

EXECUTIVE SUMMARY [NON-CONFIDENTIAL, NON-TECHNICAL ABSTRACT FOR PUBLIC INFORMATION OR PROGRAM PROMOTION]: State the application's broad, long-term objectives and specific aims, making reference to the potential public benefits of the project relevant to California. Do not include proprietary or confidential information. This may be distributed before the funding decision has been finalized.

For the past twenty years my laboratory has been investigating the roles of protein kinases and phosphatases in the regulation of cellular function, more specifically glycogen metabolism. Protein kinases are important enzymes that alter protein function by covalently attaching phosphate groups (O-phosphorylation) to amino acids serine, threonine and tyrosine. The phosphatases reverse the action of kinases by removing these phosphates. We are now interested in another modification (O-glycosylation) that also occurs on serines and threonines. In this case there is enzymatic covalent addition of a single sugar termed N-acetylglucosamine (GluNAc) on to these amino acids. The enzyme that catalyzes this reaction is called O-GlcNAc transferase or OGT. Many proteins including some kinases are O-phosphorylated as well as O-glycosylated. The role of O-glycosylation is not clear. My laboratory is very much interested in determining the functional consequences of O-glycosylation. This is a change of direction for my lab from O-phosphorylation to O-glycosylation. We are also interested in the interactions of these two types of modifications at the molecular level. Undergraduate and graduate students will work on a project in which they will determine the possible role of O-glycosylation in the regulation of the activity of an important protein kinase termed glycogen synthase kinase-3 β (GSK-3). The site of O-glycosylation and its effects on GSK-3 β activity will be determined by determining K_m and V_{max} of the non-glycosylated and O-glycosylated GSK-3 β . Because O-glycosylation of proteins increases and glycogen synthesis decreases in diabetes, the students will also determine if any of the glycogen metabolizing enzymes is/are also O-glycosylated.