

Blood Proteins as Indicators and Modifiers of Brain Function

Research Advisory Committee on Gulf War Veterans' Illnesses
San Francisco Medical Center, August 8, 2016



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Disclosure

Founder and Director of the Scientific Advisory Board
of Alkahest Inc., a company developing blood based treatments for age-related diseases

How can we study brain disease?

Healthy



Genes
Environment
Aging



Disease



How can we study brain disease?

Healthy



Genes
Environment
Aging



Disease



Neuropsychometric testing
Imaging
Postmortem analysis

Communication between CNS and Periphery

headache
sickness feeling
negative affect
memory impairment
neuroinflammation



increased memory and
learning function
positive outlook
neurogenesis



A "cold"



physical
exercise

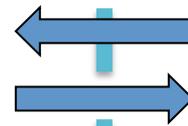
Peripheral biomarker hypothesis

CNS

BBB

Periphery

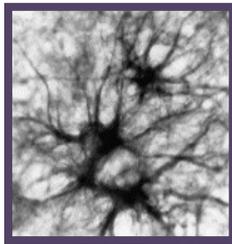
Cellular, molecular and functional changes in **brain**



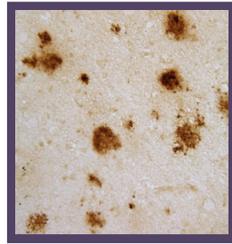
Cellular, molecular changes in **periphery**



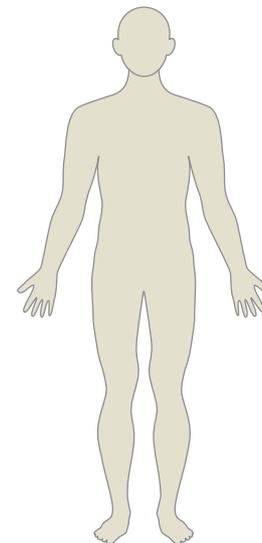
Tangles



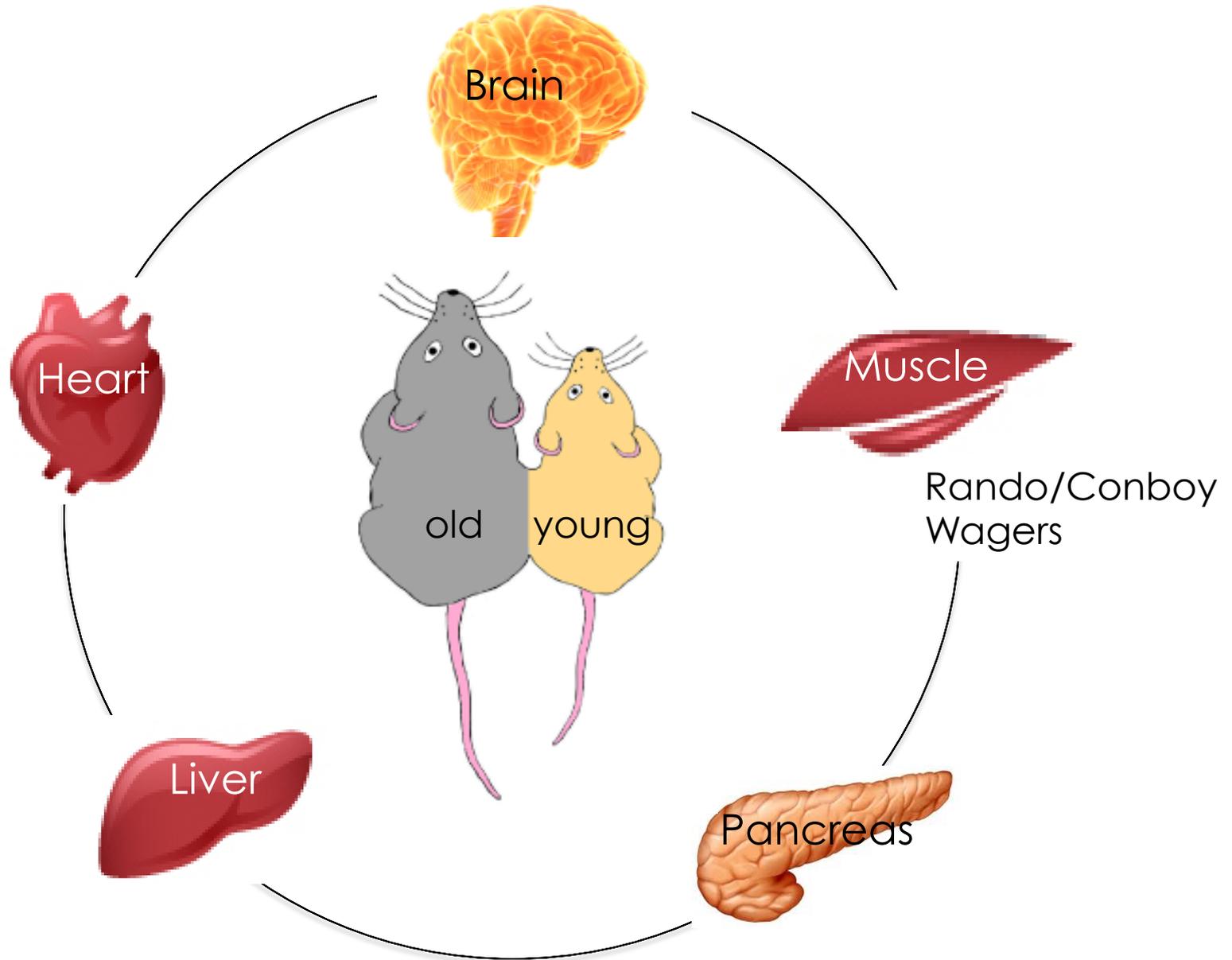
Gliosis



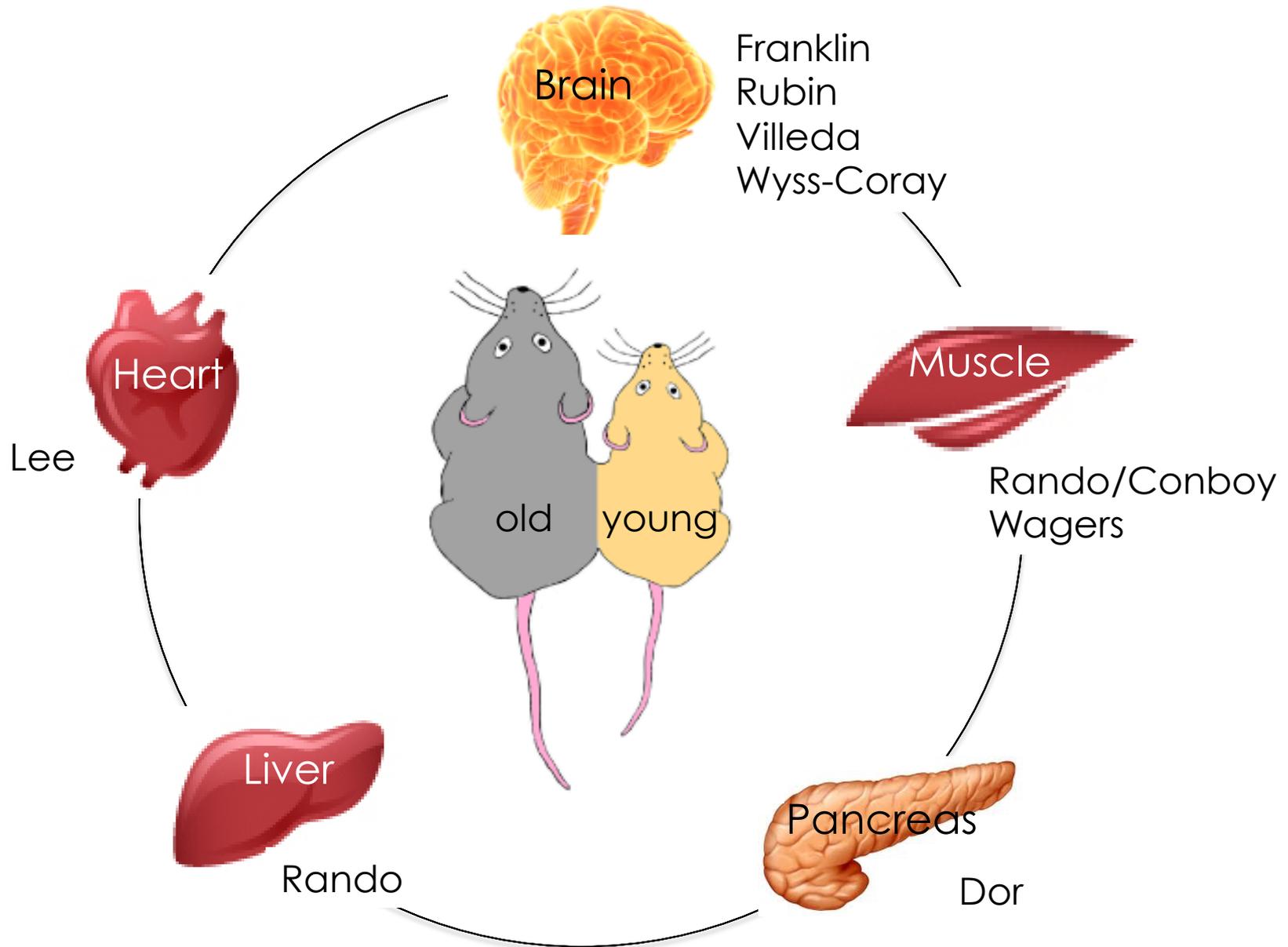
Amyloid deposits



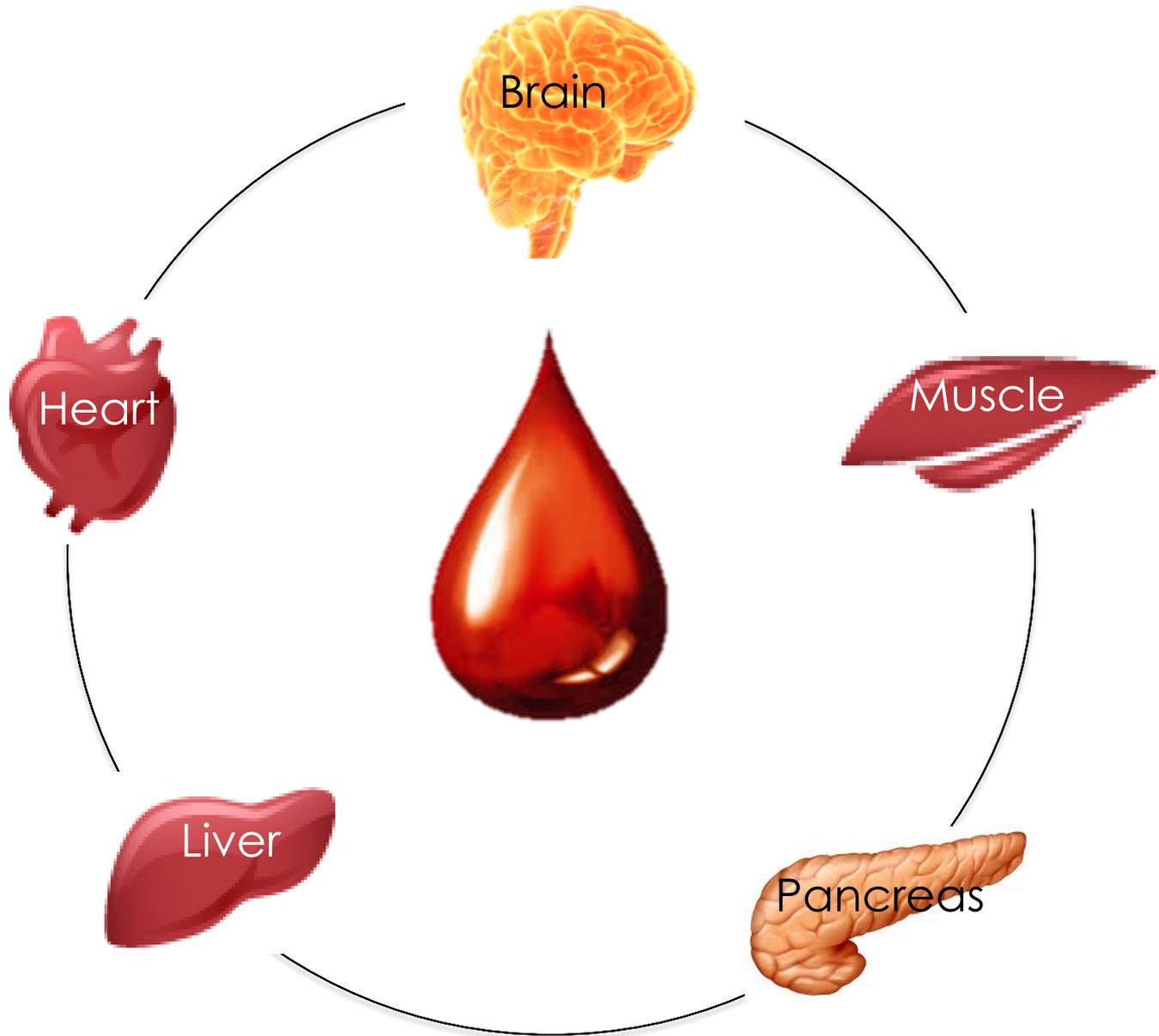
Multiple old tissues rejuvenated in mouse



Multiple old tissues rejuvenated in mouse

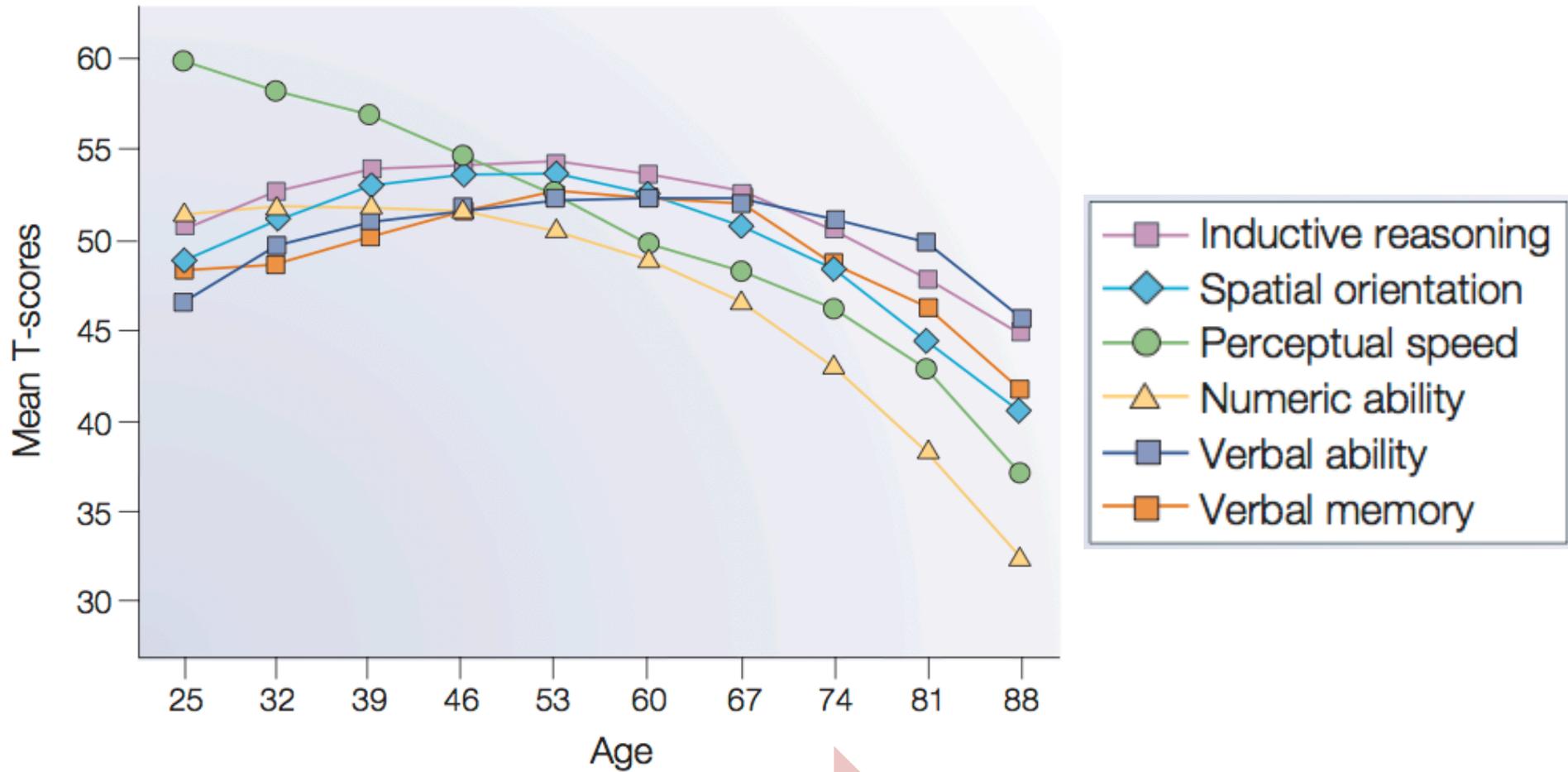


Blood connects all organs

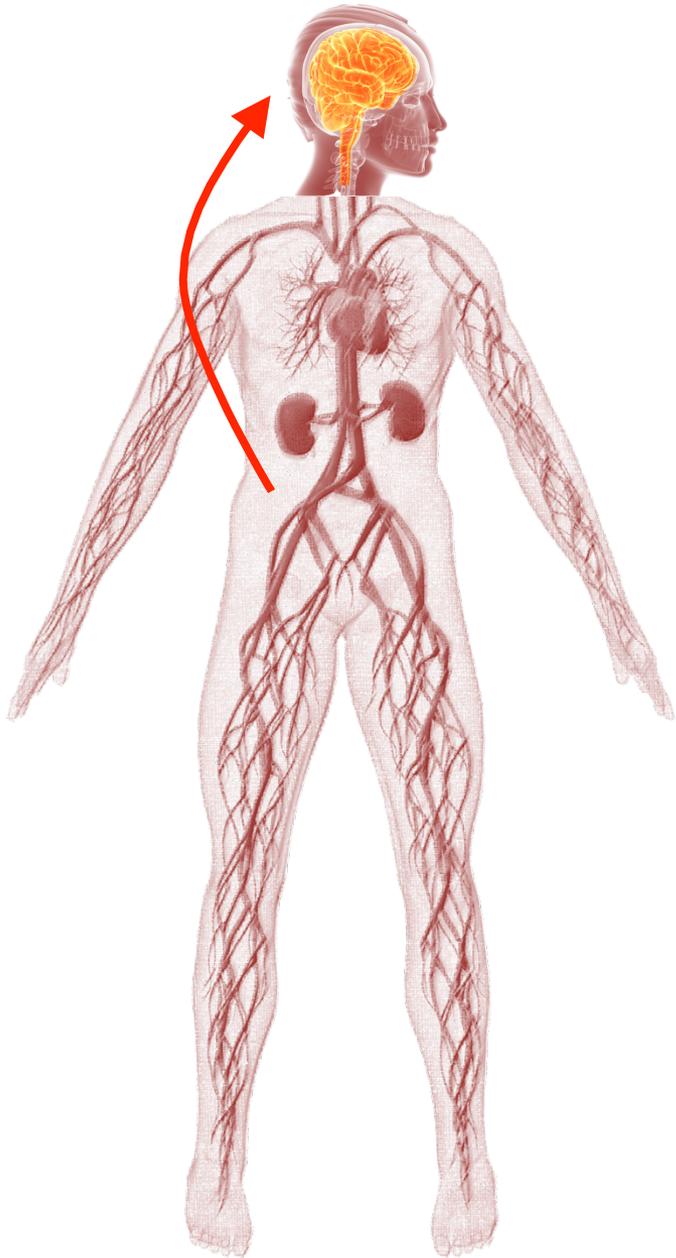


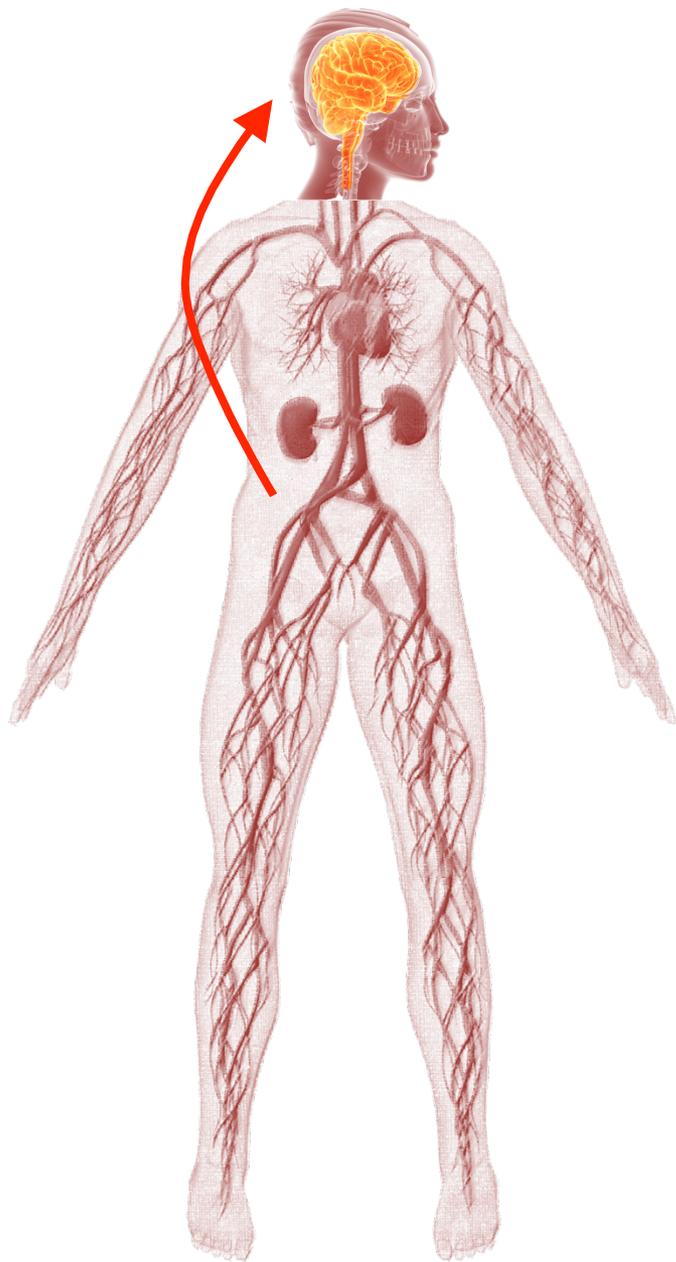
**Can we use this concept to study
cognitive aging**

Aging

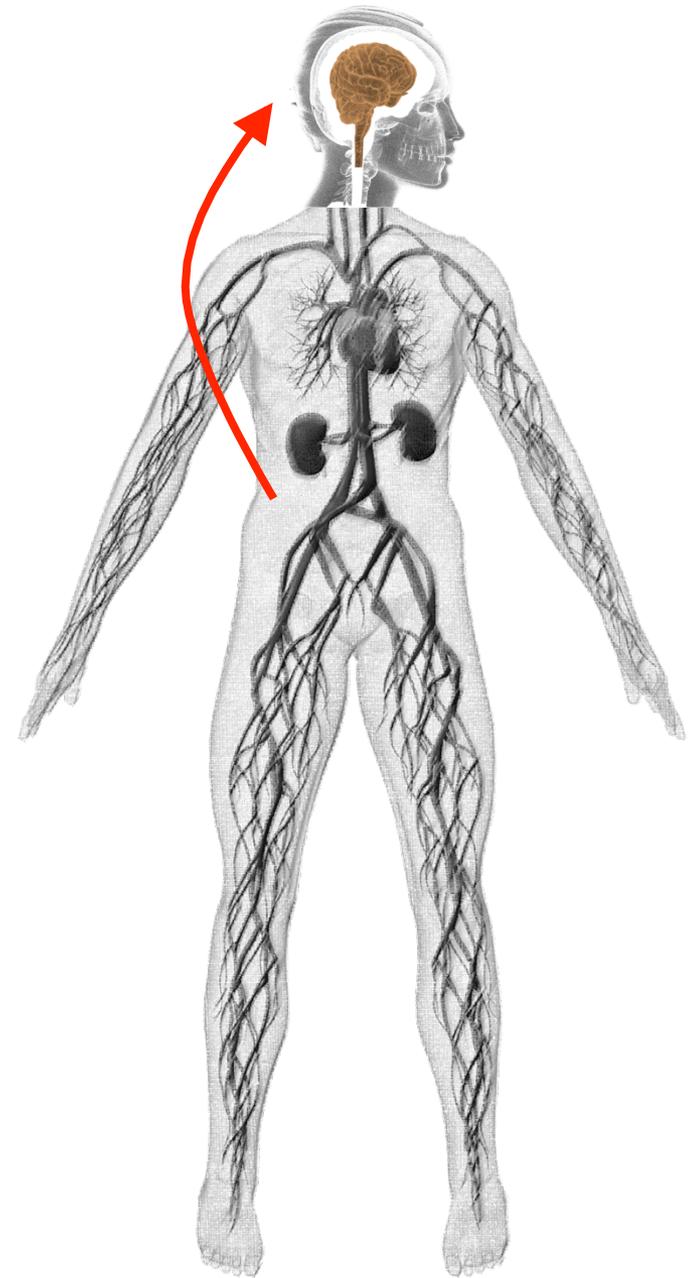


Loss in Cognition



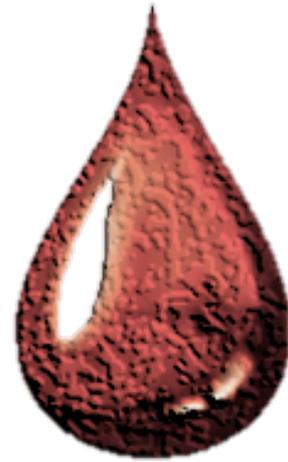


Age

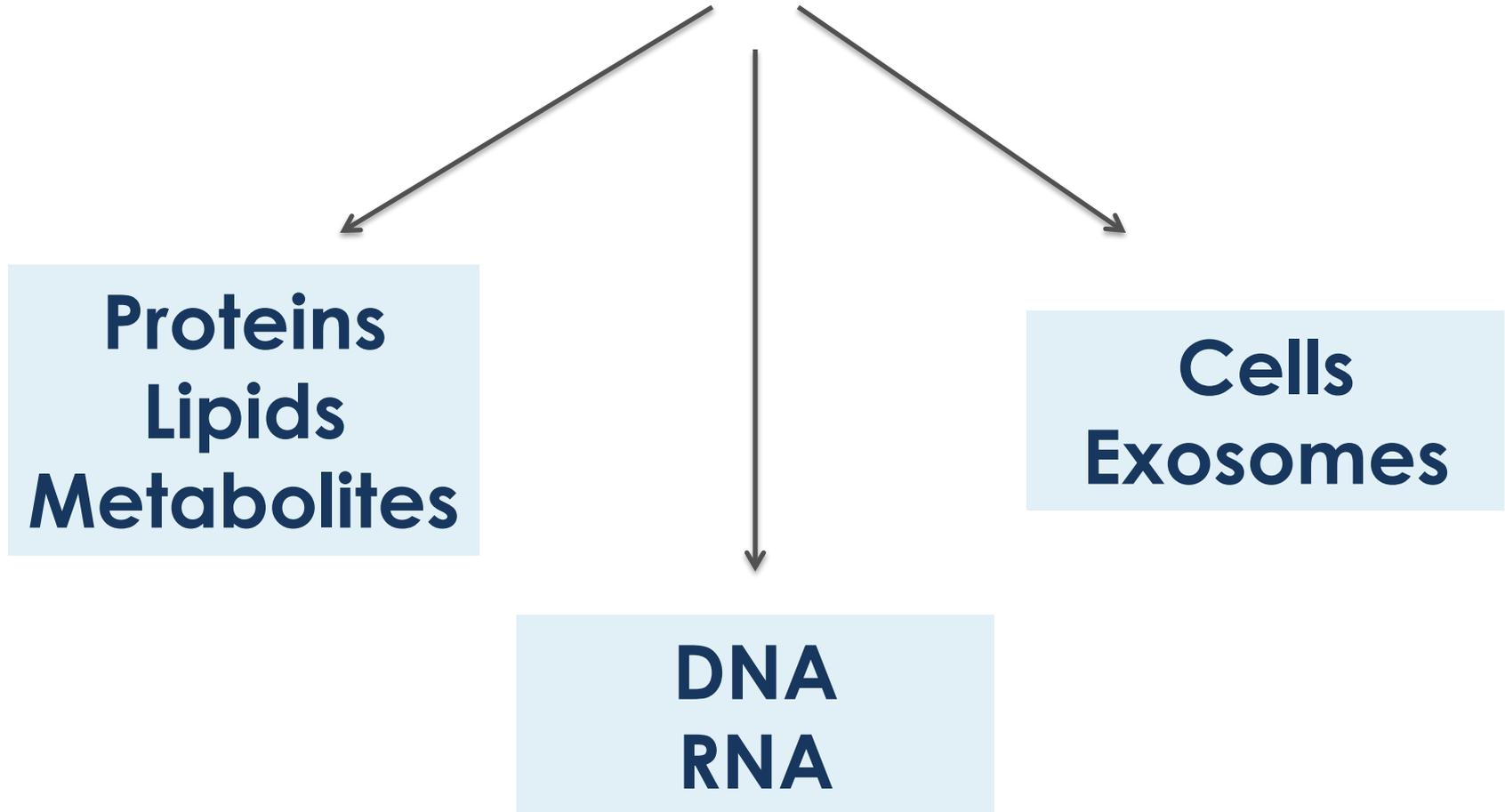




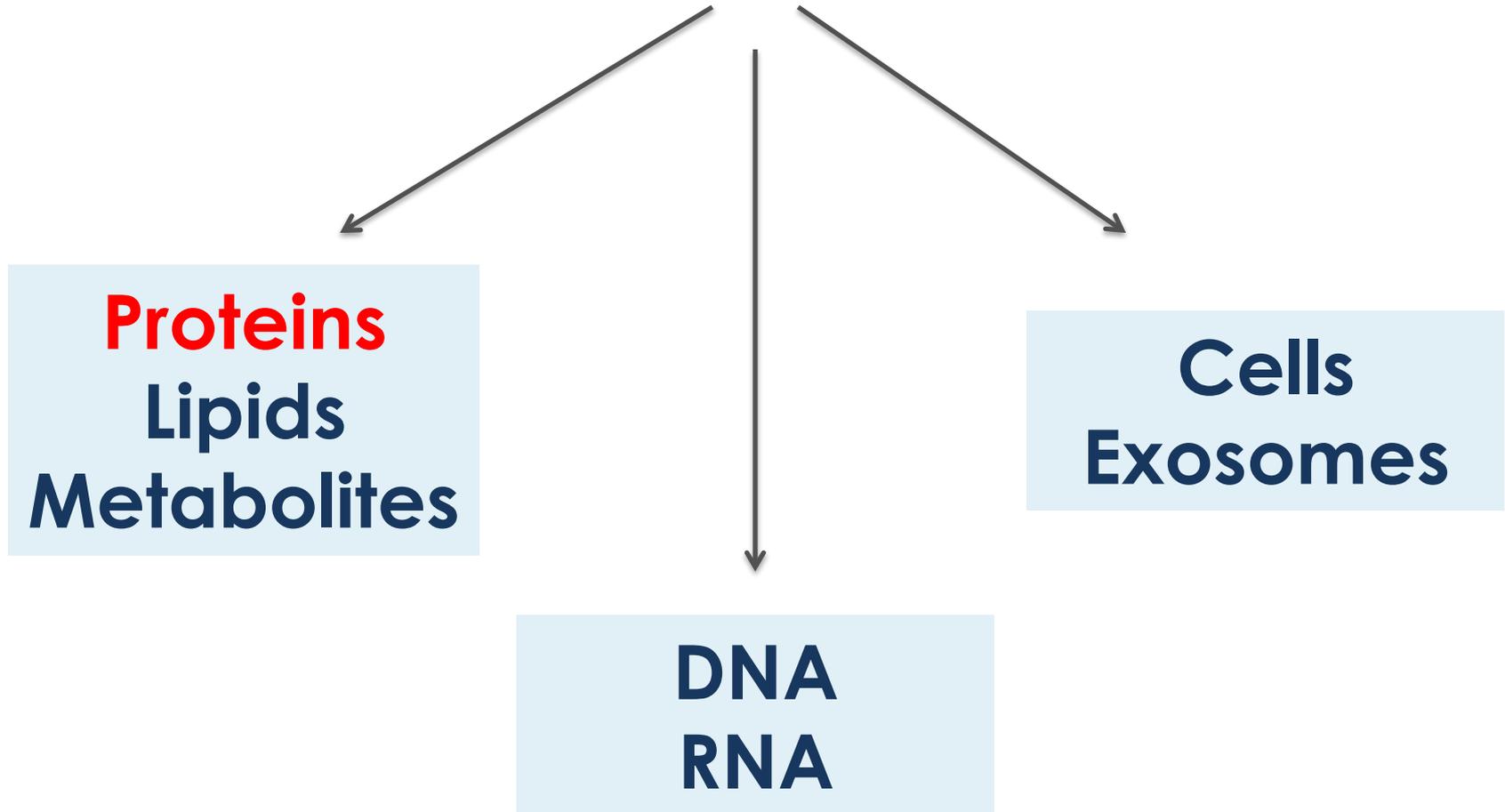
Age



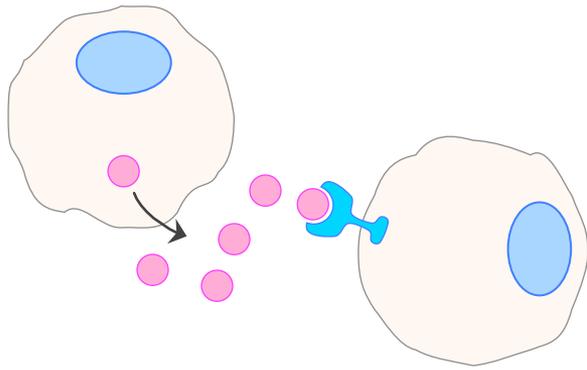
Systemic cellular and molecular changes in the periphery/blood



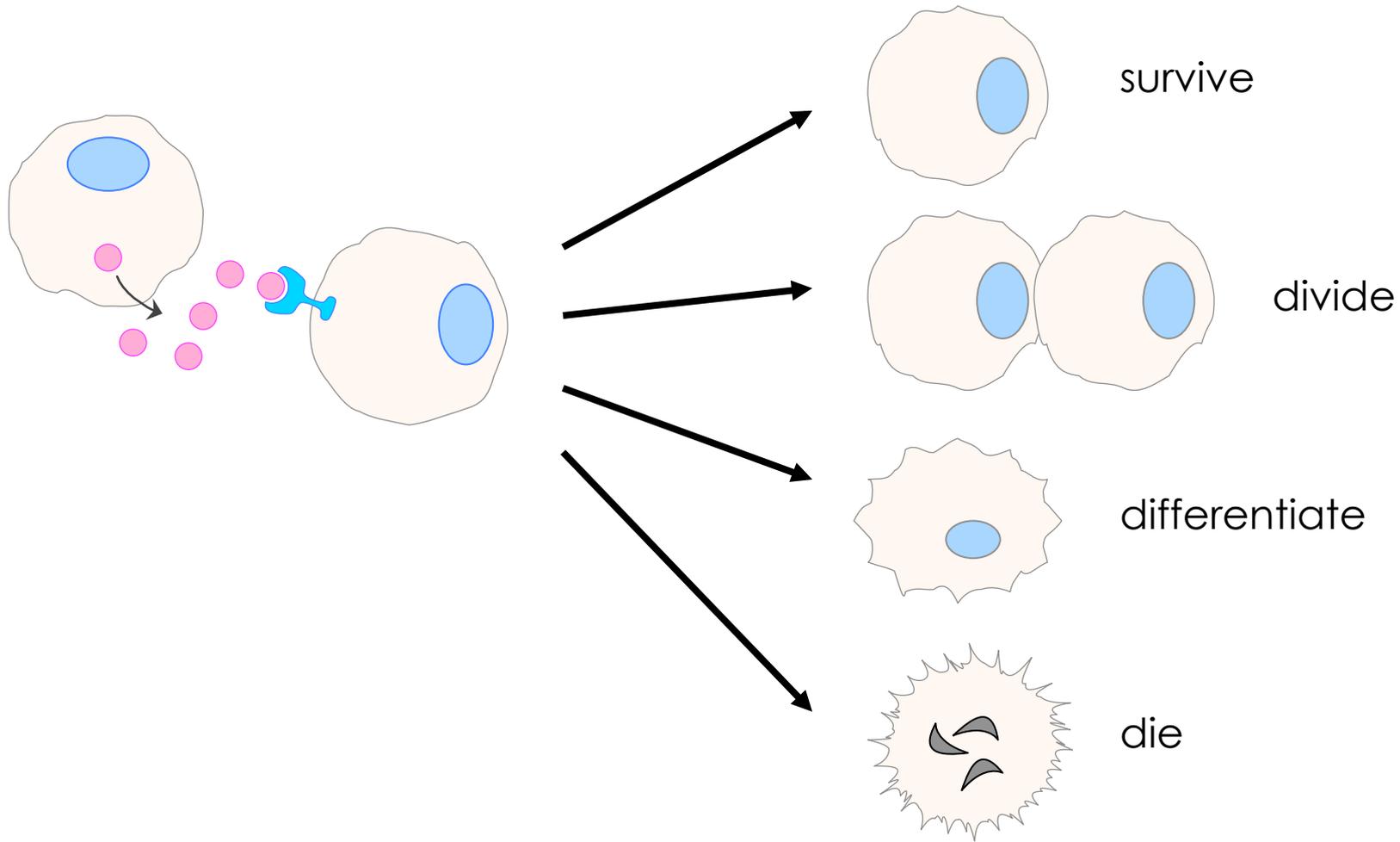
Systemic cellular and molecular changes in the periphery/blood



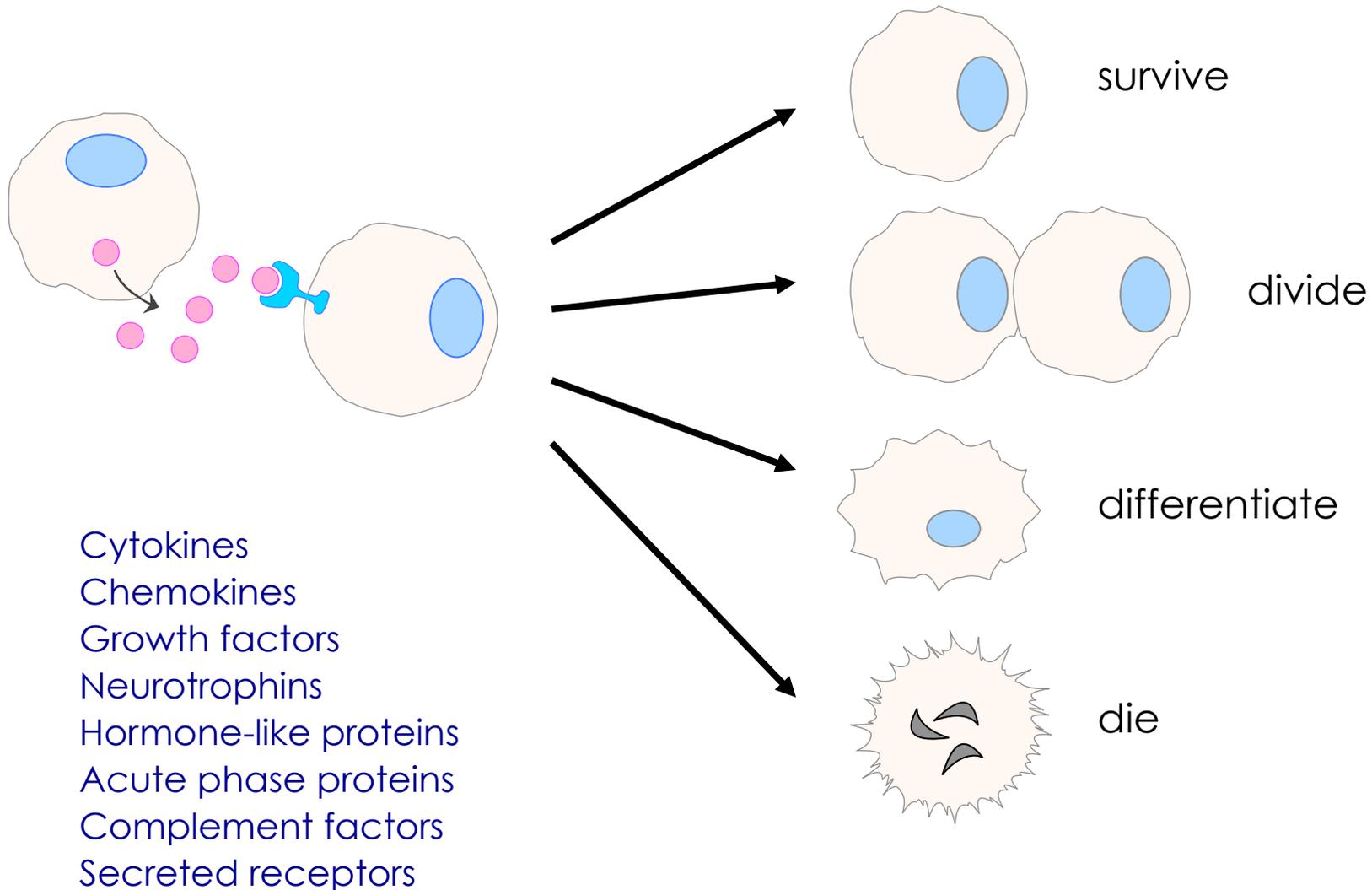
The proteome of cellular communication: the “communicome”



The proteome of cellular communication: the “communicome”



The proteome of cellular communication: the “communicome”



A blood-based signature of normal aging

295 human blood samples (20-89 years)



Measure >100 hormone-like proteins

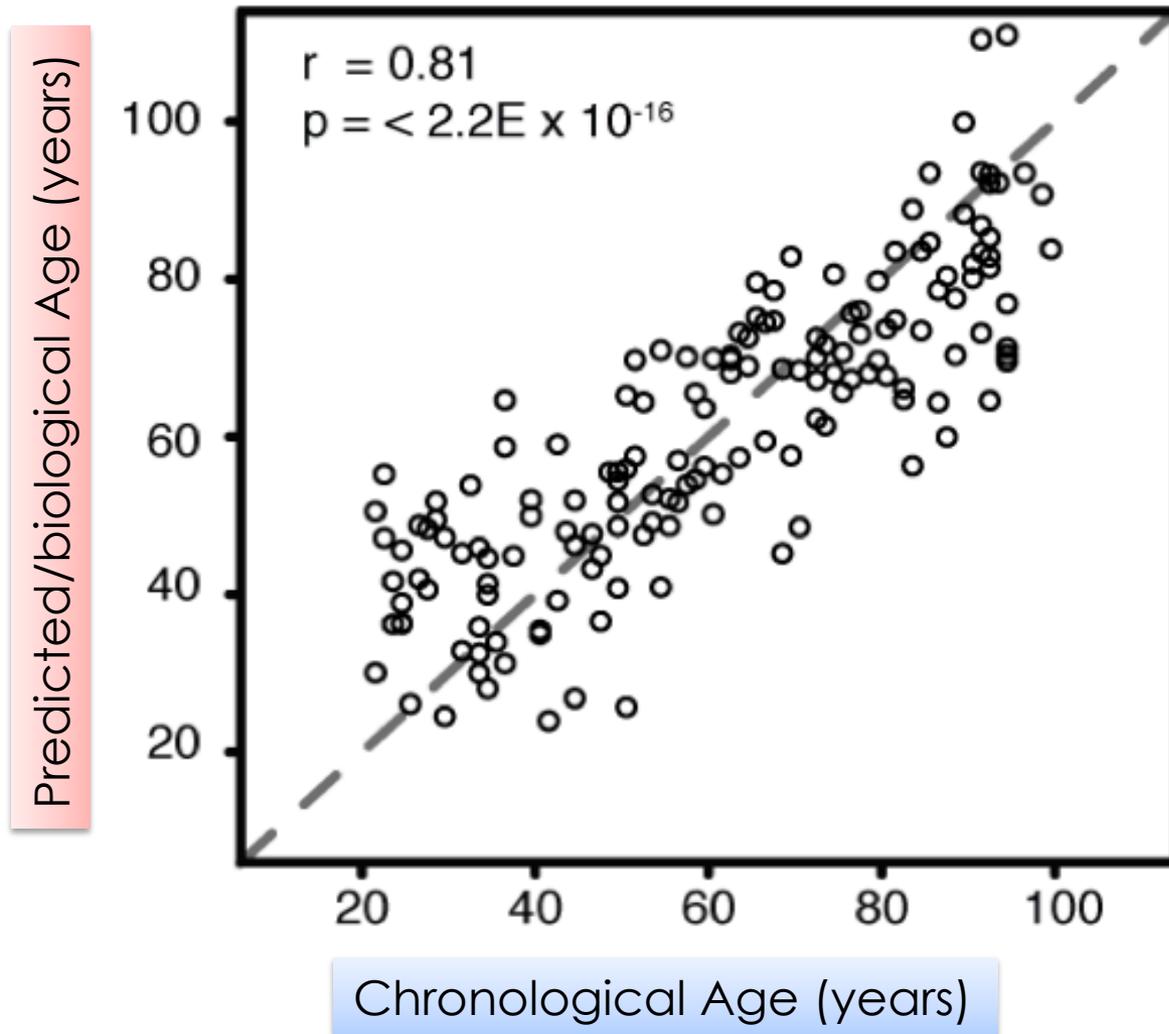


Discover protein signature of aging

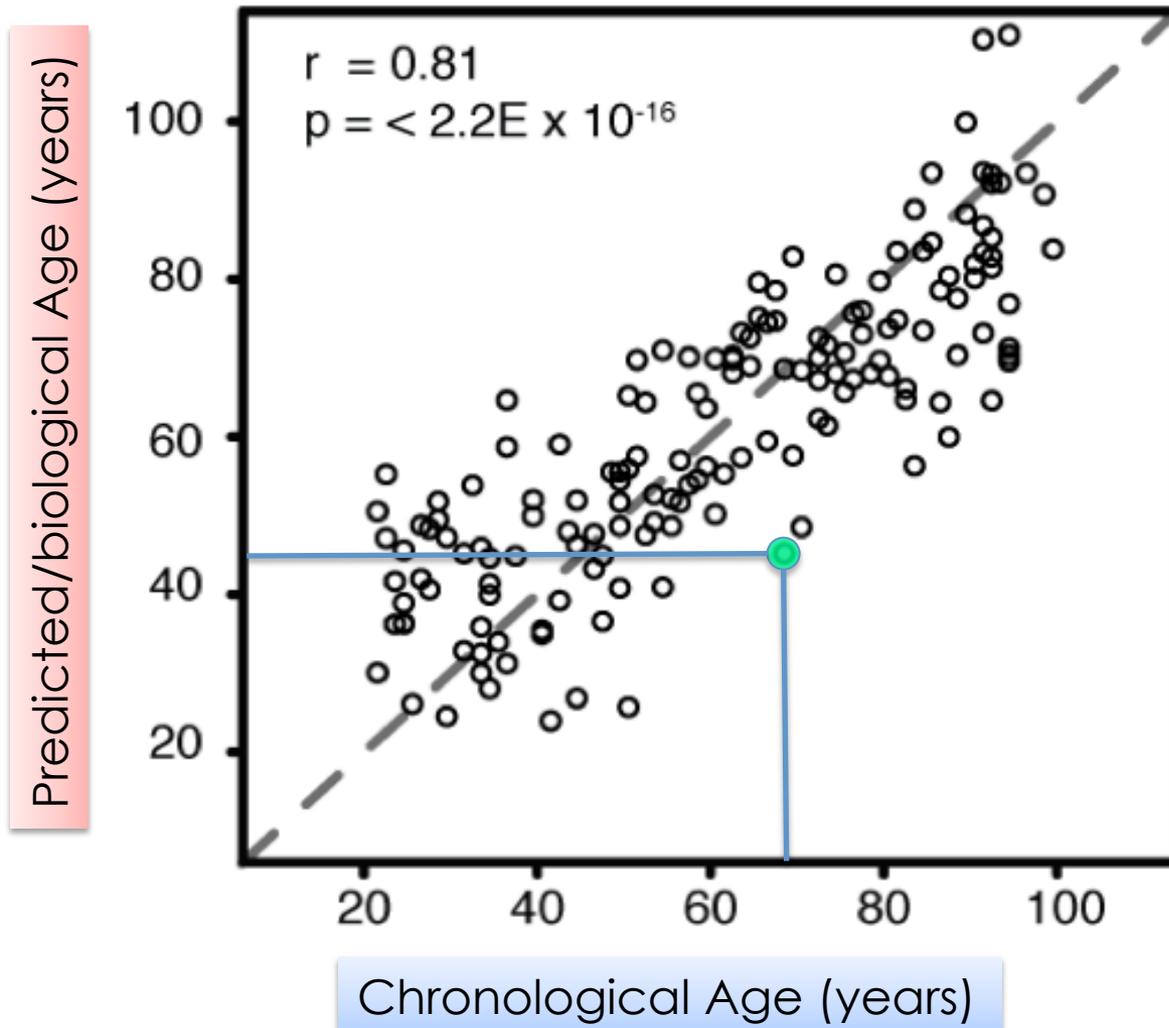


- 9 correlate highest with age
- 44 significantly changed between age groups 20-44 and 75-88 years

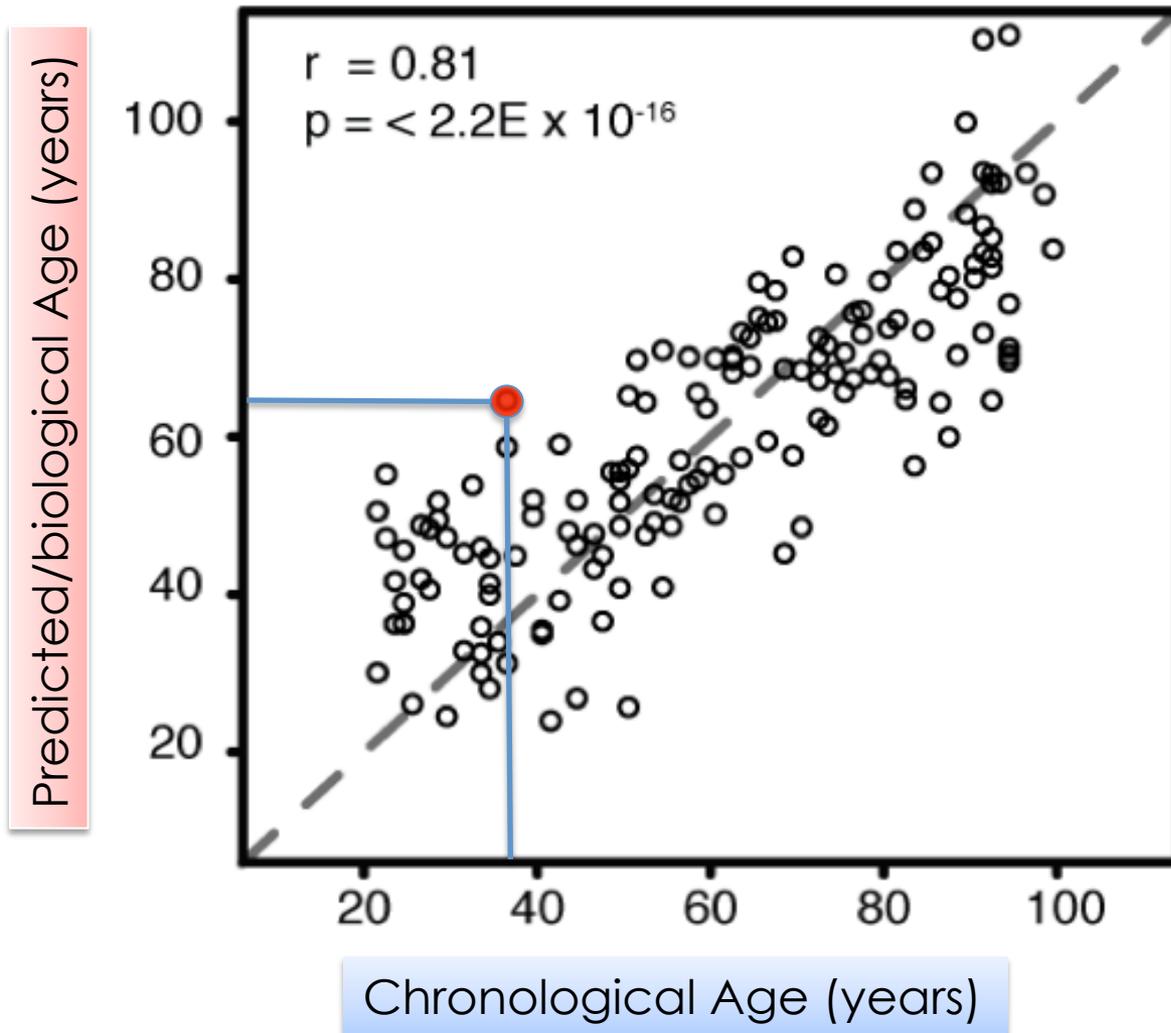
Prediction of “Biological Age” using top aging factors in human



Slowed biological aging ?

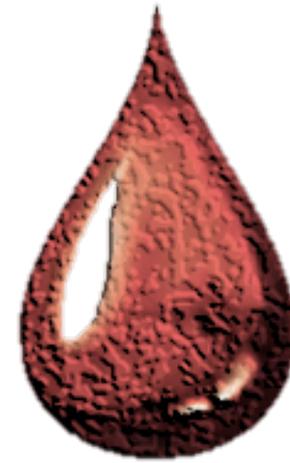


Accelerated biological aging?





Age



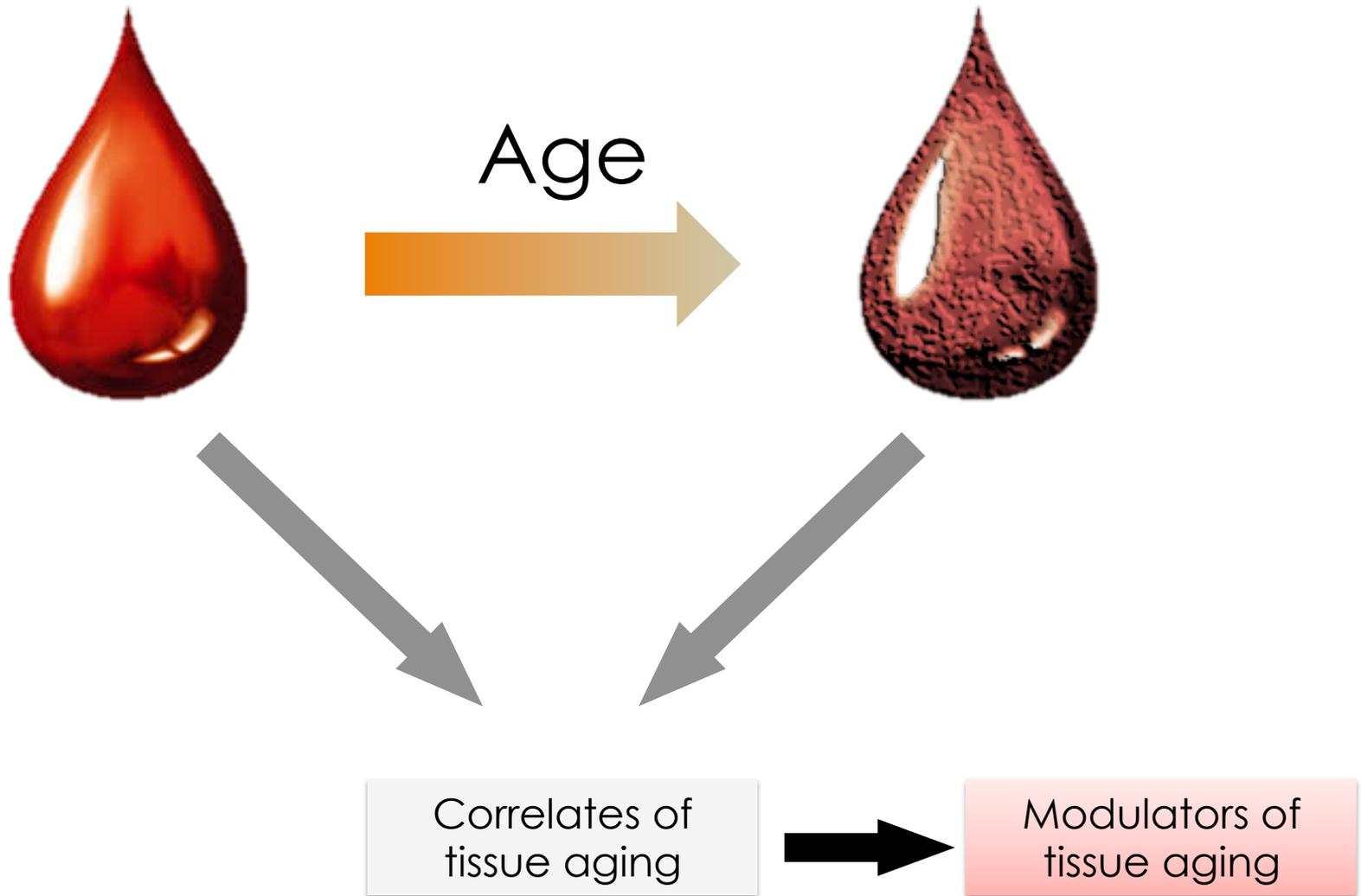
Growth and survival factors



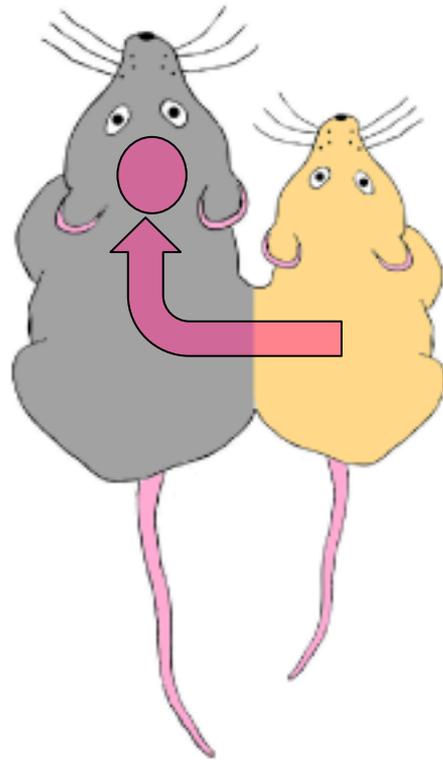
Inflammatory factors



Does blood regulate aging?



How does a young systemic environment affect the old brain?



18-month-old mouse
~
65-year-old human

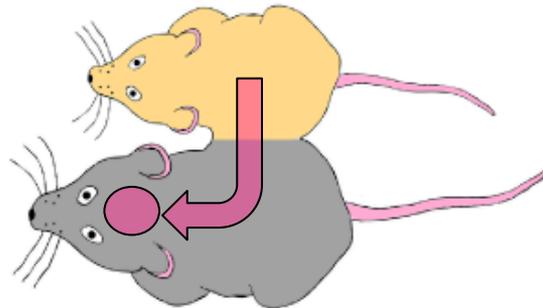
3-month-old mouse
~
20-year-old human

Old = Young

Effects: “rejuvenation”

- increased neurogenesis
- increased synaptic activity
- increased plasticity-related gene expression
- increased spine density
- improved memory
- attenuation of microglia reactivity

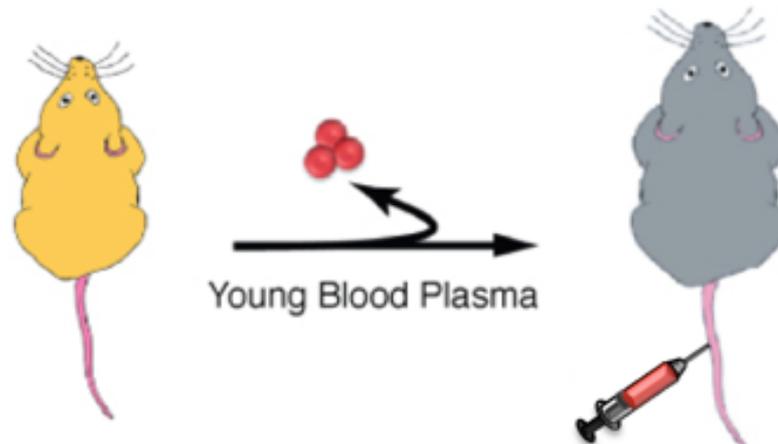
Parabiosis



Effects of a young systemic environment on the old brain: “rejuvenation”

- more neural stem cell activity
- higher synaptic activity
- higher levels of genes involved in memory
- less inflammation in the brain
- improved memory

Plasma transfer

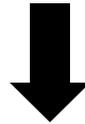


Administration of human plasma to aged mice

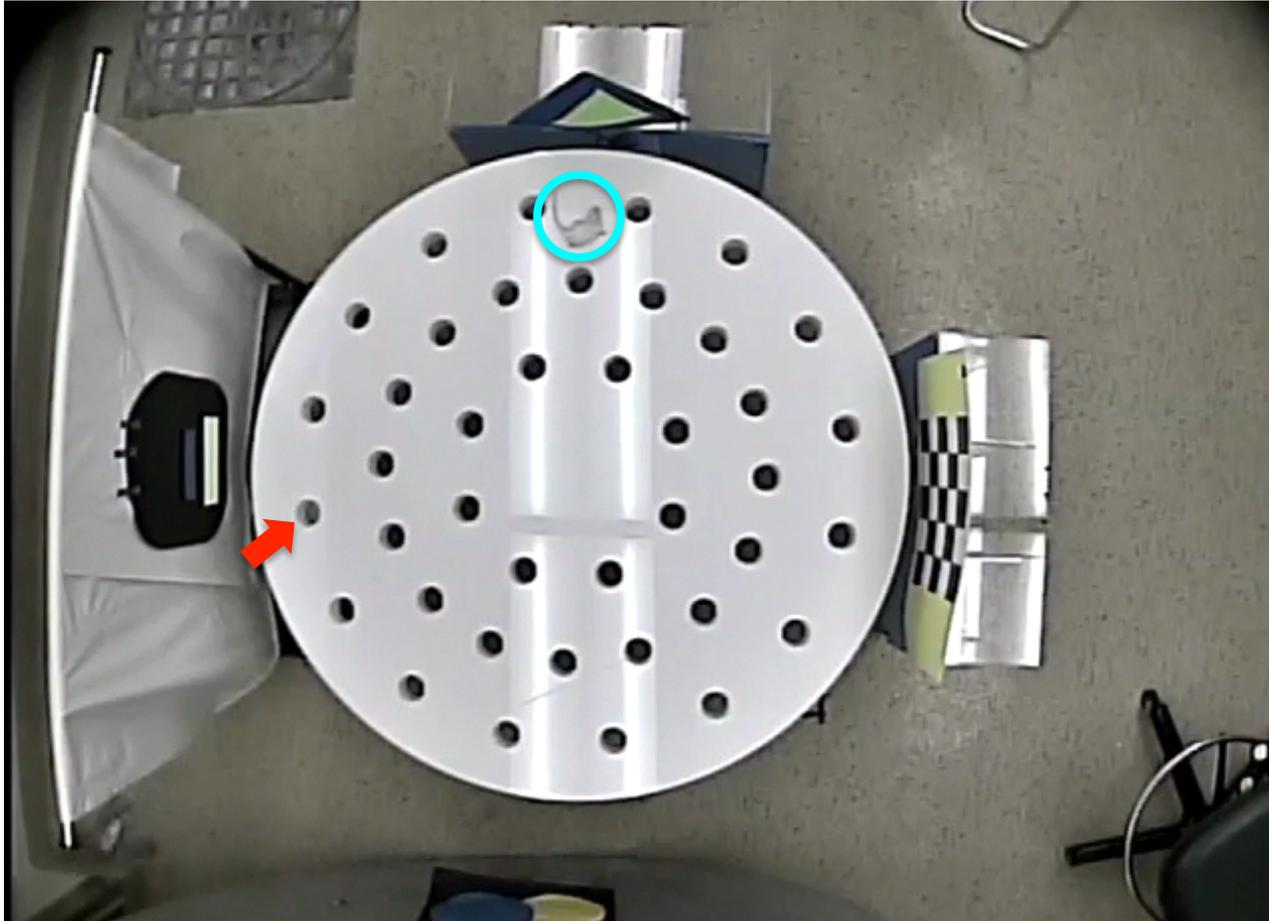
Saline



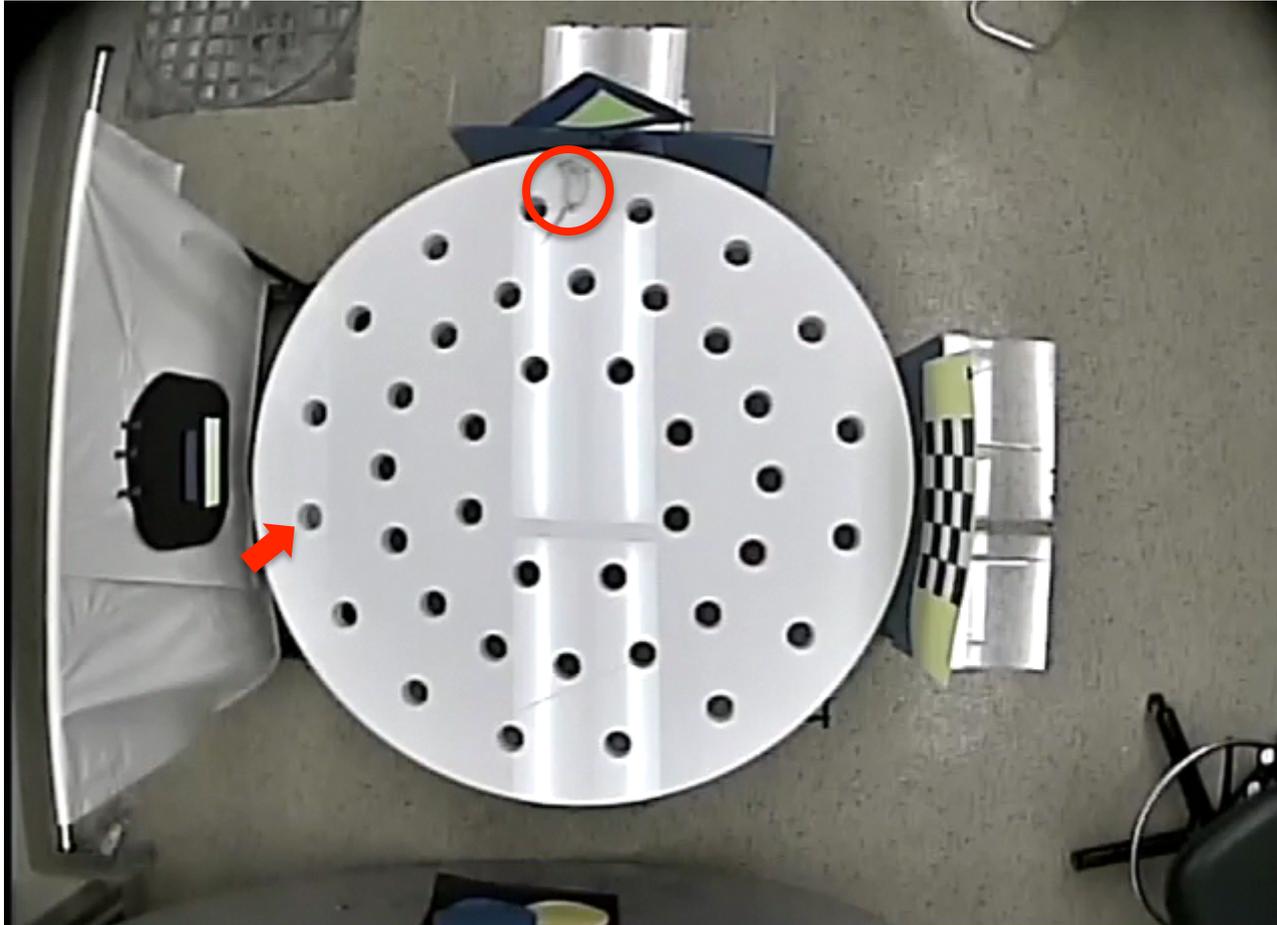
Human cord plasma



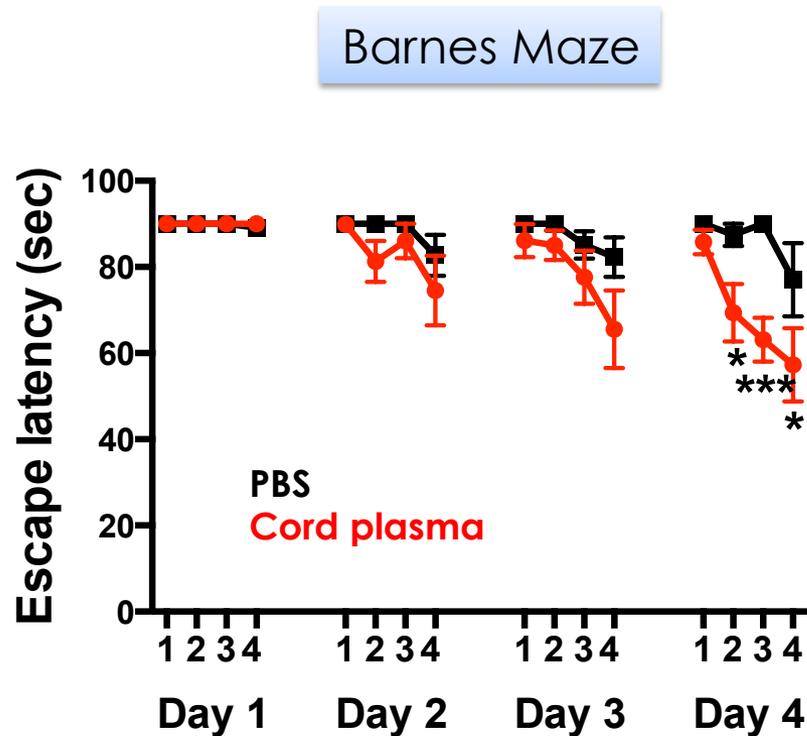
Old mouse with saline



Old mouse with cord plasma



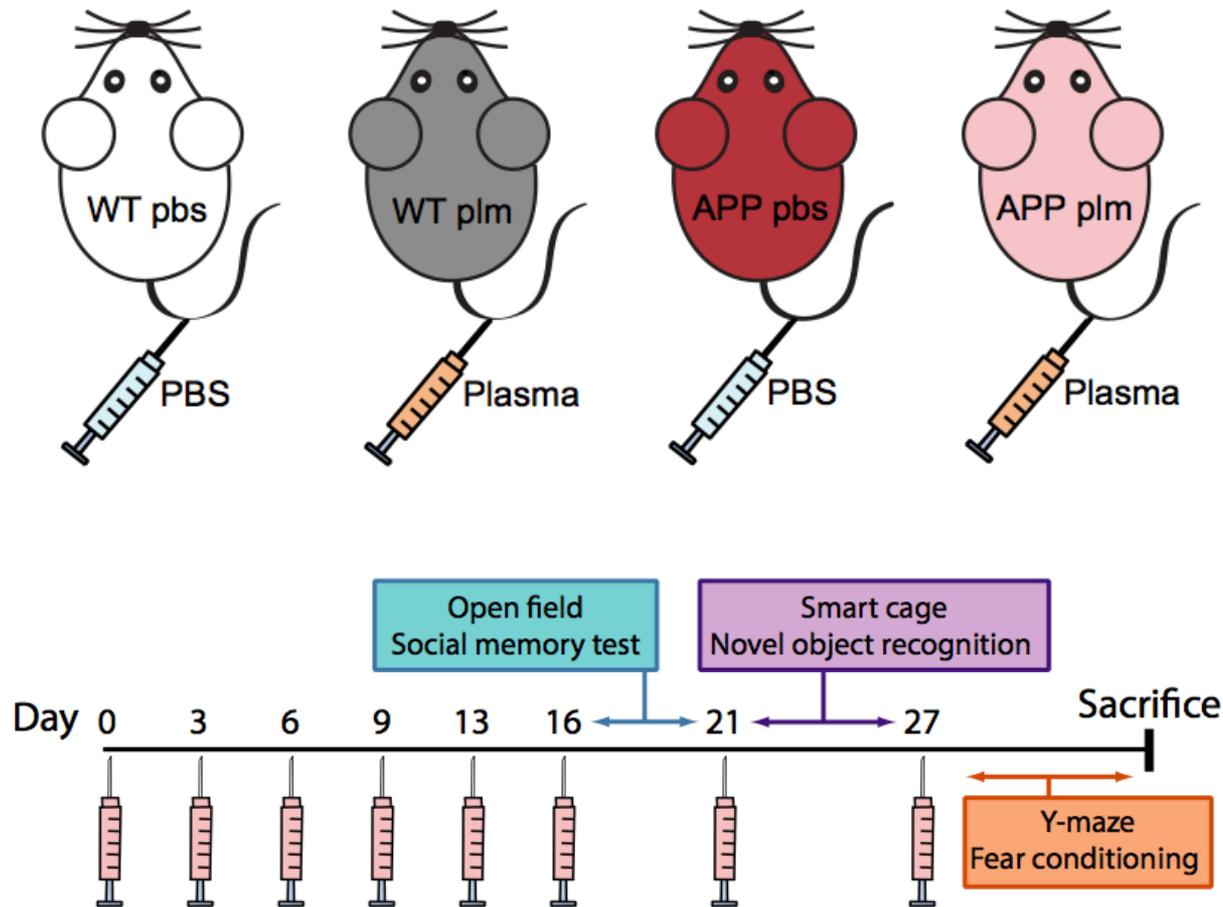
Treatment with cord plasma improves learning and memory



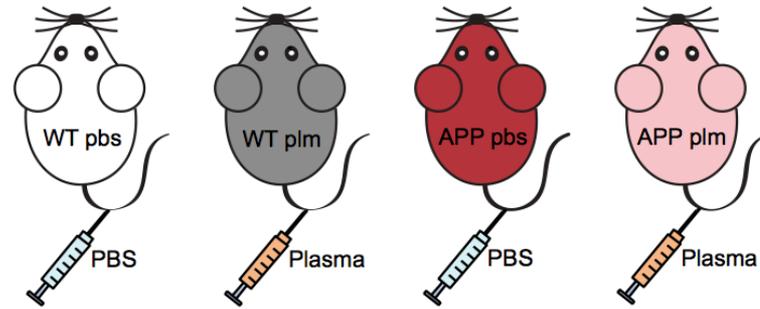
7-8 mice per group; age 12 months

Effect of young plasma in APP mice, a mouse model for Alzheimer's disease

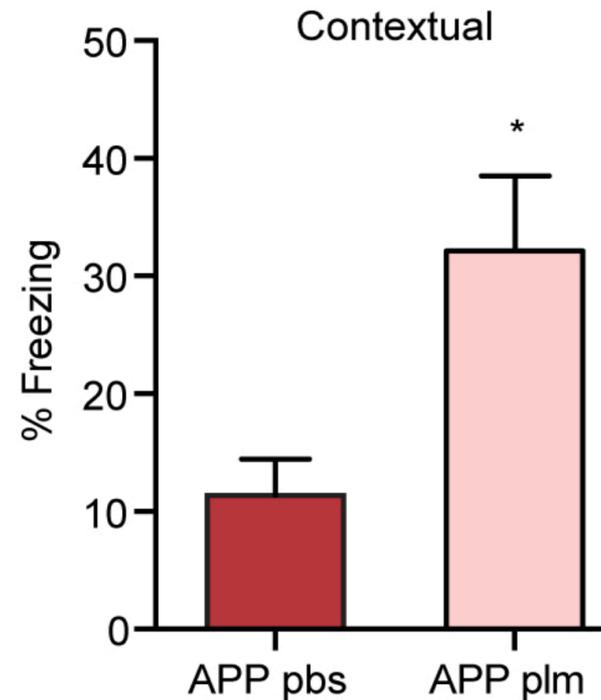
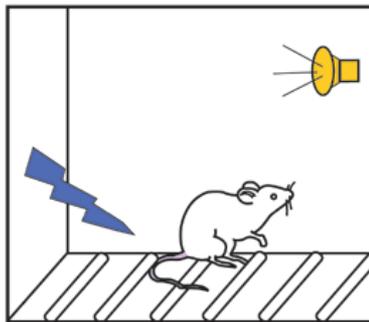
Effect of young plasma in APP mice, a mouse model for Alzheimer's disease



Young Plasma Reverses behavioral deficits in APP Mice



Spatial learning and memory:
Fear Conditioning



Clinical studies to translate rodent discoveries

First study in mild- to moderate AD – at Stanford dementia center

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

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The PLasma for Alzheimer SymptoM Amelioration (PLASMA) Study (PLASMA)

This study is currently recruiting participants. (see [Contacts and Locations](#))

Verified March 2016 by Stanford University

Sponsor:

Stanford University

Collaborator:

Alkahest

Information provided by (Responsible Party):

Sharon Sha, Stanford University

ClinicalTrials.gov Identifier:

NCT02256306

First received: September 25, 2014

Last updated: March 23, 2016

Last verified: March 2016

[History of Changes](#)

Plasma studies in humans (underway or *planned*)

- **Alzheimer's disease (Stanford/Alkahest)**
- **Progressive supranuclear palsy (UCSF)**
- ***Parkinson's disease (Stanford University)***
- ***Amyotrophic lateral sclerosis (Houston Methodist Hospital)***
- ***Depression (Stanford University)***

**What are the factors responsible for
the observed effects?**

Identification of novel factors

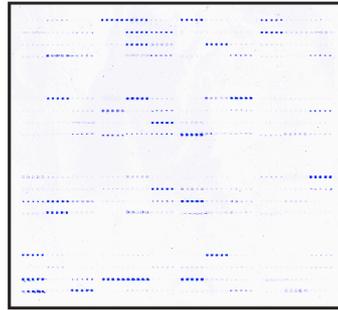
Normal aging humans

Normal aging mice

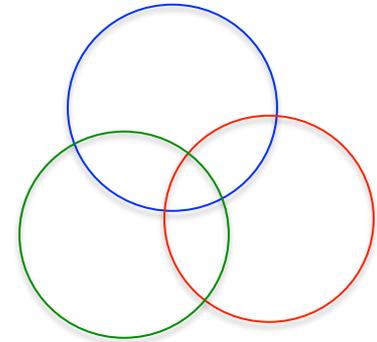
Parabiosis mice

Proteomic Assays:

- Luminex
- Aptamer Somascan
- Antibody based arrays



Top Factors



Cognitive function in B6 mice



Cellular/molecular changes in B6 wildtype mice

What are the Factors Responsible for These Effects?

Aging or deleterious factors

- Eotaxin/CCL11 (Villeda, Nature 2011)
- B2-Microglobulin (Villeda, Nat Medicine 2015)

Rejuvenating or beneficial factors

- GDF11 (Wagers, Lee & Rubin, Cell 2013, Science 2014)
- Oxytocin (Conboy, Nat. Communications 2014)
- CSF2, TIMP2 (Castellano et al., in revision)

Challenges/needs for the discovery of disease related factors

- **Carefully characterized patient population, controls**
- **High quality samples**
 - clinical characterization
 - sample collection, storage
- **Reliability and reproducibility of analytical detection method**
- **Sample number**
 - 100s but possibly 1,000s of samples
- **Statistical methods**
- **Independent validation**
- **(Animal models)**

Blood Biomarkers of Chronic Inflammation in Gulf War Illness

Gerhard J. Johnson^{1,2*}, Billie C. S. Slater¹, Linda A. Leis¹, Thomas S. Rector^{1,2}, Ronald R. Bach^{1,2}

1 Department of Veterans Affairs Health Care System, Minneapolis, Minnesota, 55417, United States of America, **2** Department of Medicine, University of Minnesota, Minneapolis, Minnesota, 55455, United States of America

* gerhard.johnson@va.gov

Table 2. Characteristics of Subjects at Time of Study.

Characteristics	GWI+	GWI-
Number of Participants (n)	57	28
Age		
Age, years (median)	46	48
Age, years (range)	(38–68)	(38–70)
BMI		
BMI (median)	31	28
BMI (range)	(19–46)	(22–47)
BMI <30 (median)	27	26
BMI ≥30 (median)	34	36
Weight		
Weight, lbs. (median)	220	200
Weight, lbs. (range)	(125–360)	(130–320)
Gender		
Female	3	1
Male	54	27
Ethnic Origin		
Black	2	2
White	53	26
Hispanic	2	0
Symptoms		
None	0	13
Single	0	15
Multiple	57	0
Cognition	57	6
Fatigue	52	6
Pain	48	1
Use of Nicotine	42%	21%
Concomitant Medications		
NSAIDS	58%	57%
OTC supplements	32%	61%
Statins	18%	32%
Antidepressants/other psych meds	14%	4%
Opiates	7%	4%

Summary

- Circulatory factors from mouse or human blood can modulate aspects of brain aging and cognitive function
- Individual proteins which replicate some of these effects can be identified and used as therapeutic agents, or possibly, as biomarkers

Acknowledgements



Former Lab Members:

- Markus Britschgi (Roche)
- Alex Eggel (Univ Bern, CH)
- Saul Villeda (USCF)
- Kira Mosher (UC Berkeley)
- Kurt Lucin (Eastern U Conn)

Collaborators

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- Martin Angst (Stanford University)
- Ludwig Aigner (Paracelsus Univ.)
- Eliezer Masliah (UCSD)

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