"Translational Studies of Neural Mechanisms of Chemotherapy-induced Cognitive Changes"

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Abstract: Cognitive changes associated with chemotherapy are an important clinical problem; yet mechanisms and treatments for chemotherapy-induced cognitive changes have not been identified. The overarching goal of this proposal to bring together an interdisciplinary team of investigators to conduct synergistic clinical and animal studies designed to examine mechanisms of and treatments for chemotherapy-induced cognitive changes. Clinical studies will evaluate breast cancer patients treated with AC-T and a cohort not exposed to chemotherapy pre- and one month post-treatment with structural and functional MRI neuropsychological tests, and measures of constitutive and oxidative DNA damage in order to test the hypothesis that chemotherapy will be associated with reduced hippocampal volume and activation and that these changes will be related to the degree of DNA damage. DNA will be stored so that genes that modulate neural and DNA repair, oxidative stress, and neurogenesis can be examined with future funding. Parallel animal studies with the agents from AC-T will examine behavioral changes in hippocampal-mediated memory tasks, disruption of hippocampal neurogenesis, and the protective effects of an antioxidant agent, ebselen. Establishment of this interdisciplinary research team, and the design of a set of convergent, hypothesis-driven, translational experiments, will provide the pilot data necessary to seek NIH/NCI funding to expand the clinical cohort and to examine long-term cognitive changes, to examine other components of breast cancer treatment (e.g., endocrine treatments, steroids) on cognition, and extent the animal model studies with the goal of identifying novel mechanisms for CNS toxicity associated with chemotherapy and the evaluation of mechanism-based interventions.