Alabama at Birmingham, Birmingham, Alabama, United States, 2. University of Vermont, Colchester, Vermont, United States, 3. Columbia University, New York, New York, United States

One of the benefits of this large, national cohort study with black and white participants is the opportunity to involve a breadth of researchers in the science. REGARDS actively solicits and engages early career and minority investigators to lead or participate in manuscripts as well as ancillary studies. REGARDS has provided opportunities for >175 ancillary studies, including those that enrich existing outcomes, provide new outcomes, assess new exposures, link with other national data, support extended analyses, and assess genetic associations. Over 70% of the 500+ publications to date have a lead author who was not a funded REGARDS investigator. In this presentation, we will discuss some of the innovative ancillary studies and high-impact manuscripts that have grown out of REGARDS, the processes for developing an ancillary study/manuscript, and the procedures for obtaining REGARDS data. We will describe opportunities for mentored research for junior investigators, as well as independent research projects.

SESSION 7715 (SYMPOSIUM)

REVERSING COGNITIVE DECLINE IN AGING: REVERSIBLE MECHANISTIC DEFECTS AND A NOVEL NUTRITIONAL INTERVENTION

Chair: Rajagopal Sekhar
Co-Chair: George Taffet

Aging is the biggest risk factor for cognitive-decline and Alzheimer's disease (AD), but underlying mechanisms are not well-understood and interventions are lacking. Cognitive-decline in AD has been associated with deficiency of glutathione, (the most abundant, intracellular, antioxidant protein), elevated oxidative-stress, insulin-resistance and increased inflammation. We identified and reported that glutathione-deficiency and oxidative-stress in older-adults occur due to decreased availability of precursor amino-acids glycine and cysteine, and can be corrected with GlyNAC (a combination of glycine and the cysteine precursor N-acetylcysteine). We hypothesized that cognitive decline in older-adults is linked to glutathione-deficiency, mitochondrial-dysfunction, oxidative-stress, insulin-resistance, and inflammation. The first abstract discusses the rationale and findings of an open-label clinical trial: compared to young-humans, older-adults had cognitive-decline, glutathione-deficiency, mitochondrial-dysfunction, abnormal glucose-metabolism and insulin-resistance, oxidative-stress, endothelial-dysfunction and inflammation. These defects were improved/reversed by supplementing GlyNAC for 24-weeks, but benefits receded on stopping GlyNAC for 12-weeks. The second abstract presents a study in 8 young (20-weeks old) and 16 aged (90-weeks old) wild-type male C57BL/6J mice where we found that aged-mice had naturally-occurring cognitive-impairment, and brain defects in glutathione-deficiency, oxidative-stress, glucose-transport, mitochondrial glucose-oxidation, insulin-resistance, endoplasmic-reticulum stress, autophagy, mitophagy, inflammation, senescence, genomic and telomere damage. Aged-mice received either GlyNAC or isonitrogenous-placebo supplementation for 8-weeks, and only GlyNAC-fed mice improved cognition and brain defects. Collectively these data highlights the discovery of novel and reversible mechanistic defects in older-adults and aged-mice with naturally-occurring cognitive-decline, and identifies that supplementing GlyNAC can improve brain-health and cognition. These findings could have important implications for reversing cognitive-decline in older-adults, and AD.

REVERSING COGNITIVE-DECLINE IN OLDER ADULTS IN AN OPEN-LABEL CLINICAL TRIAL: NOVEL MECHANISMS AND THE ROLE OF GLYNAC

Chun Liu, Rajagopal Sekhar, Premranjan Kumar, Charles Minard, and Shaji Chacko, *Baylor College of Medicine, Houston, Texas, United States*

Age-associated cognitive-decline is an important risk factor for Alzheimer's disease, but interventions are lacking. We conducted an open-label trial to test our hypotheses on whether: (1) compared to 8 healthy young adults (25y), 8 'healthy' older adults (74y) have cognitive decline, decreased glucose availability for the brain due to mitochondrial dysfunction, elevated insulin-resistance, oxidative-stress and elevated inflammation; (2) supplementing glycine and N-acetylcysteine (GlyNAC) for 24-weeks corrects deficiency of the endogenous-antioxidant Glutathione and improves these defects, and thereby cognition; (3) stopping GlyNAC supplementation for 12-weeks results in a decline in accrued benefits. Outcome measures included cognitive testing (Montreal cognitive assessment; trail-making tests; verbal-fluency tests; digital-symbol substitution-test), mitochondrial fuel-oxidation, RBC-Glutathione concentrations, plasma oxidative-stress, insulin-resistance and inflammation, and tracer-studies to measure glucose metabolism. Results validated our hypotheses and showed that GlyNAC-supplementation corrected these defects and improved cognition. This trial suggests that supplementing GlyNAC may be important for improving/preventing age-associated cognitive-decline in older adults.

REVERSING MITOCHONDRIAL, METABOLIC AND MOLECULAR DEFECTS IN THE BRAIN IMPROVES COGNITION IN AGED MICE

Rajagopal Sekhar, and Premranjan Kumar, *Baylor College of Medicine, Houston, Texas, United States*

Age-associated cognitive-decline is a risk factor for Alzheimer's disease (AD), but mechanisms are not well understood, and interventions are lacking. Rodent studies on AD have not led to therapeutic breakthroughs for cognitively-impaired humans. In an open-label trial in older-adults we found that supplementing GlyNAC (glutathione precursors glycine and N-acetylcysteine) improved cognitive-decline, defects in whole-body mitochondrial-function, and systemic insulin-resistance, oxidative-stress, and inflammation. We hypothesized that aged-mice will have similar defects in the brain, and studied male C57BL/6J mice as follows: young-mice (20w) were compared to two-groups of aged-mice (90-weeks) receiving either GlyNAC or isonitrogenous-placebo diets for 8-weeks. GlyNAC-supplementation improved cognition, and the following measures in the brain: glutathione-concentrations, glucose-transporters in blood-brain-barrier and neurons, mitochondrial glucose-oxidation, oxidative-stress, endoplasmic-reticulum stress, autophagy, mitophagy,