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Title: AGEing & RAGEing Defines Biosocial Synergism and its Role in Breast Cancer Disparities

Funding for this Team Science Project is requested to build on the team's transdisciplinary data to support the submission of an NCI Cancer Disparities Program Project Grant (P01: PAR-23-059) in September 2025. The overall objective of the Program is to gain a better molecular understanding of how "biosocial synergism" between lived experiences and individual biology contributes to the enduring nature of cancer disparities.

By addressing health inequity, disparities in overall cancer outcomes have been reduced. Despite this success however, disparities in cancer incidence and mortality persist and have even increased for some cancers. While health inequities undoubtedly remain the predominant factor, debate persists as to whether cancer disparities arise solely out of social drivers, or do other factors such as individual biology play an accompanying role. To address an unmet need, the innovative concept of the proposed Program Project is that the pathophysiological process of non-enzymatic glycoxidation and the accumulation of reactive metabolites called advanced glycation end products (AGEs) represent a biosocial driver of health that informs on the molecular consequences of biosocial synergism on enduring cancer disparities.

The overall hypothesis for the Program is that increased AGE bioavailability due to the influence of biosocial synergism on non-enzymatic glycoxidation is a key effector of malignant progression through its influence on receptor for AGE (RAGE) mediated cellular crosstalk in the tumor microenvironment (TME). The overall goals of the combined Program include: **1:** To define the reactive intermediate and AGE signatures associated with biosocial synergism and its ability to perpetuate a cycle of AGE-RAGE mediated cellular crosstalk in the TME; **2:** To show that increased glycoxidation perpetuates a cycle of AGE-RAGE mediated immune and metabolic dysfunction in the TME; **3:** To associate AGE exposure and BCa outcomes with race/ethnicity and social drivers in large patient cohorts; and **4:** To establish reducing AGE exposure through lifestyle and pharmacological intervention as a cancer prevention and control strategy.

Having shown that AGEs associated with biosocial synergism correlate with increased breast cancer risk and progression in large patient cohorts, and that increased AGE exposure through diet creates a tumor microenvironment conducive for malignant progression, funds are requested to achieve the following objectives deemed necessary before submission of the Program Project proposal: **i)** To generate additional supporting data for Research Project 2 to further deconvolute the complexities of ancestral immune differences and AGEs on breast cancer malignancy. **ii)** Establish a diabetes-cancer comorbidity mouse model to allow a mechanistic assessment of the influence of biosocial synergism on AGE biogenesis and malignant progression. Apart from generating additional data and experimental models, achieving the stated objectives will further demonstrate the strength of the research team and allow the publication of additional authored manuscripts.