Probing new generation immunotherapy approaches using a new mouse model of PSC-associated cholangiocarcinoma

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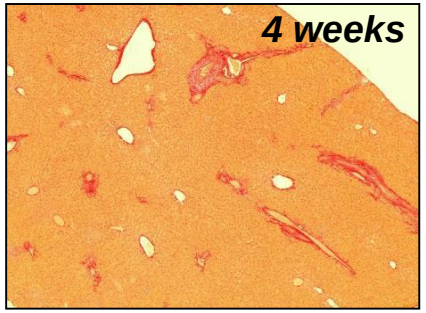
Primary sclerosing cholangitis and cholangiocarcinoma

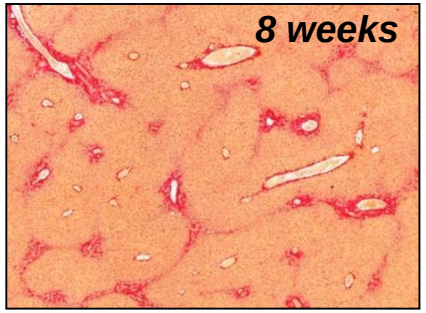
- Cholangiocarcinoma (CCA) is a dreaded complication of PSC, patients carry a **400**-fold higher risk for cholangiocarcinoma than the general population *(Khan et al. Liver Int. 2019)*

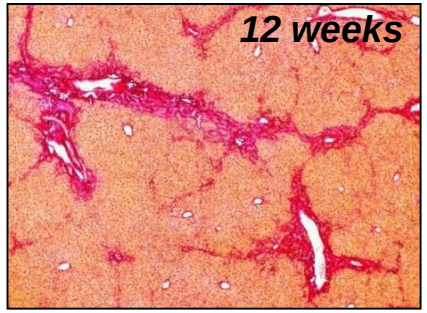
- **2016 - PSC Partners / IPSCSG meeting in Yale**:
  - FEW animal models of CCA;
  - **NO animal model mimicking human CCA in PSC background** (cholestasis, biliary injury and fibrosis)

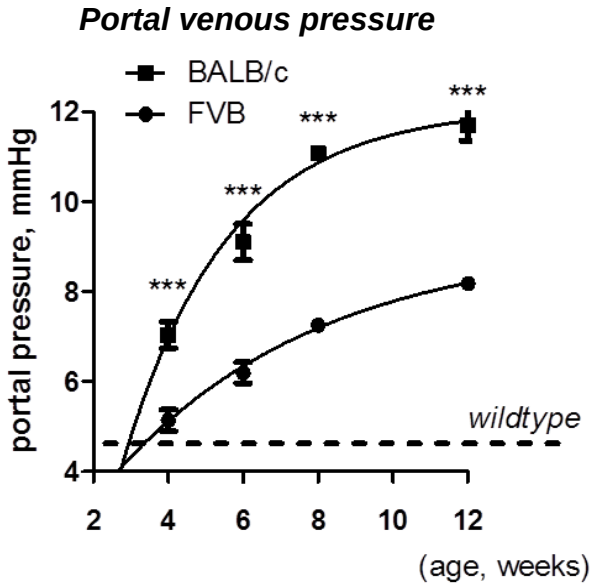
Aim: Develop a new, "high fidelity" mouse model of intrahepatic cholangiocarcinoma arising in the settings of progressive sclerosing cholangitis

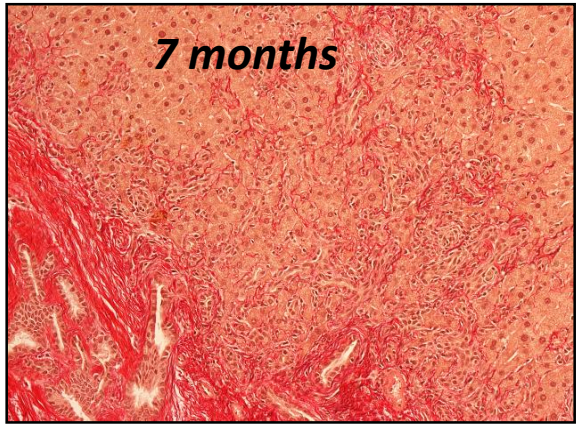
Abcb4(Mdr2)-/- mouse model of congenital, progressive PSC-like liver disease

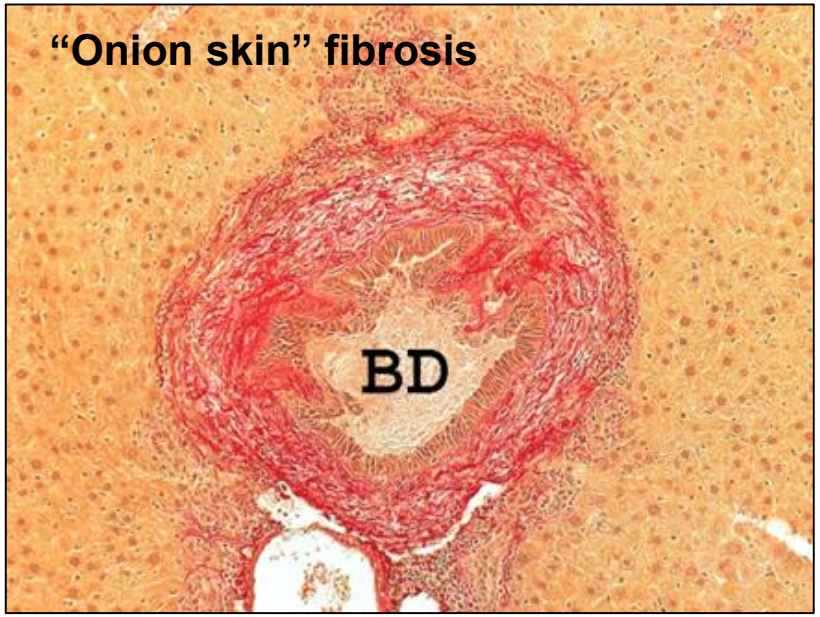












- *Early onset portal hypertension*
- *Pronounced ductular proliferations*
- *Progressive severe peri-ductal fibrosis*
- *Cirrhosis from age 7 months*

Popov et al, J Hep 2005; Ikenaga et al., Am J Pathol 2015

Multi-prong approach to create a model of PSC-CCA in Mdr2-/- mouse

- Chemical-induced: (DAPM, “Epping jaundice” inspired) – *no CCA observed, abandoned*
- Genetic manipulation with human oncogenes: retrograde biliary transduction – *low efficiency, abandoned*
- Genetic manipulation with human oncogenes: hydrodynamic transduction **(robust CCA induction in fibrotic mice, pursued)**

2017 – received pilot funding from PSC Partners Seeking a Cure (Canada) to develop and characterize PSC-CCA model

2021 – first investigational drug tested in partnership with biotech startup (TGFb and integrin inhibitors)

2024 – full scientific paper accepted for publication by Journal of Hepatology, describing the PSC-CCA model generation and validation

Research Article
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Transposon-based oncogene integration in *Abcb4(Mdr2)*$^{-/-}$ mice recapitulates high susceptibility to cholangiocarcinoma in primary sclerosing cholangitis

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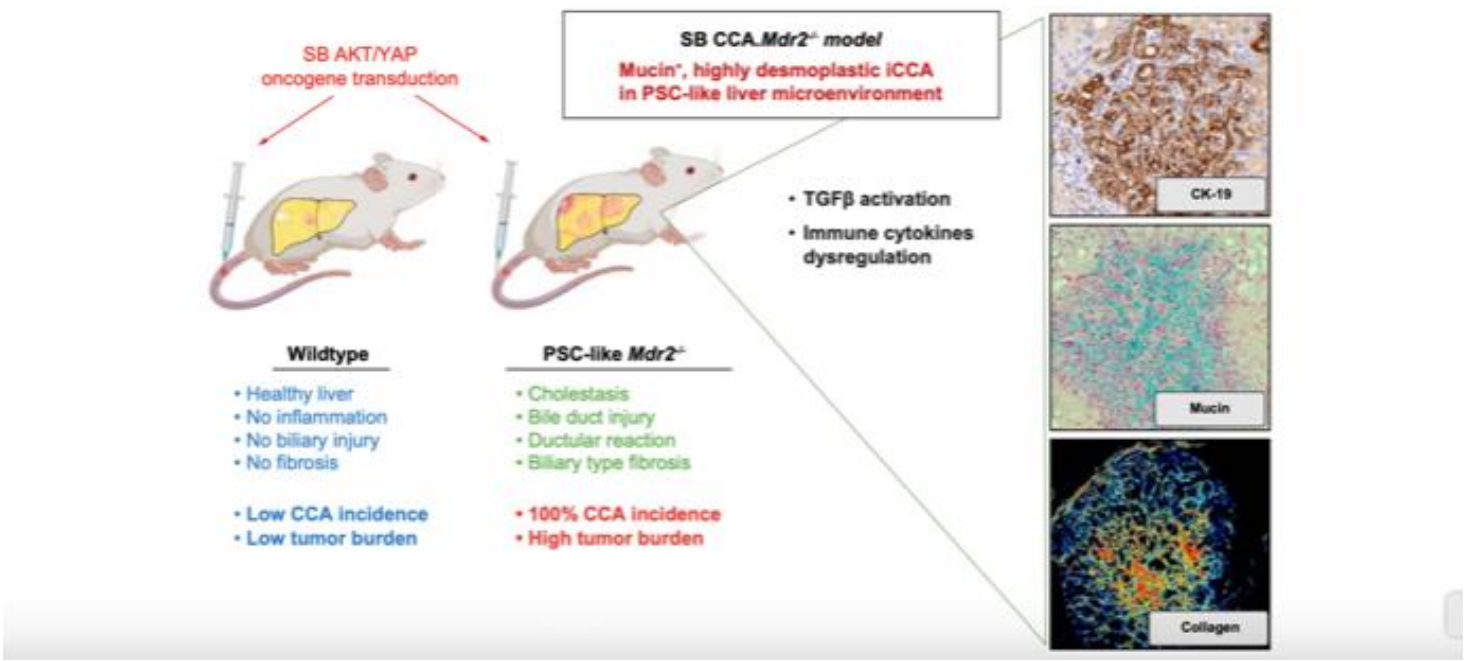
Graphical abstract



What did we learn?

- Model and AI-assisted automated drug efficacy read-out established
- PSC-CCA is immunologically distinct from sporadic CCA
- PSC-CCA tumors are “hot” but resistant to anti-PD-1 immune checkpoint therapy
- Another approach to unleash immune system via systemic TGFb blocking is effective
- **Pre-clinical evidence of efficacy obtained for clinical-stage candidate, selective avb8 integrin inhibitor**

Key takeaways

- We generated new high-fidelity CCA model (termed SB CCA.Mdr2-/- model) based on AKT/YAP oncogenic transduction that **recapitulates increased susceptibility to CCA in PSC**
- The model enabled studies into the mechanism of CCA risk in PSC and testing novel drug candidates
- Preliminary data for federal funding generated

This study represents a patient-driven, high impact study successfully addressing a knowledge gap and delivering a practical tool to advance new drugs into clinical trials