perform drug screens, requires valid and reliable measures that can be applied in vitro. Christopher Minteer who developed in cellulo epigenetic markers will demonstarte how epigenetic aging changes that can be induced in culture shed light on aging in vivo. Finally, a summarizing discussion will be held by Dr. Morgan Levine, an expert in the field.

A COMPUTATIONAL SOLUTION TO BOLSTER EPIGENETIC CLOCK RELIABILITY FOR CLINICAL TRIALS AND LONGITUDINAL TRACKING

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Epigenetic clocks are widely used aging biomarkers, but they are calculated from methylation data for individual CpGs that can be surprisingly unreliable. We report that technical noise causes six major epigenetic clocks to deviate by 3 to 9 years between replicates. We present a novel computational solution: we perform principal component analysis followed by biological age prediction using principal components, extracting shared age-related changes across CpGs while ignoring noise from individual CpGs. Our novel principal-component versions of six clocks show agreement between most technical replicates within 1 year, and increased stability in short- and long-term longitudinal studies. This requires only one additional step compared to traditional clocks, does not require prior knowledge of CpG reliabilities, and can improve the reliability of any existing or future epigenetic biomarker. The extremely high reliability of principal component epigenetic clocks makes them particularly useful for personalized medicine and clinical trials evaluating novel aging interventions.

DEEP LONGITUDINAL PROTEOMICS PROFILING REVEALS BIOLOGICAL PATHWAYS RESPONDING TO GRF6019 IN TWO AD CLINICAL TRIALS

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Blood has been widely investigated to discover biomarkers and gain insights into the biology of aging and age-related diseases. Its protein composition provides insights into complex biological processes, as proteins are often direct regulators of cellular pathways. In clinical trials, selected proteins have been used as primary and secondary endpoints, but recent methodological developments allow the measurement of thousands of proteins with very high sensitivity and specificity. In two phase 2 clinical trials testing the safety, tolerability, and feasibility of infusions of the plasma fraction GRF6019 in Alzheimer's disease (AD), we measured more than 7000 proteins in plasma over the course of the clinical trials. Differential trajectories analysis revealed groups of proteins and pathways that were responding to GRF6019. Several pathways were relevant to the biology of aging and AD and our study suggests that deep proteomics profiling can inform on specific biological processes responding to treatment in clinical trials.

LONGITUDINAL PROFILING IN PHENOTYPIC METRIC OF AGING: INSIGHTS FROM THE BALTIMORE LONGITUDINAL STUDY OF AGING

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It remains challenging to quantify the pace of aging across lifespan due to lack of comprehensive longitudinal measurements across wide range of age. In Baltimore Longitudinal Study of Aging, we have measured the longitudinal trajectories of more than 30 phenotypes across four pre-identified domain - body composition, energy regulation, homeostatic mechanisms and neurodegeneration/neuroplasticity, among participants with age between 20+ and 90+. We implemented a two-stage approach to summarize the longitudinal trajectories of these phenotypes across four domains into a summarized score. We demonstrated that higher summarized score (denoting for slower longitudinal phenotypic decline) is associated with slower decline in both cognitive and physical functions, across different stages of adulthood. Our results imply that deep longitudinal profiling contains rich information and may potentially replace diseases as an early endpoint in trials targeting at aging. Further, understanding the underpinning of longitudinal phenotypic trajectories may provide clues to the biological mechanisms of aging.

A DNAMCULTURE EPIGENETIC FINGERPRINT RECAPITULATES PHYSIOLOGICAL AGING

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Aging elicits dramatic changes to DNA methylation (DNAm), however the causes and consequences of such alterations to the epigenome remain unclear. The utility of biomarkers of aging based on DNAm patterns would be greatly enhanced if in vitro models existed that recapitulated physiological phenotypes such that modulation could garnish mechanistic insights. Using DNAm from serially passaged mouse embryonic fibroblasts, we developed a marker of culture aging and asked if culture phenotypes, like exhaustive replication, are epigenetically analogous to physiological aging. Our measure, termed DNAmCULTURE, accurately estimated passage number and was shown to strongly increase with age when examined in multiple tissues. Furthermore, we observed epigenetic alterations indicative of early cultured cells in animals undergoing caloric restriction and in lung and kidney fibroblasts re-programmed to iPSCs. This study identifies culture-derived alterations to the methylome as