Novel Zeta-Antibody ZR451 recognizes Claudin 18.2+ Tight Junctions in Gastric Adenocarcinoma

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SUMMARY:

The tight junction protein Claudin 18.2 is significantly overexpressed in gastric adenocarcinomas (GC). Reliable detection of the Claudin 18.2 achieved by the novel Zeta-Antibody clone ZR451 has the unique potential to add prognostic significance in the diagnosis of gastric and esophagogastric adenocarcinoma. Claudin 18 isoform expression is typically restricted to stomach (wt), pulmonary tissues (Claudin 18.1), and gastric tissues (Claudin 18.2) reducing the risk of isoform cross presentation. Owed to its restricted tissue specific overexpression in GC, Claudin 18.2 has become a unique target molecule for drugmakers, and their modalities currently clinically tried such as monoclonal antibodies, bispecific antibodies, and CAR-T cells.

Claudin 18.2 is a multi-pass transmembrane protein and shows membranous localization in epithelial cells of gastric tissue **(Fig. 1)**.

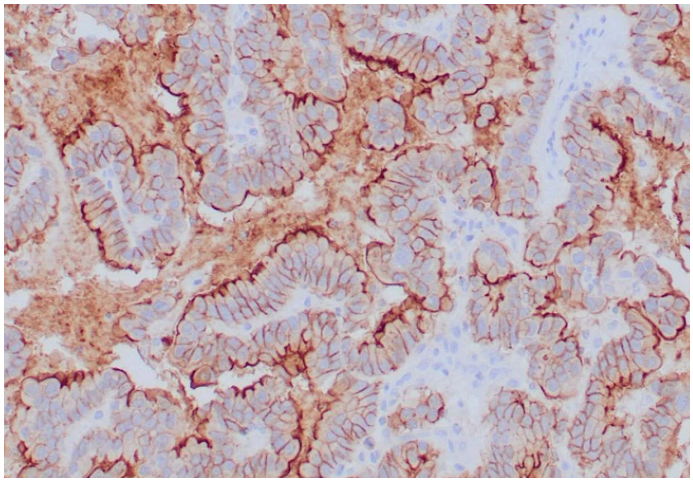

Figure 1: Zeta-Antibody ZR451 against Claudin 18.2. IHC staining of Claudin 18.2 in human gastric adenocarcinoma. Image property of Zeta Corporation.

Clinical studies observed Claudin 18.2 overexpression in 46.5% (139/299) of patients throughout the stages I-III of gastric adenocarcinoma.[1] While parental Claudin 18 overexpression was found in 22.5% primary cases and 25% metastatic cases of esophagogastric adenocarcinoma,[2] isoform Claudin 18.2 overexpression was observed in 51.1% of patients stage I, 47.9% of patients stage II, and 41.6% of patients stage III with gastric cancer, respectively.[1]

In addition to GC, Claudin 18.2 overexpression was observed in breast cancer, colon cancer, liver cancer, head and neck cancer, and bronchial cancer.[3] Moreover, Claudin 18.2 was demonstrated to contribute to proliferation, differentiation, and migration of cancer cells.[3]

The human isoform Claudin 18.2 differs from parental wt-Claudin 18 in the first 69 N-terminal amino acids only, hence the Zeta-Antibody Claudin 18.2 ZR451 maps to the extracellular loop ECL1 **(Fig. 2)**.[4]

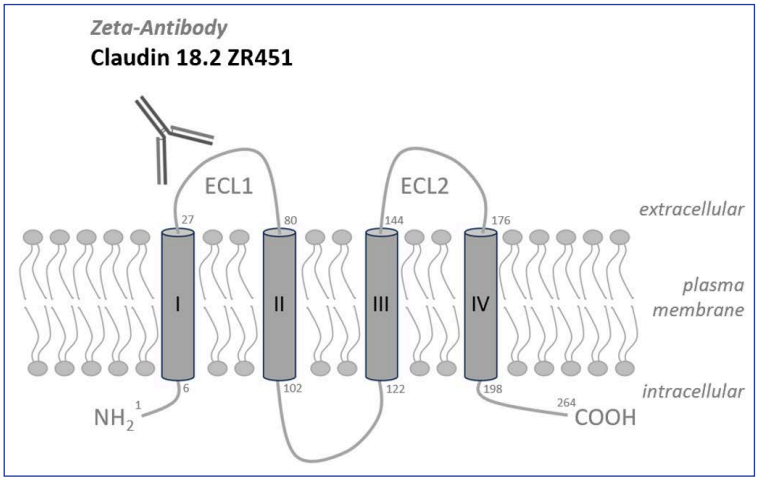

Figure 2: Zeta-Antibody Claudin 18.2 ZR451 epitope mapping to extracellular loop 1: Transmembrane protein Claudin 18.2 with its four membranous domains I-IV shown. Domain borders indicated by aa numbering. Extracellular loops ECL1 and ECL2 shown.[4] Illustration courtesy of AH.

Notably, therapeutic targeting of Claudin 18.2 by drugmakers using humanized monoclonal antibodies, bispecific antibodies, or CAR-T cells is owed to its unique expression pattern restricted to gastric tissues reducing safety risk liabilities by cross presentation in other tissues.

References:

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2. Coati, I. *et al.* Claudin-18 expression in oesophagogastric adenocarcinomas: a tissue microarray study of 523 molecularly profiled cases. *Br J Cancer* **121**:257-263 (2019).

3. Cao, W. *et al.* Claudin 18.2 is a novel molecular biomarker for tumor-targeted immunotherapy. *Biomark Res* **10**:38 (2022).

4. https://www.uniprot.org/uniprotkb/P56856/entry#sequences