Accelerating PSC Research As a Collective Network

We hope this document will serve as an educational reference and resource that you may come back to frequently as you consider your own hopes and needs for PSC research.
Don't forget that YOU are part of this Collective Network!

What progress has PSC Partners made since the last in-person conference?

In 2019, PSC Partners received training and funding through the Chan Zuckerberg Initiative Rare As One program to organize an international collaborative research network (**ICRNetwork**). Through the ICRNetwork, PSC Partners aims to make a meaningful impact on the quality of life and outcomes of PSC patients. With so many outstanding patient needs and research questions, we focused our efforts in 2021 and 2022 towards the development of a draft research agenda and strategic research plan (**SRP**).

While the SRP remains in development, the draft research agenda is complete! This agenda, detailed below, covers 5 major areas of PSC research: (1) the cause of PSC, (2) mechanisms contributing to disease progression, (3) clinical care, (4) liver transplant and PSC recurrence, and (5) cholangiocarcinoma.

Both the ROADMAP Initiative and the patient-focused drug development (PFDD) forum were key in understanding PSC patient needs and priorities. Then, after a thorough review of the scientific literature, Drs. Ruth-Anne Pai and Jesse Kirkpatrick met individually with international PSC experts to discuss future research prioritization across these topics. This expert opinion was incorporated across each of the key questions asked by patients along their journey with PSC to produce the draft research agenda.

Once implemented in 2023, this ICRNetwork and SRP will guide PSC Partners research programs over the next 5 years

What does this effort mean for me as a PSC patient or caregiver?

Your voice and needs are heard and PSC Partners will offer opportunities for YOU to listen, learn, collaborate, and advocate over the coming years through the ICRNetwork. While future events and opportunities are being developed, you can share your thoughts, ask questions, and connect with us by emailing contactus@pscpartners.org

Draft PSC Partners Research Agenda

First, let's take a look at the main sections of the draft research agenda:

1. **What is the initial cause of PSC?**

2. **What causes PSC to progress?**
    a. What is the link between the gut and liver in PSC?
    b. What is the nature of the inflammation in PSC?
    c. What is the nature of fibrosis in PSC?
    d. How do genes and the environment contribute to PSC pathogenesis?

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

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

5. **How do we improve transplantation rates and success?**

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

In the main section below, PSC Partners shares scientific questions from the draft agenda. Below each set of scientific questions, we prepared a summary of the key questions and an explanation of how these questions came to be prioritized

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1. 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?

Defining the 'cause' of PSC: When we think about the initial 'cause' of PSC, we might imagine a major life event, infection, or our family history as potential triggers. There could be one cause or multiple factors, and it's hard to pinpoint what these could be after the fact. For example, the initial cause of PSC could appear months or even years before we have symptoms or received a diagnosis. Just keep in mind that these causal factors are different from those that drive the 'progression' of PSC.

Importance of this topic: In 2022, we still don't know what causes PSC. Multiple factors have been proposed to play a role, including genetics, the environment, changes to the gut in IBD, and autoimmune disease more generally. While we do not *need* to know the cause of PSC in order to develop treatments, having a better understanding of the cause may enable us to diagnose PSC sooner and identify better treatments to stop PSC in very early disease stages.

2. What causes PSC to progress?

There are thought to be many processes that contribute to the progression of PSC. We broke these topics down into four main areas (2a. - 2d.)

2a. 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 colorectal cancer?
- 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?

Defining the gut-liver connection: Did you know that your liver is part of the digestive tract? It might not be a surprise then that there is a connection between the liver and the gut. Importantly, there is one key process that takes place across both the gut and liver in IBD and PSC: inflammation. We'll discuss inflammation in more detail in the next section. Here, we should think about how our gut and liver communicate and interact with one another, and how IBD and inflammation in the gut may contribute to the progression of PSC.

Importance of this topic: About 80% of PSC patients have IBD. In some, IBD symptoms are mild or not present, but this doesn't mean that changes to the gut aren't present or that IBD isn't playing a role in PSC progression. With so many unanswered questions, it's up to us to speak up and encourage collaboration between IBD and PSC researchers to understand exactly how the gut-liver connection contributes to progression of PSC and then identify treatments targeting the gut in order to slow progression of PSC.

2b. 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?

Defining 'inflammation' in PSC: Inflammation is caused by our immune system - a complex network of cells and proteins contributing to an orchestrated immune response. Inflammation is necessary to help us get over infections. However, in PSC, the immune response is inappropriate and leads to inflammation and scarring of the bile duct.

Importance of this topic: Because inflammation leads to damage to the bile duct and worsening of fibrosis, it's important to understand the fine details of which aspects of the immune system contribute and what we can do to dampen the inflammation. Not much is known about the early and late stages of inflammation in PSC and, in particular, immune cells and their roles in the liver. Almost all of the researchers that we spoke with highlighted how important it is to characterize immune responses in the liver, and the gut, in early, middle, and late-stage PSC.

2c. 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?

Defining 'fibrosis' in PSC: Within our liver and all the way down to our bile duct, cells communicate with one another in ways that may be harmful and worsen our PSC. One of these ways is through scarring of the liver, known as 'fibrosis'. This scarring occurs when our bile ducts and surrounding liver tissue are damaged. Ultimately, as fibrosis worsens and more liver scarring is present, we are at risk of progressing to liver cirrhosis.

Importance of this topic: The exact processes driving changes in the liver in PSC and leading to fibrosis still require investigation. And If we aren't able to prevent the initial development of liver scarring early in PSC progression, the next best thing may be to target and stop fibrosis in its tracks. As we tease apart factors like genes, proteins, and cellular responses that contribute to the fibrosis, we can develop treatments targeting those mechanisms.

2d. 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?

Defining the 'genetics' and 'the environment' in PSC: Genetics and the environment are often referred to as 'nature and nurture'. While our genes reflect our family tree and are something we're born with, our environment can be modified, and changes as we grow up and move about the world. We already know that PSC patients have certain genetic differences from people without PSC, but we don't really know how those differences contribute to PSC. Similarly, various aspects of our environment, like our diet and chemical exposures, have been proposed to impact the progression of PSC.

Importance of this topic: By studying the role of these different genetic and environmental factors, we may learn more about what causes PSC to progress. While we cannot change the makeup of our genes, we may find ways to target the downstream consequences of our genetic background. Similarly, we may find ways to modify our environment, such as our diet, to slow PSC progression. Identifying and studying these genetic risk factors and environmental exposures may lead to new PSC treatments and also impact the ways in which we detect, monitor, and treat PSC, which will be our next topic

3. 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?

Defining 'diagnosis', 'monitoring', and 'prognosis': Next, we need to leave the laboratory and return to the clinic to think about how we interact with our doctors and how we can get the best clinical care. This clinical care has three main parts: identification of PSC (diagnosis), follow-up care and testing (monitoring), and an estimation of where we are headed over the next few years (prognosis). One way to improve clinical care is to identify 'biomarkers' and screening tools to diagnose and monitor PSC, and to predict prognosis. A biomarker is a biological molecule found in blood, other body fluids like urine, or tissues, that is a sign of a condition or disease.

Importance of this topic: At the end of the day, each of us here wants to improve quality of life and outcomes for all PSC patients in our community. Our hope is that we will find biomarkers in blood, stool, saliva, or urine that can be measured easily, at low cost, and over time to aid in PSC diagnosis, management, and treatment decisions.

4. 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?

Defining 'drug development' for PSC: The process of drug development is so critical and as PSC patients, we are at the center and our voices must be heard. Drug development is the process of studying novel treatments in clinical trials to determine whether they are safe and effective in treating PSC. PSC Partners created a separate overview of drug development for the ROADMAP series, available on our website.

Importance of this topic: Clinical trials in PSC are often long and a lot is asked of participants in these trials. In order for these trials to be successful, we must work together to ensure we capture the most important clinical changes, including patient-reported changes in PSC symptom frequency and burden. In 2022, PSC Partners initiated two major projects to develop patient-reported outcome measures (PROM) and to identify biomarkers that are able to tell us early and with great accuracy whether a drug is slowing the progression of PSC.

5. 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?

Defining 'transplant' for PSC: In the absence of effective treatments to slow the progression of PSC, some of us may need a transplant at some point. But 'transplant' isn't a singular event or day in our lives. In the absence of effective drugs and as PSC progresses, we encounter many questions around transplant waitlist, access to transplant, post-transplant care, and complications.

Importance of this topic: As we work to accelerate new treatments through the drug development pathway, there still remains a great need to improve transplantation rates and success. And after transplant, many ask what the risk is of developing recurrent PSC and how we can lower this risk. The voice and needs of the post-transplant community are so important and must be heard.

6. 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?

Defining 'CCA' in PSC: Those of us living with PSC are all too familiar with the fear of developing cholangiocarcinoma (CCA), cancer of the bile duct. The lifetime risk of developing CCA is estimated to be about 10-20%, although a large proportion of CCA diagnoses come within the first year after diagnosis with PSC. While we receive imaging every year to screen for CCA, imaging doesn't catch every case. Additional tools and tests are needed to better diagnose CCA.

Importance of this topic: While the risk is low, we all want to know more about how cholangiocarcinoma develops and what we can do to prevent it or diagnose it earlier. The first three research questions above are frequently asked by researchers, but also clearly align, just as written, with our needs. Let's consider them again:

- What aspects of PSC contribute to the development of CCA?
- How can we best treat PSC in order to prevent the development of CCA?
- And how do we detect CCA while it is still curable?