TJ-CD4B (ABL111), a Claudin18.2-targeted 4-1BB tumor engager induces potent tumor-dependent immune response without dose-limiting toxicity in preclinical studies

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INTRODUCTION

- 4-1BB (CD137) is a co-stimulatory receptor that stimulates the function of multiple immune cells. Its ability to induce potent anti-tumor activity makes 4-1BB an attractive target for immuno-oncology. However, clinical development of a monospecific 4-1BB agonistic antibody has been hampered by dose-limiting hepatic toxicities. To minimize systemic toxicities, we have developed a novel Claudin18.2 (CLDN18.2) x 4-1BB bispecific antibody, TJ-CD4B (ABL111) that stimulates 4-1BB pathway only when it engages with Claudin 18.2, a tumor-associated antigen specifically expressed in gastrointestinal cancers. Previous data have shown that TJ-CD4B/ABL111 binds with high affinity to CLDN18.2, including in tumor cells that express a low level of CLDN18.2. Moreover, 4-1BB was induced to trigger T cell activation in a CLDN18.2-dependent manner, leading to a strong and long-lasting anti-tumor effect. The pharmacologic and safety profiles support the further development of TJ-CD4B/ABL111.

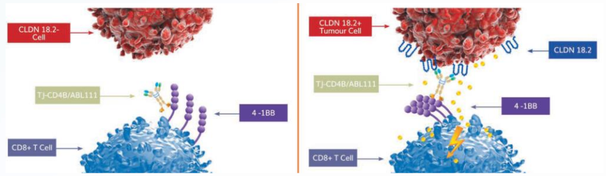
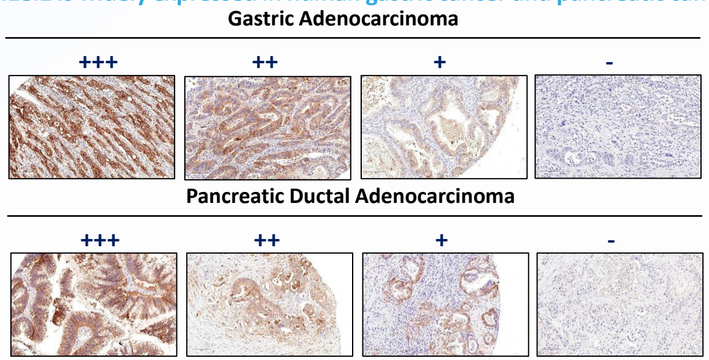


Figure 1. CLDN18.2-dependent 4-1BB activation.

RESULTS

CLDN18.2 is widely expressed in human gastric cancer and pancreatic cancer



TMA	Any positivity	2+/3+ ≥ 40% tumor	2+/3+ ≥ 70% tumor
Gastric cancer (96)	40.63% (39)	5.21% (5)	1.04% (1)
Pancreatic cancer (80)	41.25% (33)	15% (12)	3.75% (3)

Figure 1. CLDN18.2 expression was evaluated in tissue microarray of gastric cancer samples and pancreatic cancer samples by immunohistochemistry (IHC), using a monoclonal anti-CLDN18.2 antibody (Abcam)

TJ-CD4B induced dose-dependent tumor inhibition and increase of TILs.

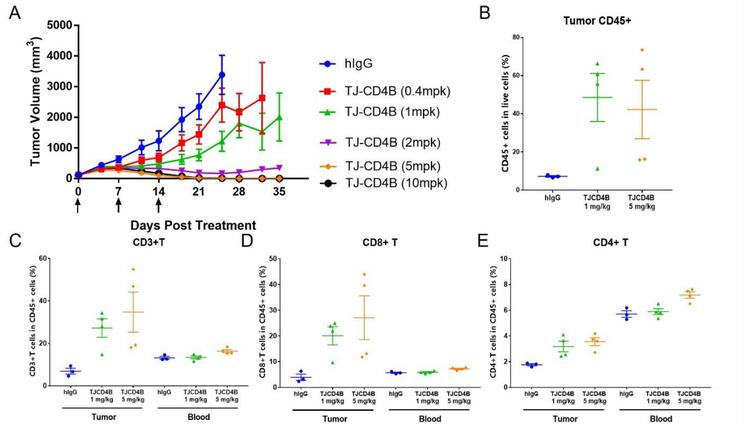


Figure 3. *In vivo* efficacy of TJ-CD4B in syngeneic mouse model (A) and *ex vivo* analysis of peripheral and tumor infiltrating lymphocytes.by FACS (B-E).

Peripheral pharmacodynamics changes after TJ-CD4B administration

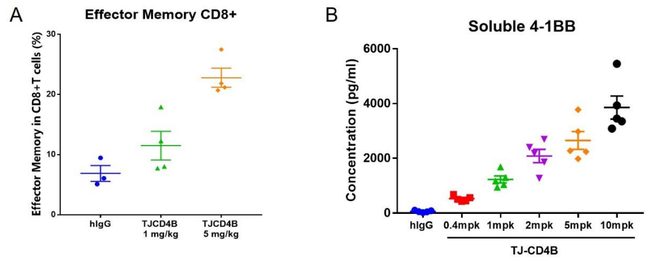


Figure 4. A. Peripheral immunophenotyping by FACS showed effector memory CD8+ expansion after TJ-CD4B. B. TJ-CD4B induced increase of soluble 4-1BB in the serum, measured by ELISA.

Treatment of TJ-CD4B induce a pro-inflammatory profile and increased IFNγ - regulated gene expression.

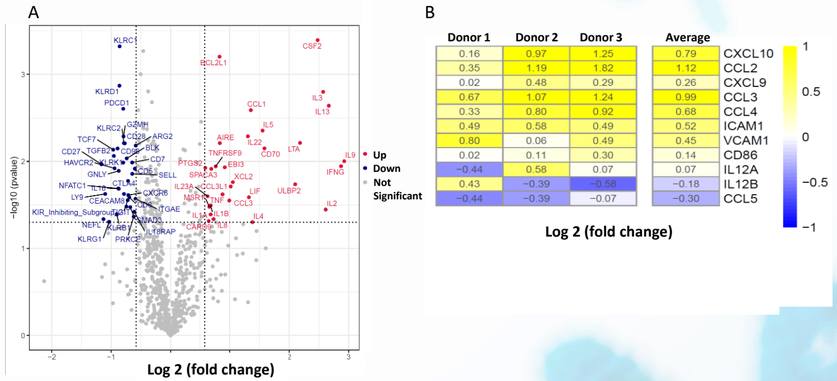


Figure 5. Gene expression analysis was performed by NanoString nCounter® on primary human CD8+ T cells that were co-cultured with CLDN18.2 expressing cells treated with TJ-CD4B. A. Volcano plot shows the mean fold change in gene expression. B. IFNγ downstream gene expression was enhanced after treatment.

TJ-CD4B was well tolerated in a pivotal GLP toxicity study in non-human primate.

- Cynomolgus monkeys were treated with TJ-CD4B up to 100mg/kg for 5 doses, followed by a recovery period.
- No elevation of liver enzymes (ALT, AST); no pathological changes was found in liver.
- No acute or delayed cytokine release was observed; no change of immune cells was observed.
- Histopathology showed on-target minimal to moderate morphological change in stomach, which resolved by the end of recovery period.
- NOAEL was determined at 100mg/kg.

CONCLUSION

- TJ-CD4B (ABL111) exhibited potent anti-tumor activity, associated with enhanced T cell proliferation in TME and memory T cell expansion in the peripheral blood. The level of soluble 4-1BB was also elevated in response to the treatment, indicating target engagement.
- TJ-CD4B (ABL111) effectively activated immune pathways characterized by IFNγ-signaling and T cell inflammation.
- TJ-CD4B (ABL111) did not induce systemic immune response nor hepatic toxicity due to the CLDN18.2 dependent 4-1BB stimulation.
- TJ-CD4B (ABL111) is now in Phase I study (NCT04900818) to assess the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy in US (NCT04900818).

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