LAY ABSTRACT

The importance of dietary factors in the prevention of chronic diseases was recently emphasized by Walter Willet in his Ancel Keys Memorial Lecture ; he stated that, “From our long-term studies, we have calculated that **modest dietary changes**……**can reduce rates of coronary heart disease by more that 80%.** Failure to take advantage of dietary and lifestyle means of preventing these diseases represents a tremendous lost opportunity for improved health and well being”. It has been estimated that, “by 2050, approximately 30% of people in industrialized countries will be 65 years old or older. Aging is associated with increased risk for neurodegenerative disorders, which can cause significant cognitive and physical impairment and shortened lifespan, thereby causing a burden to society.” Timely nutritional interventions, compared to those of synthetic pharmaceuticals, have a promise of safe and cost effective remedies that may contribute to the amelioration of age related neurodegenerative diseases.

Epidemiological data show that populations that consume diets rich in fruits and vegetables have low incidences of chronic diseases. However, intervention studies with antioxidants such as α-tocopherol (AT), vitamin C or β-carotene, which have been conducted in middle aged humans, have shown little or no efficacy. The cause(s) of this discrepancy remains to be clarified. Our **primary hypothesis** is that dietary phytochemicals modulate **epigenetic events** during early development of humans and laboratory animals and sensitize their genomes to the phytochemicals and their metabolites, for life. We further hypothesize that the molecular actions of diets enriched in phytochemicals are mediated by non-antioxidant actions through **members of nuclear receptor superfamily (NRS).** This hypothesis **may account for the data** from epidemiological studies which were obtained from cohorts who eat fruit and vegetable-enriched diets since childhood, and for the failure of dietary antioxidant-supplement interventions in adults. Our hypothesis also **predicts** that maximum effects of phytochemicals can be realized by dietary interventions EARLY during human development.

We propose to test this hypothesis in transgenic mice that display quantifiable and preventable AT-sensitive phenotypes. Extra-hepatic tissues, including the central nervous system, of our transgenic mice are AT-deficient at birth in spite of feeding a normal AT-diet. The mice **display ataxia and fail to maintain body weight with aging**; symptoms also observed in aging humans and in patients with mutations in AT transfer protein (ATTP) which determines systemic AT. The disease phenotype of our mice can be **prevented** by **increasing** dietary AT of pregnant or of young ATTP deficient (ATTP-KO) mice, and in children but not in adults with mutations in the ATTP gene. The significance of these observations is that the ATTP-KO mouse offers an *in vivo* model for defining molecular and cellular mechanisms relevant to **age-nutrition-gene** responsive ataxias, and possibly other neurological deficits in humans. In addition, our previous studies in mice fed flavonoid enriched *Ginkgo biloba* leaf extract suggest induction of synaptic genes that are also responsive to dietary AT. Thus, **phytochemicals such as AT, and polyphenols of fruits and vegetables may act through common signaling pathways, such as those offered by nuclear receptors, *in vivo* and confer protection against chronic diseases.**

If our hypothesis that EARLY nutritional interventions with phytochemicals are more effective in preventing age-related chronic diseases is validated, then the data from our research may prove useful in formulating recommendations on the composition of diets enriched in fruits and vegetables, and the timing of their interventions for optimum health benefits with aging.