Biliary diseases, also known as cholangiopathies, are a diverse group of chronic liver diseases, primarily affecting the epithelial cells (cholangiocytes) lining the intra- and extra-hepatic bile ducts. Cholangiopathies include several rare diseases but collectively are an important cause of morbidity and mortality among the pediatric and young adult population and represent a burden of modern hepatology. A major unmet need in cholangiopathies is the lack of in vitro human models to study the pathogenesis of the disease and to validate potential therapeutic targets. In this talk I will discuss novel in vitro systems of cholangiocytes based on the use of induced pluripotent stem cells (iPSC) and liver organoids. I will talk about modeling cystic fibrosis-related liver disease using iPSC-derived cholangiocytes. I will show how perturbing the extracellular matrix we can change the polarity of biliary organoids and how this can be exploited to study the interaction with other cell types and with pathogens as a tool to model more complex biliary diseases.