Malignant mesothelioma (MM) is an aggressive, devastating, cancer of the pleural/peritoneal mesothelium causally related to asbestos exposure. Despite this knowledge, the mechanism by which asbestos causes MM is poorly understood. There is an urgent need to identify mechanisms and treatment targets that will aid early detection prevention and treatment.

We have shown that asbestos exposure of human mesothelial cells (HMCs) leads to the activation of the NLRP3 inflammasome and an increase in the secretion of the inflammasome products, IL-1β and IL-18. The activation of the inflammasome by asbestos is protracted in mesothelial cells which led us to hypothesize that the inflammasome and its products play a crucial role in the tumorigenesis of MM by promoting a mesothelial to fibroblastic transition (MFT). Our studies using an EMT PCR array revealed that asbestos exposure results in the down regulation of E-cadherin and KRT19 among others. Decreases in protein expression of epithelial markers in response to asbestos exposure where observed while levels of mesenchymal markers were increased. The secretion of various cytokines including FGF2 and TFPI2 were also upregulated after asbestos exposure. Knockdown of NLRP3 by siRNA attenuated various parameters, suggesting a role for inflammasomes in the process. In vivo studies in wild type and knockout mice showed that asbestos exposure causes a thickening of the parietal peritoneal mesothelium and an early increase in IL-1β and IL-18 in the peritoneal lavage fluid. An increase in mesenchymal proteins was also observed in the mesothelium. Taken together, our results indicate that asbestos exposure increases secretion of IL-6 and IL-8 in an IL-1β dependent manner while compromising the fibrinolytic capacity of the mesothelium. This altogether leads to MFT and may eventually result in MM development.