Primary biliary cholangitis (PBC) is an incurable, long-term liver disease, characterized by the blockage of bile flow, which leads to dysfunction and in consequence, liver transplantation. The obstruction of bile flow is accompanied by the ongoing inflammation what is manifested by the presence of autoantibodies in sera of PBC patients. PBC affects primarily middle-aged women and often is associated with complications severely affecting the physical and psychological condition of patients such as: fatigue, pruritus and enhanced osteoporosis. The terminal stages of most cholangiophaties are characterized by disappearance of intrahepatic bile ducts (ductopenia), which are the results of an imbalance between cholangiocyte (epithelial cells lining bile ducts) death and proliferation. In PBC rates of proliferation and apoptosis are similar in the early-compensated stages of the diseases while, in the terminal decompensated stages, the inefficacy of proliferation leads to ductopenia, and thus to the clinical manifestations of overt cholestasis In the last years agents and mechanisms modulating cholangiocyte proliferation have been extensively investigated. In addition, estrogens stimulate the secretion of different growth factors in proliferating cholangiocytes. By acting on estrogen receptors and by activating either genomic or non-genomic pathways, estrogens play a key role in the complex loop of growth factors and cytokines, which modulates the proliferative response of cholangiocytes. Interestingly, our preliminary data have shown that DHEA - estrogen precursor enhances proliferation of cholangiocyte and protects them against oxidative stress. **Thus, the aim of this project is to establish the role of DHEA and its metabolites in PBC development. In particular, we plan to check what kind of receptor is involved in this protection and proliferation of cholangiocytes (NHC, MMNK1) and hepatocytes (HepG2, PHH) and whether DHEA and its metabolites can enhance anty-inflamatory response in those cells. This study addresses also the role of estrogens sulfation in PBC development.** Since sulfation can modulate estrogens action we will analyze the level of SULT1A1 and SULT1E1, which play a major role in the endogenous sulfation of steroids and estrogens, and their activities in the liver likely contribute to inhibition of estrogens action and in consequence may lead to the development of PBC.

To sum up, since factors responsible for the progression of PBC are still poorly understood we will investigate the potential associations between cholangiocytes proliferation and the estrogens action triggered by dehydroepiandrosterone (DHEA), which is well-known precursor of estrogens. Chemical structure of DHEA is similar to testosterone and estradiol thus it can be easily converted into them. DHEA is produced naturally in the human body and peak level of DHEA production is observed around age 20, which is followed by an age-dependent decline. Thus we suspect that DHEA might provide a new strategy for the management of PBC, which affects mostly middle-aged women.