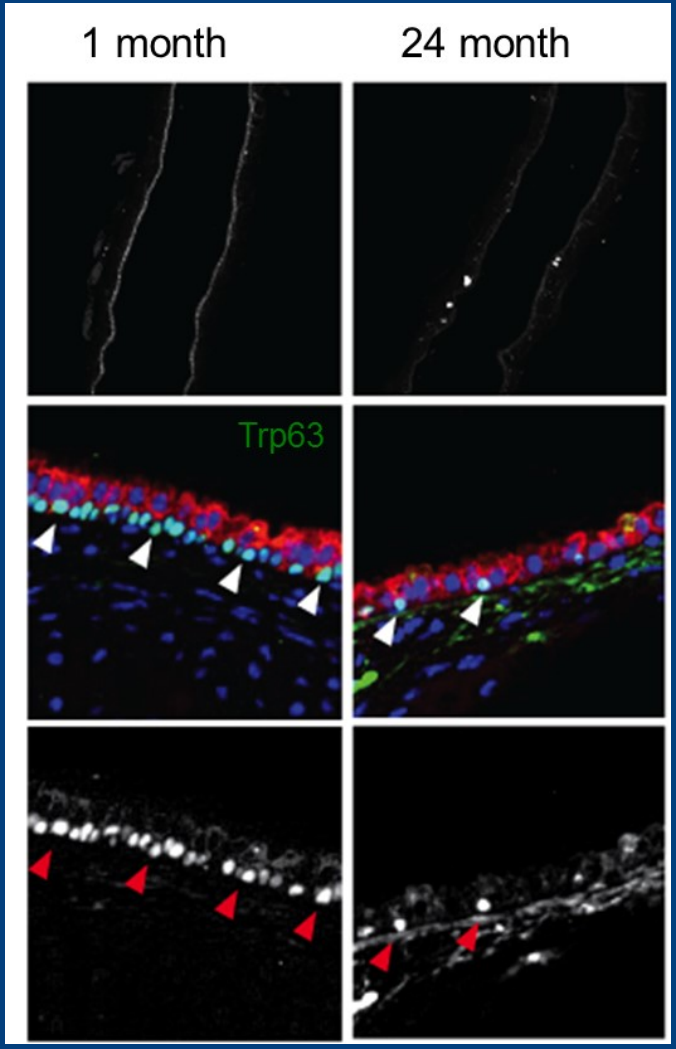
- Tracheal Stem Cells (Henri Jasper)
- Muscle Stem Cells (Jasper, Tom Rando)
- Hematopoietic Stem Cells
  (Chen et al., Sci. Signal. 2009)
- Mesenchymal Stem Cells
  (Gu et al., Aging, 8:1102 2016)

AGE-RELATED BC LOSS IN THE TRACHEA



Haller et al. Cell Stem Cell *In press*

RAPAMYCIN TREATMENT PREVENTS AGE-RELATED STEM CELL LOSS IN THE TRACHEA

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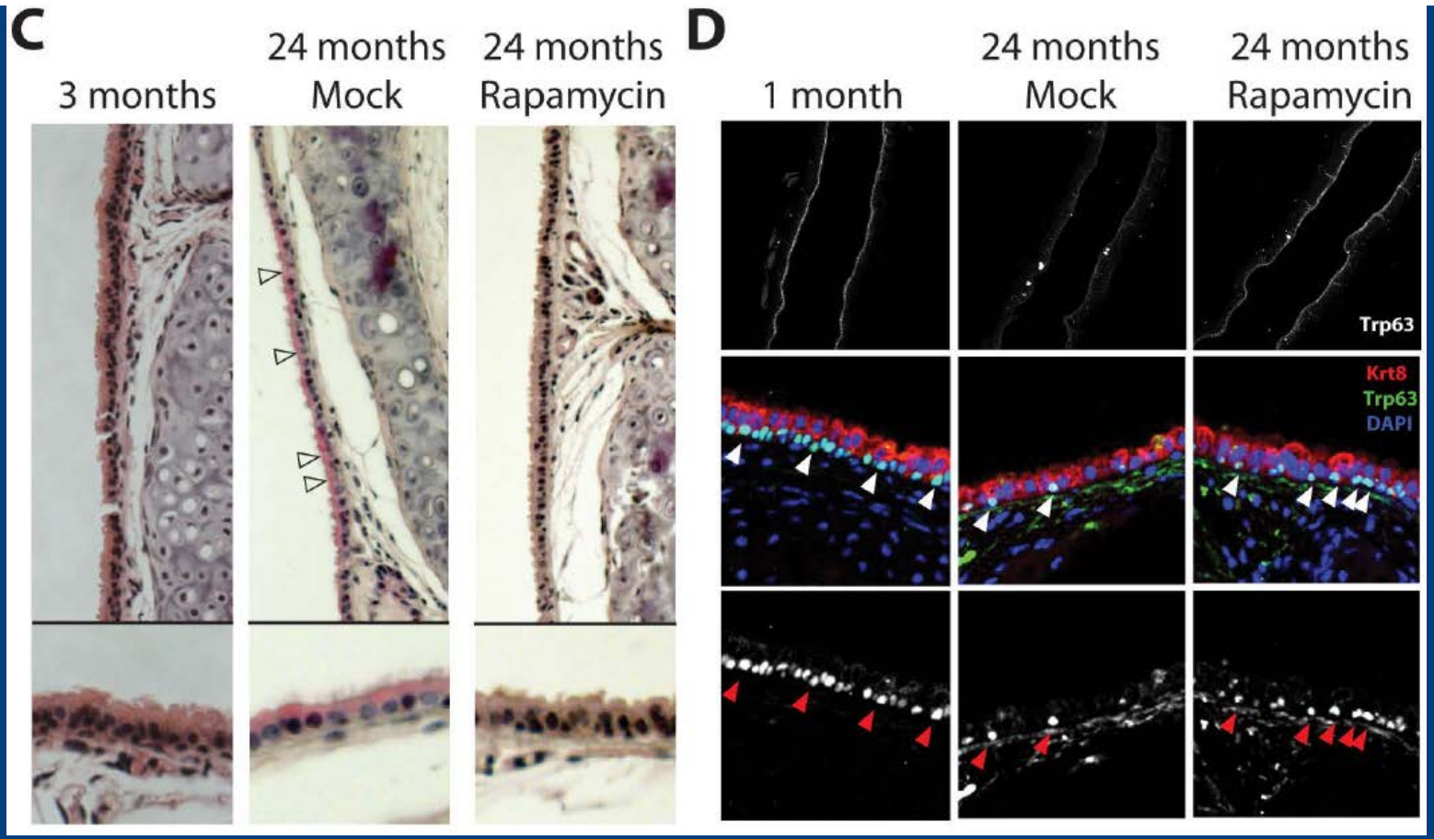
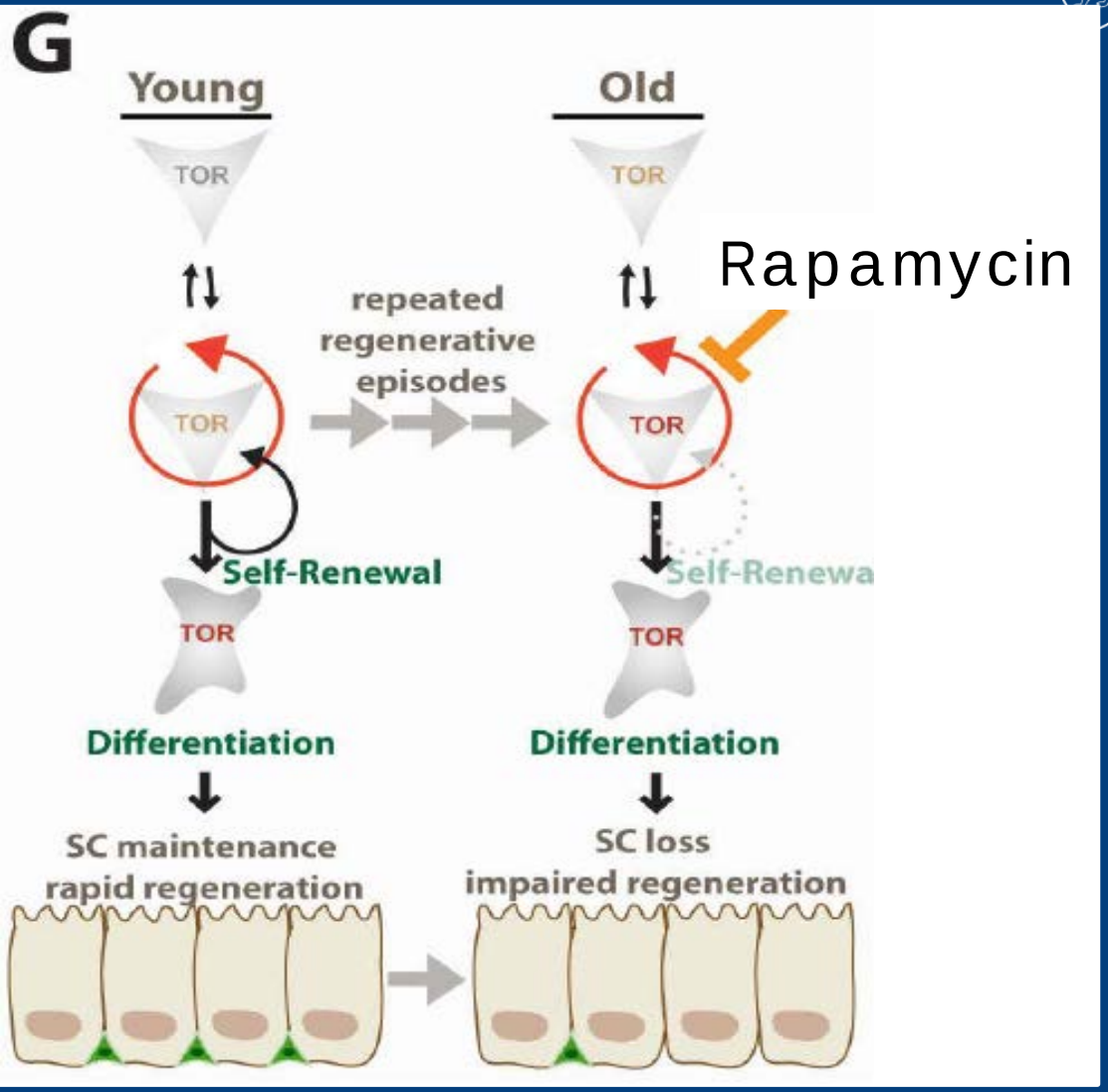


Haller et al. Cell Stem Cell *In press*

mTOR AND AGEING STEM CELLS



Haller et al. Cell Stem Cell *In press*

CENTRE FOR HEALTHY AGEING IN SINGAPORE

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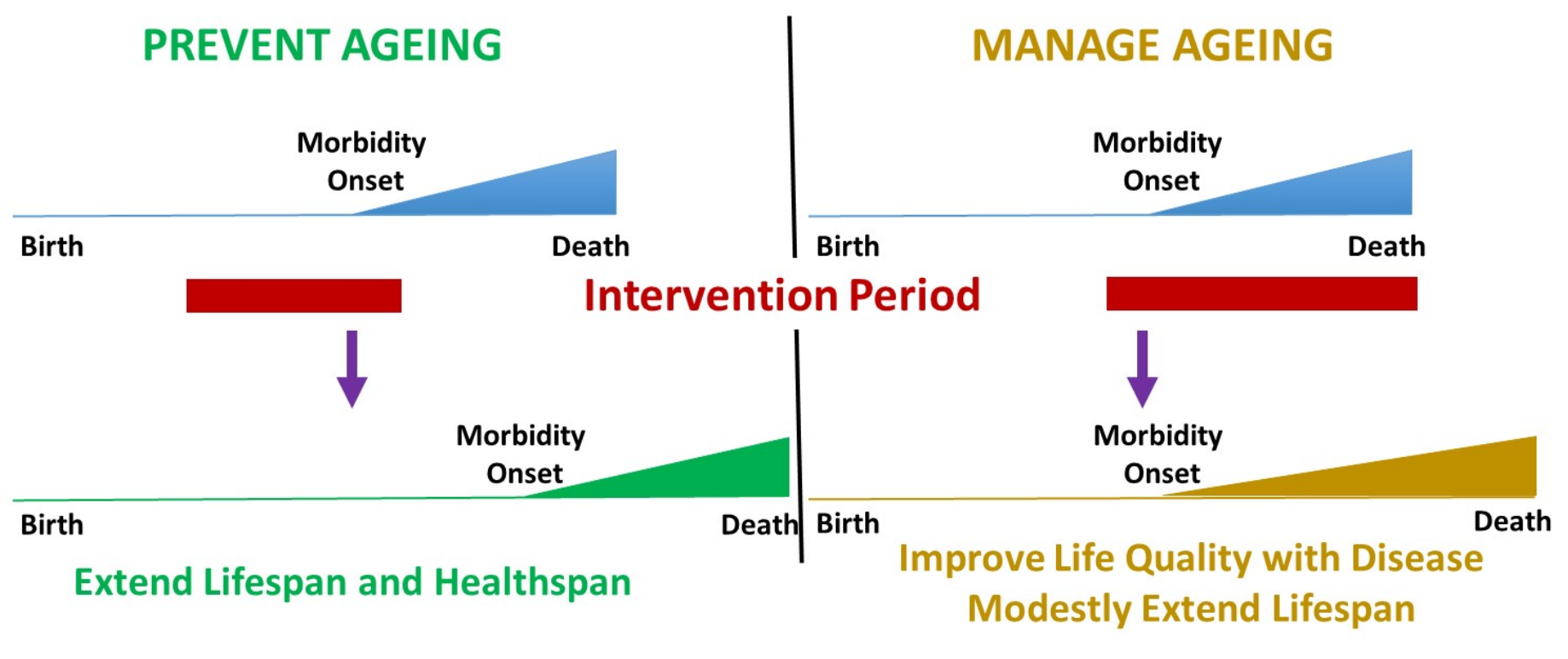
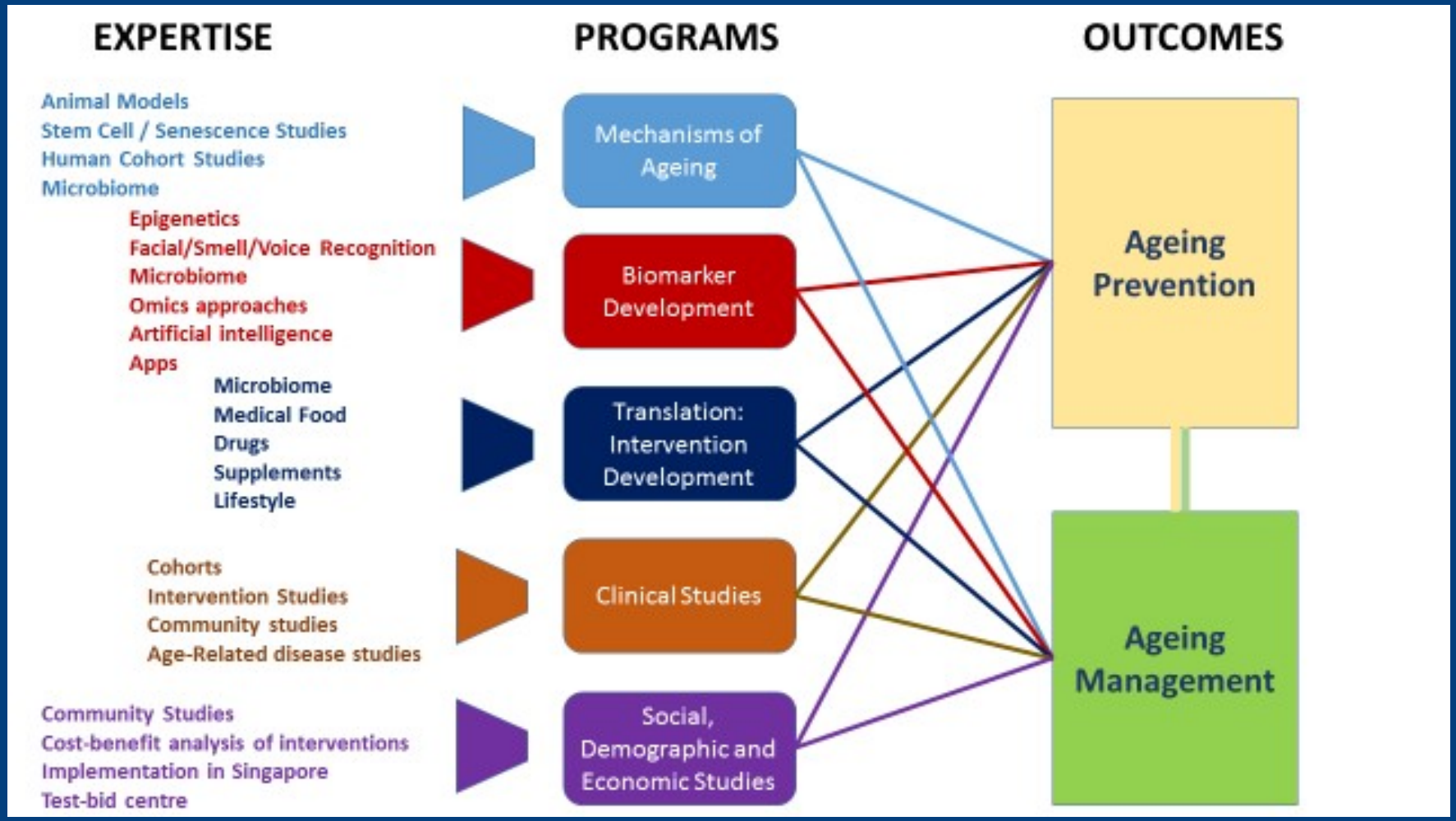
PREVENT AND MANAGE



CENTRE STRUCTURE



HEALTHSPAN INTERVENTION TRIALS

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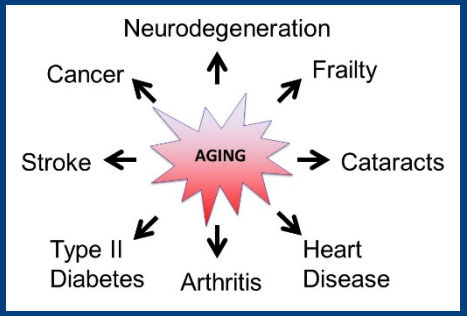
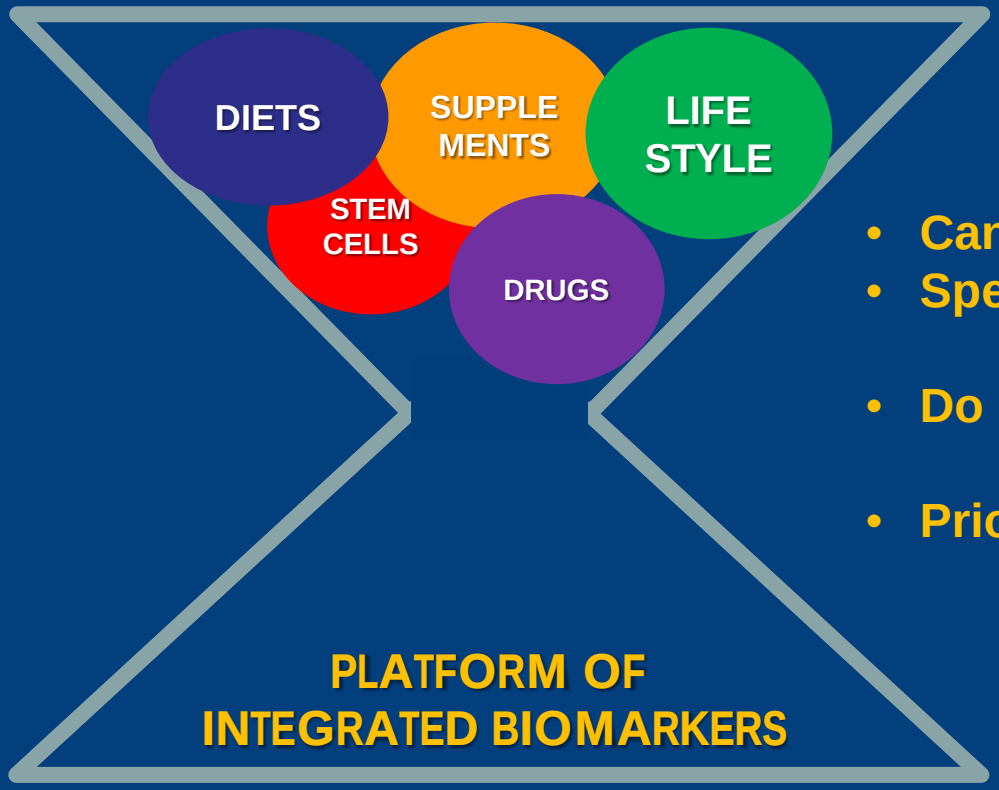
- **Short-term studies to stratify interventions**
  - **Biomarkers**
  - **50-65 years old**
  - **3 to 6 month interventions**

- **Medium-term studies**
  - **Multi-disease prevention**
  - **People at risk of chronic disease**
  - **1 to 3 year interventions**

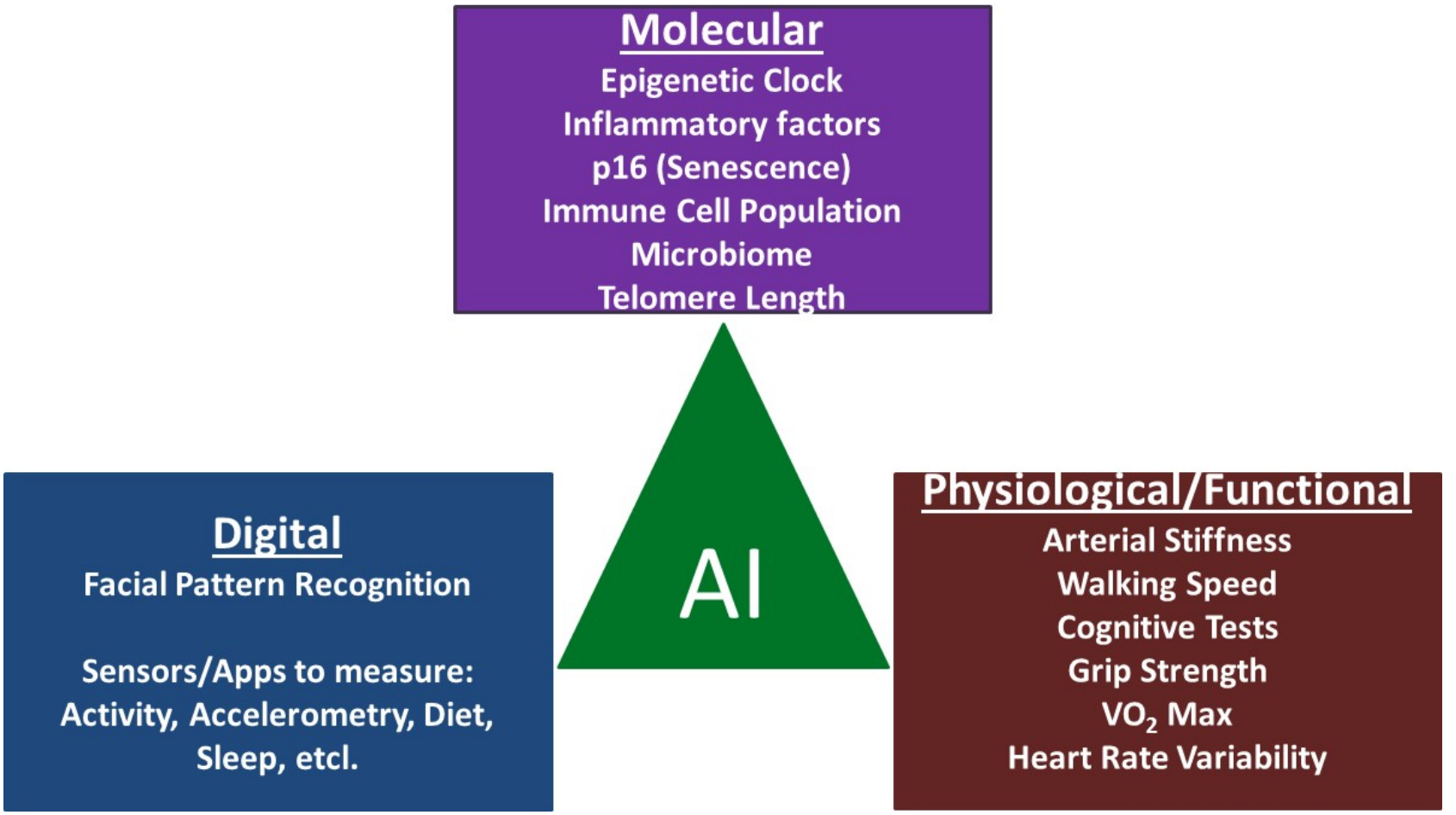


INTERVENTION TESTING

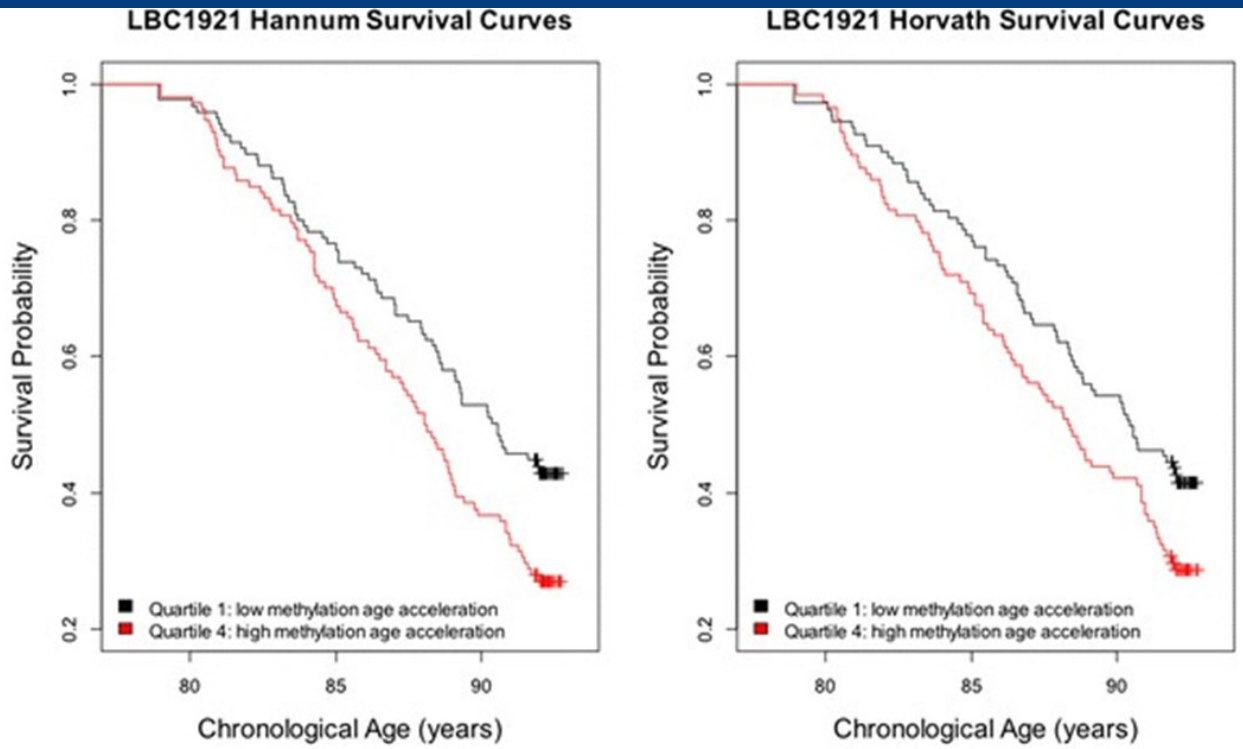


- Can ageing biomarkers be reversed?
- Specific intervention biomarker connections
- Do biomarkers relate to disease onset / functional parameters?
- Prioritization for large-scale studies

POSSIBLE BIOMARKERS



EPIGENETIC CLOCK PREDICTS MORTALITY



Genome Biol. 2015; 16(1): 25.

The association between Δ_{age} (DNA methylation-predicted age minus chronological age) and mortality was examined in four cohorts: Lothian Birth Cohort 1921 (LBC1921) (N = 446, n_{deaths} = 292), Lothian Birth Cohort 1936 (LBC1936) (N = 920, n_{deaths} = 106), the Framingham Heart Study (FHS) (N = 2,635, n_{deaths} = 238), and the Normative Aging Study (NAS) (N = 657, n_{deaths} = 226).

LONG-LIVED MUTANTS HAVE A SLOW CLOCK

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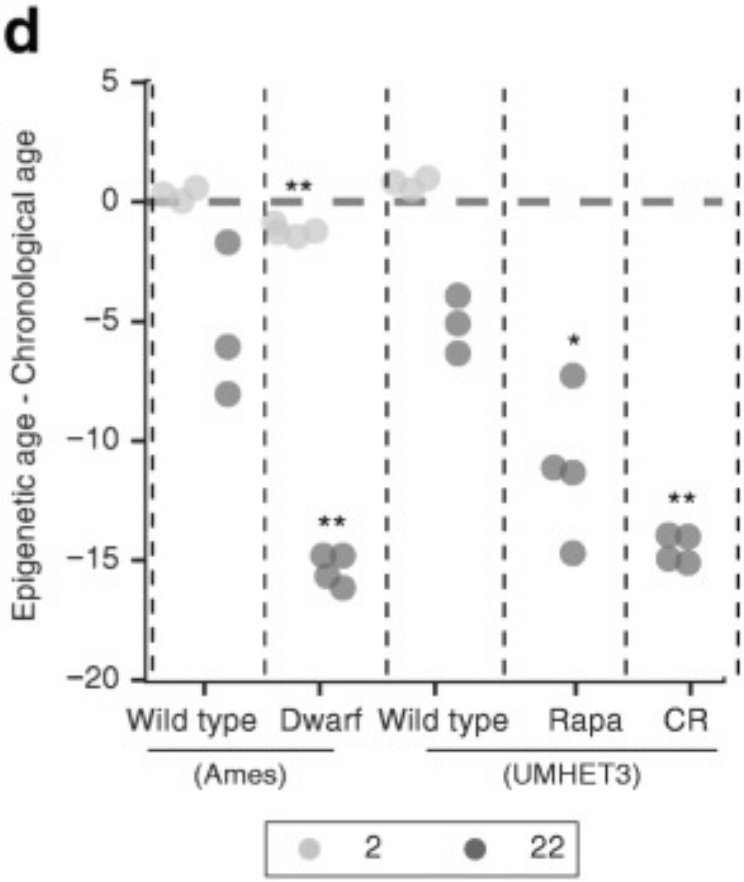


Wang et al. Genome Biology (2017) 18:57
DOI 10.1186/s13059-017-1186-2

Genome Biology

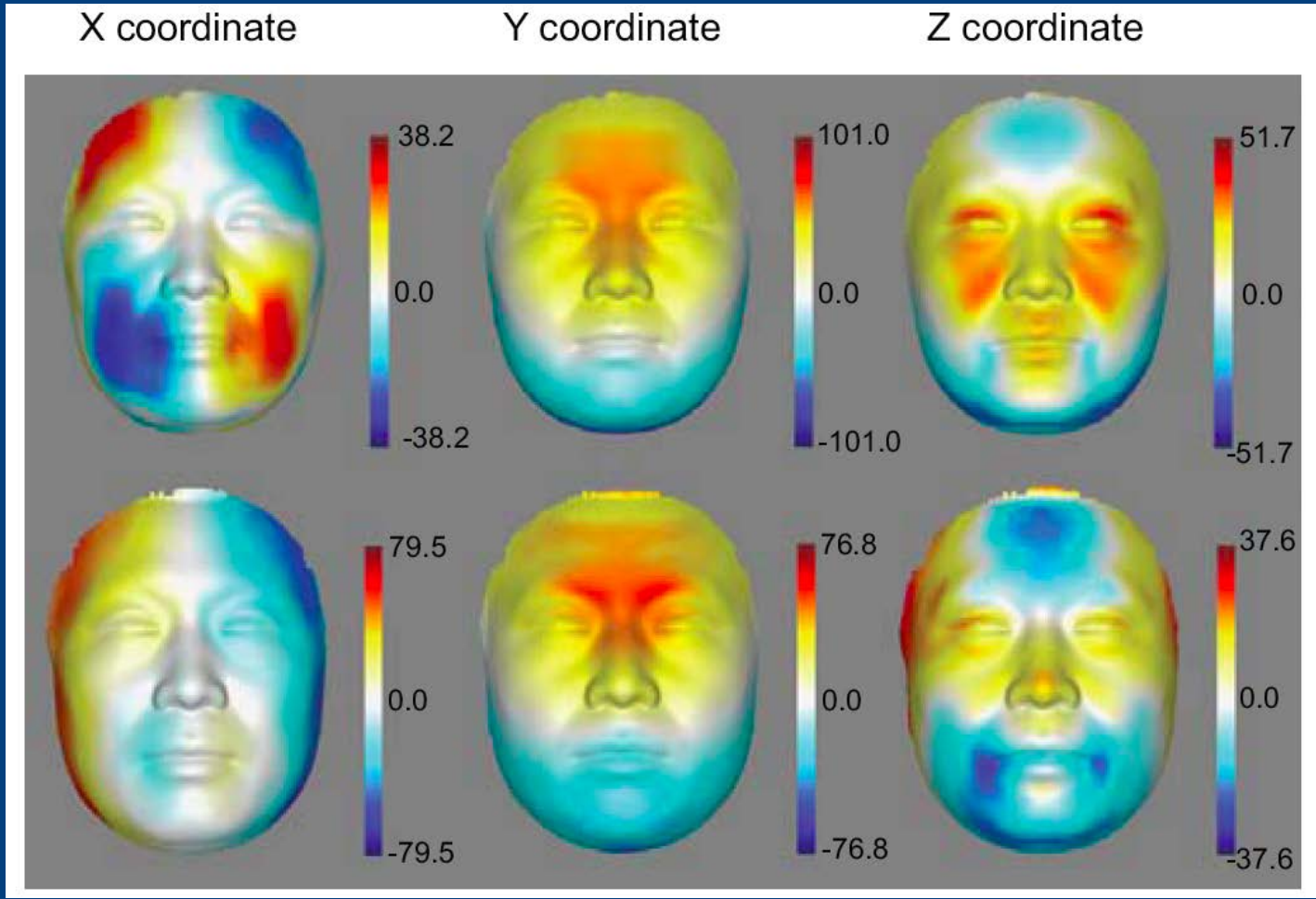
RESEARCH Open Access

Epigenetic aging signatures in mice livers are slowed by dwarfism, calorie restriction and rapamycin treatment

Tina Wang[1], Brian Tsui[1,5], Jason F. Kreisberg[1], Neil A. Robertson[2], Andrew M. Gross[1,5], Michael Ku Yu[1,5], Hannah Carter[1,5], Holly M. Brown-Borg[3], Peter D. Adams[2,4] and Trey Ideker[1*]

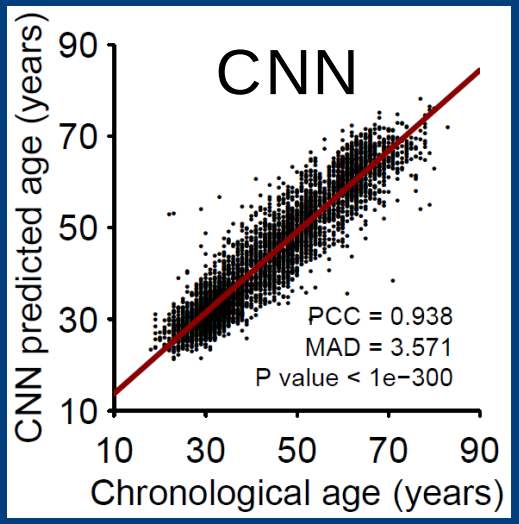
PREDICTING AGE FROM 3D FACIAL PATTERN

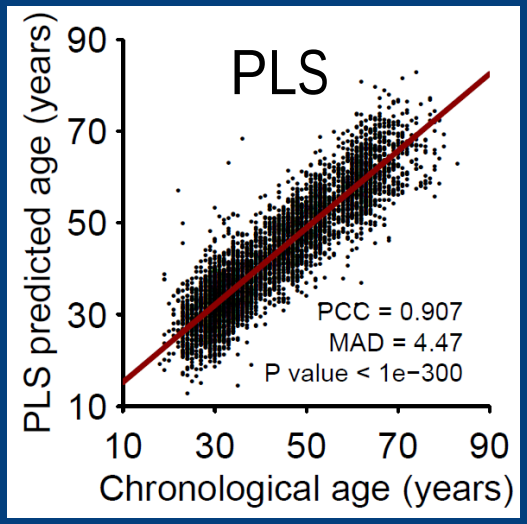
Jackie HAN
PICB, Shanghai

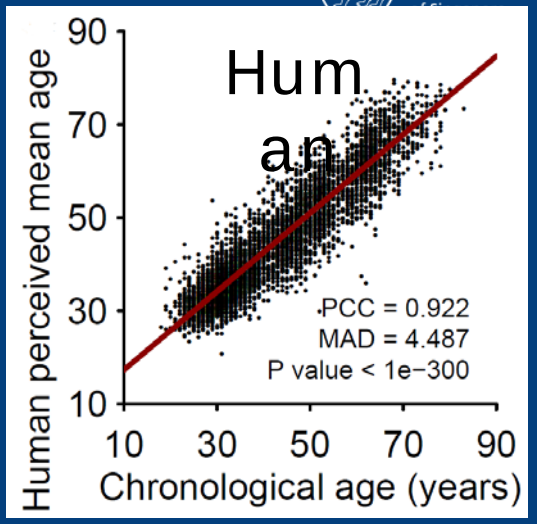


Chen *et al*, Cell Research, 2015

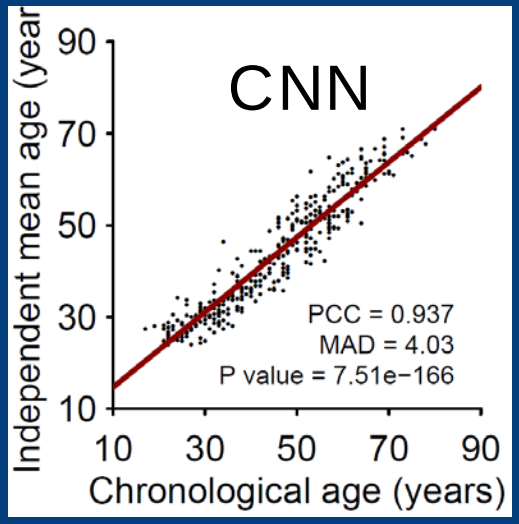
DEEP CNN ACCURATELY PREDICTS AGE

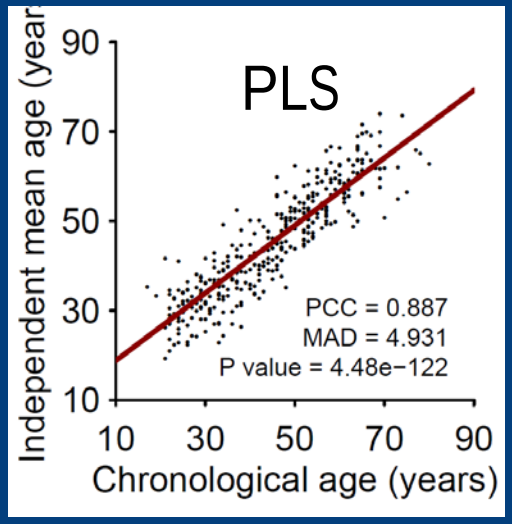






Independent validation with Beijing CDC corhort





AVERAGE FACES OF DIFFERENT DISEASES

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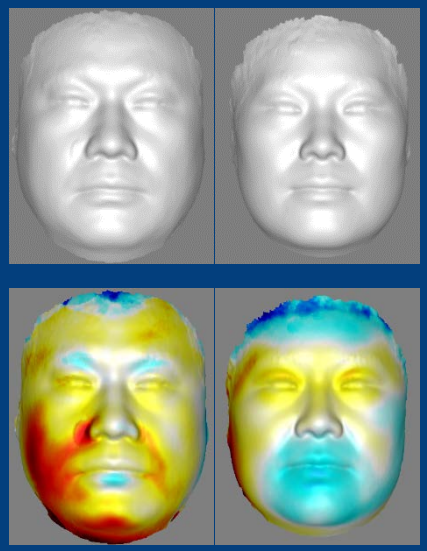
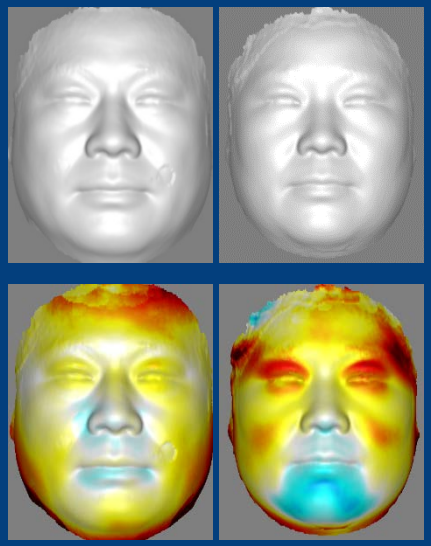
Healthy male and female

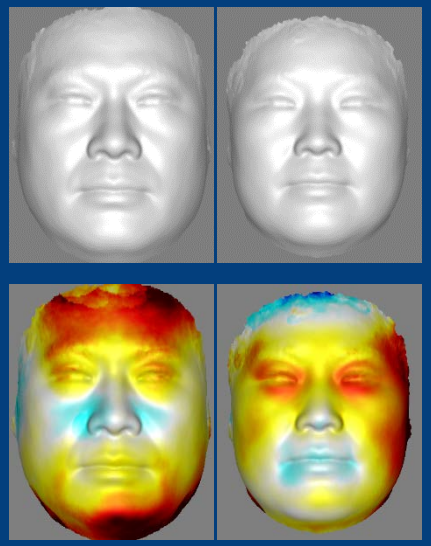
Diseases > 200 cases



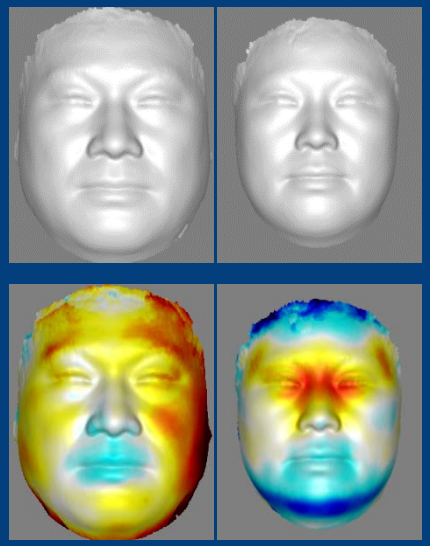
Hypertension



Diabetes

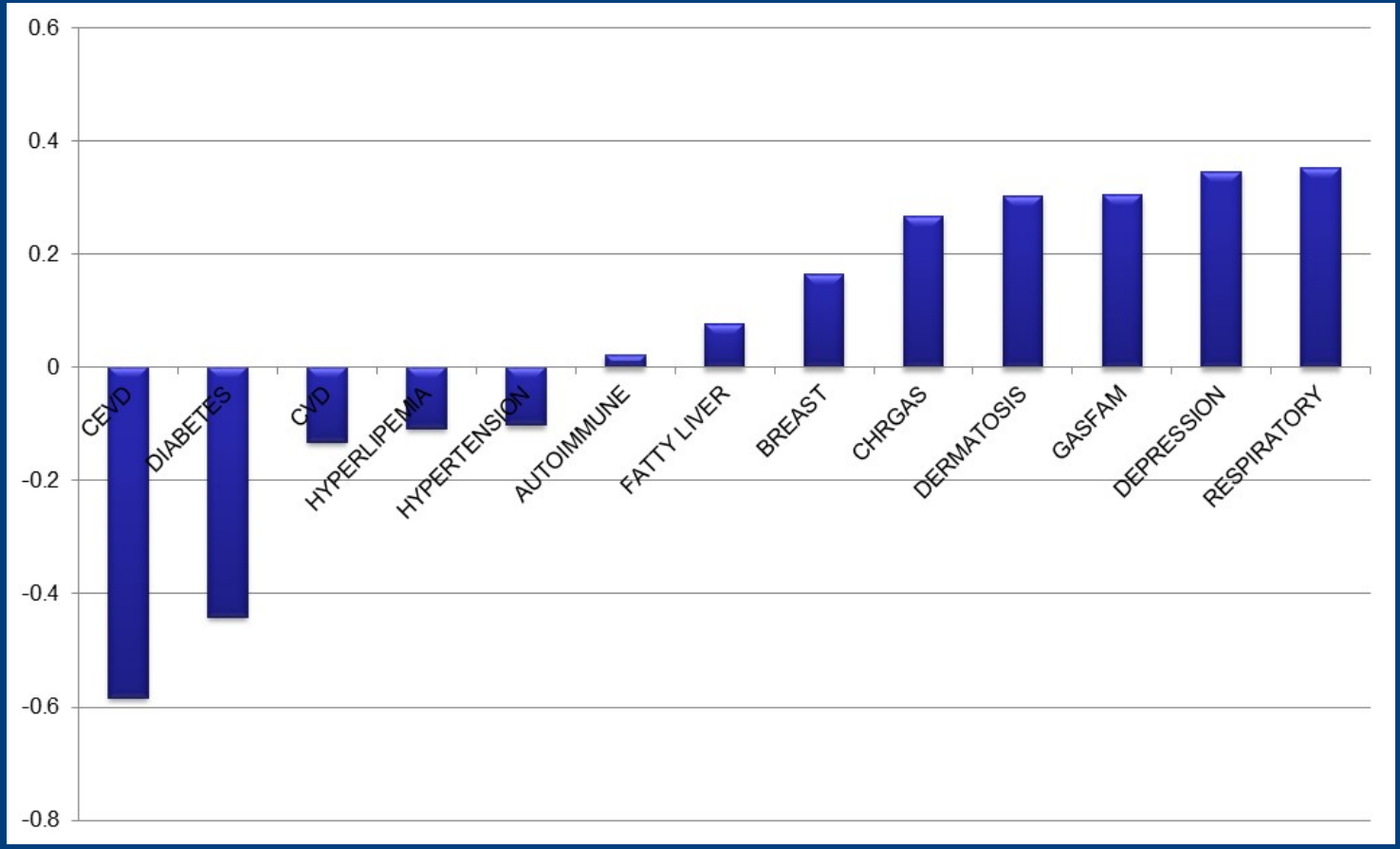


Depression



CVD

DISEASE-INDUCED AGE DIFFERENCE



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