Probody™ Therapeutics and the Target Landscape for Drug Conjugates

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Agenda

• What is a Probody therapeutic?
• Validation of the Probody concept
• Probody Drug Conjugates
  – CD166
• Summary
WHAT IS A PROBODY THERAPEUTIC?
Probody Therapeutics: Fully Recombinant Antibody Prodrugs

ANTI-CANCER ANTIBODY

PROTEASES

LINKER

MASKING PEPTIDE

TUMOR

TUMOR

TUMOR
PDC Therapeutics: Improving Balance Between Efficacy and Safety

Concept: *Creating* Therapeutic Window

Enabling New, First in Class Targets: non ADC targets such as CD166
### Our Broad Probody Therapeutic Pipeline

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Discovery</th>
<th>Lead Optimization</th>
<th>IND-Enabling</th>
<th>Phase 1</th>
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<tbody>
<tr>
<td>PD-L1 (CX-072)</td>
<td></td>
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<td>IND Anticipated 2H 2016</td>
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<tr>
<td>CD166 PDC</td>
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<td>IND Anticipated 1H 2017</td>
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<tr>
<td>PD-1</td>
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<td>CD71 PDC</td>
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<tr>
<td>ITGA3 PDC</td>
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<td>T-cell Engaging Bispecifics</td>
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<td>ProCAR-NK &amp; ProCAR</td>
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<td>Potential INDs in 2017/2018</td>
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<tr>
<td>Immuno-therapies (incl. CTLA-4)</td>
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<tr>
<td>PDCs</td>
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<tr>
<td>PDCs</td>
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**Note:**
- IND Anticipated 2H 2016
- IND Anticipated 1H 2017
- Potential INDs in 2017/2018
VALIDATION OF THE PROBODY CONCEPT
Validation of the Probody Concept

• *in vitro* and *ex vivo* protease activation
  – Tumors >> normal tissue
  – Active site antibody
  – IHZ™ technology

• Preclinical *in vivo*
  – Imaging & a non-cleavable substrate
  – Efficacy
  – Safety

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Activated Proteases are Found in Tumors But Not in Healthy Tissue

- Proteases cleave proteins into smaller pieces
- Upregulated protease activity is a hallmark of all cancers
- Protease activity is tightly controlled in healthy tissues

*matrptase: LeBeau et al., PNAS 2012

Imaging of Active Protease

Normal Colon  Primary Colon Cancer  Metastatic Colon Cancer
Validation of the Probody Concept

- *in vitro* and *ex vivo* protease activation
  - Tumors >> normal tissue
  - IHZ technology

![IHC and IHZ assay images](image-url)
Validation of the Probody Concept

- Preclinical *in vivo*
  - Imaging of cleavable and non-cleavable substrates:
  - Protease dependent activation at tumor site
Preclinical Probody Validation: Improved Safety

Improved Safety (Hair Loss)

Improved Safety (Cytokine Release)
Preclinical PDC Validation: Efficacy & Improved Safety

Similar Efficacy

Improved Safety (Body Weight)
PROBODY DRUG CONJUGATES (PDC)
# Probody Drug Conjugates Target Superior, First-in-Class Tumor Antigens

<table>
<thead>
<tr>
<th>Desired Properties</th>
<th>ADCs</th>
<th>PDCs</th>
</tr>
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<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 Modest</td>
<td>High</td>
</tr>
<tr>
<td>Tumor types addressed</td>
<td>One/Few</td>
<td>Many</td>
</tr>
<tr>
<td>Prevalence per cancer type</td>
<td>Lower</td>
<td>Very High</td>
</tr>
</tbody>
</table>

Probody Technology Enables Selection of Targets More Likely to Succeed (e.g. CD166, CD71, ITGA3)
CytomX PDC Targets Have High Expression in More Cancers than Approved ADC Targets

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Prostate</th>
<th>Pancreatic</th>
<th>Ovarian</th>
<th>NHL</th>
<th>Lung</th>
<th>Bladder</th>
<th>HD</th>
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<tbody>
<tr>
<td><strong>CytomX PDC Targets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD166</td>
<td>&gt;70%</td>
<td>80%</td>
<td>20%</td>
<td>&gt;50%</td>
<td>-</td>
<td>70%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>CD71</td>
<td>50%</td>
<td>30%</td>
<td>50%</td>
<td>60%</td>
<td>&gt;90%</td>
<td>70%</td>
<td>50%</td>
<td>TBD</td>
</tr>
<tr>
<td>ITGA3</td>
<td>15%</td>
<td>10%</td>
<td>&gt;75%</td>
<td>75%</td>
<td>-</td>
<td>15%</td>
<td>&gt;95%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Approved ADC Targets</strong></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Her2neu</td>
<td>25%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>-</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>-</td>
</tr>
<tr>
<td>CD30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>~50%</td>
<td>-</td>
<td>-</td>
<td>100%</td>
</tr>
</tbody>
</table>

CD166, CD71, and ITGA3 also show strong expression in multiple other cancer types
CD166 PDC
CD166

1. Activated leukocyte cell adhesion molecule
   - Binds CD6 receptor
   - Regulates cell adhesion, migration
   - Involved in T cell activation/proliferation

2. Role in cancer
   - Highly expressed in many human cancers
   - Marker of tumor initiating cells (e.g. prostate, colon)
CD166 Shows Very High Expression and Prevalence in Specific Tumors

- Prostate cancer: > 80%
- Breast cancer: > 70%
- NSCLC: > 70%
- SCLC: ~ 80%
- Oropharyngeal cancer: ~ 60%
- Cervical cancer: > 50%
- HNSCC: > 50%
CD166 IHZ Assay Demonstrates Activation in Tumor and No Activation on Healthy Tissue: Colon

IHC

Normal colon

Colon cancer

IHZ assay
CD166 Probody Therapeutic Does Not Bind Normal Tissue by IHZ Assay

IHC

IHZ Assay

Normal stomach

Normal bladder
CD166 is Highly Expressed in Many Normal Tissues

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>++</td>
</tr>
<tr>
<td>Brain</td>
<td>-</td>
</tr>
<tr>
<td>Colon</td>
<td>++</td>
</tr>
<tr>
<td>Esophagus</td>
<td>-</td>
</tr>
<tr>
<td>Heart</td>
<td>-</td>
</tr>
<tr>
<td>Kidney</td>
<td>+</td>
</tr>
<tr>
<td>Liver</td>
<td>++</td>
</tr>
<tr>
<td>Lung</td>
<td>+</td>
</tr>
<tr>
<td>Nerve</td>
<td>-</td>
</tr>
<tr>
<td>Ovary</td>
<td>+</td>
</tr>
<tr>
<td>Pancreas</td>
<td>++</td>
</tr>
<tr>
<td>Prostate</td>
<td>+++</td>
</tr>
<tr>
<td>Skin</td>
<td>-/+</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>++</td>
</tr>
<tr>
<td>Salivary Gland</td>
<td>++</td>
</tr>
<tr>
<td>Spleen</td>
<td>-</td>
</tr>
<tr>
<td>Stomach</td>
<td>+++</td>
</tr>
<tr>
<td>Striated/Skeletal Muscle</td>
<td>-</td>
</tr>
<tr>
<td>Testis</td>
<td>-</td>
</tr>
<tr>
<td>Uterus</td>
<td>++</td>
</tr>
</tbody>
</table>

High CD166 expression in normal tissues suggests it is not a suitable ADC target.
CD166 PDC Regressions in NSCLC Model

H292 tumor model

Mean Tumor Volume (mm³)

- Isotype Control
- CD166 ADC
- CD166 PDC

Study Day

Treatment

SPDB-DM4 from ImmunoGen
CD166 PDC Regressions in TNBC Model

**HCC1806 tumor model**

- **Mean Tumor Volume (mm$^3$)**
- **Isotype control**
- **CD166 PDC, 3 mpk**

*IV dosing on days 0 and 7*
CD166 PDC response = ADC response in Ovarian PDX Model

Ovarian PDX model

Mean Tumor Volume (mm$^3$)

- isotype-DM4; 5 mpk
- CD166 PDC; 5 mpk
- CD166 ADC; 5mpk

Treatment

study day

0 10 20 30
Anti CD166 Antibody Binds to Human and Cynomolgus With Similar Affinity

ELISA – Cyno and human binding are identical
Anti CD166 PDC Is Well Tolerated In Cynos

- 3 week tolerability study (non terminal); single dose n=2
- Stability of PDC is consistent with other DM4-conjugated antibodies
- PDC is well tolerated at 5 mpk = therapeutic dose for SPDB DM4
  - Also well tolerated at 10mpk ( standard DM4 toxicities at 15mpk )
  - No evidence of on or off-target toxicity
  - No clinical signs, weight loss or abnormal lab findings
  - Meets benchmark standards for safety
CD166 PDC Does Not Alter Toxicity Markers in Non-Human Primates

Absence of neutropenia and liver injury

**Neutrophil**

<table>
<thead>
<tr>
<th>Count x 10^3/μL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predose</td>
</tr>
<tr>
<td>CD166 PDC (M)</td>
</tr>
<tr>
<td>CD166 PDC (F)</td>
</tr>
</tbody>
</table>

**Reference range**

- Male: 2.5-20.9
- Female: 1.8-13.6

**AST**

<table>
<thead>
<tr>
<th>U/L</th>
</tr>
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<tbody>
<tr>
<td>Predose</td>
</tr>
<tr>
<td>CD166 PDC (M)</td>
</tr>
<tr>
<td>CD166 PDC (F)</td>
</tr>
</tbody>
</table>

**Reference range**

- Male: 22-260
- Female: 20-94

**ALT**

<table>
<thead>
<tr>
<th>U/L</th>
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<tbody>
<tr>
<td>Predose</td>
</tr>
<tr>
<td>CD166 PDC (M)</td>
</tr>
<tr>
<td>CD166 PDC (F)</td>
</tr>
</tbody>
</table>

**Reference range**

- Male: 24-193
- Female: 22-162
Probody Therapeutics are preferentially activated in tumors over normal tissue

Probody Therapeutics have been validated in animals across multiple MOAs for efficacy and safety
- Immuno-oncology, drug conjugates, T cell-engaging bispecifics

Platform accesses first-in-class targets for PDCs
- PDC targets generally are not targetable by conventional ADCs because of normal tissue expression
- These PDC targets generally show greater expression, prevalence and breadth of indication than conventional ADC targets

CytomX pipeline includes multiple novel drug conjugates
- CD166, CD71, ITGA3 and others
Our Vision
Transforming lives with safer, more effective therapies

Our Mission
Changing the treatment of cancer by urgently advancing our Probody pipeline

Our Values

CREATIVITY  INTEGRITY  COMMITMENT  TEAMWORK  FUN  ACCOUNTABILITY