A tumor microenvironment-targeting CD98-directed ADC confers robust anti-tumor activity in multiple cancers with favorable pharmacokinetics and safety profiles in preclinical models

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Introduction

- CD98, a subunit of the LAT1/CD98 amino acid transporter complex, is intimately involved in cell adhesion, migration, proliferation, and signal transduction [1,2,3].
- CD98 is expressed at aberrantly high levels in many solid tumors and hematological malignancies [4,5], and is frequently associated with poor prognosis [6,7], highlighting its potential as a "pan-tumor" target [8].
- However, CD98 is also expressed in some normal tissues (especially in the kidney) hence complicating the development of antibody-based therapies due to the lack of tumor selectivity, poor pharmacokinetics (PK), and safety issues.
- HH018 sesutecan is a novel ADC composed of a pH-dependent anti-CD98 monoclonal antibody (mAb) and the topoisomerase 1 inhibitor-based linker-drug, sesutecan, at a DAR of 8.

HH018 sesutecan (anti-CD98 ADC)

Anti-CD98 mAb: a novel proprietary pH-dependent human IgG1 antibody (HH018) that selectively targets CD98 in the acidic tumor microenvironment [9].

Sesutecan: a proprietary hydrophilic linker with exatecan payload, has conferred very promising anti-tumor activity associated with a manageable toxicity profile in the FRα-directed rinatabart sesutecan (Rina-S, PRO1184) [10].

CD98: A novel and promising therapeutic target in multiple cancers

CD98 is over-expressed across many cancer types

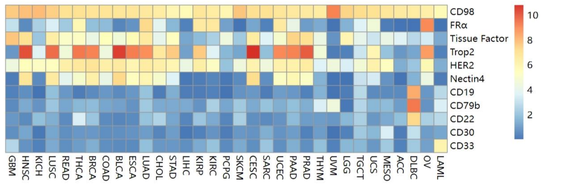


Fig. 1. mRNA expression levels of CD98 and common ADC targets were analyzed based on TCGA data. The median TPM (transcripts per million) value for each target gene was used to create the heatmap.

CD98 expression is significantly higher in tumors compared to normal tissues

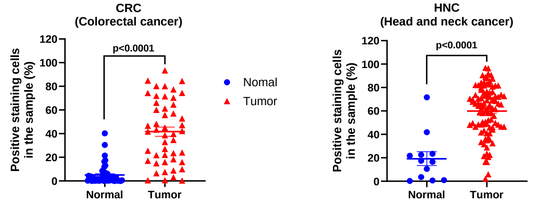


Fig. 2. Expression of CD98 in normal and tumoral tissues from patients with colorectal cancer (CRC) and head and neck cancer (HNC). Immunohistochemical (IHC) staining of CD98 in normal and tumoral tissues was analyzed. Rates of positive staining cells in the samples are shown (p value was calculated using Mann-Whitney test).

HH018 preferentially binds CD98 in tumors

HH018 accumulates predominantly in the tumors rather than in other normal tissues, whereas HH018 ctrl accumulates mainly in the kidneys rather than in the tumors.

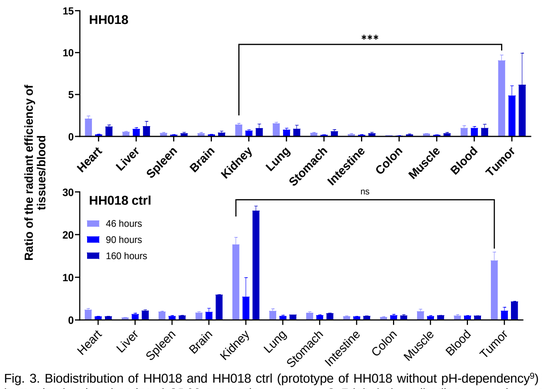


Fig. 3. Biodistribution of HH018 and HH018 ctrl (prototype of HH018 without pH-dependency[9]) in CD98-humanized mice bearing hCD98-expressing tumors. Cy7-labeled antibodies were intraperitoneally administered to the mice. The radiant efficiency for each tissue was measured post injection using IVIS imaging and the mean ± SD was calculated from 2–3 mice. ns, not significant; ***, p < 0.001 (t test).

HH018 sesutecan binds CD98 on various cancer cells in a pH-dependent manner

HH018 sesutecan binds to cell surface CD98 much more efficiently at pH6.5 than pH7.4, whereas binding of controls is insensitive to pH

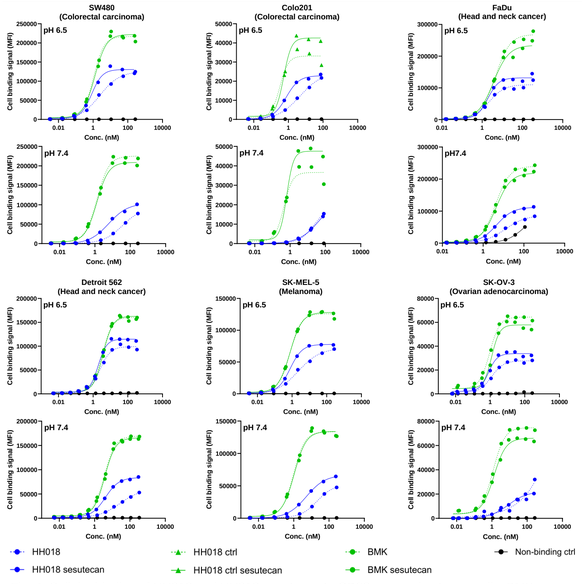


Fig. 4. Cellular binding of HH018 and HH018 sesutecan to CD98-expressing tumor cells. BMK: an anti-CD98 mAb, sequence was sourced from a patent (TW201620553A)

HH018 sesutecan exhibits high efficiency of internalization under acidic conditions in CD98-overexpressing cancer cells

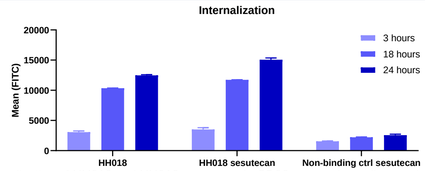


Fig. 5. Internalization of HH018 and HH018 sesutecan in CD98-expressing cells was determined using a pHrodo assay.

HH018 sesutecan exhibits higher cytotoxicity against CD98-expressing cells in acidic conditions

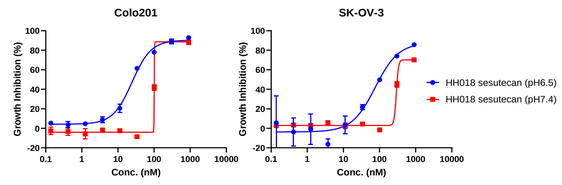
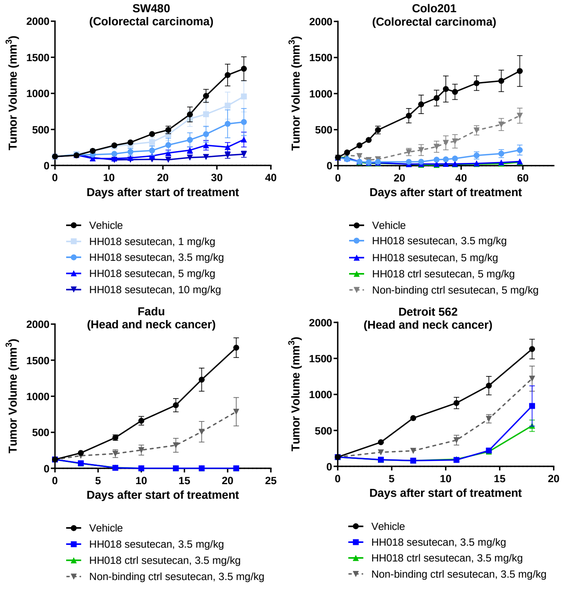


Fig. 6. Cell viability was evaluated at 5 or 6 days after drug treatment using a CCK-8 assay.

HH018 sesutecan confers potent and dose-dependent anti-tumor activity in multiple xenograft models



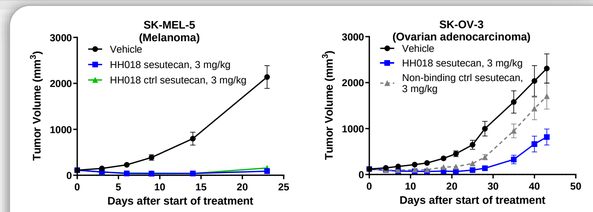


Fig. 7. Anti-tumor activity of HH018 sesutecan, HH018 ctrl sesutecan, or non-binding ctrl sesutecan with single-dose treatment in tumor cell derived xenograft (CDX) mouse models (n=4-8/group).

HH018 sesutecan exhibits favorable PK properties in CD98-humanized mice

HH018 sesutecan displays extended PK that is identical as its parent mAb; the exposure level is markedly higher than HH018 ctrl sesutecan

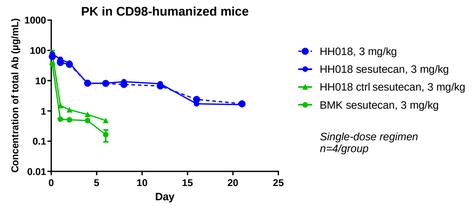


Fig. 8. Serum PK of ADCs or mAb in CD98-humanized mice.

Pilot toxicity study: HH018 sesutecan is well tolerated in monkeys

A repeat-dose (Q3W x 2) pilot toxicity study was conducted in cynomolgus monkeys at 30 mg/kg by intravenous infusion.

- HH018 sesutecan related findings included:
  - Transient slight increase in ALT
  - Reversible payload-driven toxicity (myelosuppression, manifesting as slight decreases of red cell indices and white blood counts)
- Long half-life supports Q3W dosing in the clinic

Summary

- HH018 sesutecan exhibits highly compelling preclinical profiles including efficacy, toxicity, and PK
  - Robust and crucial validation around the pH-dependency
  - Potent anti-tumor activity in a wide range of models
  - Very favorable toxicity and PK profile in pilot study in monkeys
- HH018 sesutecan is a promising novel agent that may benefit patients with a broad range of tumors

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