Clinical and Translational Approaches to Cognitive Impairments in Breast Cancer

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Background: While chemotherapy has greatly improved survival for cancer patients, the side effects of this treatment can lead to substantial detrimental effects on quality of life that can be debilitating. Chemotherapy-related cognitive impairment (CRCI) is characterized by difficulty in memory, attention, concentration and executive function. CRCI is most pronounced and severe during chemotherapy (in up to 80% of patients); however, it can last for years following treatment in up to 35% of survivors. With over 13 million cancer survivors in the US, it is estimated that up to 4 million survivors could be living with long-lasting effects of CRCI. CRCI is particularly significant because long-term cognitive impairment can develop, CRCI negatively impacts quality of life, and CRCI can affect treatment adherence. Little is known about the biological mechanisms contributing to CRCI development, though studies suggest that increased inflammation may be involved. **Methods:** This research involves a novel combination of animal modeling and human research to address the role of inflammation in CRCI, and also uses animal modeling to develop interventions that will lead to clinical research studies. We are proposing a clinically relevant CRCI mouse breast cancer tumor model with Adriamycin and Cytoxan chemotherapy to study the effects of cancer and chemotherapy on memory function using cognitive assessment and neuroimaging, as well as the contributing role of key cytokine- and chemokine-mediated immune pathways that contribute to neurotoxicity involved in CRCI. We will use the immune and neurotoxicity factors identified in the CRCI animal model to assess whether they are relevant to the human condition in a breast cancer cohort also receiving the same chemotherapy paradigm and who will also receive similar cognitive assessment and neuroimaging as in the animal study. We will also utilize our mouse model to develop and test interventions for CRCI (including anti-inflammatory target agents, supplements, and physical activity) which will allow us to move forward with the most successful interventions for testing in clinical research. **Results and Outcomes:** The goal of this work is to understand the role of inflammation and other neuro-immune factors in CRCI; develop a clinically relevant animal model of CRCI; and to develop, test, and optimize interventions for CRCI in animal models in order to move them into clinical research protocols.