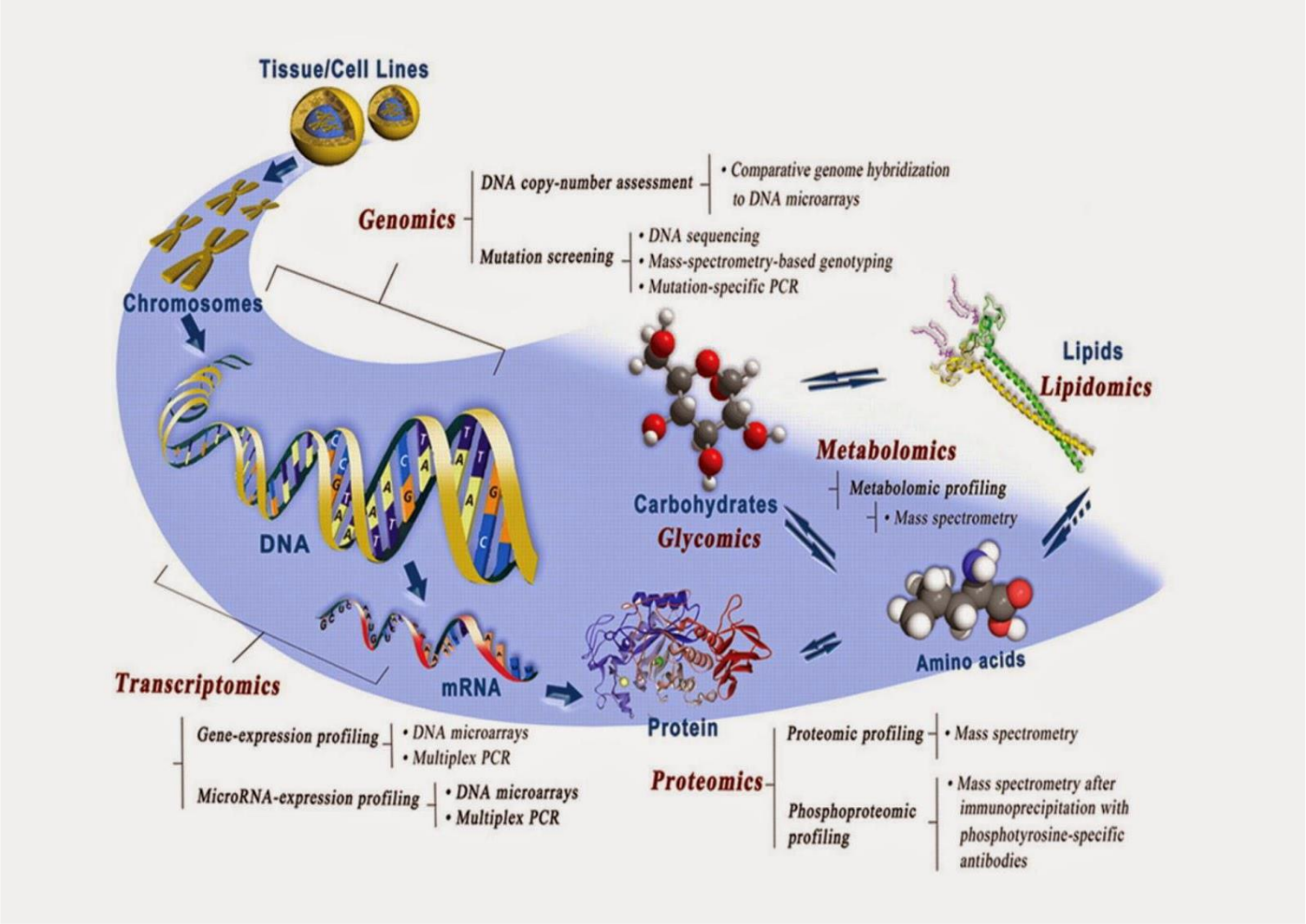
Proteomic Aging

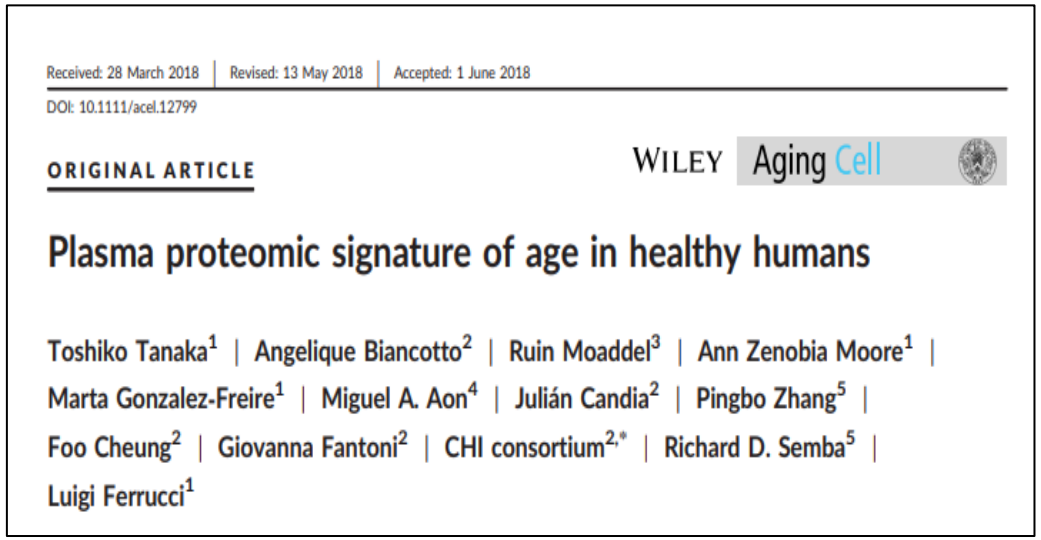
Toshiko Tanaka PhD
Longitudinal Study Section
Translational Gerontology Branch
National Institute of Aging, Baltimore, MD

Proteomics in Aging



Wu RQ, Journal of Dental research (2011)

PROTEOMICS OF CHRONOLOGICAL AGE



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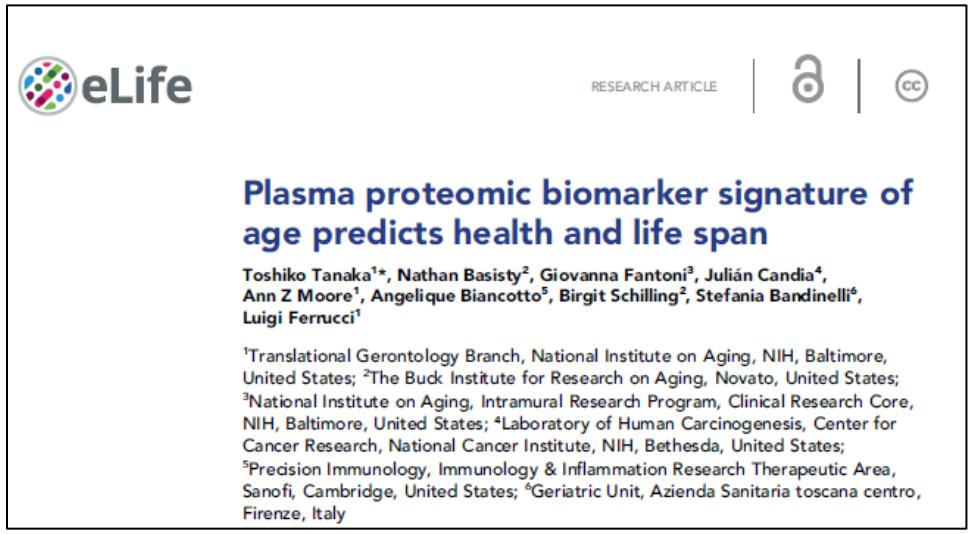
ORIGINAL ARTICLE

WILEY Aging Cell

Plasma proteomic signature of age in healthy humans

Toshiko Tanaka[1] | Angelique Biancotto[2] | Ruin Moaddel[3] | Ann Zenobia Moore[1] | Marta Gonzalez-Freire[1] | Miguel A. Aon[4] | Julián Candia[2] | Pingbo Zhang[5] | Foo Cheung[2] | Giovanna Fantoni[2] | CHI consortium[2,*] | Richard D. Semba[5] | Luigi Ferrucci[1]

Proteomic profile of chronological age in **disease-free, healthy participants**



eLife RESEARCH ARTICLE

Plasma proteomic biomarker signature of age predicts health and life span

Toshiko Tanaka[1]*, Nathan Basisty[2], Giovanna Fantoni[3], Julián Candia[4], Ann Z Moore[1], Angelique Biancotto[5], Birgit Schilling[2], Stefania Bandinelli[6], Luigi Ferrucci[1]

[1]Translational Gerontology Branch, National Institute on Aging, NIH, Baltimore, United States; [2]The Buck Institute for Research on Aging, Novato, United States; [3]National Institute on Aging, Intramural Research Program, Clinical Research Core, NIH, Baltimore, United States; [4]Laboratory of Human Carcinogenesis, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, United States; [5]Precision Immunology, Immunology & Inflammation Research Therapeutic Area, Sanofi, Cambridge, United States; [6]Geriatric Unit, Azienda Sanitaria toscana centro, Firenze, Italy

Proteomic profile of chronological age in **general sample of older adults**

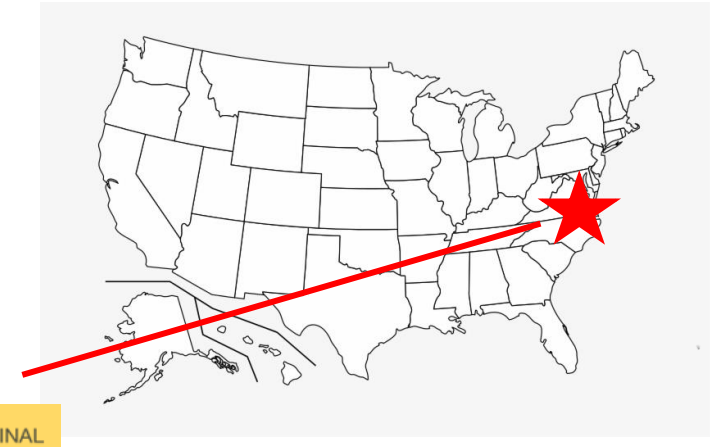
STUDY SAMPLES

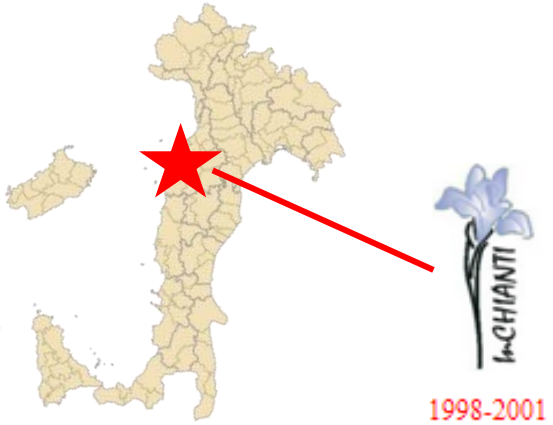
Study 1 (BLSA & GESTALT)

- Subjects are selected from two studies, the Baltimore Longitudinal Study on Aging (BLSA) and Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT) study based in Baltimore, Maryland USA
- 240 healthy subjects ranging from 22-93 years of age
- Subjects are free of mobility disability, chronic disease (except for controlled hypertension), and cognitive impairment

Study 2 (Inchianti study)

- Inchianti subjects are recruited from two cities from Tuscany, Italy, the samples are from baseline (1998-2000)
- 997 subjects ranging from 21-98 years of age
- Not all disease-free subjects

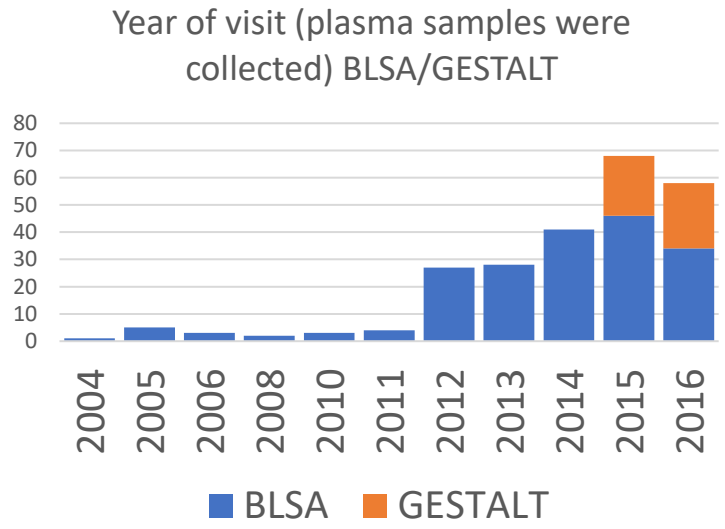




BLSA BALTIMORE LONGITUDINAL STUDY OF AGING

METHODS

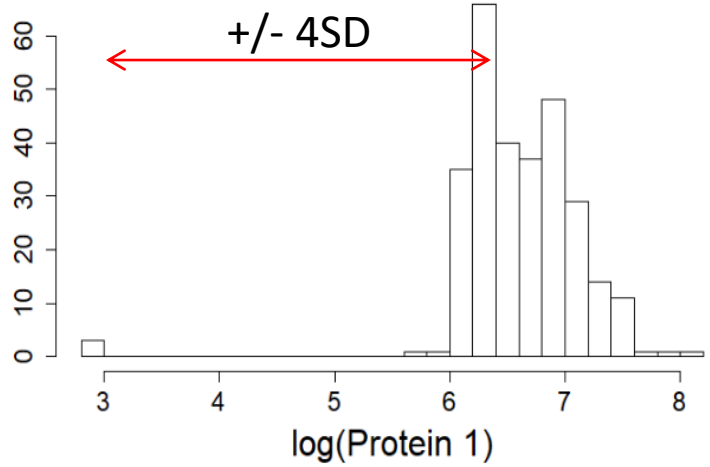
1. PROTEOMIC ASSESSMENT



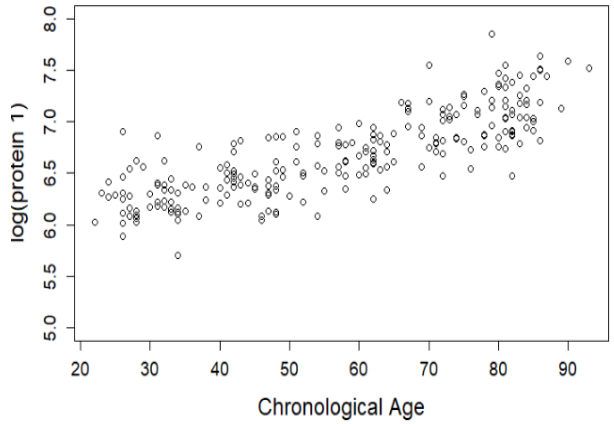
- Use stored plasma samples
- ~1300 proteins assessed using 1.3K SOMAscan assay (NIH Center for Human Immunology (CHI)

2. QUALITY CONTROL

- The data were quality controlled and normalized by the bioinformatics group
- Each protein log transformed, Outlier +/-4SD were removed



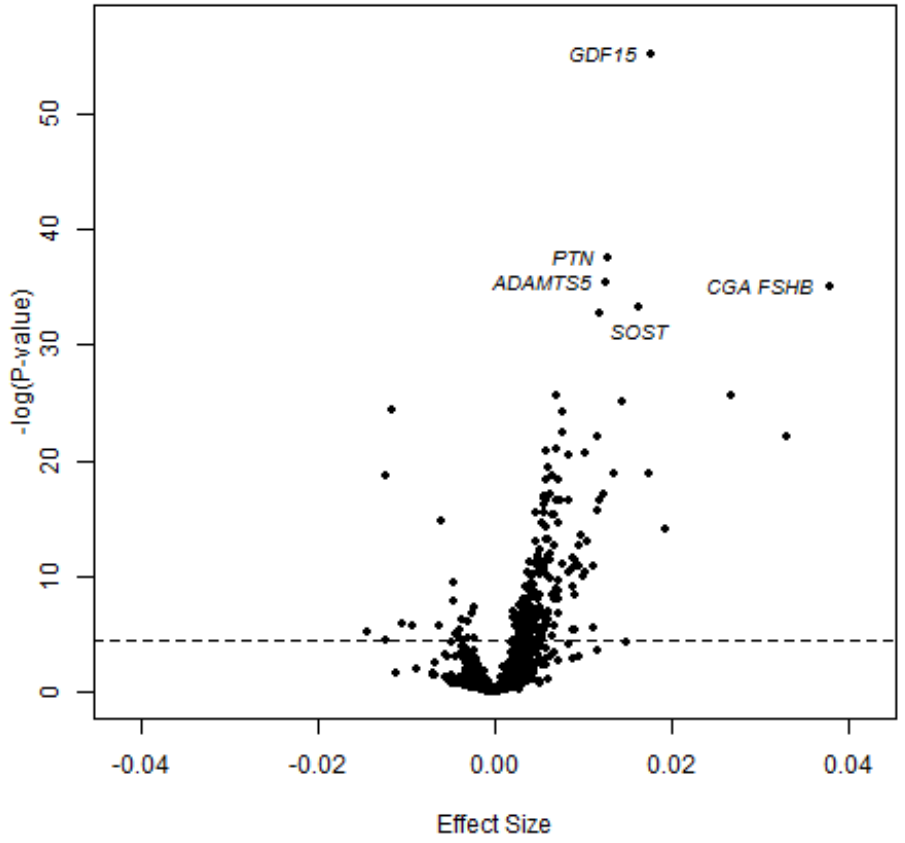
3. STATISTICAL ANALYSES



- Linear regression
  Covariates: sex, Study, WBC count
  ($p \leq 3.83 \times 10^{-5}$)
- Elastic net regression to create proteomic clock

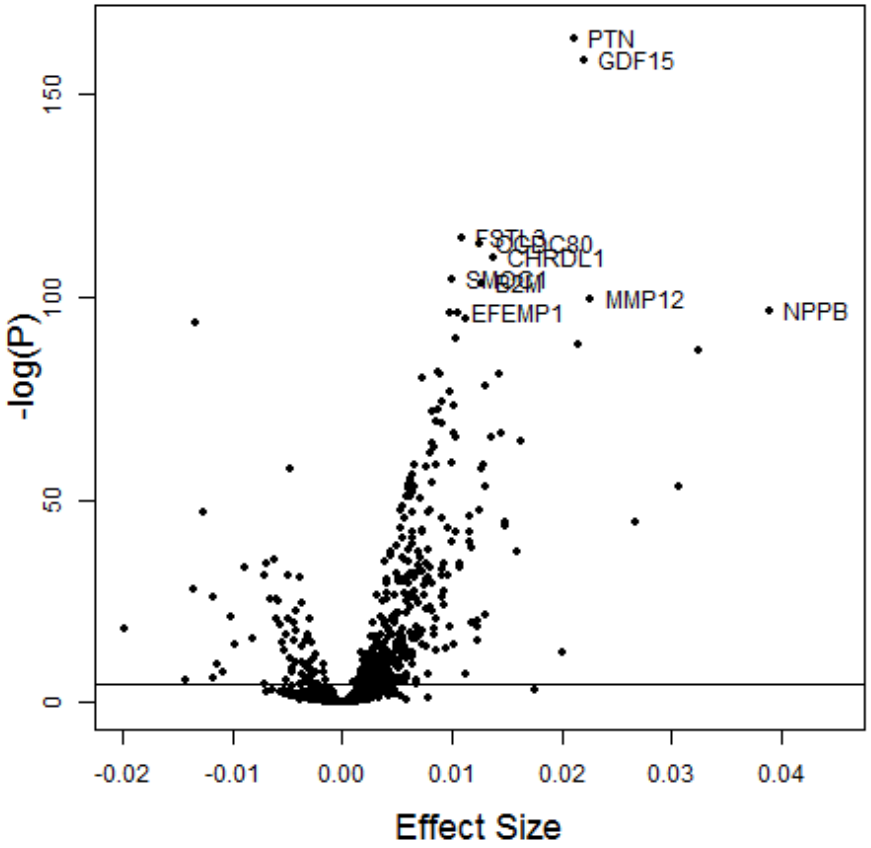
RESULTS: AGE-ASSOCIATED PROTEINS

BLSA & GESTALT study



217 proteins associated with age

InCHIANTI study



412 proteins associated with age

Of the 217 proteins associated with age in the BLSA, **211 (97%)** replicated at p<0.05 in the InCHIANTI in **consistent direction**

Of the 412 proteins associated with age in the InCHIANTI, **330 (80%)** are replicated in the BLSA

Ageing Research Reviews 60 (2020) 101070

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Systematic review and analysis of human proteomics aging studies unveils a novel proteomic aging clock and identifies key processes that change with age

Adiv A. Johnson[a,*], Maxim N. Shokhirev[b], Tony Wyss-Coray[c,d,e,f], Benoit Lehallier[c,d,e]

- Review 32 manuscripts
- 1,128 proteins associated with age in at least 2 studies
- 32 proteins associated in 5 studies

Johnson A, et al, Ageing Research Reviews 2020

Received: 25 October 2020 | Revised: 31 December 2020 | Accepted: 18 January 2021

DOI: 10.1111/acel.13325

REVIEW

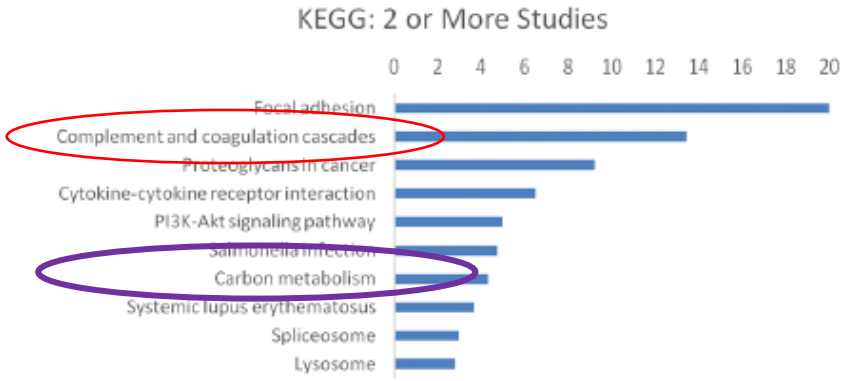
Aging Cell WILEY

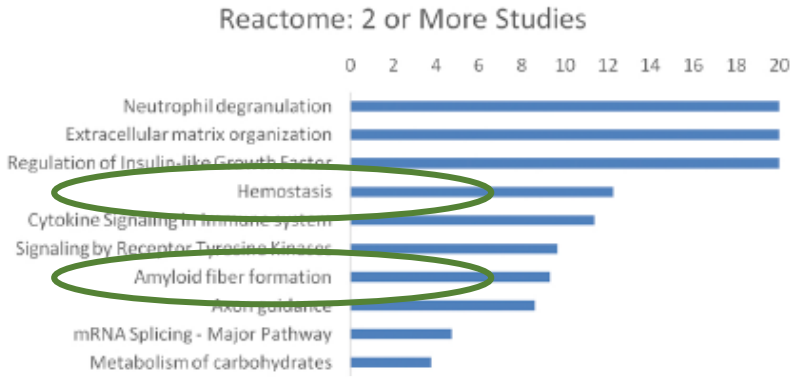
Proteomics in aging research: A roadmap to clinical, translational research

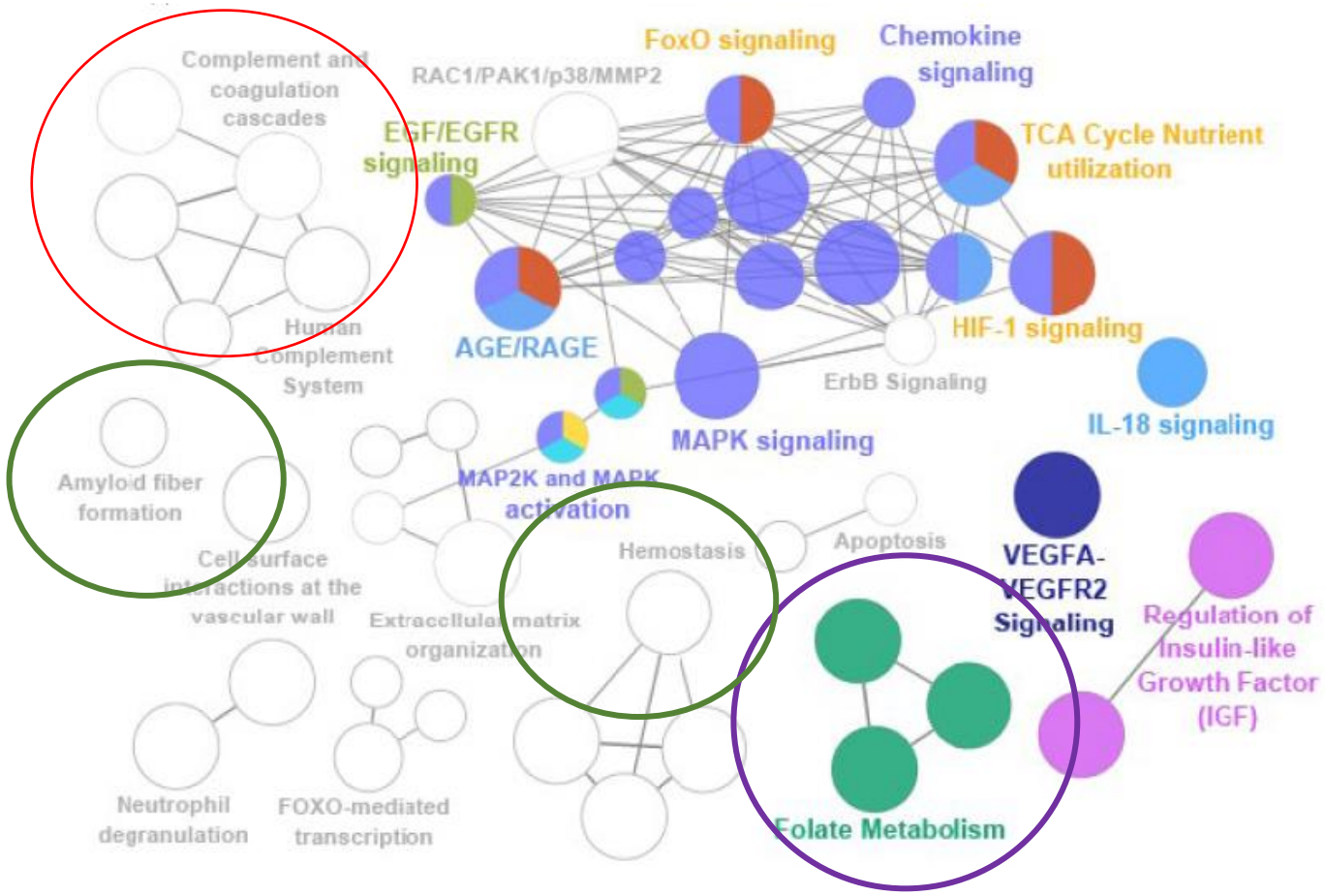
Ruin Moaddel[1] | Ceereena Ubaida-Mohien[1] | Toshiko Tanaka[1] | Alexey Lyashkov[1] | Nathan Basisty[2] | Birgit Schilling[2] | Richard D Semba[3] | Claudio Franceschi[4] | Myriam Gorospe[1] | Luigi Ferrucci[1]

- Review of 33 manuscripts
- 232 proteins associated with age in at least 2 studies
  - 154 proteins had consistent direction of association in all sample studied
  - 78 proteins consistent direction of association within plasma but different direction in other tissues

Moaddel R et al, Aging Cell 2020





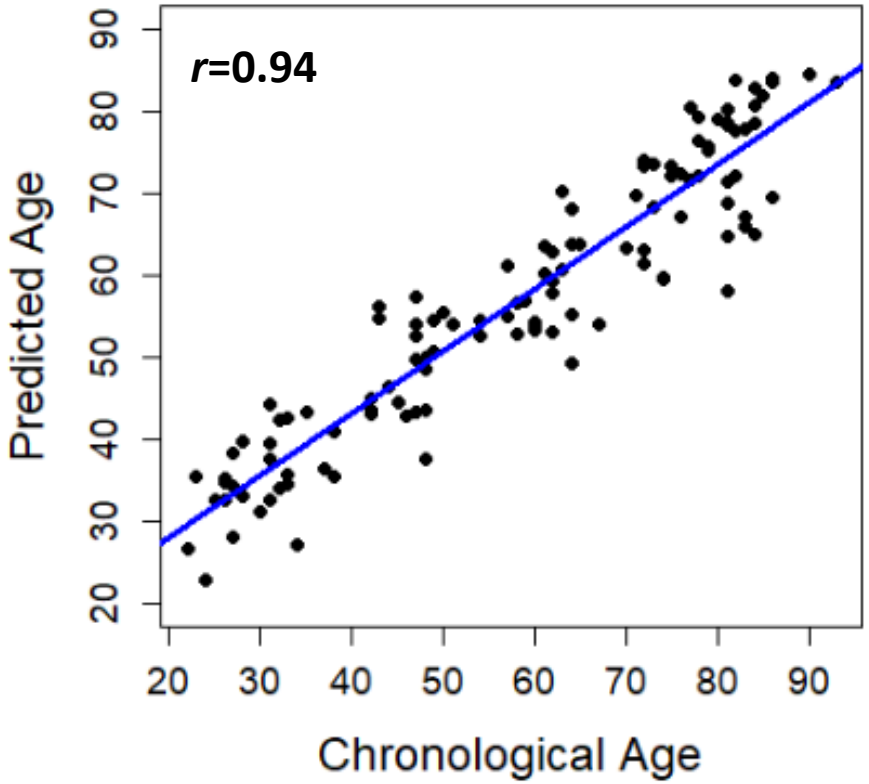


Johnson A, et al, Ageing Research Reviews 2020

Moaddel R et al, Aging Cell 2020

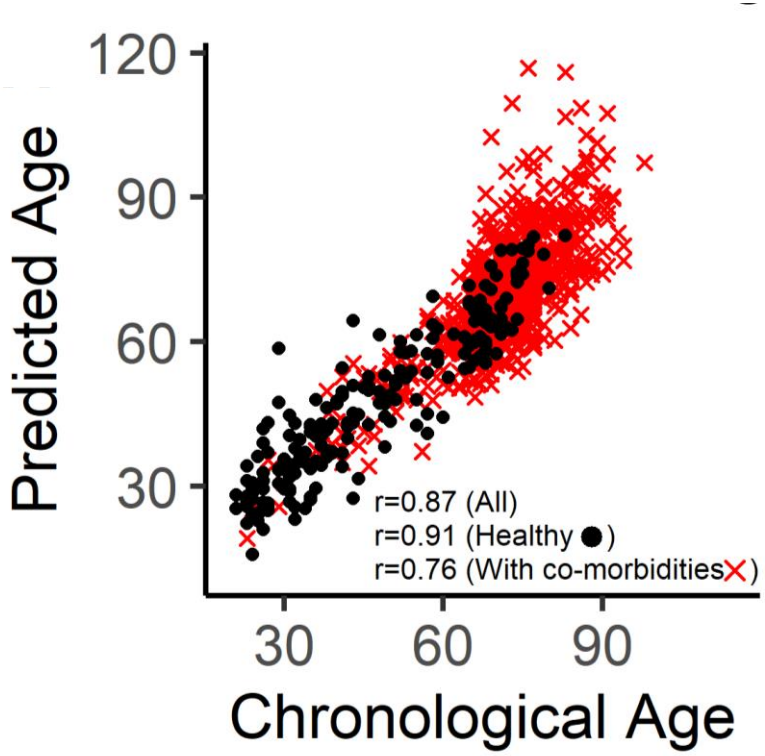
PROTEOMIC "CLOCK"

BLSA & GESTALT study



76 Proteins were selected using Elastic Net regression to predict chronological age in BLSA & GESTALT dataset

InCHIANTI study

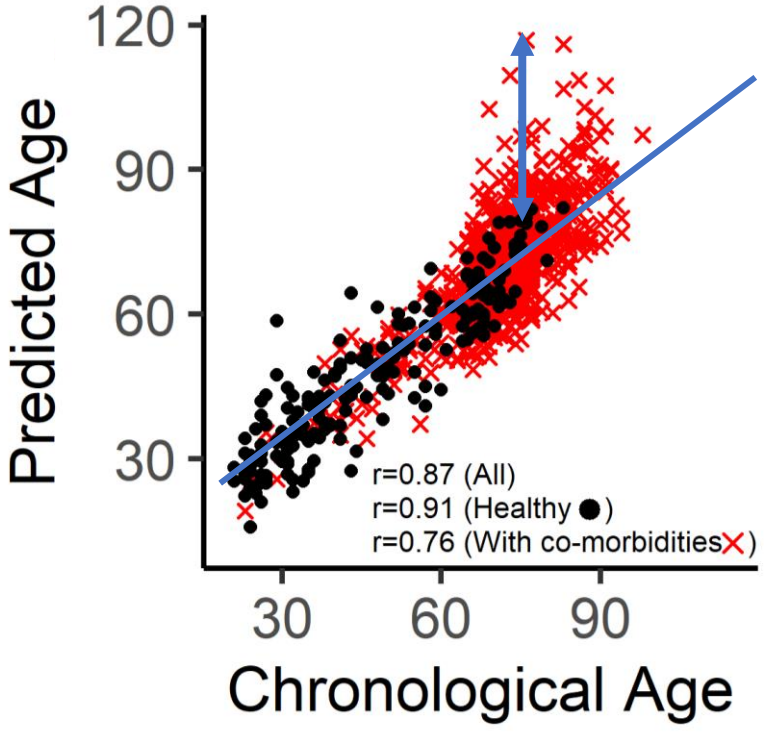


Older individuals & those with co-morbidity predicted age is older

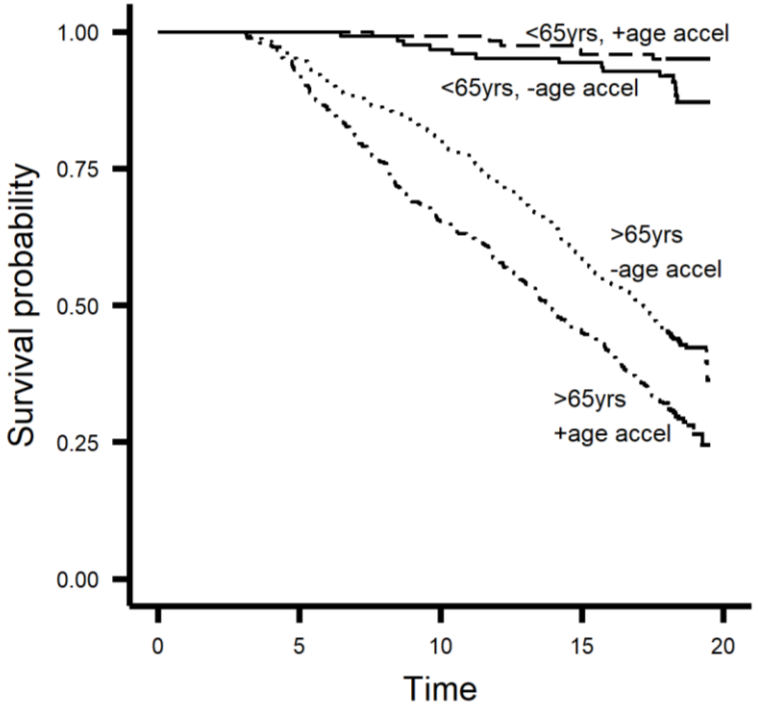
Proteomic age may have information about health status?

PROTEOMIC AGE ACCELERATION

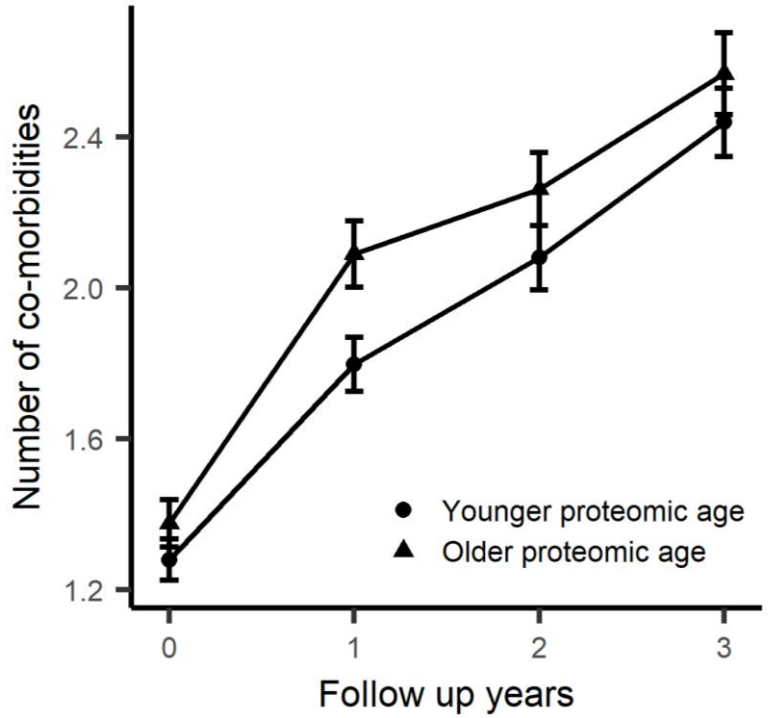
Proteomic age acceleration



All-cause mortality

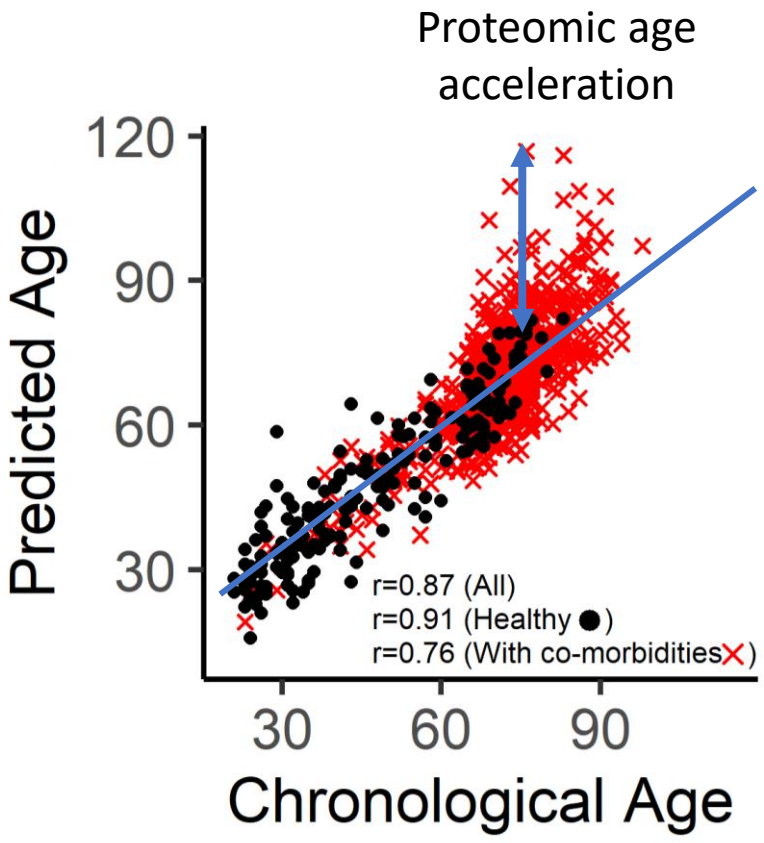


Multimorbidity

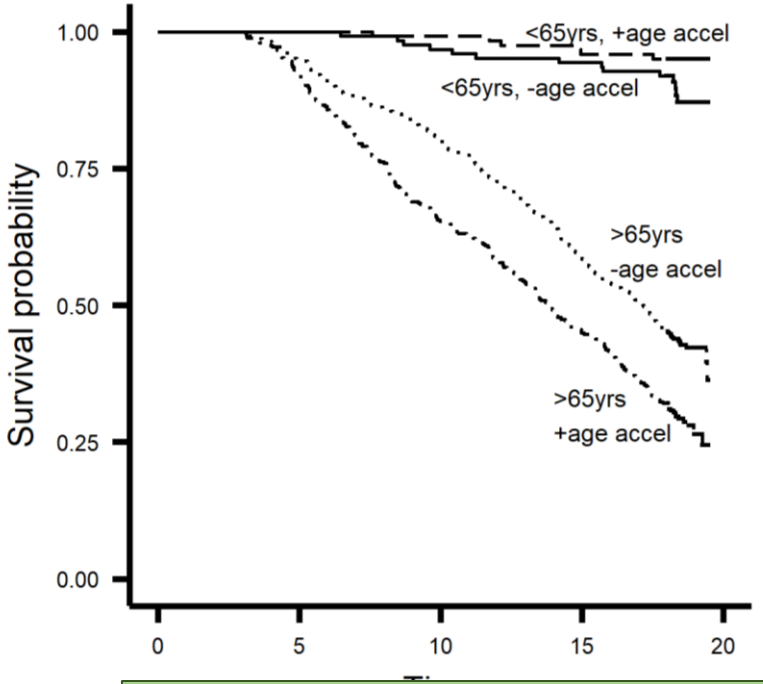


Those who are <u>predicted to be older</u> using proteomics ***higher risk for mortality***, and ***faster accumulation of disease***

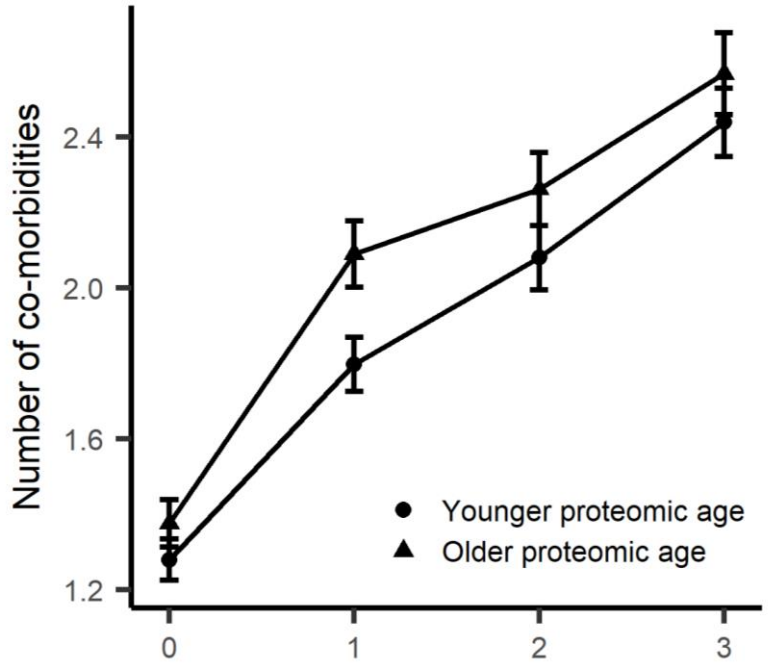
PROTEOMIC AGE ACCELERATION



All-cause mortality



Multimorbidity

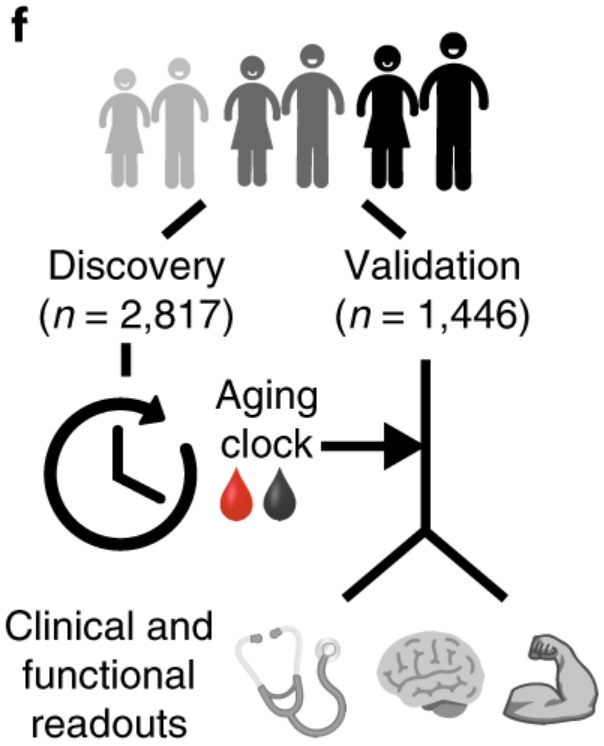


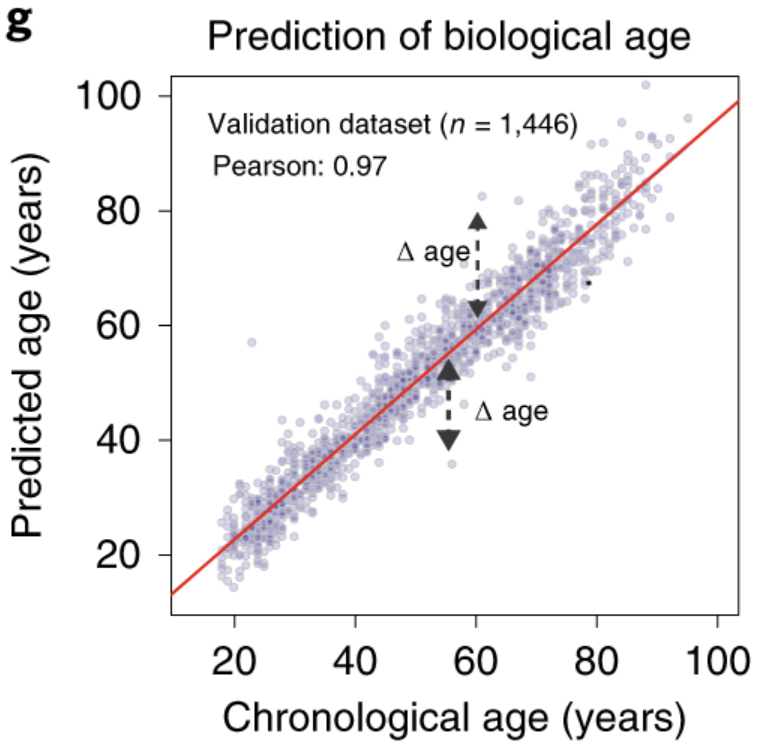
When compared to epigenetic clock:

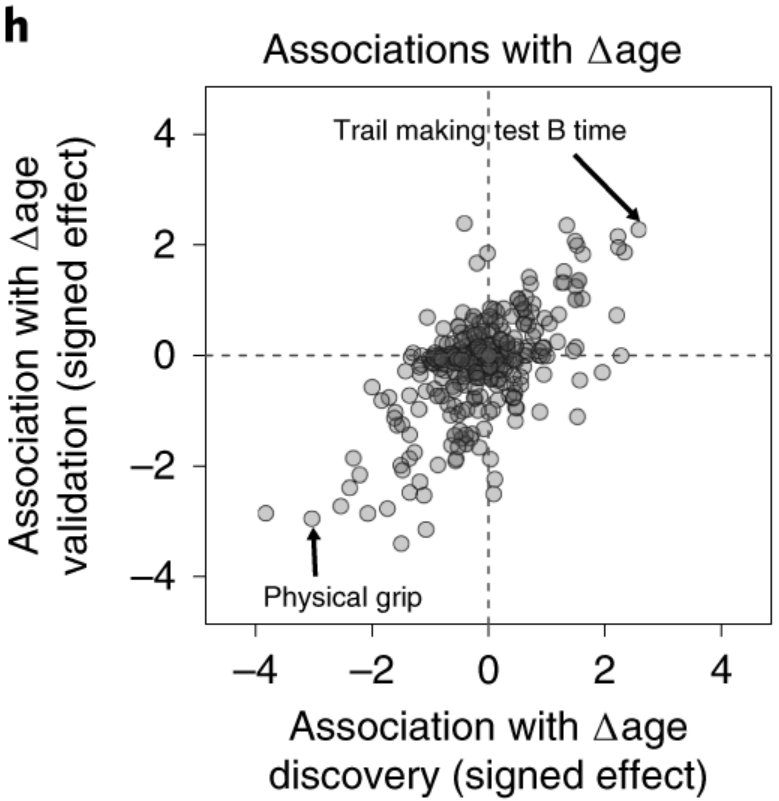
Proteomic clock >> $mDNA_{chronological\ age}$

Proteomic clock **<<** $\mathbf{mDNA_{GRIMACCEL}}$ **&** $\mathbf{mDNA_{PHENOACCEL}}$

PROTEOMIC AGE ACCELERATION







Lehallier B, Nature Medicine 2019

CONCLUSION AND FUTURE DIRECTIONS

- Great advancements in discovery of proteomic biomarkers of aging with development of new technology
  - Candidate aging biomarkers confirmed across tissue types identify
  - Elucidate which of these proteomic age biomarkers (in combination) serves as the best marker of biological age

- Circulating proteins can be used to predict chronological age
  - The deviation captures some aspect of biological age, however, requires fine-tuning

Acknowledgement

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Perry Kuo

Center for Human Immunology

Angelique Biancotto

InCHIANTI study

Stefania Bandinelli

extra

Table 2

Age-associated proteins identified in five or more different studies. For each protein, the UniProt ID, the number of studies that reported the protein, and the relevant tissues and/or cell types is provided. Proteins are organized alphabetically according to their gene abbreviation. A total of 32 proteins are listed.

Protein and Gene Names	UniProt	# of Studies	Tissues and/or Cell Types Reported
Serum albumin (ALB)	P02768	7	Liver, plasma, vastus lateralis, serum, tear fluid
Annexin A1 (ANXA1)	P04083	6	Plasma, vastus lateralis, saliva, dermal fibroblasts, tear fluid
Annexin A2 (ANXA2)	P07355	6	Plasma, vastus lateralis, liver, colon epithelial tissue
ATP synthase subunit beta, mitochondrial (ATP5F1B)	P06576	5	Plasma, vastus lateralis, colon epithelial tissue, T cells
Complement C3 (C3)	P01024	7	Plasma, liver, cerebrospinal fluid, serum
Complement C4-A (C4A)	P0C0L4	5	Plasma, cerebrospinal fluid, serum
Calpain small subunit 1 (CAPNS1)	P04632	5	Plasma, liver, lymphocytes and precursors, granulocytic precursors, dermal fibroblasts
Collagen alpha-1(XVIII) chain (COL18A1)	P39060	5	Plasma, vastus lateralis, cerebrospinal fluid
Collagen alpha-1(I) chain (COL1A1)	P02452	6	Plasma, vastus lateralis, liver, mesenchymal stem / stromal cells, urine, serum
Cathepsin S (CTSS)	P25774	5	Plasma, liver, mesenchymal stem / stromal cells, saliva
Epidermal growth factor receptor (EGFR)	P00533	5	Plasma, vastus lateralis, cerebrospinal fluid
Fibrinogen alpha chain (FGA)	P02671	7	Plasma, liver, cerebrospinal fluid
Fibrinogen gamma chain (FGG)	P02679	6	Plasma, liver, saliva
Fibronectin (FN1)	P02751	6	Plasma, mesenchymal stem / stromal cells, saliva, urine
Growth/differentiation factor 15 (GDF15)	Q99988	5	Plasma
Aspartate aminotransferase, cytoplasmic (GOT1)	P17174	7	Plasma, vastus lateralis, liver, frontal cortex
Glutathione S-transferase P (GSTP1)	P09211	5	Plasma, colon epithelial tissue, olfactory cleft, dermal fibroblasts
Hepatocyte growth factor (HGF)	P14210	5	Plasma, cerebrospinal fluid
Heterogeneous nuclear ribonucleoprotein D-like (HNRNPDL)	O14979	5	Plasma, vastus lateralis, saliva, monocytes / macrophages and precursors
Haptoglobin (HP)	P00738	8	Plasma, vastus lateralis, liver, saliva, cerebrospinal fluid, serum
Laminin subunit gamma-1 (LAMC1)	P11047	5	Plasma, vastus lateralis, liver, serum
Prolow-density lipoprotein receptor-related protein 1 (LRP1)	Q07954	5	Plasma, vastus lateralis, liver
Macrophage metalloelastase (MMP12)	P39900	5	Plasma
Protein/nucleic acid deglycase DJ-1 (PARK7)	Q99497	5	Plasma, liver, saliva, olfactory cleft, vastus lateralis
Urokinase plasminogen activator surface receptor (PLAUR)	Q03405	6	Plasma, cerebrospinal fluid
Pleiotrophin (PTN)	P21246	5	Plasma, cerebrospinal fluid
Serotransferrin (TF)	P02787	5	Plasma, liver, saliva, vastus lateralis, tear fluid
Lamina-associated polypeptide 2, isoforms beta/gamma (TMPO)	P42167	5	Plasma, vastus lateralis, liver, mesenchymal stem / stromal cells
Tumor necrosis factor receptor superfamily member 1A (TNFRSF1A)	P19438	6	Plasma, cerebrospinal fluid
Tumor necrosis factor receptor superfamily member 1B (TNFRSF1B)	P20333	6	Plasma, cerebrospinal fluid
Triosephosphate isomerase (TPI1)	P60174	6	Vastus lateralis, plasma, liver, colon epithelial tissue, dermal fibroblasts
Vascular endothelial growth factor A (VEGFA)	P15692	5	Plasma, mesenchymal stem / stromal cells

Study Characteristics

		Age Categories				
		20-35 yrs	35-50 yrs	50-65 yrs	65-80 yrs	80+ yrs
BLSA & GESTALT						
N		48	48	48	48	48
% Female (N)		50% (24)	50% (24)	50% (24)	50% (24)	50% (24)
% Gestalt (N)		27% (13)	17% (8)	21% (10)	25% (12)	6% (3)
Race						
	White	63% (30)	60% (29)	63% (30)	77% (37)	88% (42)
	Black	25% (12)	29% (14)	33% (16)	15% (7)	10% (5)
	Other	13% (6)	10% (5)	4% (2)	8% (4)	2% (1)
% Smoker		8% (4)	2% (1)	6% (3)	8% (4)	4% (2)
BMI (kg/m^2)		25.8 (5.7)	26.1 (4.4)	27.2 (4.6)	27.2 (4.1)	25.5 (3.2)
Waist Circumference (cm)		81.7 (12)	83.8 (12)	87.6 (13)	93.5 (10)	89.2 (10)
WBC ($10^3/mm^2$)		5.5 (1.4)	5.3 (1.3)	5.2 (1.4)	5.6 (1.5)	5.4 (1.5)
CRP (ug/mL)		1.6 (2.0)	1.7 (1.7)	2.0 (3.0)	2.8 (4.2)	2.3 (2.2)
InChianti Study						
N		71	78	96	623	129
% Female (N)		54% (38)	50% (39)	54% (52)	54% (336)	65% (84)
% Smoker		38% (27)	32% (25)	32% (31)	17% (103)	3% (4)
BMI		24.3 (3.8)	26.2 (4.2)	27.4 (3.7)	27.8 (4.1)	26.1 (3.9)
Waist Circumference (cm)		79.8 (10.5)	85.7 (11.8)	91.2 (11.3)	93.2 (10)	90.1 (9.4)
WBC ($10^3/mm^2$)		6.5 (1.4)	6.4 (1.7)	6.5 (1.6)	6 (1.5)	6.2 (1.4)
CRP (ug/mL)		1.9 (2.8)	3 (6.6)	3.4 (4.2)	4.3 (6.6)	5.6 (9.8)
No of co-morbidities		0.2 (0.4)	0.3 (0.6)	0.6 (0.6)	1.5 (1.3)	2.3 (1.5)