Novel Conditionally Active Biologic anti-Axl ADC Demonstrates Anti-Tumor Efficacy and Improved Safety Profile

Cathy Chang, Gerhard Frey, William J. Boyle, Leslie L. Sharp, Jay M. Short
BioAtla, 11011 Torreyana Road, San Diego, CA 92121

ABSTRACT

Axl is a TAM family receptor tyrosine kinase that has been implicated in the pathogenesis of many cancer types[1]. The high level of expression on the cancer cell surface has made it an attractive target for antibody therapeutics. However, Axl is expressed on many normal tissues and has been implicated in wide ranging requisite biological processes including response of endothelial cells to vascular injury, hematopoiesis, and regulation of immune responses. This normal tissue expression may limit Axl as a target for antibody-drug-conjugates (ADC). Conditionally Active Biologics (CAB) technology is a proprietary platform that selects antibodies that bind to target antigen in the context of diseased tissues, but not normal tissues, by taking advantage of the unique cancer microenvironment that is produced largely as a result of the Warburg effect. Using our CAB technology, we have identified anti-Axl Abs that reversibly bind to recombinant Axl and Axl expressing cells under conditions that are present in the tumor microenvironment but not in normal tissues.

CAB-Axl antibodies were then conjugated to a model toxin payload to generate CAB-Axl-ADCs. The CAB-Axl-ADCs were active against Axl positive human tumor xenografts with tumor stasis observed at 1mg/kg weekly and tumor regressions observed at 1 mg/kg twice a week dose levels. A non-specific IgG-ADC showed minimal efficacy at the same dose levels. Single dose studies in cynomolgus macaques have demonstrated that CAB-Axl-ADC has reduced liver toxicity and immune system effects compared to Axl-ADCs that bind to Axl under normal conditions.

In conclusion, our data is consistent with our work on CAB-EGFR antibodies, and suggests that ADCs generated using the CAB technology provides biologics with increased therapeutic index. Specifically, the CAB-Axl-ADC is an excellent candidate for evaluation as a treatment for human cancers that are Axl positive.

RATIONALE

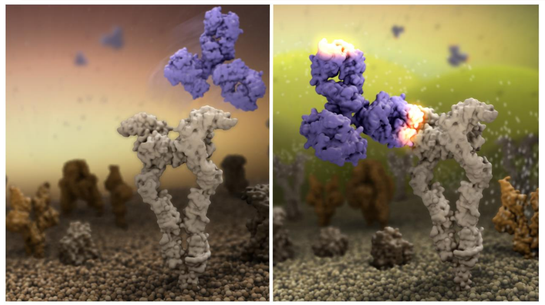

Figure 1. Condition specific binding of CABs
Left panel- CAB Abs are selected to lack binding under normal conditions present in healthy tissue
Right panel- Tumors have a unique microenvironment produced largely by Warburg effect (green). CAB Abs bind to target under conditions present in the tumor microenvironment

RESULTS

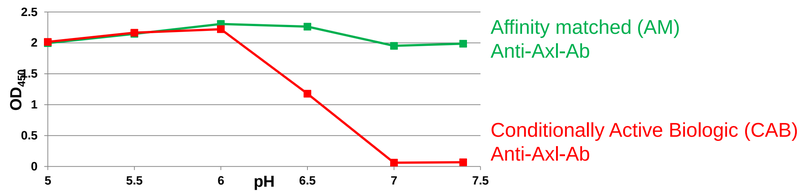

Figure 2. Differential binding capabilities of CAB-Axl-Abs. In vitro binding of affinity matched (AM) anti-Axl-Ab (green) and CAB-anti-Axl-Ab (red) to recombinant Axl protein under varying pH conditions.

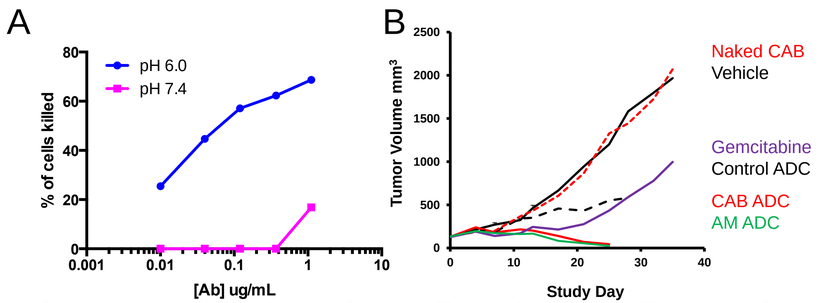

Figure 3. CAB-Axl-ADCs have anti-tumor efficacy. A) in vitro cell killing activity of CAB-Axl-ADC against A549 cells under pH 6.0 (blue) and pH 7.4 (pink) condition. B) Mice bearing MiaPaCa2 xenograft tumors were were dosed at 1mg/kg twice weekly for 3 weeks with Abs or ADC. CAB-Axl-ADC (solid red), affinity matched (AM)-Axl-ADC (solid green), CAB-Axl-Ab (dotted red), non-tumor-specific-ADC (dashed black). Vehicle PBS (solid black), and gemcitabine (purple) we included as controls.

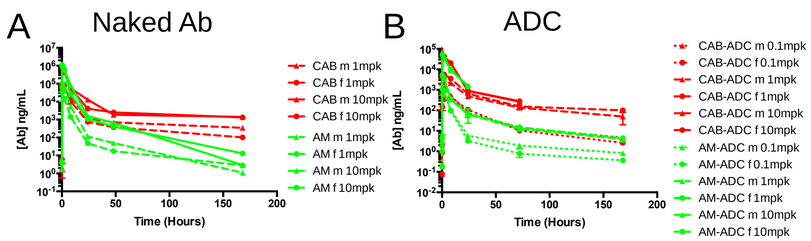

Figure 4. CAB-Axl-Ab and CAB-Axl-ADCs have increased serum concentration in cynomolgus non human primates compared to affinity matched comparator. A) serum Ab concentration of CAB-Axl-Ab (red) and affinity matched AM-Axl-Ab (green) B) serum Ab concentration of CAB-Axl-ADC (red) and affinity matched AM-Axl-ADC (green). 0.1 mg/kg dose-dotted line, 1mg/kg dose-dashed line, 10 mg/kg dose- solid line, males-triangle, females-circle. Serum Ab concentration measured by FLAG ELISA.

RESULTS

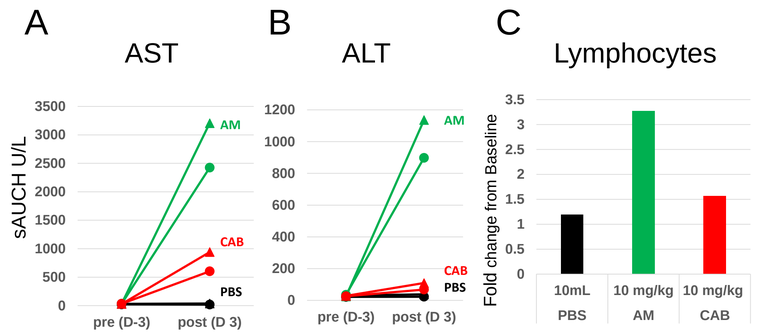

Figure 5. CAB-Axl-ADCs have reduced toxicity in cynomolgus non human primates compared to affinity matched Axl-ADC and phenocopy TAM$^{-/-}$ mice [2,3]. A) amount of AST B) amount of ALT and C) Fold change in lymphocyte numbers at Day 3 post-dose relative to pre-dose (Day -3) in animals dosed with 10 mg/kg ADCs. PBS treated animals (black), AM-Axl-ADC treated animals (green) CAB-Axl-ADC treated animals (red)

CONCLUSIONS

CAB-Axl-ADC that bind to Axl under tumor but not normal conditions have been generated

CAB-Axl-ADC are efficacious in a pancreatic xenograft model

CAB-Axl-Ab and CAB-Axl-ADC have increased serum concentration of Ab compared to affinity matched Axl-Abs and Axl-ADC

CAB-Axl-ADC have reduced toxicity compared to affinity matched Axl-ADC and phenocopy liver and immune system effects found in TAM$^{-/-}$ mice

CAB-ADC have opportunity for increased therapeutic index

REFERENCES

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3. Qi N, Peipei L, Zhang Y, Wu H, Chen Y, Han D. *PLoS ONE.* 2013 8(6) e66604

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