Immunosynthen: STING-Agonist ADC Platform

November 16, 2020
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Agenda

• Anna Protopapas, President & Chief Executive Officer
  – Opening remarks & introductions

• Tim Lowinger, PhD, Chief Science & Technology Officer
  – Therapeutic rationale for a STING-agonist ADC
  – Development & optimization of Immunosynthen platform

• Marc Damelin, PhD, Executive Director & Head of Biology
  – Preclinical data supporting Immunosynthen ADC pipeline

• Tim Lowinger, PhD, Chief Science & Technology Officer
  – Potential of the Immunosynthen ADC pipeline and next steps

• Q&A
We Intend to Answer Key Questions Today

- Why activate innate immunity with a STING-Agonist ADC?
- How is Immunosynthen different than other approaches to stimulate innate immunity (SITC 2020, Abstract #620)?
- How did Mersana build and optimize the Immunosynthen platform?
- How deep is the pipeline of Immunosynthen ADCs, and which indications might be addressable?
- When will we reach the clinic?
Targeted Stimulation of Innate Immunity has the Potential to Deliver Breakthroughs

Innate Immunity
- Includes STING
- “Step on the gas”

Adaptive Immunity
- Includes CTLA4, PD1/PD-L1
- “Release the brakes”

- The immunotherapy revolution has focused on adaptive immunity and serves only a fraction of patients

- Innate immune stimulation could address unmet medical needs in
  - Checkpoint refractory tumors
  - Checkpoint relapsed tumors
  - Tumor types where checkpoints have minimal activity

*Nature Reviews Cancer 4, 11–22 (2004)*
STING Pathway Activation has Shown Intriguing Signs of Activity

- In clinical trials, intratumoral injection of STING agonists has induced:
  - Tumor shrinkage (top panel)
  - Immune cell infiltrates (bottom panel)

- In preclinical studies, compelling genetic and pharmacological evidence for anti-tumor potential of STING activation

- STING activation leads to a potent Type I interferon response without general inflammation

Selected preclinical references:
Hypothesis: An ADC Approach Could Address Administration Issues, Systemic Tolerability, and Activity

- Systemic administration with targeted delivery to the tumor
- Improved anti-tumor activity compared to free agonist
- Improved tolerability compared to free agonist
### What We Thought

- STING pathway is silenced in tumor cells
- The STING mechanism of action is limited to immune cells

### What We Now Know

- Tumor cells activate STING in the presence of immune cues
  - Field has been misled by standard monoculture conditions
- Our studies employed:
  - CRISPR-mediated STING knockout cancer cells
  - Fc mutant ADCs
  - Co-cultures of tumor cells and immune cells
  - Conditioned media from immune cells

### The ADC Modality Is Ideally Suited

- Immunosynthen ADCs enable target-dependent activation of STING in tumor-resident immune cells and tumor cells
  - Active internalization into both cell types in the tumor (via FcγR and via tumor antigen)
- Immunosynthen ADCs avoid STING activation in undesired cell types (e.g., T and B cells)

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**Immunosynthen ADCs Activate STING in Immune and Tumor Cells**

Presented at SITC 2020
STING: The One-Two Punch
Presented at SITC 2020

Tumor

Myeloid cell

Target-Dependent FcγR-Mediated Internalization

STING Activated in Myeloid Cell

Hit the tumor-resident immune cells

STING Activated in Tumor Cell

Hit the tumor cells

Tumor cell

No internalization into undesired immune cells (T, B)

No internalization into immune cells

Periphery

No stimulation of immune cells

No internalization into immune cells
Punch One: Fc-Mediated Delivery to Immune Cells is Target Dependent

- Specific tumor antigen binding provides high local concentration, which promotes FcγR binding on tumor-resident immune cells.
- FcγR binding results in internalization into tumor-resident immune cells and STING activation.
- STING activation by ADC is ~40-100x more potent than free agonist.

**Antibody variants**

**Free Payload**

**Targeted**
- Antigen and FcγR binding

**Control**
- No antigen binding

**Fc mutant**
- No FcγR binding

**Human immune cell**

STING pathway activation (Luciferase reporter)

**Luciferase Activity**

Payload (nM)

0 0.1 1 10 100

0 10000 20000 30000

~40x
**Punch Two: STING Activation in the Tumor Cell Also Contributes to Efficacy**

- Surprising observation that Fc-mutant ADCs are active in co-culture – which indicates tumor intrinsic STING activation
- Previously believed that STING pathway is silenced in tumor cells
- Co-cultures with STING knockout cancer cells demonstrate the direct contribution of tumor intrinsic STING
The One-Two Punch: *In Vivo* Data Consistent and Differentiated

- Significant anti-tumor activity is maintained by the Fc-mutant ADC, which cannot internalize into the immune cells
  - Demonstrates the contribution of tumor cell STING to anti-tumor activity
  - Demonstrates the contribution of immune cell STING to activity
  - The One-Two Punch
Holistic Approach to Building a STING-Agonist ADC

1. Design novel STING agonist for use in ADC
2. Optimize linker and scaffold for the novel agonist
3. Validate multiple targets for Immunosynthen
4. Select optimal antibody for each target
5. Build pipeline of Development Candidates
Mersana’s ADC Expertise Drives Platform Optimization

ADC Optimization via Modular Approach

- Antibody
- Bioconjugation
- Aqueous solubility
- Charge balance
- Drug load per scaffold
- Proprietary STING agonist

Optimizing Activity With the Same Antibody and Same STING agonist
(single, equivalent IV dose for all ADCs)

High Stability and Extended Exposure of Immunosynthen ADC

Parallel curves reflect stability of Immunosynthen ADC

Space between curves reflects higher molecular weight of antibody relative to STING-agonist payload
Defined Success Criteria Have Been Achieved

- Antigen-dependent targeted delivery to the tumor
- Sustained tumor regressions
  - Consistent results across tumor models and mouse strains
- Proof of mechanism
  - Induction of STING pathway cytokines in the tumor
  - Induction of STING genes in the cancer cell
  - Immune memory
- Well-tolerated; minimal systemic inflammation; favorable NHP
- Compatible with many antigens
  - Enables a portfolio to address many clinical indications
Comprehensive Approach to Target Selection

- Innate immune activation with STING enables many target classes
  - Immune cells
  - Tumor cell antigens
  - Tumor-associated antigens
- Potential broad target space encompasses multiple indications of high unmet medical need
Single, Low Dose of Immunosynthenen ADC Dramatically Outperforms Benchmark

Tumor Growth Inhibition

Legend

- Vehicle
- Control ADC (1 mg/kg)
- Control ADC (3 mg/kg)
- Unconjugated Antibody (3 mg/kg)
- *Benchmark IV agonist (5 mg/kg)
- Targeted ADC (1 mg/kg)#
- Targeted ADC (3 mg/kg)#
  - All groups dosed IV
  - ADC Doses by mAb [mg/kg]

*Benchmark described in J.M. Ramanjulu et al. (2018) Nature
#1 mg/kg by mAb = 0.03 mg/kg by STING-agonist payload
# Target-Dependent Immune Cell Infiltration into Tumor

## CD45 Immunohistochemistry

<table>
<thead>
<tr>
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<th>Vehicle</th>
<th>Targeted ADC</th>
<th>Control ADC</th>
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<td><strong>12 hrs.</strong></td>
<td><img src="image1" alt="Vehicle 12 hrs." /></td>
<td><img src="image2" alt="Targeted ADC 12 hrs." /></td>
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<td><strong>72 hrs.</strong></td>
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<td><img src="image5" alt="Targeted ADC 72 hrs." /></td>
<td><img src="image6" alt="Control ADC 72 hrs." /></td>
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Brown staining indicates immune cells (CD45+)
Punch One: Immunosynthen ADC Induces STING Pathway Cytokines in the Tumor-Resident Mouse Immune Cells *In Vivo*

- **Mouse** cytokines in tumor microenvironment measured by qPCR
- ADC targets the human tumor cells

<table>
<thead>
<tr>
<th>Mouse cytokines induced in the tumor microenvironment</th>
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<tbody>
<tr>
<td>Mouse CXCL10</td>
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<td>mRNA Expression (relative to GAPDH)</td>
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<tr>
<td><strong>Vehicle</strong></td>
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<td>5</td>
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<td>20</td>
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<td>25</td>
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</table>
Punch Two: Immunosynthen ADC Induces STING Pathway in Human Tumor Cells *In Vivo*

- **Human** cytokines in tumor microenvironment measured by Nanostring

**Human cytokines induced in the tumor cells**

- **Human CXCL10**
  - Vehicle: 0
  - Targeted ADC: 4000
  - Control ADC: 0

- **Human IFNβ**
  - Vehicle: 0
  - Targeted ADC: 800
  - Control ADC: 0

- **Human IL6**
  - Vehicle: 0
  - Targeted ADC: 1200
  - Control ADC: 0
Down for the Count: Immunosynthen ADC Triggers Tumor-Specific Immunological Memory

Tumor Growth Inhibition Study

- Tumor free mice re-implanted with targeted tumor on one flank (blue) and a non targeted tumor on the other flank (red).
- Untreated age matched mice also implanted as a control (black line).

Tumor Rechallenge Study (Dual Flank)

- Tumor free mice re-implanted with targeted tumor on one flank and a non targeted tumor on the other flank.
- Untreated age matched mice also implanted as a control.

- 6/9 tumor-free animals

Mean Tumor Volume ± SEM (mm³) for:
- Vehicle
- Control ADC 1 mg/kg
- Targeted ADC 0.9 mg/kg

Single IV dose
Dramatically Lower Systemic Cytokine Levels After Immunosynthen ADC Compared to Benchmark IV Agonist

Serum cytokines measured with Luminex assay

- **CXCL10**
- **IL-6**
- **CXCL1**
- **TNF-α**
- **MIP-1a (CCL3)**
- **IFNγ**

**Vehicle control**
- **Targeted ADC (0.09 mg/kg STING agonist)**
- **Control ADC (0.09 mg/kg STING agonist)**
- **Benchmark IV agonist (5 mg/kg ~ maximum tolerated dose)**

Systemic immune activation

Tumor, no immune activation

Tumor with STING-Mediated Innate Immune Activation
Immunosynthen ADCs Well-Tolerated in Non-Human Primate Studies After Repeat IV Dosing

• NHP studies with Immunosynthen ADCs based on 5 antibodies
  • 4 fully cross-reactive antibodies for 4 therapeutic targets
  • 1 non-reactive antibody to assess platform safety profile

• Intravenous administration; single-dose and repeat-dose studies

• Pharmacokinetics
  • High exposure; dose dependent; overall profile similar to non-STING ADCs
  • ADC highly stable in circulation; minimal free payload in plasma

• Serum Cytokines
  • Transient, modest elevation of 5 cytokines out of 24 tested; similar to results in mouse

• No adverse changes in hematology or clinical chemistry

• No adverse findings in histopathology to date
Immunosynthen ADCs Active Against Diverse Tumor Antigens and Tumor-Associated Antigens in Multiple Models After Single, Low IV Dose

Legend

Vehicle
Control ADC
Targeted ADC

Tumor Antigen A
3.0 mg/kg

Tumor Antigen B
3.0 mg/kg

Tumor-AssOCIated Antigen A
2.2 mg/kg

Tumor Antigen C
2.8 mg/kg

Tumor Antigen D
2.5 mg/kg

Tumor-AssOCIated Antigen B
0.88 mg/kg
Opportunity to Build a Robust Pipeline to Treat a Broad Range of Cancers

- Bladder Cancer
- Breast cancer
- Colorectal cancer
- Endometrial Cancer
- Gastric cancer
- Head & Neck Squamous Carcinoma
- Lung cancer
- Melanoma
- Ovarian cancer
- Pancreatic cancer
**XMT-2056: First Immunosynthen Development Candidate**

**Summary of Data**

**Fc-mediated uptake and THP1 cell activation**
- IRF3 Reporter (THP1)
  - EC$_{50}$ = 0.08 nM

**Tumor cells with PBMCs**
- CXCL10 ELISA
  - EC$_{50}$ = 0.11 nM

**In vivo Activity**
- 0.96 mg/kg antibody / 0.033 mg/kg STING
  - Single dose IV

**NHP Results**
- Single-dose and repeat-dose studies at 9 mg/kg antibody
- Intravenous administration
  - No clinical signs, no mortality
  - High exposure, high ADC stability in circulation
  - Transient elevation of 5 cytokines out of 24 tested
  - No adverse changes in clinical pathology
  - No adverse findings in histopathology

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**Graphs:**
- RLU vs Payload [nM]
- O.D. 450nm vs Payload [nM]
- Mean Tumor Volume ± SEM (mm$^3$) vs Days on study
  - > 1,000x Free payload
XMT-2056 Shows Excellent PK after Repeat IV Dosing and a Wide Therapeutic Index

**Plasma Concentrations in Non-Human Primate**
(Total Antibody △ and Conjugated STING agonist ▲)

- High stability as indicated by parallel curves of antibody and conjugated drug
  - Space between curves reflects higher molecular weight of antibody relative to STING-agonist payload
- Comparable PK profiles after 1st and 2nd dose

**Plasma Concentrations in Non-Human Primate vs. Mouse**
(Conjugated STING agonist)

Exposure of XMT-2056 at well-tolerated dose in non-human primate is ~10-fold higher than the exposure required for sustained tumor regression in mouse

**Graphs:**
- **Non-Human Primate, 9 mg/kg**
- **Mouse, 1 mg/kg**
### The Immunosynthen Platform is Already Delivering Multiple Product Candidates

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<thead>
<tr>
<th>Program</th>
<th>Target</th>
<th>Target Validation</th>
<th>Discovery</th>
<th>IND-Enabling Studies</th>
<th>P1 Dose Escalation</th>
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<tbody>
<tr>
<td>XMT-2056</td>
<td>Tumor Antigen A</td>
<td></td>
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<tr>
<td>To Be Named</td>
<td>Tumor Antigen B</td>
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<td>To Be Named</td>
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<td>To Be Named</td>
<td>Tumor Antigen D</td>
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<tr>
<td>To Be Named</td>
<td>Tumor-Associated Antigen A</td>
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<tr>
<td>To Be Named</td>
<td>Tumor-Associated Antigen B</td>
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• Immunosynthen ADCs have the potential to address the limitations of current approaches to activate innate immunity / STING

• Immunosynthen ADCs deliver One-Two knockout punch from STING activation in tumor cells and tumor-resident immune cells (SITC 2020)

• We have optimized the platform using our ADC expertise

• We are building a deep pipeline of Immunosynthen ADCs with a broad range of clinical indications and potential for value-creating partnerships

• XMT-2056 has been selected as the first Immunosynthen ADC with initiation of Phase I Dose Escalation expected in Q1 2022
Q&A