Development of a Probody™ Drug Conjugate (PDC) Targeting CD166 for the Treatment of Multiple Cancers

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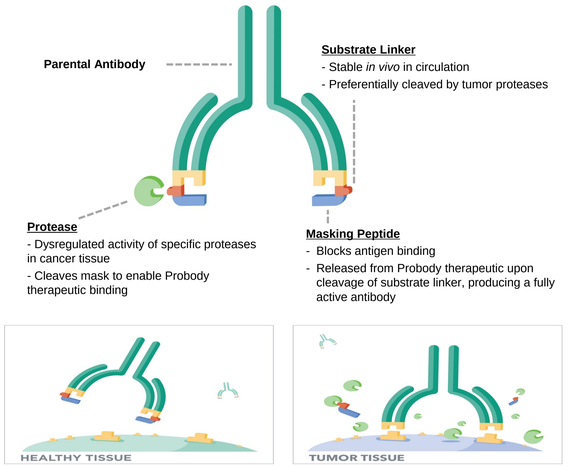
ABSTRACT

Antibody drug conjugates (ADCs) have shown their greatest clinical utility when targeting antigens expressed at very high levels on cancer cells. This is exemplified by the approvals of trastuzumab emtansine for her2neu 3+ breast cancer and brentuximab vedotin for CD30+ Hodgkin's Disease and Anaplastic large-cell lymphoma. There are other cell surface antigens that are highly expressed on cancer cells and are therefore attractive for ADC targets, but the utility of such antigens is restricted by their corresponding expression in normal tissues and their potential for mediating on-target toxicities. One such target is CD166 (ALCAM), which shows 3+ expression by IHC in most samples of multiple cancer types, but also expression in multiple normal tissues including lung, GI tissues, and liver. Thus CD166 has not been progressed as a target for ADCs.

Probody™ therapeutics are fully recombinant antibody prodrugs that are converted to active antibodies by tumor-associated proteases. Preclinical *in vivo* studies show that Probody therapeutics remain substantially unable to bind target in normal tissues and in circulation. As such, Probody drug conjugates (PDCs), unlike ADCs, enable targeting of high expression tumor targets that are also expressed in normal tissues. We have developed an anti-human CD166 Probody therapeutic selected for specific binding, internalization, and cross reactivity to cynomolgus macaque. This therapeutic has been conjugated to spdb-DM4 and tested in preclinical models for efficacy and safety. Treatment with the PDC has led to complete regressions in models of lung and breast cancer at therapeutically relevant doses. These same doses were demonstrated to be well-tolerated in cynomolgus monkeys. The safety and efficacy profiles for the anti-CD166 PDC are supportive of progression to clinical development of this anti-CD166 Probody drug conjugate.

INTRODUCTION

Probody™ Therapeutics are Protease-Activatable Antibody Pro-Drugs

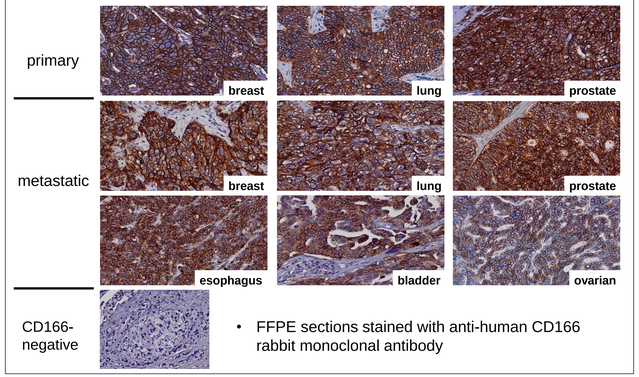


RESULTS

Probody Drug Conjugates Have the Potential to Target a Densely Concentrated Tumor Antigen, Regardless of Expression on Normal Tissue

		ADCs	PDCs
Desired Properties	Expression in healthy tissue	Low	Low or High
	Expression of target in tumor	High	High
Resulting properties	Homogeneity of expression in tumor	Often Modest	High
	Tumor types addressed	One/Few	Many
	Prevalence per cancer type	Lower	Very High

Figure 1: CD166 is Highly Expressed in Many Human Cancers – Primary and Metastatic



- FFPE sections stained with anti-human CD166 rabbit monoclonal antibody

Table 1: Prevalence of CD166 Expression in Human Cancers

Cancer type*	high CD166 expression (IHC ≥ 2+)	# cores
Prostate	> 80%	75
Breast	> 70%	196
NSCLC	> 70%	150
Endometrial	~ 70%	150
Ovarian	> 50%	80
Neuroendocrine	~ 65%	82
Head & Neck	> 50%	155

* Candidate indications (DM4/maytansine-sensitive)

Figure 2: CD166 PDC Renders Complete and Durable Responses in Mouse Models of Human Xenograft Tumors at Doses Equal to or Below the Predicted Human Dose

IV dosing on days 0 and 7

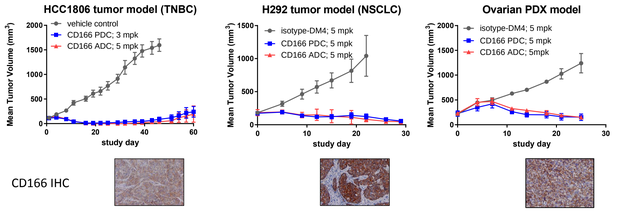
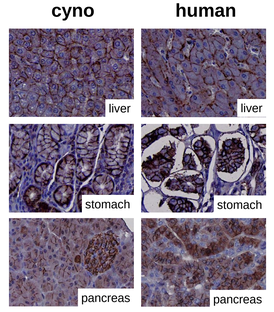


Figure 3: CD166 is Widely Expressed in Normal Human and Cynomolgus Monkey Tissues

Tissue Type	Cyno*	Human*
Adrenal Gland	+/-	+/-
Bone Marrow	-	-
Breast	+++	++
Cerebrum	+/-	+/-
Cerebellum	+	+
Colon	++	+++
Esophagus	+	+
Heart	+/-	-
Kidney	++	++
Larynx	+	+
Liver	++	++
Lung	++	++
Nerve	+	+
Ovary	+	+
Pancreas	++	+++
Prostate	++	+++
Skin	+/-	+
Small Intestine	++	++
Salivary Gland	++	++
Spleen	+	+
Stomach	+++	+++
Testis	-	-
Thyroid	+	+++
Thymus	+	+/-
Uterus	+++	+++



High CD166 expression in normal tissues suggests CD166 may not be a suitable target for conventional ADCs in human patients

* IHC

Figure 4: CD166 PDC Shows Significantly Extended Exposure in Cynomolgus Monkeys, Consistent with Reduced Binding in Normal Tissues

- ELISA PK assay shows increased exposure of CD166 PDC (total IgG) compared with CD166 ADC (single dose, 5mpk, i.v., n=2)
- Extended exposure is consistent with CD166 PDC avoidance of the antigen sink in normal tissues

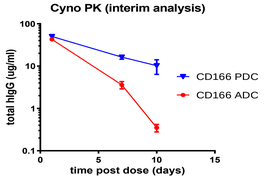
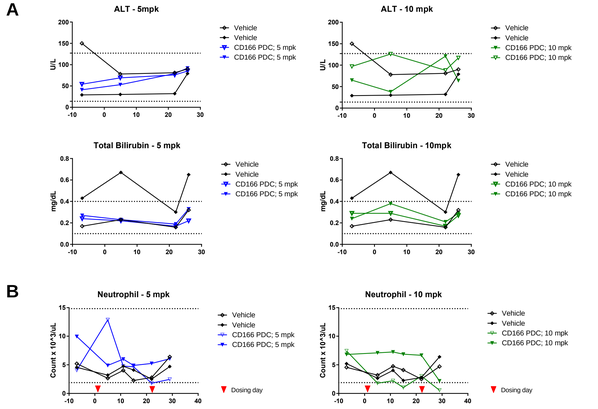


Figure 5: CD166 PDC is Well-Tolerated in Cynomolgus Monkeys at a Therapeutically Relevant Dose



- Cynomolgus monkeys (1male, 1 female) were treated IV with vehicle or CD166 PDC at the indicated doses on days 1 and 22
- CD166 PDC is well-tolerated at 5 mpk. No treatment-related adverse effects were observed, even in tissues with high CD166 expression (e.g. liver). Representative LFTs are shown (Figure 5A)
- Adverse hematologic effects (i.e. neutropenia) observed at 10 mpk are consistent with expected off- target toxicity of DM4 (Figure 5B)

SUMMARY/CONCLUSIONS

- **Probody drug conjugates (PDCs) have the potential to safely target highly expressed tumor antigens, regardless of expression on normal tissue, thus expanding the utility of ADCs**
- **We have developed a Probody drug conjugate (PDC) targeting CD166, a highly expressed antigen in many cancers but also in normal tissue**
- **CD166 PDC is efficacious in mouse models of human xenograft tumors at doses equal to or below the predicted human dose**
- **CD166 PDC is well-tolerated in cynomolgus monkeys and shows extended exposure compared with CD166 ADC, consistent with avoiding the target sink in normal tissues**
- **The safety and efficacy profiles of CD166 PDC are supportive of clinical development**

CytomX THERAPEUTICS