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 HER2+ breast cancer and brentuximab vedotin for CD30+ Hodgkin’s Disease and Anaplastic large-cell lymphomas. 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™ therapies are fully recombinant antibody produgs that are converted to active antibodies by tumor-associated proteases. Preclinical in vivo studies show that Probody therapies 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 expanding activity in non-human macaque. This therapeutic has been conjugated to spDM4 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 studies 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.

### RESULTS

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

<table>
<thead>
<tr>
<th>Desired Properties</th>
<th>ADCs</th>
<th>PDCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression in healthy tissue</td>
<td>Low</td>
<td>Low or High</td>
</tr>
<tr>
<td>Expression of target in tumor</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Homogeneity of expression in tumor</td>
<td>Often Blended</td>
<td>High</td>
</tr>
</tbody>
</table>

**Resulting Properties**

- **Tumor types addressed**: One/Pew Many
- **Prevalence per cancer type**: Lower Very High

### INTRODUCTION

**Probody™ Therapeutics are Protease-Activatable Antibody Pro-Drugs**

<table>
<thead>
<tr>
<th>Property</th>
<th>CD166- negative</th>
<th>CD166- sensitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>- FFPE sections stained with anti-human CD166 rabbit monoclonal antibody</td>
<td>- FFPE sections stained with anti-human CD166 rabbit monoclonal antibody</td>
<td></td>
</tr>
</tbody>
</table>

### Table 1: Prevalence of CD166 Expression in Human Cancers

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>CD166 Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>++</td>
</tr>
<tr>
<td>Bladder</td>
<td>+</td>
</tr>
<tr>
<td>Lung</td>
<td>++</td>
</tr>
<tr>
<td>GI tissues</td>
<td>++</td>
</tr>
<tr>
<td>Pancreas</td>
<td>++</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>++</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>++</td>
</tr>
<tr>
<td>Thyroid</td>
<td>++</td>
</tr>
<tr>
<td>Thyroid</td>
<td>++</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>++</td>
</tr>
<tr>
<td>Stomach</td>
<td>++</td>
</tr>
<tr>
<td>Esophagus</td>
<td>++</td>
</tr>
<tr>
<td>Bladder</td>
<td>+</td>
</tr>
<tr>
<td>Breast</td>
<td>++</td>
</tr>
<tr>
<td>Bladder</td>
<td>++</td>
</tr>
</tbody>
</table>

**Candidate indications (DNA/mayartransverse-serradine):**

- BREAST
- GI tissues
- Pancreas
- Salivary gland
- Adrenal gland
- Thyroid
- Cerebrum
- Stomach
- Esophagus
- Bladder

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**Shouchun Liu, Jennifer Richardson, W. Michael Kavanaugh, Jonathan A. Terrett, Luc R. Desnoyers
Cytomx Therapeutics, Inc., South San Francisco, CA**

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

**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**

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

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

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

**CONCLUSION & SUMMARY**

- **Probody drug conjugates (PDCs) have the potential to safely target highly expressed tumor antigens, regardless of expression on normal tissues, 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 favorable retention consistent 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.**