Understanding the interplay between DNA damage and metabolism in aging

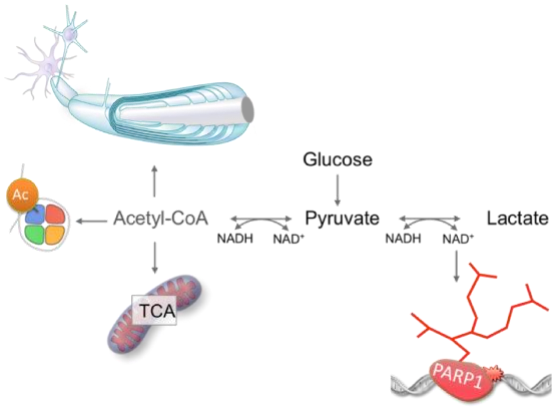

Figure 1. Intersection of markers of aging, DNA damage/repair with metabolism, as well as neurological and epigenetic outcomes

The goal of my PhD was to understand the effects of DNA damage on metabolism and how these two phenomena interact with age (Figure 1). There were four main outcomes from this work:

1) The ketogenic diet and furthermore ketones alleviate age-related phenotypes of Cockayne syndrome (CS).
2) Age-related metabolic remodeling takes place in order to compensate for decline in oxidative stress compensatory mechanisms, with age
3) Gait speed declines in both humans and mice, for different reasons: mice have a similar decline in cadence of the legs with age, while human gait speed decline is driven by a decline in overall step length.
4) Automated phenotyping of animal models with a newly developed platform and company, Tracked.bio.

Figure 2. Several model organisms were used in the first study along with computational methods

In the first and main outcome of this work, we unveiled two major findings: 1) a fruit fly homologue to the mammalian gene CSB 2) that ketones rescue features of CS. CS patients have a range of phenotypes from short lifespan (12 years average), neurodegeneration, and photosensitivity. This study employed three model organisms (fruit flies, cells and mice) as well

as an array of computational methods (Figure 2) to understand if a ketogenic diet was a viable option for CS patients, since no known treatment exists.

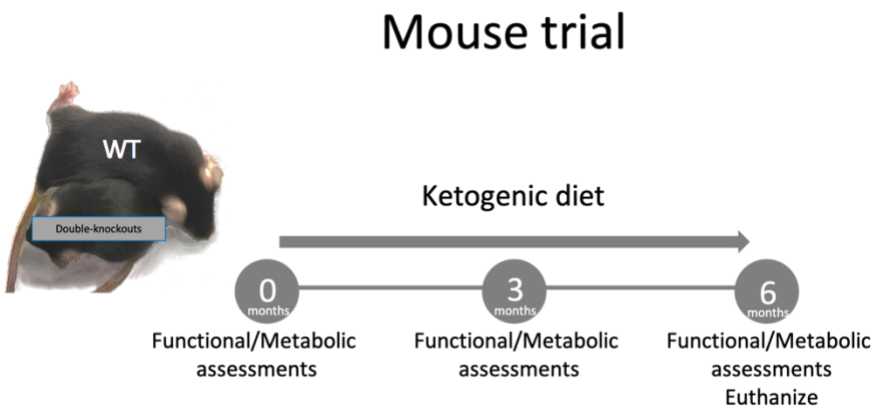

Figure 3. Mouse trial of ketogenic diet study

In order to obtain a comprehensive phenotypic understanding and ensure the study translatable to humans, we employed a mouse cohort (Figure 3), including double-knockout mice in order to exacerbate the phenotype of the single knockout $Csb^{-/-}$mice, which typically have a mild CS phenotype. The next major result from this first study was the discovery of a novel homologue in fruit flies to CSB. When knocking down this new homologue, lifespan is significantly reduced as well as producing other CS phenotypes similar in humans. We next wanted to understand why ketones are beneficial for Cockayne syndrome models, therefore we sought after the mechanism involved, which was also a major finding in this study.

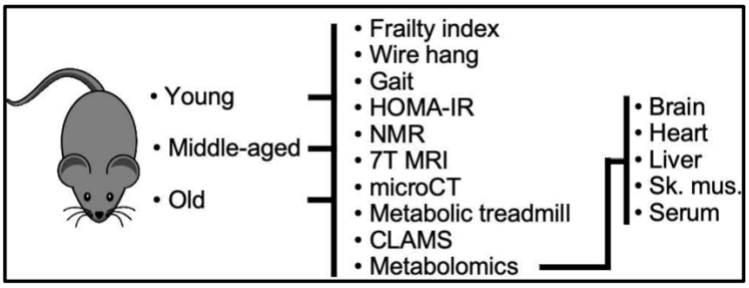

Figure 4. Battery of mouse metrics used in studies from outcomes 2 and 3.

The second and third outcomes of my PhD are overlapping in objective and mice cohorts. They utilize the same cohort of mice and both sought to discover trends with age in mice, and understand the comparison to humans and an established aging intervention. In outcomes 2 and 3, we assessed a battery of metrics (Figure 4) in mice over a wide range of ages. In outcome 3, we compared the aging gait trends of our mouse cohort to a human clinical trial cohort.

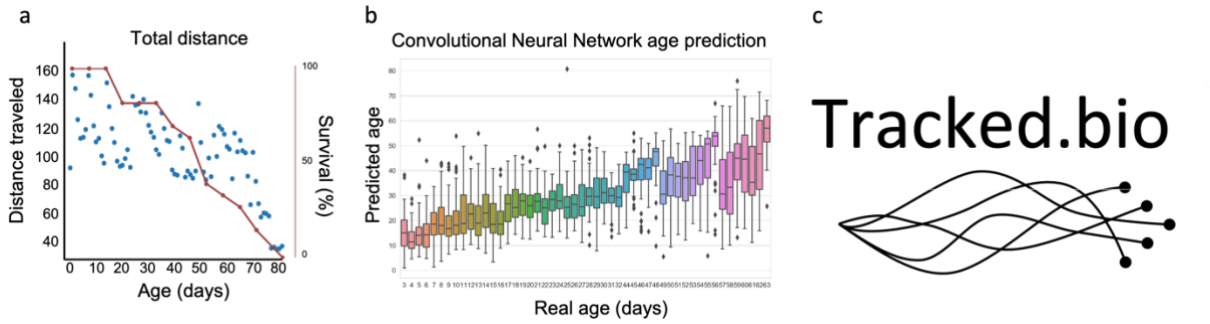

Figure 5. Tracked.bio a) Lifespan and distance traveled versus age, b) Age prediction using neural networks c) Tracked.bio logo

In the fourth and final outcome of my PhD, we developed a platform that automatically analyzes our animal models continuously. This was inspired by the very laborious nature of the fruit fly work. Additionally, we can obtain much richer information with this platform, such as continuous lifespan analysis combined with unique healthspan metrics (Figure 5a), and as well as age prediction (Figure 5b). This platform led to the spinout of our company, Tracked.bio (Figure 5c). This platform has recently since been expanded to mouse models as well.

In summary, my PhD consisted of 1) discovering a mechanism that could explain why a ketogenic diet benefits the premature aging disease Cockayne syndrome, 2) creating an understanding of the age-related changes of mice metabolically and functionally, and how a dietary, CR, reverses this metabolic change with age, and 3) developed a platform, Tracked.bio, which was utilized in my PhD research is spun-out into a company of its own.