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Novel conditionally active ADCs (CAB ADCs): A novel class of molecules targeting solid tumors

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ABSTRACT

Conditionally Active Biologics (CAB) technology is a proprietary platform that selects antibodies binding to target antigens in the context of diseased tissues, but not normal tissues, taking advantage of the unique conditions in the tumor microenvironment. Using our CAB technology, we have developed CAB ADCs to various well-established tumor associated antigens (TAA), including Nectin4, Her2 and CD46. All these molecules play important roles in cancer biology and are attractive targets for the development of therapeutic antibodies. These targets, however, are expressed on many normal tissues and have been implicated in wide ranging biological processes, therefore limiting the use of regular ADCs as cancer therapy. Using CAB technology, we have developed conditionally active ADCs that have no or very little binding to the target antigen in healthy tissue (normal physiological conditions), but have strong binding in the context of diseased tissues (tumor microenvironment) based on the glycolytic tumor metabolism (e.g.Warburg effect).

In vitro pH binding profiles demonstrating higher binding affinities of CAB ADCs to antigens in tumor conditions compared to normal physiological conditions, together with *in vivo* efficacy data demonstrating the abilities of CAB ADCs to inhibit tumor growth in human tumor xenograft models are presented here. In conclusion, our data is consistent with our previous work on EpCAM, AXL and ROR2 CAB ADCs and further supports that conditionally active ADCs generated using the CAB technology platform will provide a new generation of biologics with increased therapeutic index in the clinic.

RATIONALE

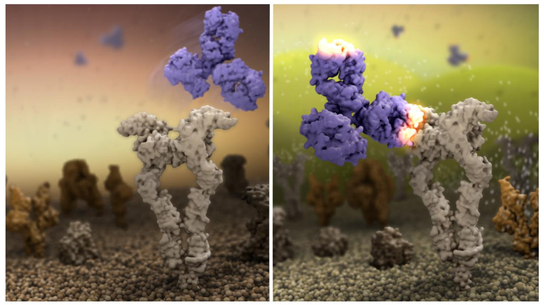
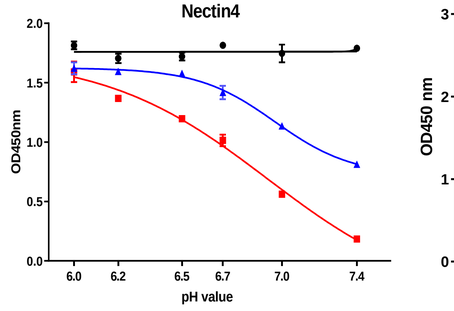


Figure 1. Condition specific binding of CABs
Left panel- CAB Abs are selected to lack binding under normal conditions present in healthy tissue
Right panel- Tumors have a unique microenvironment produced by glycolysis including the Warburg effect in oxygenated regions of the tumor (green). CAB Abs bind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

RESULTS

2A



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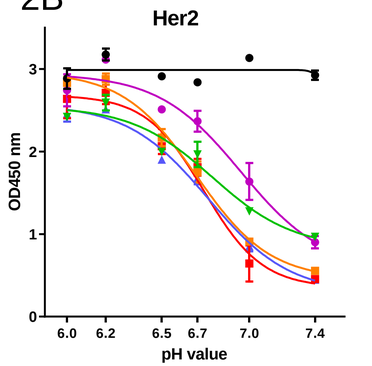

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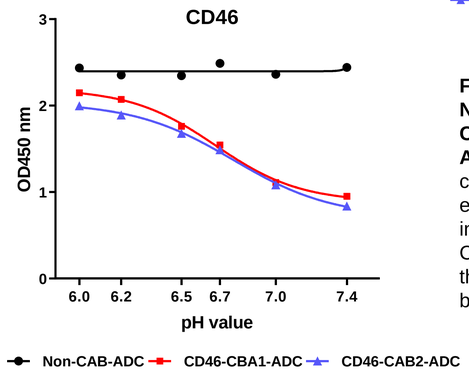


Figure 2. pH binding profile of anti-Nectin4 CAB ADCs (A), anti-Her2 CAB ADCs (B) and anti-CD46 CAB ADCs (C). CAB ADCs bind to the corresponding recombinant human extra cellular domain (ECD) antigens in ELISA. The binding signal of the CABs drops from pH6.0 to pH7.4 while the binding signal of the non-CAB benchmark clones stay the same.

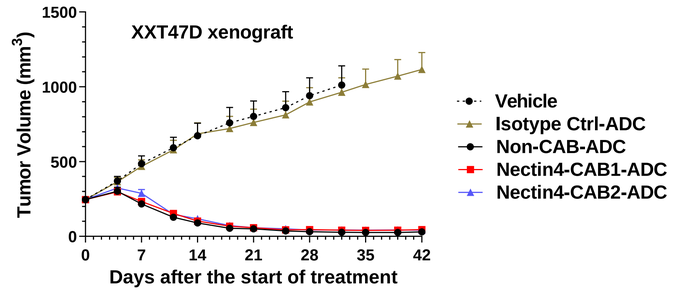
CONCLUSIONS

Compared to tumor conditions, CAB ADCs have reduced binding to target antigens under normal conditions, which endues CAB ADCs with an increased therapeutic index.

CAB ADCs are efficacious at a low dose of 3mg/kg in cell line derived xenograft models *in vivo* without any intolerability.

RESULTS

3A



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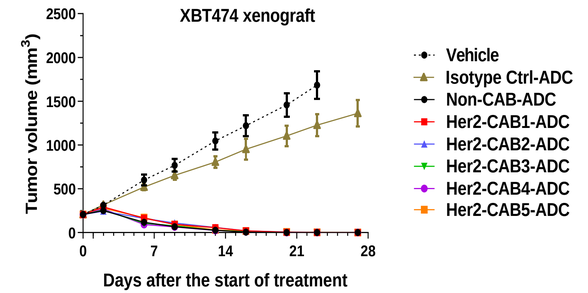

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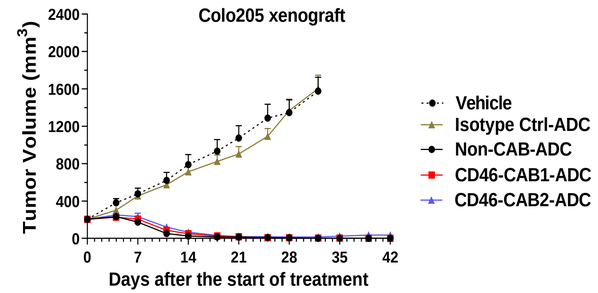

Figure 3. *In vivo* efficacy of CAB ADCs in tumor cell line derived xenograft models. Tumor cells were implanted in immunodeficient mice. When the tumor volume reached approximately 80-100 mm^3, following randomization, animals (n=8 per group) were dosed with the indicated test articles (3 mg/kg, Q4Dx4). No significant difference in body weights was found among different groups, indicating CAB ADCs have comparable tolerability as non-CAB ADCs.

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