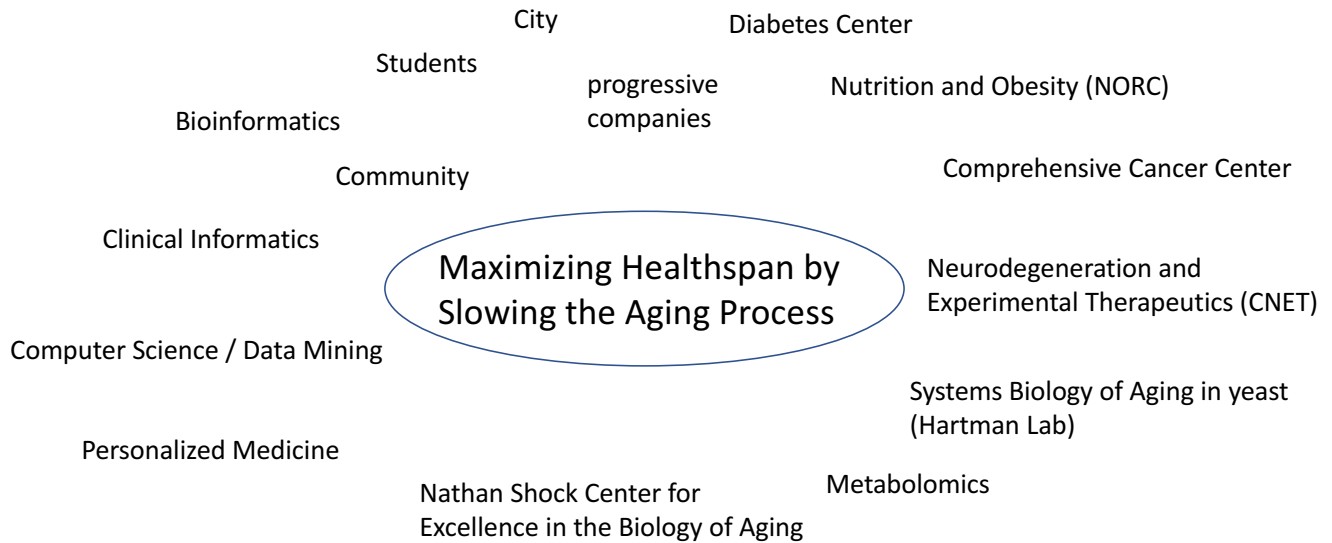**Cover Page**

Name of UAB Grand Challenge: **Maximizing Healthspan - Birmingham and Beyond**

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Potential Team Members: To this point, I have conceptualized and drafted the ideas for the grand challenge. The two main factors in my selection were impact of the challenge itself and feasibility, i.e., leverage existing strengths and interests at UAB. However, I have not vetted this plan with others at UAB. Thus, the list of participants below is neither comprehensive or approved. If the ideas are judged worth pursuing, I would seek these and likely other participants to further develop them.

City　　　　　Diabetes Center

Students

Bioinformatics　　　progressive　　　Nutrition and Obesity (NORC)
　　　　　　　　　　companies

Community　　　　　　　　　　　　　Comprehensive Cancer Center

Clinical Informatics

　　　Maximizing Healthspan by　　Neurodegeneration and
　　　Slowing the Aging Process　　Experimental Therapeutics (CNET)

Computer Science / Data Mining

　　　　　　　　　　　　　　　　Systems Biology of Aging in yeast
　　　　　　　　　　　　　　　　(Hartman Lab)

Personalized Medicine

　　　　　　　Nathan Shock Center for　　Metabolomics
　　　　　　　Excellence in the Biology of Aging

Aging is among the **most familiar experiences in our human existence**. Physical and mental transitions people undergo with age are universal on the one hand and define us as individuals on the other. Yet the science of aging and development of strategies to maximize not only the quantity, but, distinctly, the *quality of life* is relatively new and emerging. I propose a UAB Grand Challenge of "**Maximizing Healthspan - Birmingham and Beyond**". If successfully, outcomes will include a more vibrant community and healthier society, along with establishment of "blue prints" useful for communities throughout our state, nation and world to reap the benefits and build on our success.

Healthspan is a term coined by the National Institute on Aging to emphasize the importance of the distinction between *quality vs. quantity* of life. For example, healthspan can be lengthened without altering lifespan and *vice versa*. *Healthspan equates to the duration of a desirable, high quality of life*, while lifespan is thought of as correlating primarily with duration. We want to live healthier, not merely longer. Healthspan is a diverse and active area of research at UAB and nationwide, thus suited to galvanize an interdisciplinary health-focused initiative, engaging lay and academic communities in a multi-faceted effort to greatly improve our individual, community, and societal experience.

The rate of declining physical and mental function and the associated rise of age-associated disease varies substantially between individuals. The factors influence aging include genetic, dietary, and environmental. Biochemical and cellular **processes that influence aging are conserved across evolutionarily distant species** such that knowledge about aging in yeast, worms, flies, mice are mutually informative regarding aging and age-associated disease in humans. UAB is home to one of the **UAB Nathan Shock Center**, one of six NIH-funded centers of Excellence in Aging Research.

The potential payoffs for maximizing healthspan and the "grandness" of addressing the challenge of the basic biology underlying aging and age-related disease can hardly be overstated. Aging-related diseases with great economic and societal impact include **cancer, diabetes, and dementia**. *Delaying the aging process could* prevent, postpone, and/or reduce affliction by such illnesses. The healthspan concept is relatively new, and the opportunity is ripe for it to advance health and society.

Outlined below is how integration of different lines of research in this grand challenge would achieve outcomes that maximize healthspan and produce other community and societal benefits:

(1) **Integrative Biology**: Mechanisms and thus interventions that modulate lifespan are biologically conserved and operate across species as evolutionarily distant as mice and yeast, a single-cell eukaryotic organism. Thus aging, at the cellular level, is predictive of aging at the organismal level. The most well recognized example of cellular / organismal regulation of aging by an evolutionarily conserved biological process is nutrient signaling through the **Target or Rapamycin (TOR)** pathway. TOR Complex 1, which is conserved from yeast to mammals is inhibited by rapamycin, a natural product that modulates lifespan in yeast, worms, flies, and mice. TOR-relevant nutrient interventions, such as methionine restriction or other alterations in dietary composition also show evolutionarily conserved effects. Thus, there is opportunity to integrate knowledge from complementary disciplines to address the mechanistic cellular details underlying aging and age-related disease.

(2) **Systems Biology and Informatics**: The Hartman laboratory has developed novel technology, named Quantitative High Throughput Cell Array Phenotyping (**Q-HTCP**), which we apply to the complete, genomic collection of 6000 haploid *S. cerevisiae* (budding yeast) gene knockout (**yko**) and knockdown (**kd**) strains to characterize the influence of every gene on cell proliferation. Q-HTCP is used to measure yeast chronological lifespan (**CLS**), which is the decline in viability of yeast cultures in stationary phase. Hartman was one of two RFA awardees (R01) from **NIH-NIA** for **Systems Biology of Aging in *S. cerevisiae*,** and has since become a frequent *ad hoc* member of the Cellular Mechanisms of Aging and Development (CMAD) NIH study section. Q-HTCP applied to CLS of the YKO/KD library serves as a powerful experimental tool for ***phenotypic* data acquisition, discovery, and knowledge generation** to address the grand challenge. To complement yeast phenomics, the Hartman laboratory has also developed a state of the art **metabolomics** approach to enable systems

biology of aging, with the help of a pilot grant from the Southeast Center for Integrated Metabolomics (collaborations with Chris Beecher from IROA technologies and Stephen Barnes at UAB). Initiatives in **informatics of healthspan** would be synergistic for systems and integrative biology of aging aimed at genetics and metabolism, utilizing multiple experimental systems and clinical / translational research in age-related disease (cancer, diabetes, neurodegenerative disorders, etc.). Informatics of healthspan would **leverage both bioinformatics** to leverage new and existing biological information as well as **clinical informatics**, which would integrated translational and clinical science. There are ongoing informatics initiatives to collect and biobank clinical patient samples and to a organize and integrate patient clinical data with genomic information in order to advance capabilities for personalized diagnosis and treatment of disease. The Grand Challenge put forth here would serve as a cross-cutting theme of not only bioinformatics (i.e., basic science focus), but also for clinical informatics (e.g., influence of genetics and metabolism on prevalent diseases). The health relevance of aging is both for primary phenotypes and a broad range of age-associated clinical disorders. Thus it would serve as a point of integration campus-wide (e.g., Cancer, Diabetes and Neurodegeneration Centers) as well as in the College of Arts and Sciences (Chair of Biology, Steven Austad, is the PI/Director for the Nathan), and also the School of Public Health (e.g., Department of Nutrition). Aging, like all biological processes is subject to functional genetic variation, natural selection and evolution. Thus, this Grand Challenge is also cross cutting for **personalized medicine**.

(3) **Translational science leads to community engagement, commercialization, and broader impacts**: The Grand Challenge vision proposed here extends beyond the basic and clinical science of aging to broadly impact community engagement, science education, civic services, and commerce. Achievements reached and benefits resulting from the Grand Challenge would include:

(a) Community Engagement: Using the modern tools of **social media and internet marketing**, lay realization and understanding about the scientific initiatives to address aging, and opportunities afforded within our community for individuals to engage and contribute to extending their own healthspan and that of future generations and potentially the world will be empowering and galvanizing. Thus, an early initiative will be to engage the broader community. This will bolster **community participation, fund raising, political support** for related initiatives, etc.

(b) Science Education: Engaging the community would spur education. Too often, the lay community and even area students feel disconnected from science. The biology of aging and age-related diseases provides a **familiar context for the community to engage with education-based initiatives**. These include ideas such as evolution, the use of model organisms biomedical research, and appreciation for relationships between lifestyle choices such as diet and exercise with healthspan.

(c) Civic Services: Just as **examples**: Birmingham's park system, among other things (bike lanes, pollution and other environmental controls, etc.) could be improved in order to support the active lifestyle and clean environment that promotes healthspan. Community engagement and Science Education would eventually promote initiatives that **attract people to our city**, both from surrounding areas and from out of state. This would also lead to attracting **progressive companies** looking to our city over others that currently attract their business due to value-added to employs in a competitive professional marketplace.

(d) Commercialization: In addition to attracting companies to the Birmingham healthspan initiative, a relating industry would be born, derived from the numerous synergistic initiatives described above. Moreover, the interdisciplinary and integrated approaches developed to solve this grand challenge would create a powerful **infrastructure** that could be generally applied to all disease, whether aging-related or not.