Developing biomarkers for human clinical trials to lower Advanced Glycation Endproducts (AGEs) in cases of diabetic pathologies, dementia and obesity.

Investigators: Pankaj Kapahi and Birgit Schilling

Unmet Need: Aging and hyperglycemia are two of the most significant risk factors for several age-related diseases, including diabetes, cardiovascular and neurodegenerative diseases in humans. However, there is a lack of therapeutics and biomarkers to target these risk factors in humans.

Background: Aging and hyperglycemia remain a major risk factor for the onset of several age-related diseases including diabetes, cardiovascular and neurodegenerative diseases in humans. Diabetes almost doubles the risk of death and onset of Alzheimer’s disease. However, the mechanism of this increase in mortality and enhanced risk of dementia are not currently understood. We hypothesize that AGEs, which accumulate with age and hyperglycemia are a driving force in causing several diabetic pathologies and dementia. Thus to develop viable therapeutics that lower AGEs we need to develop a panel of biomarkers that can report the status of AGEs in humans. AGEs are a form of molecular damage in which distorted sugars attach themselves to proteins and DNA. Previous work using both in vivo and in vitro approaches supports the notion that AGEs can contribute to increased diabetic pathologies and neurofibrillary tangle formation due to glycation of tau protein which makes it more prone to aggregation, contributing to AD pathology. The Kapahi Lab has screened for compounds to lower AGEs. Some of these compounds activate a conserved cellular pathway through which AGE can be sensed and detoxified, which was recently identified by the Kapahi lab. The Kapahi lab has created a cocktail of 5 commonly used supplements in humans that can significantly lower the damage from accumulation of AGEs in worms and mammalian neurons and mice. These compounds protect mammalian neurons from the toxic effects of several stressors tested. Furthermore, this cocktail provides significant protection in a mouse model of obesity by reducing diabetic pathologies and weight gain.

Novel Hypothesis: We hypothesize that AGEs that are known to accumulate with age and in hyperglycemia, are drivers of dementia and diabetic pathologies. A cocktail of therapeutics that lower AGEs will lower the risk of dementia and diabetic pathologies in humans. To determine which individuals are the best to receive such AGEs lowering therapy and determine the efficacy of clinical trials there is a need to develop appropriate biomarkers in mammals.

Proposal: The Kapahi and Schilling lab proposes to develop human serum and urinary biomarkers to track the efficacy of compounds that lower AGEs and identify the appropriate patients to receive this treatment. These markers will include measurements of AGEs, glycated
proteins, and markers of inflammation and senescence that accompanies diabetes. We will use both mouse and human samples from controls and patients with diabetes and dementia for the study.

**Aim 1.** Measurement of biomarkers of AGEs in diabetic mice treated with a cocktail of compounds that lower AGEs. The Kapahi lab has identified a cocktail of 5 compounds that are ‘generally recognized as safe’ (GRAS) that prevent diabetic pathologies, weight gain and shortened lifespan in a mouse model of obesity (Figure 1). We will measure multiple biomarkers of AGEs, glycated proteins and markers of inflammation and senescence that accompany diabetes in the sera, urine, and tissues of these mice.

**Aim 2.** Measurement of biomarkers of AGEs in human patients with diabetes and dementia. We will measure multiple biomarkers of AGEs, glycated proteins, and markers of inflammation and senescence in human samples. We will use serum and urine samples from controls and patients with diabetes and dementia for this study.

**Impact:** This project will provide evidence of whether our biomarkers for AGEs change in diabetic and obese mice that have been treated to lower AGEs. Furthermore, the proposal will determine whether human patients that suffer from diabetes also show relevant biomarkers related to AGEs. This work will set us up to conduct clinical trials with our unique cocktail of 5 compounds to slow diabetic pathologies and dementia. As these compounds are safe in humans this will not need approval from the FDA. Our work will enable the identification of molecular targets for drug discovery that could prevent Alzheimer's diseases and related dementias in both diabetics and non-diabetics.

**Specialized Equipment Needs:** the Schilling lab has most of the equipment necessary for the project.

**Figure 1.** The impact of treating obese mice (missing the leptin receptor) with a cocktail of compounds that reduces advanced glycation endproducts (AGEs). On the left is the untreated mouse and on the right is a mouse treated with the cocktail for 2 months.