Draft PSC Partners Research Agenda

Note: More specific research questions have been identified, but will not be presented at the conference in the interest of time. After receiving feedback at the conference, PSC Partners will begin to prioritize 5-10 questions into a Strategic Research Plan. With support from the ICRNetwork, we will detail the most important research projects, experimental strategies, and resources under each bullet point.

What is the initial cause of PSC?

- How do genetic risk factors predispose to PSC?
- How do environmental risk factors predispose to PSC?
- Is PSC an autoimmune disease?
- To what extent does recurrent PSC recapitulate the initial injury in PSC?
- What role does the gut-liver axis, including intestinal inflammation and microbiota, play in the initiation of PSC?

What causes PSC to progress?

What is the link between the gut and liver in PSC?

- How do microbes in the gut and bile ducts contribute to liver inflammation, fibrosis, and cirrhosis?
- How do bile acids contribute to PSC progression?
- Is there a role for homing of gut-primed T cells to the liver in PSC?
- What is the relationship between PSC and IBD?
- How does the IBD phenotype associated with PSC differ from that observed in patients without PSC?
- What are the factors impacting the clinical features of IBD in PSC?
- Is there a role for gut barrier dysfunction in PSC?
- How does PSC-UC increase the risk of CRC?
- How do we modulate the gut-liver axis to slow or stop the progression of PSC?
- How do we target mechanisms of microbial metabolite synthesis, conjugation, and signaling in order to slow or stop progression of PSC?

What is the nature of the inflammation in PSC?

- What are the phenotypes and functions of the different immune cell subsets in the gut, peribiliary glands, and bile duct in PSC? Is there evidence for a common antigenic target?
- Do autoantibodies in PSC contribute to pathogenesis?
- Do Th17 cells and neutrophils contribute to PSC pathogenesis?
- What is the ideal therapeutic strategy to target immune mechanisms in PSC? How does the effectiveness of immune-targeted therapy change over the course of disease progression?

What is the nature of fibrosis in PSC?

- What causes the initiation and progression of fibrosis in PSC?
- What are the phenotypes of cell types involved in the fibrotic scar in PSC?

- To what extent are fibrotic mechanisms unique to PSC?
- What role do cholangiocytes play in perpetuating inflammation and fibrosis in PSC?
- How do we target mechanisms of fibrosis in order to slow or stop progression of PSC? Can fibrosis be reversed?

How do genes and the environment contribute to PSC pathogenesis?

- What role do risk alleles play in the progression of PSC?
- How do environmental exposures modify the progression of PSC?
- Do somatic mutations in the bile duct contribute to the progression of PSC?
- How does diet modify the progression of PSC?
- What are the shared and divergent genetic risk factors among diverse populations?
- How do we modulate environmental factors to slow or stop progression of PSC?
- How can we use genetic findings to identify and therapeutically target pathways driving PSC pathogenesis?

How do we detect PSC early, monitor it effectively, and predict long-term prognosis?

- What are the best tools to measure inflammation, fibrosis, and cholestasis in PSC?
- In striving to diagnose PSC earlier, which biomarkers and tools are needed to screen patients at risk for developing PSC?
- How can we predict long-term treatment response and treatment efficacy using noninvasive biomarkers?
- How can we predict the course of disease upon diagnosis with PSC?

How do we improve and accelerate the development of new treatments for PSC patients?

- What are the best surrogate endpoints to predict treatment response?
- How do we reduce the number of PSC patients enrolled in placebo arms in clinical trials?
- How can we leverage patient-reported outcome measures to support clinical trials?
- What factors contribute to heterogeneity in PSC? How do we define PSC?
- How do the mechanisms driving PSC progression change throughout disease course?
- How do we support effective patient recruitment into clinical trials?

How do we improve transplantation rates and success?

- How do we increase access to liver transplant?
- How do we improve post-transplant outcomes in PSC?
- Can we pursue novel technologies for liver replacement in PSC?

How do we prevent the development and progression of cholangiocarcinoma (CCA) in PSC?

- What aspects of PSC contribute to the development of CCA?
- How can we best treat PSC in order to prevent the development of CCA?
- How do we detect CCA while it is still curable?
- How is the CCA associated with PSC different from sporadic CCA?
- How does the transition of PSC to CCA inform our understanding of the underlying mechanisms of PSC?