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Claudin-1 is a target for treatment of advanced liver fibrosis and cancer prevention

Houssein El Saghire[1 2], Antonio Saviano[1 2 3], Natascha Roehlen[1 2], Emilie Crouchet[1 2], François H.T. Duong[1 2], Frank Jühling[1 2], Sara Cherradi[1 2], Marine Oudot[1 2], Victor Gonzalez-Motos[1 2], Sarah Durand[1 2], Patrick Pessaux[1 2 3], Emanuele Felli[1 2 3], Christine Thumann[1 2], Olga Koutsopoulos[1 2], Bryan C. Fuchs[4], Yujin Hoshida[5], Greg Elson[6], Markus Meyer[6], Roberto Iacone[6], Tamas Schweighoffer[6], Mathias Heikenwälder[7], Laurent Mailly[1 2], Mirjam Zeisel[1 2], Catherine Schuster[1 2], Joachim Lupberger[1 2], Thomas Baumert[1 2 3 8]

[1]Inserm U1110, Institut de Recherche sur les Maladies Virales et Hépatiques, Strasbourg, France, *[2]Université de Strasbourg, Strasbourg, France*, *[3]Institut Hospitalo-Universitaire, Pôle Hépato-digestiv, Nouvel Hôpital Civil, Strasbourg, France*, *[4]Massachusetts General Hospital Cancer Center, Harvard Medical School, Charlestown, MA, United States*, *[5]Liver Tumor Translational Research Program, Harold C. Simmons Comprehensive Cancer Center, Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX, United States*, *[6]Alentis Therapeutics, Basel, Switzerland*, *[7]Division of Chronic Inflammation and Cancer, German Cancer Research Center, Heidelberg, Germany*, *[8]Institut Universitaire de France, Paris, France*

Email: thomas.baumert@unistra.fr

Background: Tissue fibrosis is the key driver of end-stage organ failure, accounting for up to 45% of death in developed countries. Advanced liver fibrosis is the main risk factor for hepatocellular carcinoma (HCC). Despite the urgent medical need, approved antifibrotic therapies are absent and compounds in clinical development have limited anti-fibrotic efficacy. Claudin-1 (CLDN1) is a cell membrane protein mediating cell adhesion, signaling and epithelial-mesenchymal differentiation (EMT). Furthermore, CLDN1 is a cell entry factor and signal transducer of hepatitis C virus, a major cause of liver fibrosis and HCC worldwide.

Aims and Method: Using highly specific humanized monoclonal antibodies (mAbs) targeting non-junctional CLDN1 and a large series of patient-derived cell-based and mouse models combined with loss-of-function studies, we aimed to investigate the role CLDN1 as a therapeutic target for liver fibrosis.

Results: CLDN1 was overexpressed in liver tissues derived from patients with NASH, liver fibrosis and HCC. Targeting non-junctional CLDN1 on the hepatocyte basolateral membrane by highly specific mAbs markedly and significantly inhibited fibrosis and suppressed tumorigenesis *in vivo* in two state-of-the-art NASH fibrosis mouse models including humanized liver chimeric mice. Antifibrotic effects were further confirmed in NASH F3/F4 patient-derived precision-cut liver slices, 3D bioprinted liver tissues and NASH patient-derived liver spheroids. Perturbation studies revealed that CLDN1-targeting mAbs suppress pro-fibrogenic differentiation of liver myofibroblasts and Kupffer cells as well as EMT of hepatocytes by interfering with host cell signaling. Treatment with humanized anti-CLDN1 antibodies is considered to be safe, as administration in non-human primates and mouse models did not reveal any major toxicity even when high doses largely exceeding the therapeutic need were repeatedly applied.

Conclusion: Our results provide robust preclinical proof-of-concept for CLDN1-specific mAbs for treatment of advanced liver fibrosis and prevention of HCC. A key differentiator of CLDN1-targeting approach is the combination of a robust direct anti-fibrotic and HCC

preventive effect complementing compounds in clinical development mostly targeting metabolism.

Figure: N/A