PROJECT TITLE: **Understanding the molecular connection between Hyperglycemia and Cancer**

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**Project Description**

Background: Epidemiological studies indicate an association between type 2 diabetes (T2D), obesity and cancer. Diet rich in saturated fat and simple sugars has been identified as a risk factor for T2D. The scientific premise of this application is that, while epidemiological data is strong, very little is known about the molecular mechanisms by which high glucose utilization, alone or in combination with specific mutations determine cancer risk and disease progression. This is a relatively new and highly significant area of investigation. Despite strong epidemiological evidences showing co-occurrence of several human cancers including breast cancer with diabetes and obesity, the mechanisms are unclear. Particularly, whether excess tissue glucose utilization per se affects epithelial cell biology in hyperglycemic individuals is not well understood. The overarching challenge of this proposal is to objectively test if hyperglycemia causes aberrant glycosylation in mammary epithelial cells to increase the risk of breast cancer development and progression.

Objective/Hypothesis: The objective of this application is to examine if high glucose alters O\(^\text{GlcNAcylation}\) expression and stability of proteins involved in cell cycle and DNA damage response (DDR) pathway, and contribute to the development of breast cancer. O\(^\text{GlcNAcylation}\) is a process by which glucose is added to proteins; this process is known to be elevated in breast cancer patients. We are interested in studying these proteins because of the critical role of O\(^\text{GlcNAcylation}\) on cell cycle regulation and DDR pathway. In addition, many of these proteins are well known to be directly implicated in cancer progression. Our central hypothesis is that high glucose utilization induces alterations in O\(^\text{GlcNAcylation}\), expression and function of proteins involved in cell cycle and DNA damage response (DDR) pathway, and promotes mammary epithelial cell hyperplasia, alone or in combination with BRCA?predisposing mutations. To achieve this objective, we will use human primary mammary epithelial cells in culture, mouse models of breast cancer (with or without hyperglycemia), and patients with breast cancer (with or without hyperglycemia). This proposal addresses the following specific aims.

a) Specific Aim 1. To determine if high glucose impairs functions of cell
cycle and DDR proteins through aberrant OGlcNAcylation in human primary mammary epithelial cells in an insulin-independent manner.

b) Specific Aim 2: To determine if hyperglycemia promotes cancer development and progression in mouse models of breast cancer.