

Specific Aims — Living Longer, Living Better

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Specific Aims

Aging-genomics extends the pharmacogenomics paradigm: where pharmacogenomics personalizes therapy by genotype, aging-genomics personalizes the negotiation each individual conducts with their genes across genome, epigenome, mitochondrial state, and real-time physiology. Mechanistically, the mitochondrial-inflammaging axis (NLRP3 inflammasome activation by mtDNA damage and oxidized cardiolipin) drives accelerated aging, and lifestyle factors modulate this axis through epigenetic regulation. Maternal mtDNA inheritance and numts (Mills) layer a largely-overlooked genetic dimension onto this story.

Aim 1 — Longevity & Cardiovascular Health Index (LCI). Integrate nuclear and mitochondrial WGS, cardiorespiratory fitness (METs), standard clinical risk factors, and real-time BioIntelliSense BioButton physiologic data into a clinically-deployable predictive index. Train across MGI (~90{,}000 UM patients), MPOG (Kheterpal, millions of records), and federal exercise-stress-test cohorts (DoDSR, USAFSAM, Cooper, VETS); validate against Oracle Health 150 M EHR via Ellison Institute partnership.

Aim 2 — Epigenetic & Mitochondrial Health Panel (EMHP). Build a blood-based panel calibrated against BioButton-captured behavioral/physiologic states. Phase 1 = small inflammatory and mitochondrial-regulator gene set (NLRP3, sirtuins, GDF-15, FGF-21, etc.) with paired methylation + expression + circulating-protein assays. Phase 2 = genome-wide methylation (EPIC arrays → RRBS/WGBS where justified) and CRISPR Perturb-seq for causal-flow discovery in patient-derived iPSCs.

Aim 3 — Targets, Therapies, and Precision Longevity Programs. Pathway analysis across all data layers prioritizes epigenetic enzymes (DNMTs, TETs, HDACs, sirtuins) and mitochondrial regulators for therapeutic modulation. An aging-genomics decision framework (Athey) outputs individualized lifestyle prioritization and therapeutic-candidate identification, designed for Oracle Health clinical workflows and EIT-affiliated longevity clinics.

Closed-loop deliverable: measure → model → intervene → re-measure, with the same rigor that pharmacogenomics has brought to oncology and cardiology.