Slow aging and thereby delaying the onset of all age-related diseases (e.g., heart disease, cancers) simultaneously is the ultimate preventative medicine, and it would increase life expectancy more than curing all cancers. Severely restricting dietary protein is one of the most effective ways to extend lifespan in lab animals, but it comes with costs including reduced reproduction and extreme hunger. Research on extending lifespan while minimizing these costs has focused on dietary protein. Eating high-quality protein (i.e., with the composition of the amino acid building blocks matching the needs of the animal) at the right quantity (less than generally recommended) can extend healthspan in some lab animals. Our recent research has sought to identify this ideal mix of dietary protein quantity and quality while also examining metabolic responses to these diets.

We have used the lubber grasshopper for our research with undergraduate students for 20 years. These unusual insects are large, flightless, poisonous to birds, and ubiquitous in the SE US in the spring and summers. They are easy to rear and large enough for harvesting multiple tissues for biochemical analysis. Grasshoppers in general, and locusts in particular, are major agricultural pests, and because of this grasshopper biology is well understood. We have capitalized on this body of knowledge to use grasshoppers as a biomedical research model. Further, because cellular and molecular mechanisms are well conserved across all animals, what we learn about the metabolism of grasshoppers has the potential to be applied to research on mammalian biomedical models such as mice, and potentially to clinical research.

My students and I have developed a custom diet with which we can adjust most of the amino acid composition of the dietary protein, and on which grasshoppers can thrive. The diets are custom prepared, and include a small amount of horse feed, lots of cellulose (aka., fiber), all the individual amino acids, two carbohydrates, cholesterol, and vitamins. Using this diet, we have identified that dietary protein composition matched to the composition of grasshopper egg yolk protein allows not only better reproduction, but also better development of juvenile males. In adult females, when offered at the right quantity, this diet statistically breaks the reproduction vs longevity trade-off. That is, when compared to the standard lab diet of lettuce, grasshoppers on the diet matched to egg yolk protein reproduce similarly (only 20% less, which was not statistically significant) yet they live 30% longer (statistically significant, and equivalent to ~25 years for humans). Therefore, we have identified a diet that mostly breaks the reproduction vs longevity trade-off that is ubiquitous in biology of aging research. This makes our lab primed for important discoveries on the physiological responses to this healthy, life-extending diet.

One such physiological response is a shift in the nutrients that are burned for fuel (i.e., to make ATP, the usable chemical energy in cells). Most animal tissues preferentially burn glucose, with burning fats the second choice, and burning amino acids a distant third. However, a recent body of literature has shown that burning some amino acids is critical to good health, and dysfunction in burning these amino acids is associated with age-related disease (diabetes, Alzheimer’s, Polycystic Ovarian Syndrome). We have found that the rate of burning the amino acid leucine is very low on a full diet of lettuce (which produces high reproduction but the shortest lifespan), very high on diets with an unbalanced mix of amino acids (which produces long lifespan but low reproduction), and intermediate on diets with the best balance of amino acids (which produce long lifespan and sustained reproduction). The rate of burning each amino acid affects the levels of metabolic intermediates, which in turn can affect health and lifespan (potentially through epigenetic changes). Taken together, we have identified a diet that mostly breaks the reproduction vs longevity trade-off, and in concert moderately increases the rate of leucine burning.

We hypothesize that this leucine burning (and not just leucine levels) is a critical component of a hale and hearty life. We intend to first characterize the association of longevity and leucine burning more fully. This will include testing some diets low in one amino acid (to increase burning of all other amino acids) or low in leucine and one other amino acid (to suppress burning of leucine specifically while burning of other amino acids is increased). In addition, on our (moderately) leucine-burning diet we will test other components of healthspan, such as anti-oxidant activities. Finally, we intend to experimentally test several predictions of the hypothesis, by pharmacologically increasing burning of leucine or using genetic manipulations to block burning of leucine.

In addition, in September 2025 I am submitting a proposal for an NIH Support for Research Excellence (aka., SuRE or R16) award. This project also addresses dietary protein quality, healthspan, and metabolism. Essential amino acids are required in our diet, because we cannot make them from other compounds. Non-essential amino acids are one that we can make from other compounds, but nonetheless are incorporated in our proteins (as are Essential Amino Acids). Nutritional epidemiological research (i.e., surveys of what people eat, linked to their health outcomes) supports high intake of protein for long-term health. Specifically, most research identifies consuming *plant* protein as healthiest. Plant proteins are higher in non-essential amino acids (non-EAAs) than are animal proteins. My proposed research will test an array of different dietary protein qualities, all with the same total amount of protein and calories, but varying in the EAA:non-EAA ratio, all without the potentially confounding variables of plant secondary compounds. Because survey research supports the benefits of eating plant protein, we predict that eating diets with relatively low EAAs and relatively high non-EAAs will be healthiest. The proposal is titled Sickening essentials, salubrious non-essentials: roles of dietary amino acids in healthspan. First, we will test the phenotypic outcomes on this array of diets, measuring metrics such as anti-oxidant activities, reproduction, lifespan, and muscle integrity. Next, after identifying the diets that produce full reproduction, long lifespan, and the best health, we will run a full metabolic analysis (aka, metabolomics) on grasshopper fat bodies (analogous to vertebrate liver). This study will identify the diet that produces the greatest healthspan, and then characterize the metabolism underlying this long-term health.