Translational approach to the treatment of COPD

Exposure to tobacco smoke is a major risk factor for chronic obstructive pulmonary disease (COPD) with the ultimate tissue destruction in emphysema resulting from an imbalance in protease/antiprotease activity. Our laboratory has demonstrated that lung parenchymal cells in patients with emphysema express MMP-1 as opposed to smokers without the disease and through in vitro and in vivo studies we demonstrated that cigarette smoke can directly induce MMP production in epithelial cells in a MAP Kinase dependent fashion. Subsequent studies identified a novel cigarette smoke responsive (CSR) element within the promoter region of MMP-1. We further delineated the upstream signaling pathway regulating MMP1 induction by cigarette smoke and identified TLR4 as an important regulator of the induction of MMP1. After the identification of the CSE in MMP-1 we used this knowledge to develop a novel mammalian cell–based assay to screen for inhibitors to the smoke induced MMP1 pathway by transfecting a human cell line (HEK 293T) with a vector containing a luciferase reporter gene under the control of the MMP-1 promoter. Using this novel cell based system we screened an NIH library of compounds and identify novel compounds that exhibited strong activity in our assay. This screening has led to several candidate molecules we are pursuing for the treatment of emphysema. We also screened a plant-based library in our system and were able to identify a new depside, jaboticabin, isolated from the fruit jaboticaba, in our assay. Future studies will elucidate the role of these compounds in treating emphysema.