To date, there are no effective therapies that can counteract the damaging effects of cigarette smoke exposure in the lung. In fact, the age-adjusted mortality for chronic obstructive pulmonary disease(COPD) has risen 71% over the past thirty years. To improve this trend more effective strategies of treating the underlying disease mechanisms need to be developed. We have recently published that superoxide dismutase-1 (SOD1), a lung antioxidant, prevents cigarette smoke-induced inflammation and emphysema formation in mice. Further in our laboratory demonstrate that the transgenic expression of human SOD1 and glutathione peroxidase-1 (GPX1) decreases JNK activation and AP-1 signaling within the lungs of mice. Importantly, these events correlate with the antioxidant-mediated increase in protein phosphatase 2A (PP2A) activity. This is significant since PP2A is the primary serine threonine protein phosphatase present in all eukaryotic cells. It dephosphorylates and inactivates both JNK and IKK; thus, PP2A is a major regulator of TNF signaling in the lung. PP2A is a heterotrimer enzyme composed of distinct isoforms of a structural subunit (A), a regulatory subunit (B) and a catalytic subunit (C). Post-translational modifications of the C subunit and dynamic exchange of variable B subunits regulate PP2A substrate specificity, activity, and intracellular distribution. PP2A activity is decreased by tyrosine phosphorylation of Tyr307 and disulfide cross-linking of the catalytic (C) subunit of the enzyme which are processes that are affected by reactive oxygen species(4, 5). SOD1 and GPX1 markedly increased protein phosphatase 2A (PP2A) activity in the lungs of these mice without altering PP2A expression or protein levels. Based on these findings, we hypothesize that redox balance can alter TNF signaling and smoke-induced lung injury by modfying PP2A activity in the lung.

Reversible phosphorylation of proteins is the most important reaction for regulating protein function in eukaryotic cells. The intracellular phosphorylation of proteins enables the cell to respond to environmental and nutritional stresses by regulating gene expression, cellular proliferation and cell differentiation. The cell contains a tightly coordinated network of kinases and phosphatases that switch proteins from the phosphorylated to the dephosphorylated state in order to cope with various physiological challenges. While a significant body of research has elucidated the role that protein kinases exert in this process, much less is know about the effects of protein phosphatases. As noted above, PP2A is the major serine-threonine protein phosphatase in all eukaryotic cells. In fact, it accounts for as much as 1% of total cellular protein and for a large fraction of overall cellular phosphatase activity. However, its effects on inflammatory lung diseases such as COPD have not been well studied. This proposal will advance public health by specifically determining how PP2A regulates the TNF signaling pathway which plays a pivotal role in the development of smoke-induced lung injury. This project will achieve these goals by addressing three fundamental questions:

1) Does redox balance affect PP2A activity by modifying the holoenzyme complex?

2) Does modifying PP2A activity alter TNF signaling and affect the development of injurious responses to cigarette smoke exposure in the lung?

3) Does PP2A alter TNF signaling within the lungs of emphysema subjects?

It is hoped that the insights gained from these studies will provide a more targeted approach of treating this disease. Importantly, our findings will have important implications for other diseases where TNF signaling and inflammation play a central role.