

# CCL24 overexpression resulting from bile duct injury induces an inflammatory-fibrotic vicious cycle in primary sclerosing cholangitis

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## INTRODUCTION

Primary Sclerosing Cholangitis (PSC) is characterized by damaged peribiliary space, in which immune cells, reactive bile epithelial cells and fibroblasts interact. This interaction leads to elevation of cytokines, chemokines and a variety of other secreted factors that masters the inflammatory-fibrotic process.

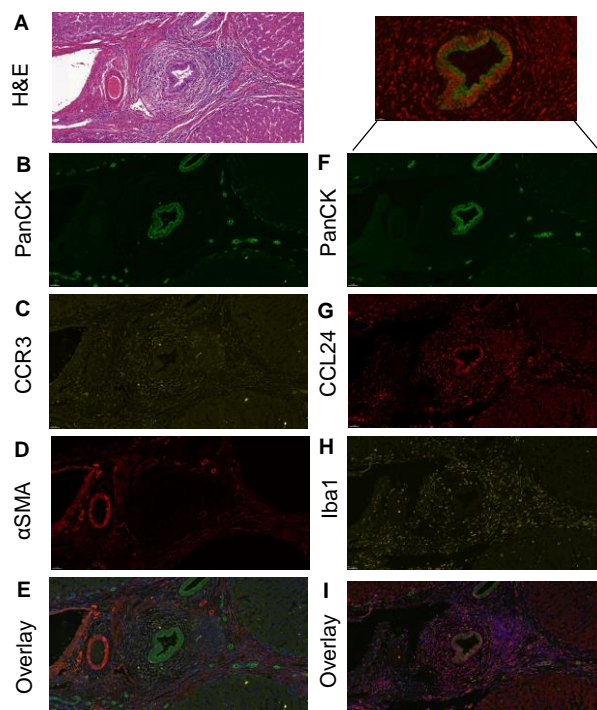
## AIM

In this work we studied the role of CCL24, a chemokine involved in promoting immune and fibrotic biliary damage, in PSC pathophysiology. Specifically, we focused on the bile duct injured areas that play a key role in the development and progression of the disease.

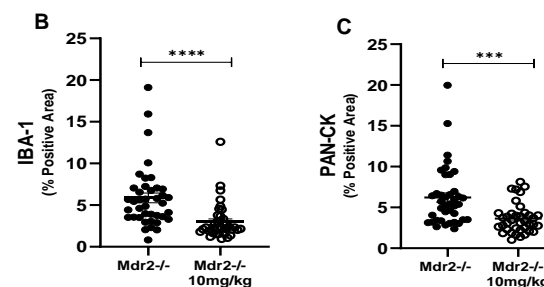
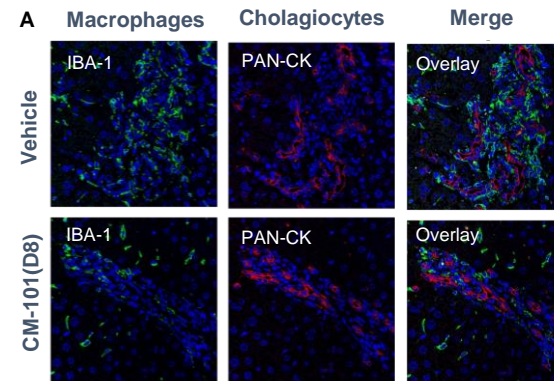
## MATERIALS & METHODS

PSC patients human liver biopsies and liver sections from an animal model of PSC were evaluated for their inflammatory-fibrotic and biliary damage. Patients' biopsies were stained for H&E and by immunofluorescence for bile epithelial cells (PAN-CK), macrophages (IBA-1), and for CCL24 and its receptor CCR3. In-vivo, Mdr2 deficient mice were treated with CM-101, a CCL24 neutralizing mAb. Liver sections from this model were stained for PAN-CK, IBA-1 and  $\alpha$ -SMA.

## RESULTS



CCL24 staining in human PSC liver biopsies shows high CCL24 expression in bile duct epithelial cells and recruited inflammatory cells. Importantly, CCR3, the receptor for CCL24, was found to be expressed on immune cells and activated myofibroblasts (co-stained with  $\alpha$ -SMA). This co-expression highlights the ability of these cells to respond to CCL24.



Treatment of Mdr2<sup>-/-</sup> mice with anti-CCL24 mAb resulted in reduction of liver inflammation, liver fibrosis and cholangiocytes proliferation. (A) Immunofluorescent staining of Mdr2<sup>-/-</sup> liver sections, IBA-1 staining for macrophages and PAN-CK staining for cholangiocytes (N=5). (B) and (C) Quantification of IBA-1 and PAN-CK staining (N=38-40 fields).

## CONCLUSION

In PSC the affected area surrounding the bile ducts is characterized by creation of a localized inflammatory niche. High expression of CCL24 by recruited and tissue resident inflammatory cells as well as by bile duct epithelial cells promotes tissue damage. This further support recruitment of immune cells which results in additional CCL24 secretion. The CCL24 reach vicious cycle promotes inflammation and fibrosis.

In a PSC related mice model inhibiting CCL24 activity using CM-101, breaks the vicious cycle leading to improvement of liver injury.

CM-101, is currently being studied in a Phase 2 trial as a treatment for PSC.

## DISCLOSURES

MSS, AA and AM are employees of Chemomab; AP is a consultant to Chemomab

## CONTACT INFORMATION

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