Due to the increased prevalence of obesity, non-alcoholic fatty liver disease (NAFLD) has become a major public health problem in the Western world and Asian countries. Approximately a third of the general population in the US has NAFLD. NAFLD includes a spectrum of histological characteristics ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis and can be characterized into two major phenotypes: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Water disinfection byproducts like trihalomethanes can act as crucial risk factors for NAFLD progression. Here I have studied the molecular mechanisms of a water disinfection byproduct, Bromodichloromethane, in induction of hepatic inflammation and fibrogenesis. I found that Bromodichloromethane (BDCM) can induce hepatic fibrogenesis and NASH by inducing leptin mediated activation of NADPH oxidase and subsequent increase in microRNA21 expression, resulting in augmented hepatic TGFβ signaling. I also explored the hepatoprotective effects of a plant derived TLR4 antagonist Sparstolonin B (SsnB) and found that it inhibited BDCM induced TLR4-Flottilin co-localization, decreased microRNA21 expression and reduced the expression of a myriad of inflammatory markers in liver when administered in vivo. Similar effects of SsnB were also observed in cell
culture model of kupffer cells. Anti-fibrotic and anti-proliferative mechanisms of SsnB were observed in a BDCM induced mice NASH model and in hepatic stellate cell (HSC) culture. Mechanistically, SsnB decreased activation and pro-fibrogenic proliferation of
HSCs. SsnB could inhibit hedgehog signaling pathway, decreased proliferation and induced apoptosis in HSCs. SsnB decreased TGFβ signaling by upregulating BAMBI and decreased STAT3 activation in HSCs. SsnB also changed the morphology of fibrogenic stellate cells by downregulating focal adhesion adaptor protein and stress fibers. Thus my research unravels novel molecular mechanisms of hepatic fibrogenesis in NASH and proposes the use of Sparstolonin B to ameliorate hepatic inflammation and fibrosis in NASH.