A humanized Claudin-1 specific monoclonal antibody for treatment of hepatocellular carcinoma

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ILCA conference
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2 - 5 September 2021
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INTRODUCTION & AIM

Hepatocellular carcinoma (HCC) is a fast rising and leading cause of cancer death. While new therapeutic modalities have been recently approved, treatment response and survival in patients remain poor.

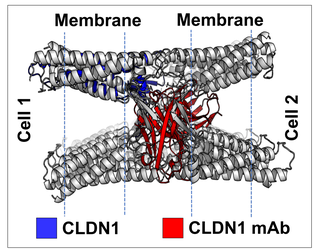
Claudin-1 (CLDN1) is a cell membrane protein mediating cell-cell adhesion, cell fate, and differentiation. Functionality of CLDN1 in solid tumors including HCC has been demonstrated by gain- and loss-of-function studies, yet its impact as a therapeutic target is unexplored.

The present study aims to evaluate the **non-junctional CLDN1 as a therapeutic target** for the treatment of **HCC.**

METHODS

Using humanized monoclonal antibodies (mAbs) specifically targeting the 1st extracellular loop of human non-junctional CLDN1 and a large series of patient-derived model systems we investigated the role of CLDN1 as a therapeutic target in HCC.

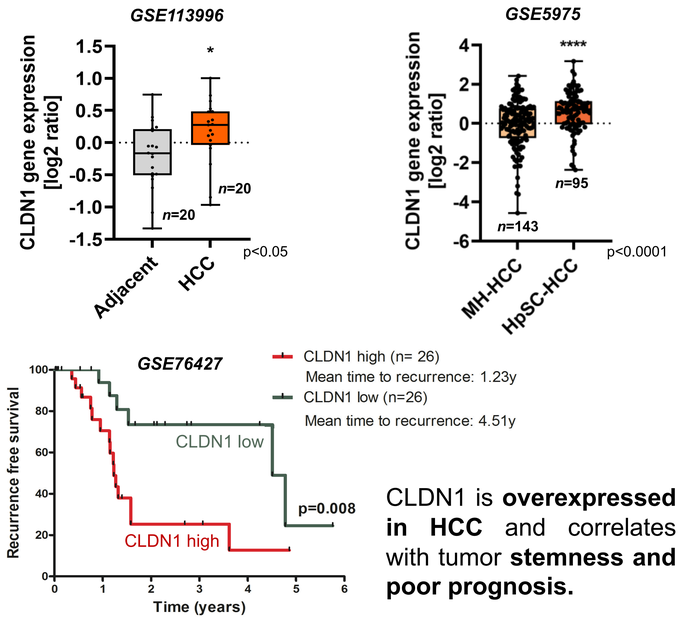
CLDN1 in TJ is not accessible to CLDN1 mAb



RESULTS

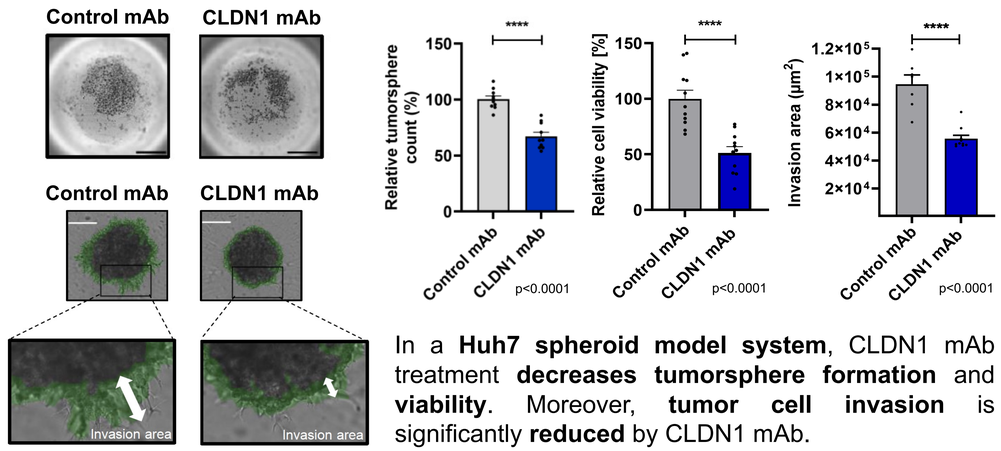
HpSC-HCC = hepatocyte progenitor/stem cell
MH-HCC = mature hepatocyte

1. CLDN1 is overexpressed in HCCs of poor prognosis



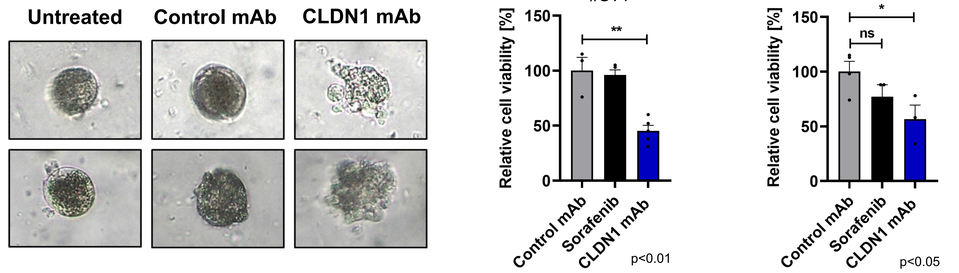
CLDN1 is **overexpressed in HCC** and correlates with tumor **stemness and poor prognosis.**

2. CLDN1 perturbation suppresses tumorsphere growth and invasion



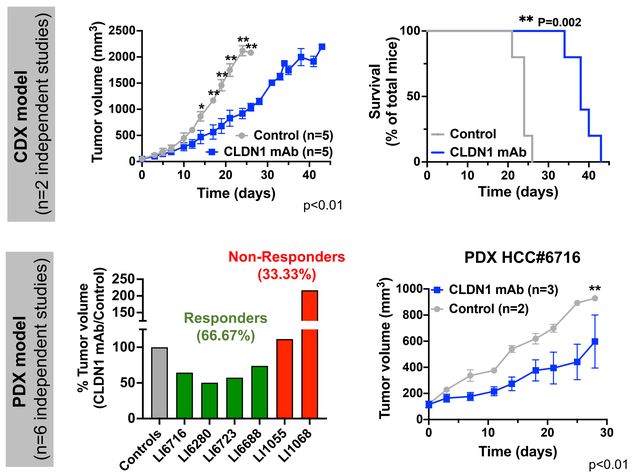
In a **Huh7 spheroid model system**, CLDN1 mAb treatment **decreases tumorsphere formation** and **viability**. Moreover, **tumor cell invasion** is significantly **reduced** by CLDN1 mAb.

3. CLDN1 mAbs suppress primary HCC spheroid growth



In a **HCC patient-derived spheroid model system**, CLDN1 mAb treatment strongly **disrupts** the **architecture of spheroids** and **suppresses tumor cell viability** with superior efficacy compared to sorafenib, a clinical multi kinase inhibitor.

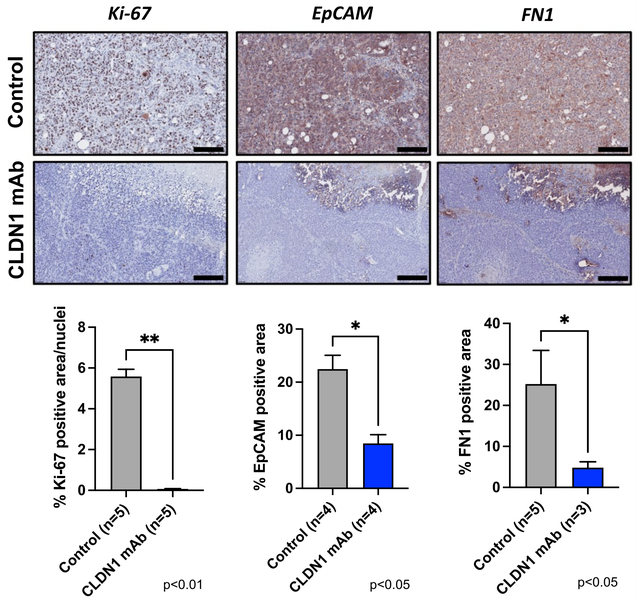
4. CLDN1 mAbs suppress tumor growth in CDX and PDX mouse models



Effects of CLDN1 mAb therapy were assessed in a **Huh7 cell-line derived xenograft** (CDX) mouse model and 6 independent **patient-derived xenograft** (PDX) mouse models.

CLDN1 mAb treatment **strongly suppresses tumor growth** with increasing effects over time of treatment in the CDX model and a response rate of 66.67% in PDX mice.

5. CLDN1 mAbs suppress cell proliferation, liver cancer stemness and EMT *in vivo*



Histological assessment of Ki-67, EpCAM, and Fibronectin markers in Huh7 CDX mice revealed that **CLDN1 mAb** strongly **suppresses cell proliferation**, **liver cancer stemness**, and **EMT**.

CONCLUSIONS

These results provide a **robust** pre-clinical **proof-of-concept** for humanized **CLDN1-specific mAbs** for the **treatment of HCC** and pave the way for **clinical development of CLDN1-targeting therapies** using monoclonal antibodies.

The **unique** and **distinct mechanism of action** provides opportunities to **break the plateau of limited response** and **survival,** which is limiting in currently approved therapies.

CONTACT INFORMATION

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