JAB-BX610, a First-in-Class Tissue Factor-Directed Antibody Drug Conjugate Delivering a Novel KRAS G12D Inhibitor

Peng Wang[1], FangJie Liu[2], Rui Zhou[1], Haijun Li[3], Dan Liu[1], Amin Li[3], Andrea Wang-Gillam[4], Xin Sun[5], Yiwei Lin[6], Baohua Cao[2], Yanping Wang[7]

[1]Jacobio Pharmaceuticals, Biology, Beijing, China; [2]Jacobio Pharmaceuticals, Antibody Engineering, Beijing, China; [3]Jacobio Pharmaceuticals, Chemistry, Beijing, China; [4]Jacobio US Pharmaceuticals, Medicine, Burlington- MA, USA; [5]Jacobio Pharmaceuticals, Translational Medicine, Beijing, China; [6]Jacobio US Pharmaceuticals, Translational Medicine, Burlington- MA, USA; [7]Jacobio Pharmaceuticals, Preclinical Pharmacology, Beijing, China.

Abstract # PB-076

Background

- KRAS G12D is a dominant oncogenic driver, present in about 40% of pancreatic ductal adenocarcinoma (PDAC) cases. While current KRAS G12D inhibitors show promising efficacy in PDAC patients, significant room for improvement of therapeutic window remains.
- TF is a clinically validated target in cervical cancer, and highly expressed in various solid tumors, especially in PDAC. In preclinical cancer models, TF overexpression promotes acquired resistance to KRAS inhibition, and combinational treatment with TF-blocking antibody leads to a robustly enhanced antitumor efficacy toward KRAS mutant tumors.
- Utilizing antibody-drug conjugates (ADCs) to deliver KRAS G12D inhibitors directly to tumors offers a promising approach to enhance therapeutic outcomes. JAB-BX610 was developed as a TF-directed ADC to achieve tumor-specific delivery of a novel, highly potent KRAS G12D inhibitor, with drug-antibody ratio (DAR) 8.

Superior Cellular Activity and Selectivity

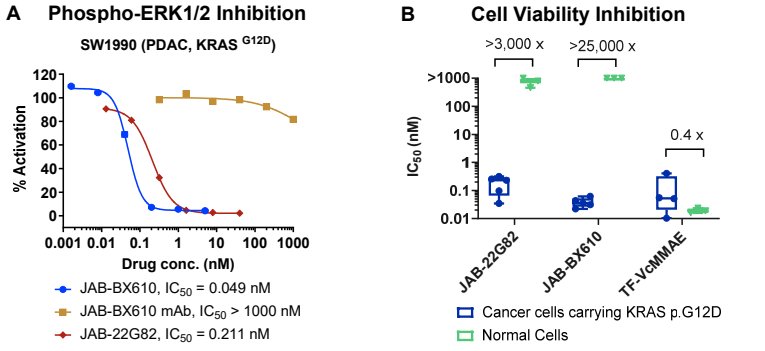

Figure 1. Cellular Activities of JAB-BX610
A. Phospho-ERK1/2 levels in SW1990 cell lysates were evaluated by HTRF after a 24-hour drug treatment. **B.** Cells were treated with the indicated drugs in culture medium for 6 days, followed by viability assessment using a luminescence-based assay. Cancer cells carrying KRAS p.G12D and with TF expression: AsPC-1, SW1990, PK-1, PK-59, HPAF-II. Human normal cells with TF expression: HaCaT (skin cells), HCE-T (corneal epithelial cells) and HBEC3-KT(bronchial epithelial cells). TF-VcMMAE (DAR4) was synthesized by Jacobio using a clinical stage TF Ab as the delivery antibody.

High Binding & Bystander Killing, Lacking ADCC & Coagulation Toxicity

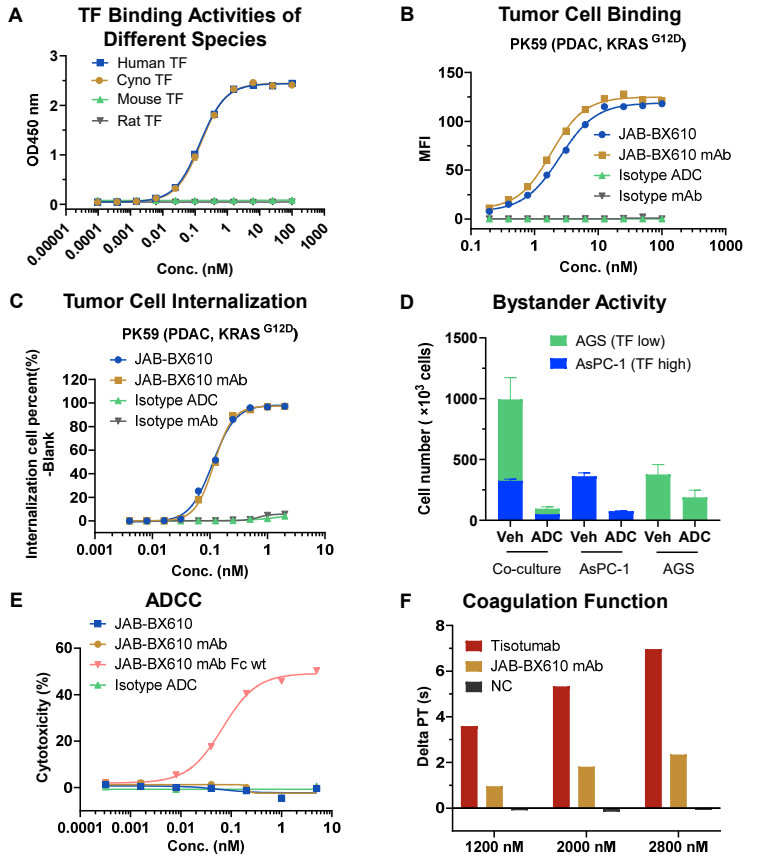

Figure 2. *In Vitro* Profile of JAB-BX610
A. Species cross-reactive binding activities were assayed by ELISA. **B.** Binding affinity of antibody and ADC to human TF on PK59 cells was detected by FACS. **C.** Internalization to PK59 cells was assessed by FACS. **D.** AGS and AsPC-1 monocultures, as well as their co-cultures, were treated with 1 nM JAB-BX610 for 6 days. Viable cells were detached and counted using an automated cell counter. To determine the AGS/AsPC-1 ratio, the harvested cells were stained with an anti-TF-FITC antibody and analyzed by flow cytometry. The absolute numbers of cells in each well were calculated based on the total cell count and the ratio of TF-low and TF-high populations. **E.** ADCC (Antibody-Dependent Cell-mediated Cytotoxicity) of antibody and ADC was detected using A431 and hPB-NK cells. **F.** Effects of antibody on coagulation function were assayed by prothrombin time (PT) test. NC: a non-relevant negative control mAb.

Robust Anti-tumor Efficacy in TF-Positive Models

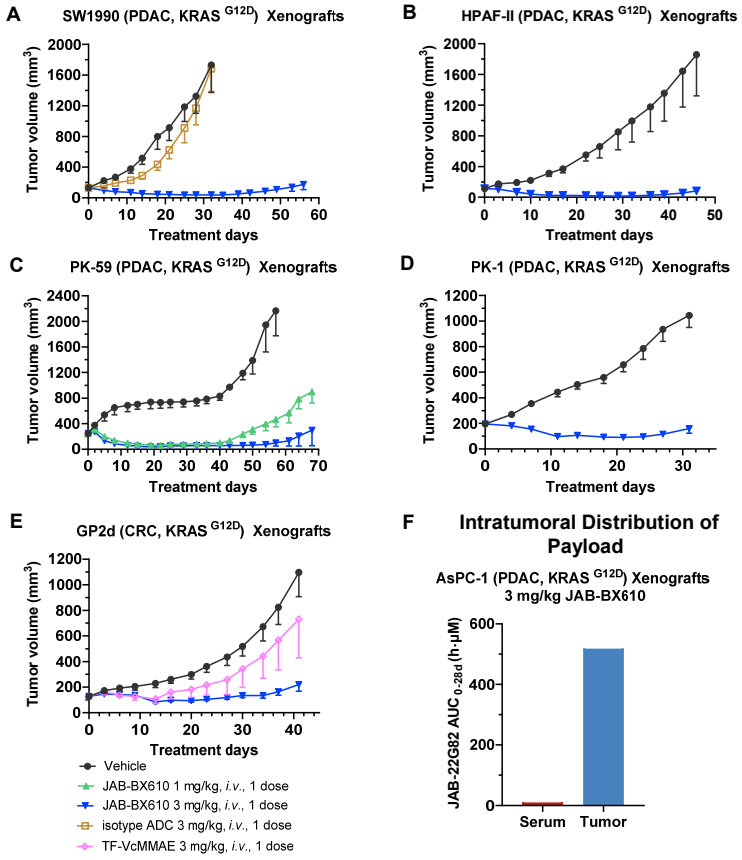

Figure 3. *In Vivo* Efficacy of JAB-BX610
A-E. Tumor-bearing mice were treated with drugs at indicated doses. Isotype ADC: anti-HEL mAb conjugated with the same linker-payload as JAB-BX610. **F.** AsPC-1 tumor-bearing mice were treated with a single dose of JAB-BX610 at 3 mg/kg, and tumor tissue samples were collected at different time points. The concentration of JAB-22G82 in serum and tumor was quantified by LC-MS/MS.

Favorable PK Profile

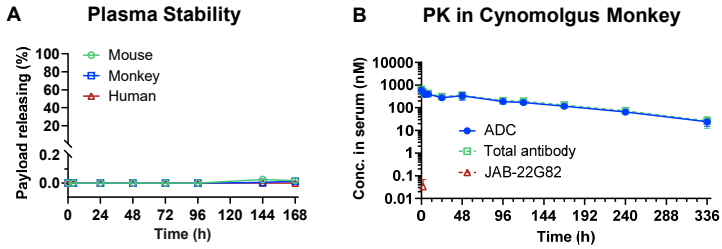

Figure 4. PK profile of JAB-BX610
A. Mouse, monkey, and human plasma samples were incubated with 125 nM JAB-BX610 at 37 °C for the indicated times, and the released payload (JAB-22G82) was subsequently quantified by LC-MS/MS. **B.** Cynomolgus monkeys(1 female and 1 male) were treated with 3 mg/kg JAB-BX610. Total antibody concentration of JAB-BX610 in serum was measured by ELISA. The concentration of JAB-22G82 in serum was quantified by LC-MS/MS.

Conclusion

- The free payload JAB-22G82 and the ADC JAB-BX610 exhibit superior cellular potency, displaying 3,000-fold and 25,000-fold selectivity over human skin cells, corneal epithelial cells and bronchial epithelial cells, respectively, whereas TF-VcMMAE showed no such selectivity.
- JAB-BX610 shows potent TF binding, efficient internalization, and bystander killing, lacking ADCC and coagulation toxicity.
- A single administration of JAB-BX610 at 3 mg/kg can induce tumor regression in PDAC animal models, with high intratumoral payload distribution and minimal payload release in blood.
- JAB-BX610 is stable in plasma, and demonstrates favorable monkey PK.
- JAB-BX610 is ready to enter IND-enabling studies, for the treatment of multiple cancer types, such as PDAC, cholangiocarcinoma, cervical cancer, lung cancer, etc.

Acknowledgement

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Oncogene 43, 668–681 (2024).
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For more information about Jacobio Pharma and our KRAS programs, please refer to the website: https://www.jacobiopharma.com/en/pipeline