Novel Conditionally Active Bispecific T Cell Engagers Targeting Solid Tumors

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Disclosure Information

- ***AACR 2020 Virtual Annual Meeting II***
  Speaker: Ana Paula G Cugnetti, PhD

I have the following financial relationships to disclose:

Consultant for: N/A

Speaker's Bureau for: N/A

Grant/Research support from: BioAtla, LLC

Stockholder in: BioAtla, LLC

Honoraria from: N/A

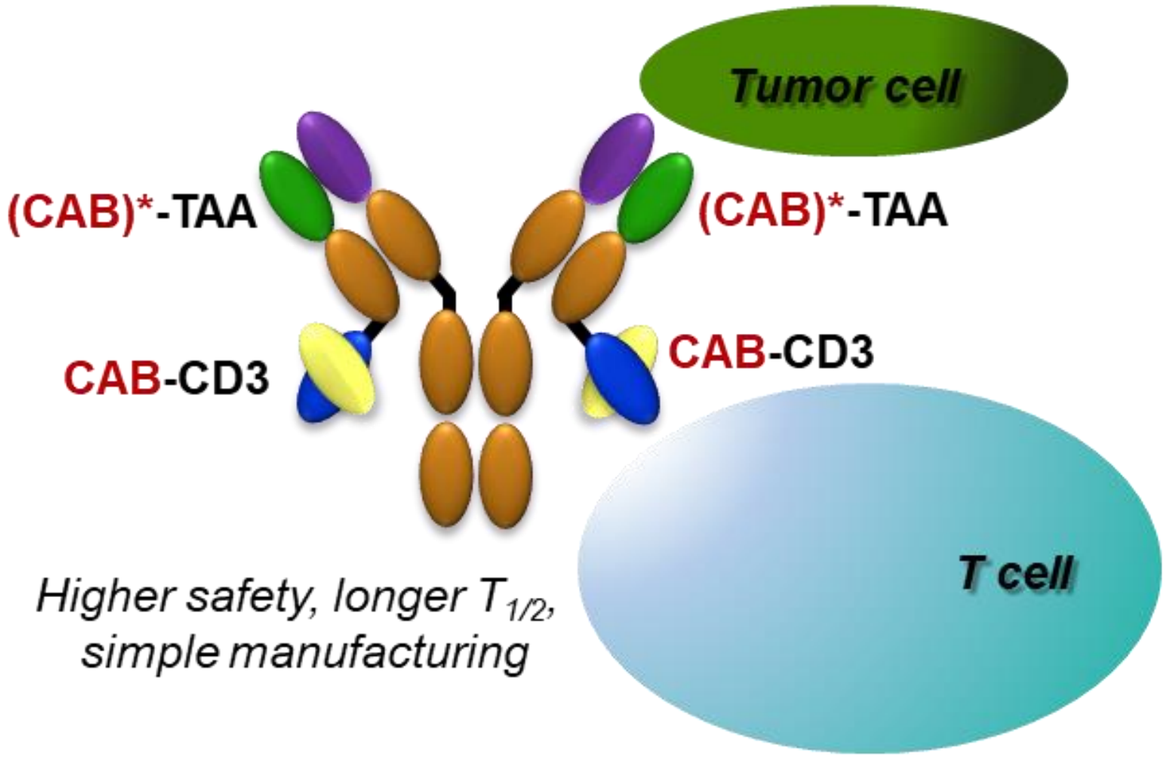
Employee of: BioAtla, LLC

I will discuss the following off label use and/or investigational use in my presentation:

- *BioAtla's CAB Technology*
- *BioAtla's CAB Butterfly Bispecifc Antibodies Targeting EpCAM and B7H3 TAAs*

Conditionally Active Biologics (CAB) Bispecific Platform

Butterfly CAB Bispecific Platform

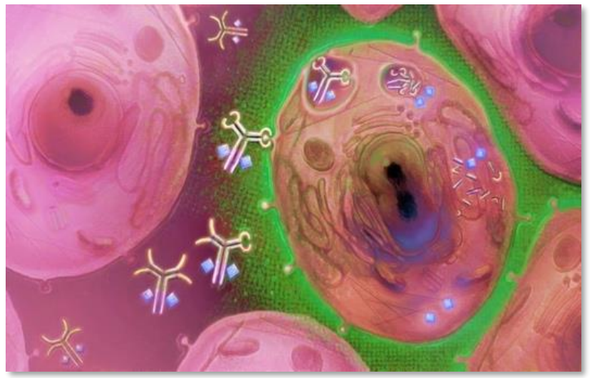


*Optional CAB directed against the tumor associated antigen (TAA)

CAB Technology Leverages Differential pH of Cancer Cells

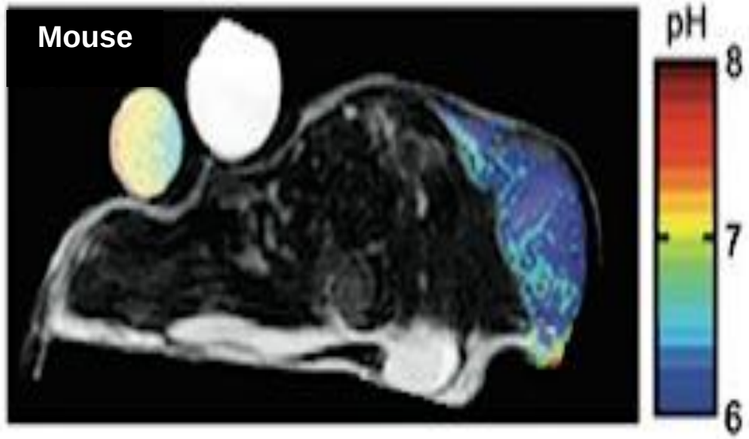
CABs designed to be active only under certain conditions found in disease tissue

- **Ability to generate antibodies that are only active in the Tumor Microenvironment (TME)**
  - Increased safety
  - Higher potency



- **Warburg Effect**
  - Cancer cells have high rate of glycolysis (reduces immune attack and apoptosis)
  - Well established in scientific literature since the 1920's by Prof. Otto Warburg
  - Glycolysis theorized to be required for single cell neoplastic transformation
  - Glycolysis is required for active proliferating cells

- **High glycolysis creates a unique TME**
  - High external lactic acid levels leading to acidic pH (5.5-7.0) in the tumor
  - Contrasts with alkaline pH (7.4) in healthy tissue



Liu G et al. (2012) Imaging *in vivo* extracellular pH with a Single PARACEST MRI Contrast Agent. Molec Imaging 11(1): 47-57

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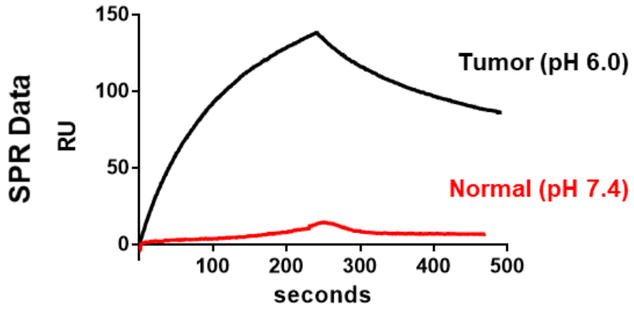
CABs Bind Selectively and Reversibly Based on the Cellular Microenvironment

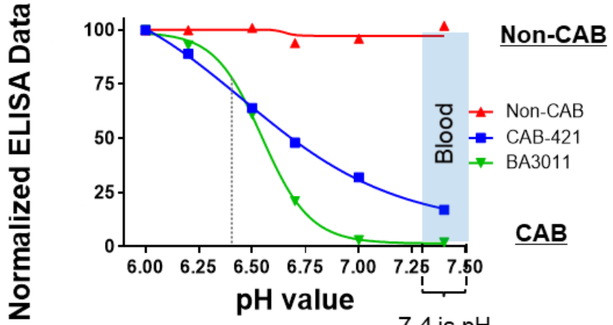
CABs Bind Selectively in the TME…

CAB antibody binds to target antigen under TME conditions



Adjustable CAB pH binding inflection point

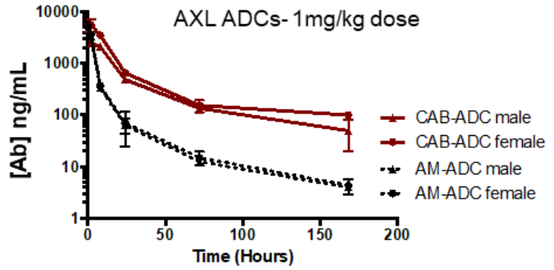
CAB mAbs Undisclosed Targets



…Enhancing Therapeutic Exposure and Reducing Toxicity

CAB enhances therapeutic exposure

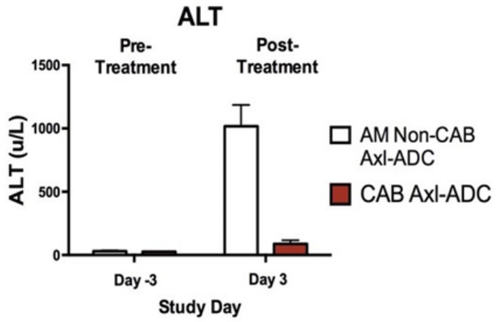
CAB improves PK by eliminating Tissue Mediated Drug Deposition (TMDD)



Non-human primate studies

CAB lowers liver toxicity, no on-target tox

CAB lowers liver ALT levels compared to affinity matched (AM) non-CAB-ADC



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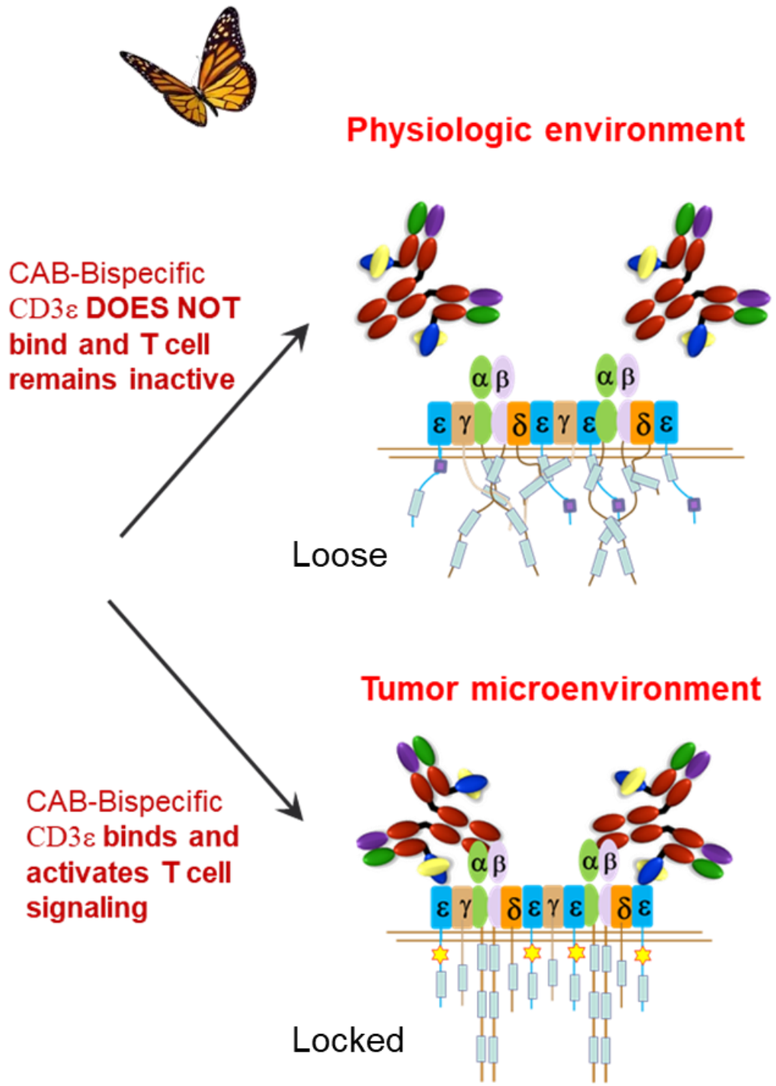
CAB Bispecific Antibody Activates T cells in the Tumor Microenvironment Minimizing Toxicity while Maintaining Potency

- T cells are physically linked to tumor cells via Bispecific mAbs composed of a T cell-binding domain and a tumor-binding domain
- Bispecific mAbs activate T cells through binding of CD3ε in the TCR complex, thereby bypassing MHC restriction and epitope specificity of the TCR.
- CD3 e engagement changes the TCR complex to a locked configuration that promotes signaling and T cell activation.

Advantages of CAB Bispecific Platform

- Potential to increase safety by reducing systemic activation, *i.e.* reduce cytokine release syndrome, neurological toxicity and anaphylaxis
- Enables T cell engaging therapies with high potency *in vitro* and *in vivo*
- Expands the universe of targets for drug development in the context of T cell engagers



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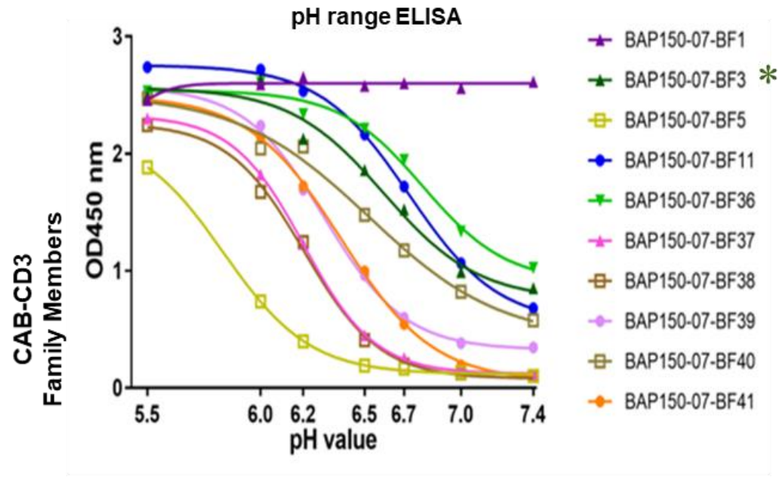
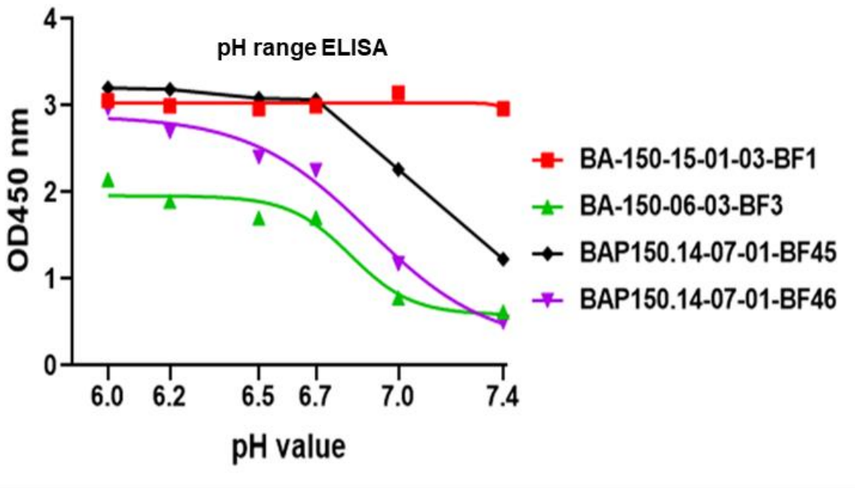
CAB T Cell Engagers Family for Rapid Generation and Maximum Therapeutic Index





- Potent and selective CAB-CD3 T cell activators
- Long $T_{1/2}$ with high safety
- Rapid conversion of mAbs to potent a CAB bispecific
- CAB-CD3 family enables cost-effective selection of optimal target-effector combination bispecific antibody
- Reduce T cell exhaustion by activation selectively in the TME
- Optional CAB on the tumor targeting arm for higher selectivity and reduction of potential Target Mediated Drug Deposition (TMDD)

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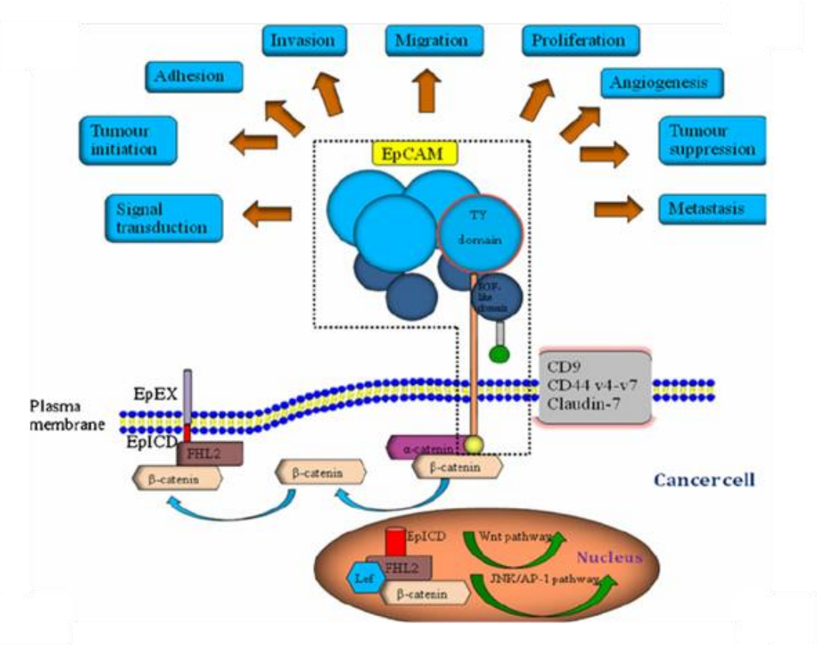
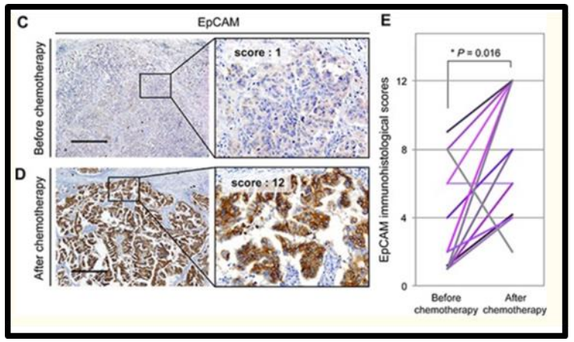
EpCAM (Epithelial Cell Adhesion Molecule)

- Highly expressed on adenocarcinomas
  - Lung, colon, Ovarian, Prostate, Breast.
- Epithelial cell proliferation is driven through EpCAM signal transduction
- Expressed in virtually all epithelia containing tissues
- Loss of function in normal tissues causes significant pathology and morbidity
- CAB-EpCAM ADC drug concept
  - High solid tumors expressing high levels.
  - Internalization to deliver conjugated cytotoxin.
  - Minimize on-target normal tissue toxicity – Micromet EpCAM-CD3 (Solitomab) is toxic, development stopped.
- Attractive target for immunotherapy of cancer; significant commercial potential
  - EpCAM is overexpressed in many cancers (epithelial carcinomas).
  - Lack of selectivity for affected tissues and cells is a significant concern for use in the clinic.





Biology of EpCAM; modified from Ni, J., et al. (2012). "Role of the EpCAM (CD326) in prostate cancer metastasis and progression." Cancer Metastasis Rev 31(3-4): 779-791

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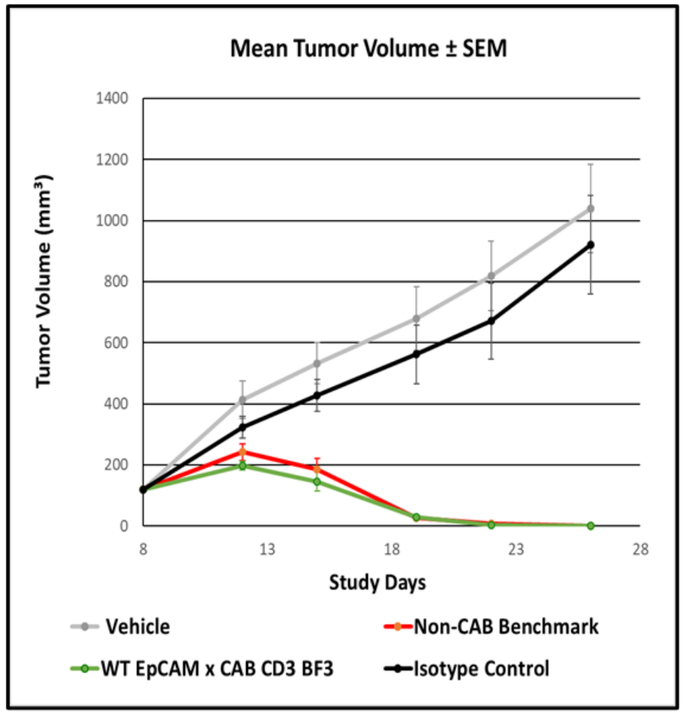
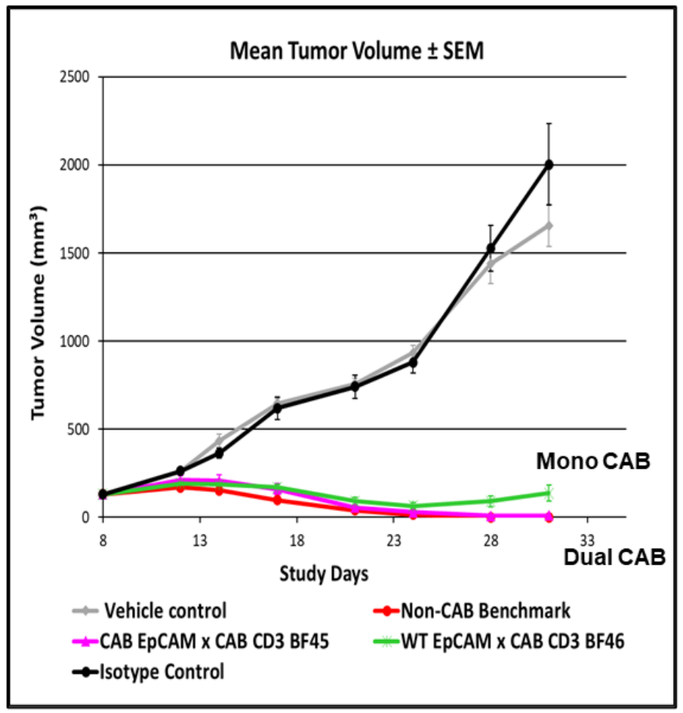
EpCAM x CD3 Mono and Dual CAB Bispecific mAbs MiXeno HCT116 Xenograft Studies

Mono CAB



Mono CAB and Dual CAB



Mixeno Model with HCT116 Colorectal Cancer Cell Line
2.5mg/kg twice/week in mice
(equivalent to 0.2mg/kg in non-human primates)

Both WT-EpCAM x CAB-CD3 and CAB-EpCAM x CAB-CD3 demonstrated high efficacy in in vivo Mixeno xenograft studies

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Lower Inflammatory Response is Observed in Non-Human Primates Treated with Mono CAB WT-EpCAM x CAB-CD3

Lower levels of IL-6 and higher level of CD3+ cells observed in the serum of NHPs 4h after treatment with WT-EpCAM x CAB-CD3 vs WT-EPCAM x WT-CD3 antibody

Non-human Primates
WT-EpCAM x WT-CD3
0.25mg/kg = 2 expired
0.05mg/kg = 1 expired; 1 ill (recovered)
0.025mg/kg = 2 ill (recovered)

- GI and kidney function was impacted.
- Marked increase in ALP, ALT, AST, TBIL, CK were noted in these animals.
- Hepatocellular and cholestatic injury was identified based on the current clin path data.

Non-human Primates
WT-EpCAM x CAB-CD3
0.25mg/kg = 1 healthy;1 ill (recovered)
0.05mg/kg = 2 healthy
0.025mg/kg = 2 normal

- At high dose see some early signs of toxicity
- No toxicity observed at the lower doses

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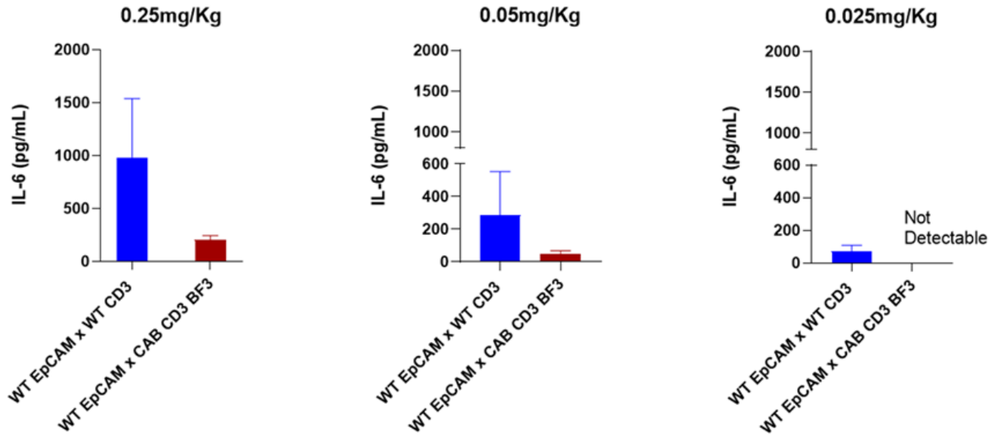
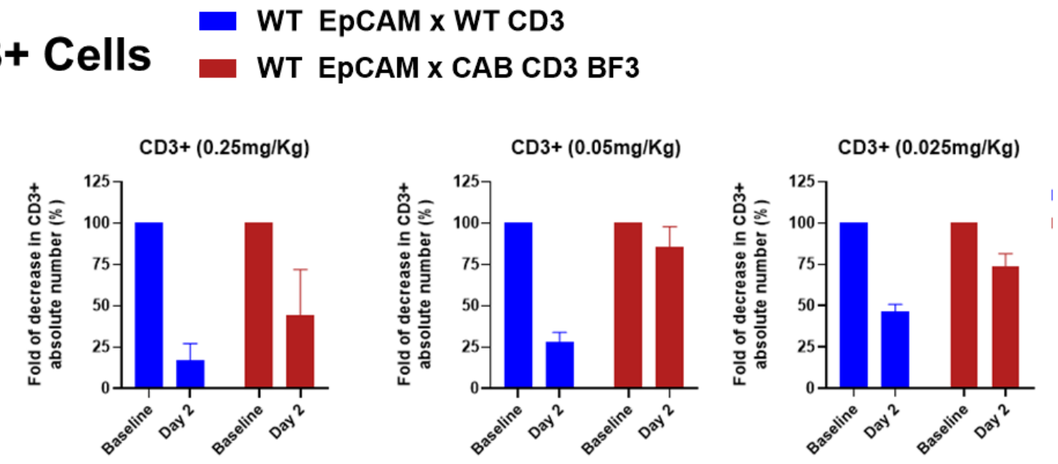
IL-6



CD3+ Cells

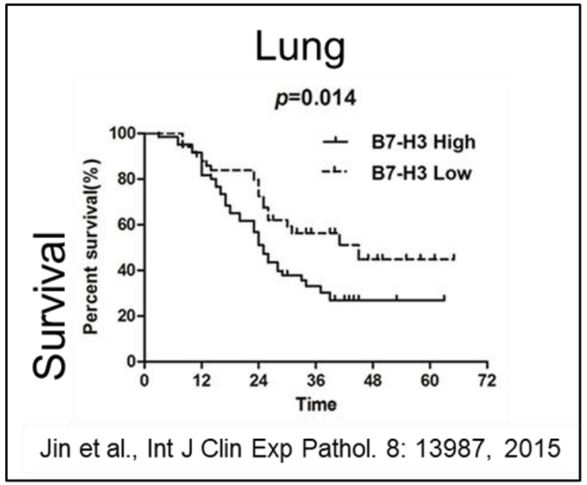


Expected dosing in Non-human Primates <0.25mg/kg w/ current CABs

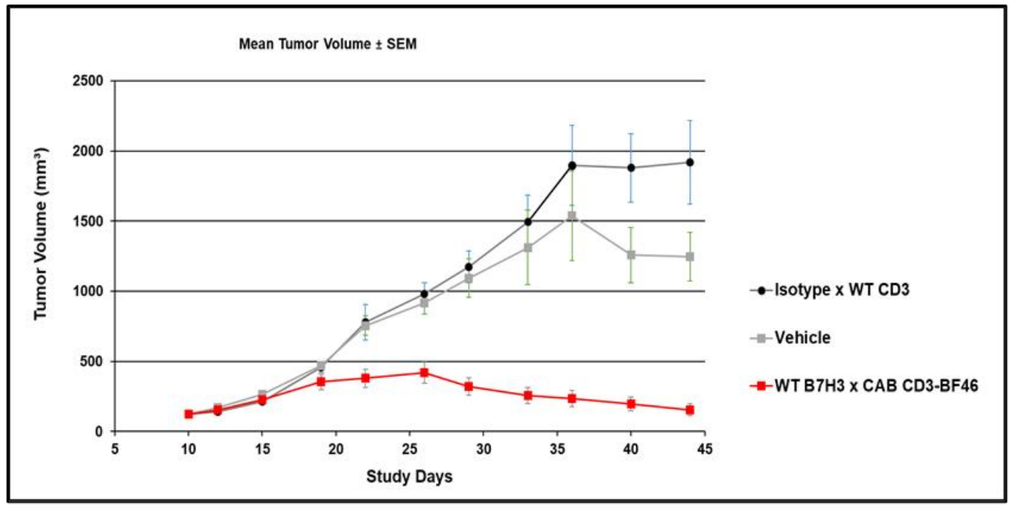
Immuno-oncology B7 Family Member- B7-H3

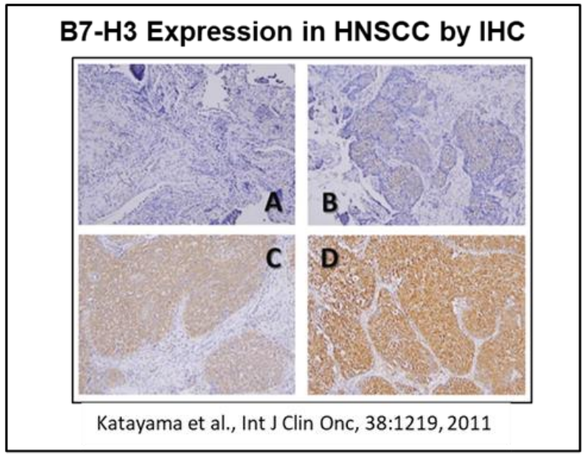
Target Expression in Cancer

- **B7-H3 overexpression correlates with poor prognosis in multiple tumor types including:**
  - Head and Neck, Lung, Melanoma, Pancreatic, Prostate, Sarcoma
- **Overexpression of B7-H3 in cancer cell lines**
  - increases tumor growth *in vivo*
  - Increases glucose uptake *in vivo*
- **Potential toxicity risk due to expression in normal tissues**
  - Small and large intestine
  - Skin
  - Esophagus



Jin et al., Int J Clin Exp Pathol. 8: 13987, 2015





Katayama et al., Int J Clin Onc, 38:1219, 2011

WT-B7H3 x CAB-CD3 demonstrates high efficacy in in vivo Detroit-563 Mixeno xenograft studies

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Summary of CAB CD3 Bispecific Antibodies

- Mouse tumor xenograft efficacy data demonstrated that WT and CAB CD3 bispecific antibodies which target WT EpCAM have equivalent efficacy (nominal value = 1).

- NHP administered with single doses of either WT-EpCAM x CAB-CD3 or WT-EpCAM x WT-CD3:
  - CAB-CD3 has an MTD that is about 10 times higher than WT-CD3 (CAB-CD3 MTD is 0.25mg/kg vs WT-CD3 MTD of 0.025mg/kg).
  - In the WT bispecific antibody, there is a dose dependent decrease in the level of CD3 positive T cells (both for CD4 and CD8 positives) in the peripheral blood, but not for the CAB-CD3 bispecific antibody indicating that the T cell pool is likely being deposited to tissues/cells expressing EpCAM.

- Overall, harmful inflammatory cytokines and toxicity-related clinical signs are ~10x greater with the WT-CD3 vs the CAB-CD3 bispecific antibodies in non-human primates.

- Dual CAB bispecific antibodies also show good efficacy and may further widen the therapeutic window as will soon be determined in ongoing non-human primates.

- WT-B7-H3 x CAB-CD3 bispecific antibody show good efficacy *in vivo.*

Summary

- CAB Technology platform allows the generation of biologics with conditional and reversible binding activity.
- Broadly applicable to antibody formats including ADCs, bispecifics, CAR-Ts and other therapeutic proteins.
- CABs are active in the tumor microenvironment, but not under physiological conditions, enhancing the therapeutic index by increasing both potency and safety.

Acknowledgement

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