Serum Proteomics Reveals Unique Association of CCL24 with Disease-related Pathways and Signatures in Primary Sclerosing Cholangitis

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Presentation ID# 44663
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• Presenter: Ilan Vaknin

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CCL24’s Dual Role in Inflammation and Fibrosis-related Pathology

Inflammation

- Directly activates fibroblasts
- Enhances local immune cell recruitment

Fibrosis

- Data shows unique role vs. other chemokines
- Correlates with fibrotic biomarkers and disease outcome

Low in Healthy Tissue; Elevated in Fibrotic Tissue
- Liver, skin, lung, kidney, others
- Wide therapeutic margin

THE POWER OF CCL24

Dual Role in Promoting Fibrosis & Inflammation
- Directly activates fibroblasts
- Enhances local immune cell recruitment

Differentiated Activity
- Data shows unique role vs. other chemokines
- Correlates with fibrotic biomarkers and disease outcome

Low in Healthy Tissue; Elevated in Fibrotic Tissue
- Liver, skin, lung, kidney, others
- Wide therapeutic margin
CM-101 Neutralizes CCL24 and Reduces Inflammation and Fibrosis

CM-101 Reduces In Vivo Monocyte Recruitment

Number of Migrated Monocytes (x1000)

- PBS
- CCL24
- CCL24 + CM-101

CM-101 Inhibits Primary Fibroblast Activation

Proliferation: Relative Change from Baseline

- PBS
- CCL24
- CCL24 + CM-101

CM-101 Neutralizes CCL24 and Reduces Inflammation and Fibrosis

CCL24 Regulated Cells
- Monocytes
- Fibroblasts

CM-101 The Antibody

CCL24 The Target

CR3 The Receptor

Immune cell recruitment ATTENUATED

Fibroblast activation ATTENUATED
Clinical Relevance of CM-101 Supported by Elevated CCL24 Levels in PSC Patients

CCL24 LEVEL IN HEALTHY VS PSC PATIENT LIVER TISSUE

Healthy Liver

PSC Livers

CCL24 (brown) overexpressed in damaged bile duct area

CCL24 (red) overexpressed in bile epithelial cells (green) and immune cells (yellow)

CCL24 AND CCR3 EXPRESSION IN PSC PATIENT LIVER TISSUE

Greenman et al, JCI Insight 2023
CM-101 Reduces Liver Injury & Fibrosis in Multiple PSC Animal Models

Segal-Salto et al, JHEP reports 2020

Greenman et al, JCI Insight 2023
Serum Proteomics to Reveal Disease-Related Pathways

HC, Healthy Controls
ELF, Enhanced Liver Fibrosis

3 Comparison Groups:
- Disease (PSC vs HC)
- Fibrosis Severity (PSC: high vs low ELF score; 9.8 as cutoff)
- CCL24 Levels (PSC: high vs low CCL24; median as cutoff)

HC, N = 30
PSC, N = 45
Serum Proteomics
Olink Explore 3072

Canonical pathways
Upstream regulators
Liver-related toxicity functions

Comparison Groups:
- Disease (PSC vs HC)
- Fibrosis Severity (PSC: high vs low ELF score; 9.8 as cutoff)
- CCL24 Levels (PSC: high vs low CCL24; median as cutoff)
Disease-Related Canonical Pathways Are Elevated in Patients with High CCL24 Levels

Top Overlapping pathways:
1. Pathogen Induced Cytokine Storm Signaling Pathway
2. Granulocyte Adhesion and Diapedesis
3. Agranulocyte Adhesion and Diapedesis
4. Hepatic Fibrosis / Hepatic Stellate Cell Activation
5. Wound Healing Signaling Pathway

* Similar effects in other overlapping canonical pathways, including fibrosis, chemotaxis and inflammation pathways
Disease-Related Upstream Regulators Are Elevated in Patients with High CCL24 Levels

Top 20 regulators: Fibrosis CCL24

Overlapping regulators:
[5] Immunoglobulin

HC, Healthy Controls

* Similar effects in other overlapping upstream regulators, including fibrosis and inflammation regulators

Overlapping Regulators#

Mean Expression of Proteins Within a Given Pathway (NPX)

* p<0.05, **** P<0.0001 Welch 2-sample t-test
Disease-Related Toxicity-Functions Are Elevated in Patients with High CCL24 Levels

Overlapping toxicity functions:
[1] Degeneration of liver
[2] Hepatocellular carcinoma
[3] Liver Cirrhosis
[4] Liver Damage
[5] Liver Enlargement
[6] Liver Fibrosis
[7] Liver Hyperplasia/Hyperproliferation
[8] Liver Inflammation/Hepatitis
[9] Liver Necrosis/Cell Death
[10] Liver Proliferation
[11] Liver Steatosis

Overlapping Toxicities#

Mean Expression of Proteins Within a Given Pathway (NPX)

*p<0.05, **** P<0.0001 Welch 2-sample t-test

HC, Healthy Controls

# Similar effects in other overlapping tox-functions, including liver inflammation, liver necrosis and liver proliferation
Unique Association of CCL24 with Key Disease-Related Pathways and Regulators

- CCL11 (Eotaxin-1)
- CCL24 (Eotaxin-2)
- CCL26 (Eotaxin-3)

ns, nonsignificant, * p<0.05, ** p<0.01; Welch 2-sample t-test
CM-101 Phase 2 Trial in Primary Sclerosing Cholangitis

Key Enrollment Criteria
PSC patients with large duct disease of >24 weeks duration
- ALP > 1.5 ULN
- Stable IBD allowed
- Stable UDCA treatment allowed

Outcome Measures
Primary – Safety and tolerability
Secondary - Change from baseline to Week15 in:
- Serum alkaline phosphatase
- ELF score
- FibroScan®
- Fibrotic biomarkers/liver enzymes (e.g., AST, ALT, Pro-C3, Pro-C5)
- Pharmacokinetics
- Pharmacodynamic parameters

Topline data expected in 2H 2024
Key Takeaways

• CM-101 Reduces Liver Injury & Fibrosis in Multiple PSC Animal Models

• Disease-related canonical pathways, upstream regulators and toxicity-functions are elevated in PSC patients with high CCL24 levels

• Unique Association of CCL24 but not other eotaxins with Key Disease-Related Pathways and Regulators

• CCL24 is associated with both inflammatory and fibrotic mechanisms

• Preclinical and patient derived serum proteomics data support further clinical investigation of an anti-CCL24 therapy in PSC