

## ***Bile acid-regulation of mast cells in models of primary sclerosing cholangitis and cholangiocarcinoma***

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### **Lay summary of progress to date:**

**Background:** Primary Sclerosing Cholangitis (PSC) and the primary liver cancer, cholangiocarcinoma are devastating liver diseases that target cells within the liver called cholangiocytes. These diseases have limited treatment options. Patients that present with PSC have a higher incidence of developing cholangiocarcinoma. When cholangiocytes (that line bile ducts where bile flows out of the body) become damaged and ducts become blocked, cholangiocytes will increase in number and this disrupts the normal state of the liver and bile flow. Bile acids are synthesized by the liver to aid in the digestion of foods and the secretion of bile. Patients with liver disease are frequently treated with bile acid therapy to improve liver function. Ursodeoxycholate is a secondary bile acid that is used in patient therapy for PSC and has been found to have beneficial effects in patients suffering from these diseases. Besides cholangiocytes, mast cells (inflammatory cells that release histamine in the body) are found in the liver and increase in number during liver disease. When mast cells are treated with bile acids there is a release or blockage of histamine release (depending on the type of bile acid).

**Update on research:** To date, we have found that mast cells infiltrate the liver during PSC and cholangiocarcinoma progression. Once these cells migrate to the liver they release numerous mediators that can negatively impact a patient's prognosis. One of the main factors released is histamine that can contribute to the progression of liver injury or tumor growth. Since we have found a large number of mast cells in the liver following injury, we recently developed a technique to isolate or extract these cells from rodent liver giving us a tool to better examine their effects on PSC and cholangiocarcinoma models. Further, following treatment with cromolyn sodium, a compound that blocks the release of histamine from mast cells, we have demonstrated that there is a decrease in liver fibrosis (which is a consequence of diseases like PSC) and tumor growth. We have found that treatment with ursodeoxycholate decreases the release of histamine from mast cells, which may also be an important finding in the treatment of fibrosis or cholangiocarcinoma. Our results demonstrate that targeting mast cells may be a potential therapy for patients suffering from PSC and cholangiocarcinoma.