Harnessing the Power of Multi-Omics to Advance Understanding of Biological Aging and Healthspan in Older Women

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UC San Diego

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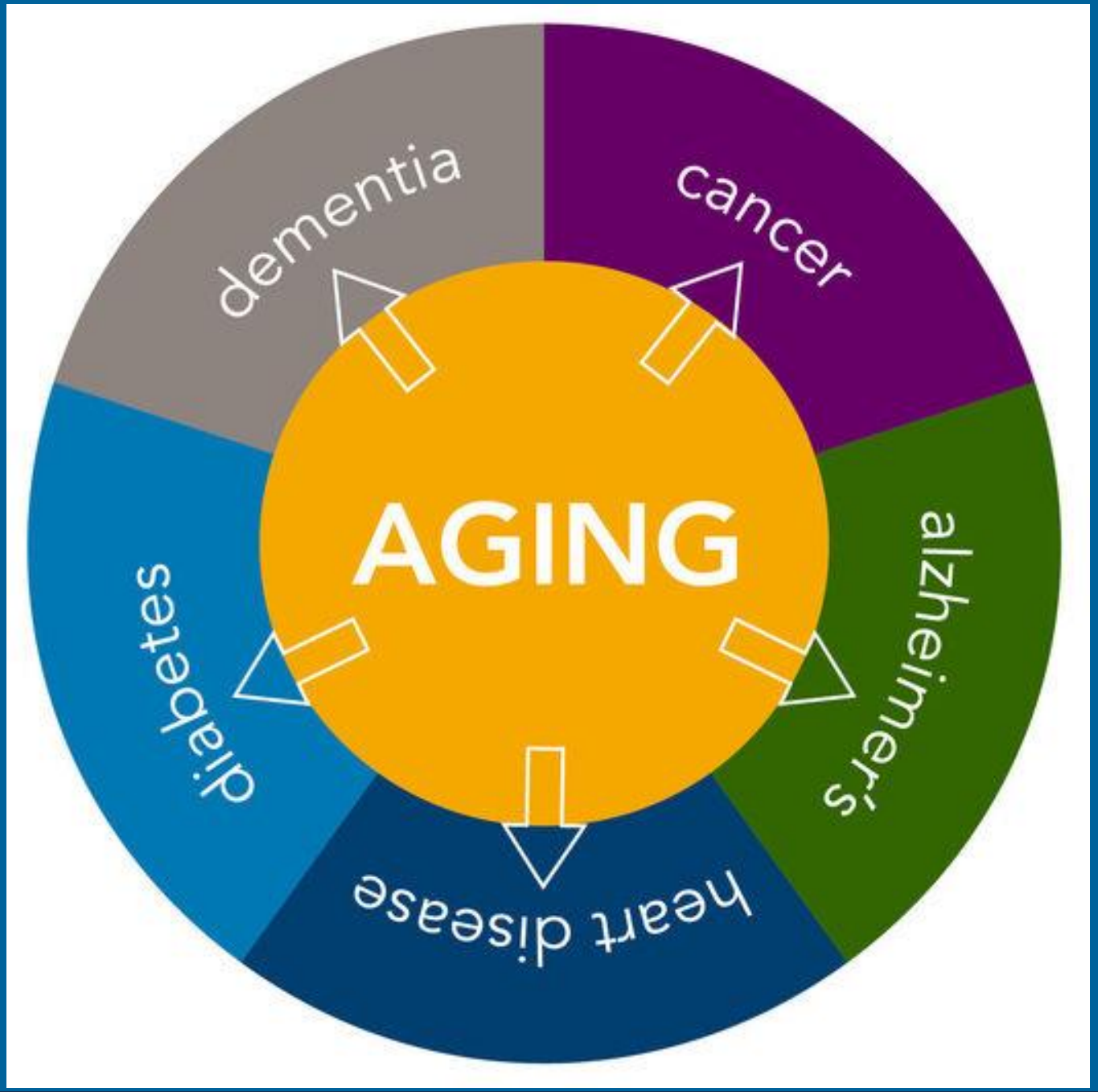
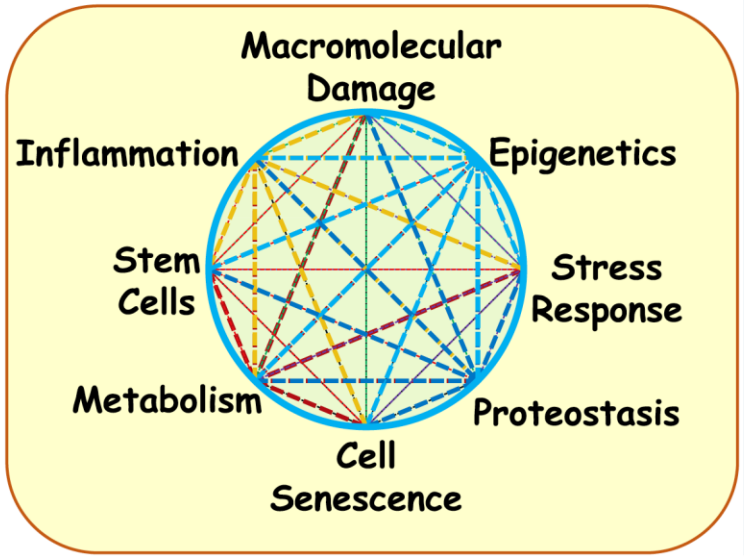
HUMAN LONGEVITY SCIENCE

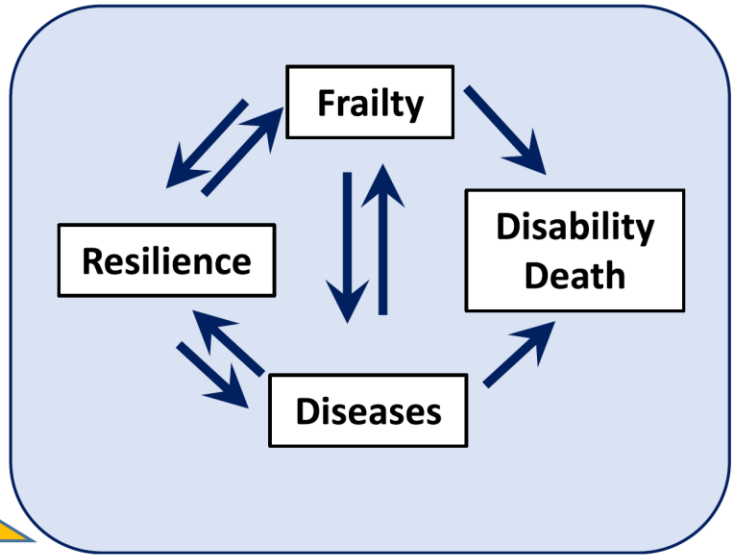

dementia
cancer
AGING
alzheimers
diabetes
heart disease

Biological Aging (Geroscience)

Biological drivers of aging



Geroscience: Targeting Biological Drivers of Frailty and Multiple Chronic Diseases



Sierra et al. *JAGS* 2021;69:2455-63.

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Epigenetic Aging Biomarkers of MCI, ADRD, and Brain Aging

R01 (2021-2026)

Role: Principal Investigator

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Epigenetic Data Resource

- Epigenetic profiling (>900K CpGs) among 6,400 WHIMS women (2,000 longitudinal measures)
- Among the largest cohorts with epigenomic data (EPIC v2)
- **Data resource to study epigenetics of diverse phenotypes (CVD, cancer, geriatric syndromes, functional decline, etc.)**

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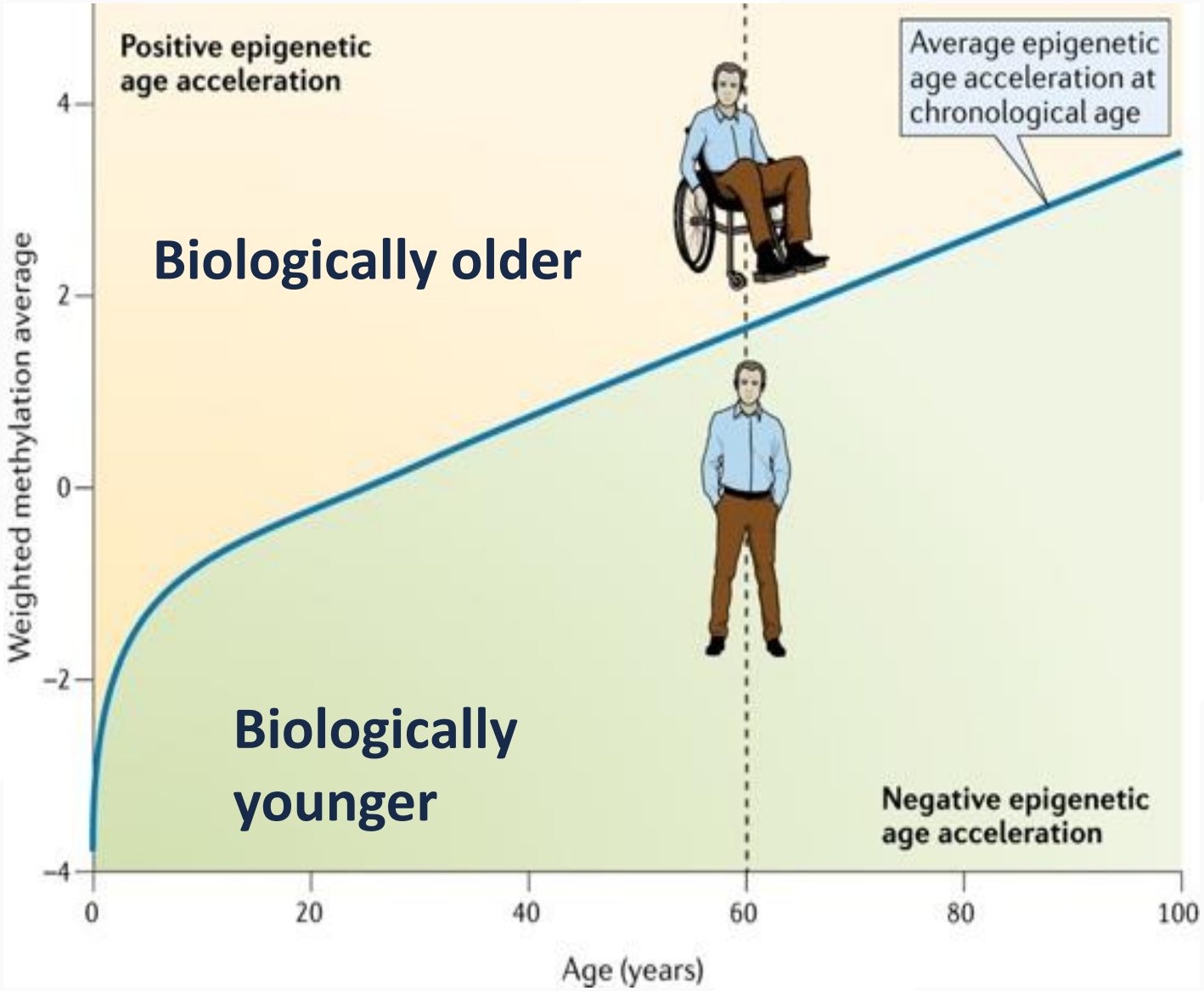
Epigenetic Clocks



Nat Rev Genet 2018;19:371-84.

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Plasma Proteomic Signatures for Alzheimer's Disease and Related Dementias

R01 (2022-2027)

Role: Multiple and Contact PI

NIH NIA

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Proteomic Data Resource

- Proteomic profiling (11k proteins) among 2,836 WHIMS women (1000 longitudinal measures at baseline and LLS)
- Plasma AD biomarkers at baseline and LLS (ptau-217, ptau-181, GFAP, NfL, Ab42/40)
- Among the few cohorts with 11k Somascan
- **Data resource to study proteomics of diverse phenotypes (CVD, cancer, geriatric syndromes, functional decline, etc.)**

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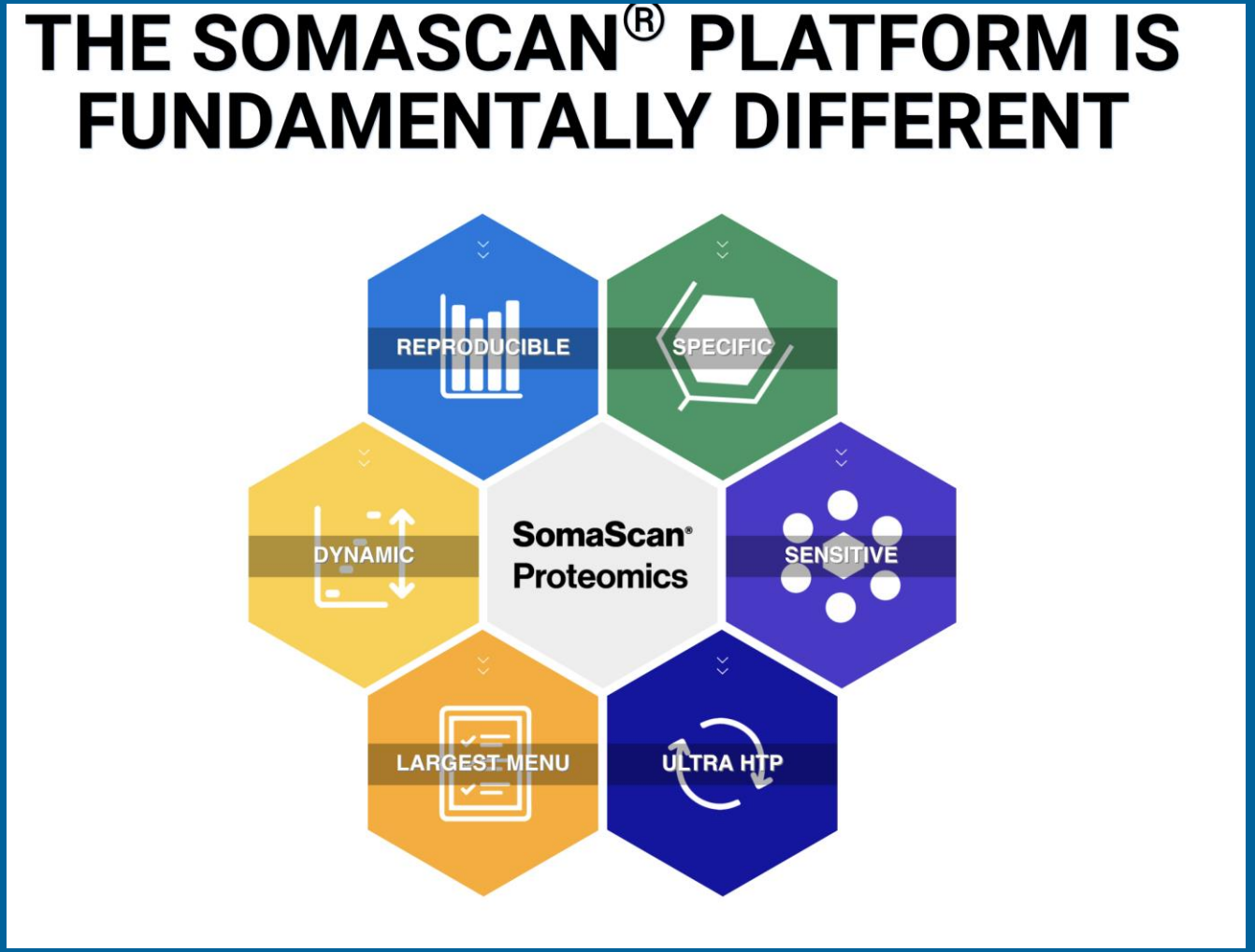
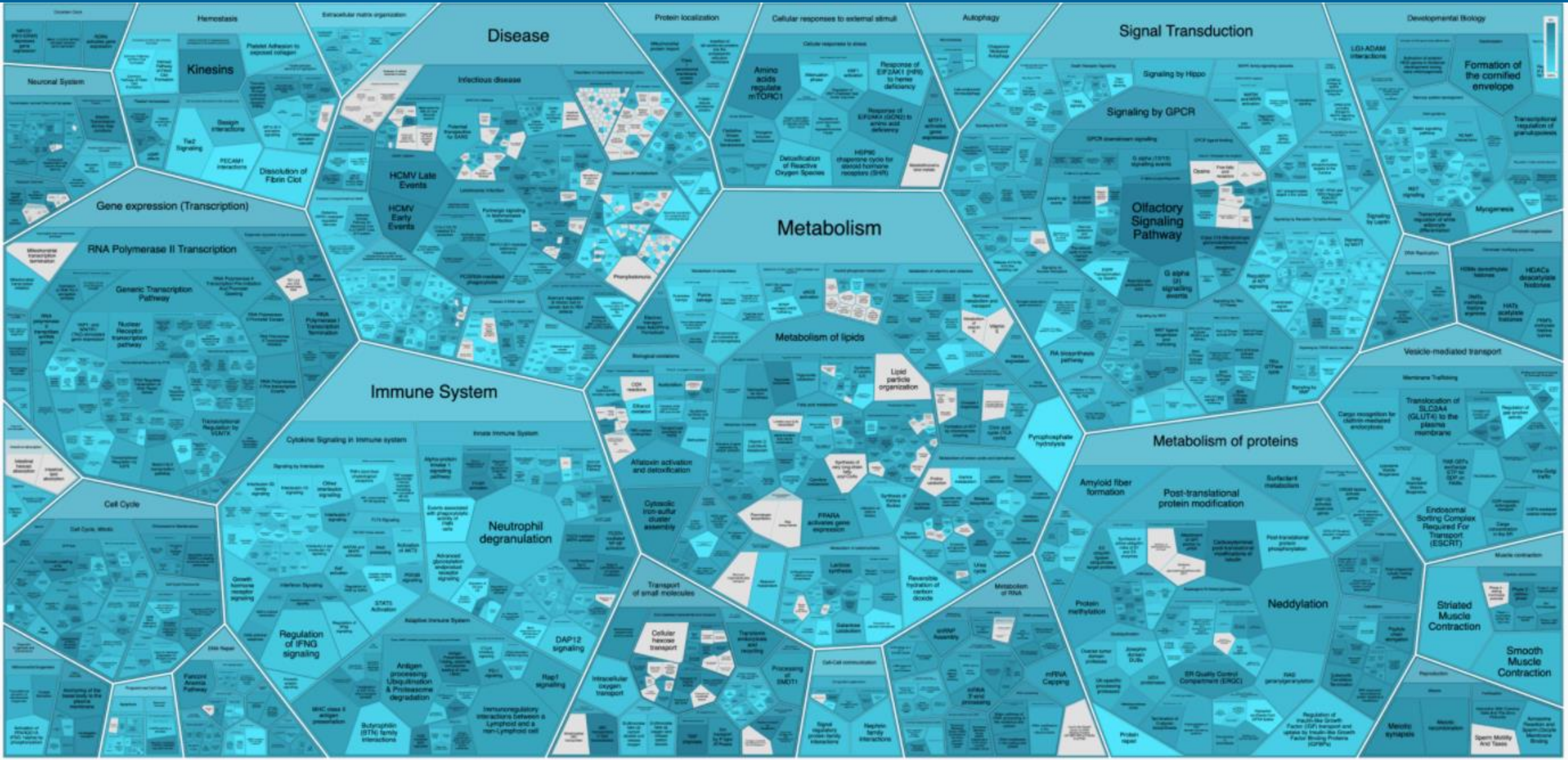
SomaScan: Biomarker Discovery

- Next generation proteomics tool
- >11,000 proteins
- 35 ul plasma
- Discovered and validated proteins for diverse phenotypes (e.g., cancer, CVD, diabetes, etc)





Disease
Signal Transduction
Metabolism
Immune System
Metabolism of proteins
Gene expression (Transcription)
RNA Polymerase II Transcription
Generic Transcription Pathway
Kinesins
Hemostasis
Neuronal System
Protein localization
Cellular responses to external stimuli
Autophagy
Developmental Biology
Infectious disease
HCMV Late Events
HCMV Early Events
Amino acids regulate mTORC1
Signaling by GPCR
Signaling by Hippo
Olfactory Signaling Pathway
Formation of the cornified envelope
Metabolism of lipids
Lipid particle organization
Vesicle-mediated transport
Cytokine Signaling in Immune system
Innate Immune System
Neutrophil degranulation
Regulation of IFNG signaling
DAP12 signaling
Cell Cycle
Aflatoxin activation and detoxification
Cytosolic iron-sulfur cluster assembly
Transport of small molecules
Cellular hexose transport
Amyloid fiber formation
Post-translational protein modification
Neddylation
Striated Muscle Contraction
Smooth Muscle Contraction
Pyrophosphate hydrolysis
mRNA Capping
Protein methylation
Dissolution of Fibrin Clot
Tie2 Signaling
PECAM1 interactions
Detoxification of Reactive Oxygen Species
HSP90 chaperone cycle for steroid hormone receptors (SHR)
Endosomal Sorting Complex Required For Transport (ESCRT)
Antigen processing: Ubiquitination & Proteasome degradation
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell
Butyrophilin (BTN) family interactions

Proteomic Clocks

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]

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Abstract Older age is a strong shared risk factor for many chronic diseases, and there is increasing interest in identifying aging biomarkers. Here, a proteomic analysis of 1301 plasm proteins was conducted in 997 individuals between 21 and 102 years of age. We identified 6 proteins associated with age (506 over-represented, 145 underrepresented with age). Media analysis suggested a role for partial *cis*-epigenetic control of protein expression with age. Of age-associated proteins, 33.5% and 45.3%, were associated with mortality and multimorbidit respectively. There was enrichment of proteins associated with inflammation and extracellula matrix as well as senescence-associated secretory proteins. A 76-protein proteomic age sign predicted accumulation of chronic diseases and all-cause mortality. These data support the u proteomic biomarkers to monitor aging trajectories and to identify individuals at higher risk disease to be targeted for in depth diagnostic procedures and early interventions.

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nature medicine LETTERS
https://doi.org/10.1038/s41591-019-0673-2

Undulating changes in human plasma proteome profiles across the lifespan

Benoit Lehallier[1,2,3]*, David Gate[1,2,3,4], Nicholas Schaum[5], Tibo Hanadie Yousef[1,2,3,4], Patricia Moran Losada[1,2,3], Daniela Berdnik Joe Verghese[8,9], Sanish Sathyan[8,9], Claudio Franceschi[10,11], Sofiy and Tony Wyss-Coray[1,2,3,4]*

Aging is a predominant risk factor for several chronic diseases that limit healthspan[1]. Mechanisms of aging are thus increasingly recognized as potential therapeutic targets. Blood from young mice reverses aspects of aging and disease across multiple tissues[2–10], which supports a hypothesis that age-related molecular changes in blood could provide new insights into age-related disease biology. We measured 2,925 plasma proteins from 4,263 young adults to nonagenarians (18–95 years old) and developed a new bioinformatics approach that uncovered marked non-linear alterations in the human plasma proteome with age. Waves of changes in the proteome in the fourth, seventh and eighth decades of life reflected distinct biological pathways and revealed differential associations with the genome and proteome of age-related diseases and phenotypic traits. This new approach to the study of aging led to the identification of unexpected signatures and pathways that might offer potential targets for age-related diseases.

Aging underlies declining organ function and is the primary risk factor for several diseases[1]. Thus, a deeper understanding of aging is likely to provide insights into mechanisms of disease and to facilitate the development of new antiaging therapeutics. A growing number of investigators have applied genomic, transcriptomic and proteomic assays (collectively referred to as 'omics') to studies of aging[11]. Human genetic studies have uncovered relatively few modifiers of aging, yet other omics modalities, which measure more dynamic gene modifications or products, have provided valuable insights. For example, the transcriptome varies greatly during aging across tissues and organisms[12], pointing to evolutionarily conserved, fundamental roles of developmental and inflammatory pathways[13]. The protein composition of cells, bodily fluids and tissues changes similarly with age and provides insights into complex biological processes, as proteins are often direct regulators of cellular pathways. In particular, blood, which contains proteins from nearly every cell and tissue, has been analyzed to discover biomarkers and gain insights into disease biology. Accordingly, organismal aging results in proteomic changes in blood that reflect aspects of aging of different cell types and tissues.

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Results

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Received: 15 June 2020 | Revised: 21 August 2020 | Accepted: 15 September 2020
DOI: 10.1111/acel.13256

ORIGINAL ARTICLE

Aging Cell WILEY

Data mining of human plasma proteins generates a multitude of highly predictive aging clocks that reflect different aspects of aging

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ABSTRACT

We previously identified 529 proteins that had been reported by multiple different studies to change their expression level with age in human plasma. In the present study, we measured the q-value and age coefficient of these proteins in a plasma proteomic dataset derived from 4263 individuals. A bioinformatics enrichment analysis of proteins that significantly trend toward increased expression with age strongly implicated diverse inflammatory processes. A literature search revealed that at least 64 of these 529 proteins are capable of regulating life span in an animal model. Nine of these proteins (AKT2, GDF11, GDF15, GHR, NAMPT, PAPPA, PLAU, PTEN, and SHC1) significantly extend life span when manipulated in mice or fish. By performing machine-learning modeling in a plasma proteomic dataset derived from 3301 individuals, we discover an ultra-predictive aging clock comprised of 491 protein entries. The Pearson correlation for this clock was 0.98 in the learning set and 0.96 in the test set while the median absolute error was 1.84 years in the learning set and 2.44 years in the test set. Using this clock, we demonstrate that aerobic-exercised trained individuals have a younger predicted age than physically sedentary subjects. By testing clocks associated with 1565 different Reactome pathways, we also show that proteins associated with signal transduction or the immune system are especially capable of predicting human age. We additionally generate a multitude of age predictors that reflect different aspects of aging. For example, a clock comprised of proteins that regulate life span in animal models accurately predicts age.

KEYWORDS
age-related disease, aging, aging clock, health span, life span, longevity

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