Current Research

Interventions that delay aging have been correlated with improved maintenance of cellular components and cellular homeostasis[1]. Consequently, aging research has been heavily focused on studying the protective and homeostatic mechanisms within cells. However, cells are surrounded by extracellular matrices (ECM) and components of the ECM become fragmented, damaged, modified and cross-linked during aging[2-8]; thereby potentially impairing cellular functions and intercellular communications, which are major hallmarks of aging[9].

In our previous research, sponsored in part by the Swiss National Science Foundation, we established the first insight into the importance of the ECM for healthy aging during longevity in *C. elegans* (Ewald *et al., Nature* 2015). We discovered that almost all longevity-promoting interventions enhance ECM gene expression and this ECM enhancement is essential and sufficient for delaying aging[10]. Furthermore, we uncovered tantalizing evidence for conservation of such an ECM gene expression enhancement in mice using published expression profiles[10]. Interestingly, long-lived mice have been characterized by a prolonged preservation of ECM integrity[11,12], suggesting that longevity interventions might also protect or maintain extracellular components through as yet unknown mechanisms.

Although numerous studies have pointed to a progressive decline in ECM integrity during aging, studying the *in vivo* role of ECM homeostasis during aging in mammals is complicated and is virtually unexplored in any organism. The model organism *C. elegans* provides unique opportunities to explore ECM integrity during aging, since: 1) *C. elegans* is transparent thereby allowing ECM components to be tagged by fluorescent proteins to directly monitor ECM homeostasis and integrity non-invasively *in vivo;* and 2) *C. elegans* is a well-established aging model because of its short lifespan and powerful genetics. For these reasons, using *C. elegans* is an innovative approach that enables us to gain insights into the mechanisms underlying how enhanced ECM gene expression extends healthspan, which remains unknown. Furthermore, our previous research suggests an exciting hypothesis of an active and probably conserved process (ECM gene expression enhancement) initiated by many longevity interventions. To address this hypothesis, we will address the following specific aims:

1. **Characterize the pro-longevity transcriptional program initiated by ECM enhancement.**
2. **Determine which cellular effects of ECM enhancement extend healthspan.**
3. **Identify novel regulators of ECM enhancement through unbiased genetic screening.**

With a panel of novel reagents including transgenic *C. elegans* strains, we approach this with a multifaceted plan consisting of functional, genetic, and molecular approaches to understand the link between ECM quality and aging. We will establish a platform to discover new mechanisms that are mobilized to promote healthy aging. We intend to use the pioneering work of identifying genes and mechanisms in *C. elegans* to build on, and to test these hypotheses in mice and in mammalian cell culture system as a long-term goal for our lab. We are particularly excited about the ability to translate results that spin off from our work to higher organisms “in house”. The Department of Health Sciences and Technologies (D-HEST) at the ETH Zürich is an excellent environment to succeed with our research goals because of the outstanding experts on yeast, mouse, and human aging, ECM architecture, ECM biomechanics, and ECM signaling integration working there, all of which contribute to a unique composition of interdisciplinary groups focusing on healthy aging. Our ultimate goal is to extend our new findings to humans and to initiate collaborations to establish novel therapeutic targets for clinical applications.

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