Yan Sanders, MD, Assistant Professor in the Division of Pulmonary, Allergy, and Critical Care Medicine, recently earned recognition and support for her different research efforts. Dr. Sanders was the primary investigator for the recently-published “Epigenetic Regulation of Caveolin-1 Gene Expression in Lung Fibroblasts.” Dr. Sanders was also awarded a National Institutes of Health R01 Grant for the project “Histone H4 Lysine16 Acetylation in Aging and Lung Fibrosis.”

In “Epigenetic Regulation of Caveolin-1 Gene Expression in Lung Fibroblasts,” Dr. Sanders and her colleagues examined Caveolin-1, or Cav-1, expression levels, DNA methylation status, and histone modifications associated with the Cav-1 promoter. Prior research showed that Cav-1 gene suppression by the pro-fibrotic cytokine TGF-β1 contributes to fibroblast proliferation and apoptosis resistance. Cav-1 has been shown to be constitutively suppressed in idiopathic pulmonary fibrosis (IPF). Dr. Sanders hypothesized that epigenetic processes contribute to Cav-1 down-regulation in IPF lung fibroblasts and fibrogenic stimuli.

Dr. Sanders and her colleagues discovered that methylation-specific PCR demonstrated methylated and unmethylated Cav-1 DNA copies in all groups. Despite significant changes in Cav-1 expression, there were no observed DNA methylation changes in CpG islands (CGIs) or CGI shores of the Cav-1 promoter by pyrosequencing of lung fibroblasts from IPF lungs, in response to TGF-β1, or after bleomycin-induced murine lung injury. In contrast, the association of Cav-1 promoter with the active histone modification mark, H3K4Me3, correlated with Cav-1 downregulation in activated/fibrotic lung fibroblasts.

This data indicated that Cav-1 gene silencing in lung fibroblasts is actively regulated by epigenetic mechanisms that involve histone modifications, in particular H3K4Me3. DNA methylation does not appear to be a primary mechanism. These findings support therapeutic strategies that target histone modifications to restore Cav-1 expression in fibroblasts participating in pathogenic tissue remodeling.

In “Histone H4 Lysine16 Acetylation in Aging and Lung Fibrosis,” Dr. Sanders aims to determine the mechanisms that regulate H4K16Ac in persistent lung fibrosis associated with aging, the role of H4K16Ac in regulating pro-fibrotic phenotypes in fibrotic lung fibroblasts, and the efficacy of targeting H416Ac in an aging mouse model of persistent lung fibrosis. The active histone mark H4K16Ac epigenetically regulates gene expression. Preliminary data demonstrated the dysregulation of this histone modification in IPF fibroblasts.

Dr. Sanders hypothesizes that age-related histone modifications, in particular H4K16Ac, mediate fibrotic cell phenotype, promote senescence, and induce apoptosis resistant lung fibroblasts which cause persistent fibrosis in aging. Targeting this histone modification will alter pro-fibrotic cell phenotypes and promote resolution of fibrosis. This study will evaluate the efficacy of modulating specific histone modification to be used as a therapeutic method for IPF.