LITE PAPER

PROJECT OUTLINE AND VISION STATEMENT

Rakhan Aimbetov

r@overlake.bio

ABSTRACT

This document outlines the vision and project pipeline of **overlake.bio**, a research initiative focused on understanding and intervening in the aging process, with a particular emphasis on the extracellular matrix (ECM) and its role in age-related decline. The initiative encompasses several projects that leverage advancements in generative AI and machine learning to accelerate research and develop innovative therapeutic strategies. The overarching goal is to extend healthy lifespan by targeting key mechanisms of aging, such as ECM stiffening and proteostasis loss, through engineered interventions and comprehensive data analysis.

Keywords: aging, longevity, space biology

Contents

1 EXECUTIVE SUMMARY

overlake.bio is a research initiative focused on understanding and intervening in the aging process, with a particular emphasis on the *extracellular matrix* (ECM) and its role in age-related decline. The initiative encompasses several projects that leverage advancements in generative AI and machine learning to accelerate research and develop innovative therapeutic strategies. The overarching goal is to extend healthy lifespan by targeting key mechanisms of aging, such as ECM stiffening and proteostasis loss, through engineered interventions and comprehensive data analysis.

2 SCOPE

The projects within **overlake.bio** are designed to explore various aspects of aging, from the molecular and cellular mechanisms to potential therapeutic applications. The scope includes:

- AI for data mining and hypothesis generation; especially at the non-conventional intersection of metabolism, proteostasis, and extracellular matrix dynamics.
- Engineering of enzymes to target specific age-related damage, such as *advanced glycation end products* (AGEs).
- Development of comprehensive databases, such as the *Extracellular Matrix Aging Atlas*, to aggregate and analyze aging-related data across different tissues and contexts.
- Exploration of novel hypotheses regarding the accelerated aging in space and the potential for optimizing human phenotypes for space exploration.

3 PROJECTS

Currently, the pipeline includes the following projects, each with its own focus and objectives:

3.1 The Spacefarer Phenome

The *Spacefarer Phenome* is the concept of an optimized collection of human phenotypic traits, dictated by genetics, that are specifically adapted for the rigors of space exploration and life in extraterrestrial environments. It encompasses the idea of identifying or engineering these traits to **enhance human resilience against space-related challenges**, such as increased radiation, microgravity, and isolation, aiming to improve the feasibility and sustainability of long-duration space missions and off-world colonization.

- **Description:** https://www.notion.so/6df641ad372c4ac5a64b8a666d30a179
- **Short deck:** https://overlake.bio/pdf/spacefarer-phenome-deck-brief-resized.pdf
- **Long deck:** https://overlake.bio/pdf/spacefarer-phenome-deck-v3-resized.pdf

3.2 Enzyme engineering for crosslinked collagen turnover

The project posits extracellular matrix stiffening as the upstream cause of the hallmarks of aging and proposes leveraging generative AI to **engineer matrix metalloproteinases** (MMPs) capable of degrading sugar-modified, or glycated, collagen that resists normal remodeling. The work aims to overcome hitherto irreparable forms of damage through engineered ECM turnover, offering its first therapeutic application in diabetic nephropathy using enhanced *glyoxalase I* and *MMPs-3*, *-9*, targeting both intracellular and extracellular glycation damage in kidneys.

- **Description:** https://www.notion.so/17f3fc8f169f80079fbfe1fdaed87d0a
- **Deck:** https://overlake.bio/pdf/vitalabs-slides.pdf

3.3 The Extracellular Matrix Aging Atlas

The *Extracellular Matrix Aging Atlas* is a knowledge base that collects time-resolved matrisome signatures extracted from public proteomic datasets. The ECM is a complex substance localized in the extracellular space, serving as a medium where cells reside. It provides anchoring support and is a mechanical and biochemical environment directing cellular functions and processes through a variety of stimuli, prompting gene expression profiles to reflect developmental and physiological contexts. As a dynamic structure, the ECM's composition changes as a function of age, but there has been a lack of unified, consensual understanding of these qualitative and quantitative aspects. The *ECM Aging Atlas* aims to aggregate published datasets into a **database of the ECM aging signatures** to better understand how the ECM composition and its changes impact aging across different tissues.

- **Description:** https://www.notion.so/10e0f2ecd2f545afad43fd971cce5be7
- **Deck:** https://overlake.bio/pdf/ai-hackathon-slides.pdf

3.4 Advanced glycation end product (AGE)-degrading enzymes

The project addresses a critical gap in aging research by targeting the issue of tissue stiffening caused by random irreversible chemical damage in the extracellular matrix. This damage, primarily in the form of crosslinks and adducts, is largely due to the accumulation of *advanced glycation end products* (AGEs), which are closely linked to pathomechanisms of aging. The proposed solution involves **developing specialized enzymes engineered to break down AGEs**, thereby potentially reversing or mitigating one of the key contributors to the aging process.

- **Description:** https://www.notion.so/ce317852187b4639b5e5debe42b62290
- **Deck:** https://overlake.bio/pdf/psi-slides.pdf

3.5 Glycation of ribosomes as a driver of proteostasis loss

In this exploration, we propose a novel hypothesis centered on the abundant potential for glycation within the ribosome, suggesting that such modification could lead to an altered error rate in protein synthesis. This presumed increase in errors could, in turn, enhance the production of improperly

folded polypeptides, unveiling a previously unexplored pathway through which *proteostasis*—the delicate balance of protein maintenance—is compromised. This mechanism intricately links the precise regulation of proteostasis to the random nature of glycation. By delving into this novel aspect of translation fidelity, especially its connections to metabolism, our research aims to chart a path toward innovative interventions for extending healthy life, offering new **strategies to combat the pathologies associated with protein misfolding**.

- **Description:** https://www.notion.so/d8971d87778846349d8f4fc29a91a30b
- **Deck:** https://overlake.bio/pdf/ribo-slides.pdf
- **Preprint:** https://dx.doi.org/10.2139/ssrn.4566939

4 OBJECTIVES

The projects are at different stages of development, with some in the early research phase and others progressing towards preclinical validation. The overarching objective is to advance our understanding of aging mechanisms and develop interventions that can extend healthy lifespan, with a particular focus on the extracellular matrix and its role in age-related decline. The recent advancements in generative AI and machine learning have been instrumental in accelerating our research, enabling us to analyze complex datasets, generate novel hypotheses, and design innovative therapeutic strategies. We are committed to leveraging these technologies to drive our projects forward and achieve our goals.