Efficacy of Anti-ICOS Agonist Monoclonal Antibodies in Preclinical Models Provides a Rationale for Clinical Development for cancer immunotherapy

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- Jounce Therapeutics

SITC 2015
Disclosures

Dr. Michael J. Briskin

The following relationships exist related to this presentation:

• Current VP of research at Jounce Therapeutics
Jounce Translational Approach: Iterative Clinical and Preclinical Data to Pursue Relevant Targets and Drive Programs

Translational Science

- Human Cells
- Tumor Samples
- Clinical Studies

Drug Discovery

- Mouse Cells
- Tumor Samples
- *In vivo* Efficacy Studies
ICOS: A Member of the B7/CD28-Superfamily

- ICOS is up-regulated on activated CD4+ T effector and CD4+ T regulatory cells
- Its ligand (ICOSL) is expressed on APCs and B cells
- ICOS ligation via ICOSL stimulates activation of Teff cells
- ICOS binding to ICOSL on B cells leads to antibody production

Adapted from Yao et al. Nature (2013)
ICOS is Up-regulated on CD4\(^+\) T cells of Patients Who Respond to Anti-CTLA-4 Therapy: Clinical Observations Translated to a Pre-clinical Model

- Sustained increase in ICOS on peripheral CD4\(^+\) T cells associated with positive clinical outcome
- Increase in ICOS\(^+\) TILs also observed post-anti-CTLA-4 treatment
- In a pre-clinical tumor model. ICOS agonism in the context of anti-CTLA-4 mAb results in enhanced mouse survival

**Hypothesis:** Up-regulated ICOS activates an immune-based anti-tumor response to provide therapeutic benefit
Mechanisms of a Jounce Anti-ICOS Antibody
Mechanisms of Jounce Anti-ICOS Antibodies

Primary mechanism
Agonism of Teff
Anti-ICOS mAb Displays Agonistic Activity

**Effect of Anti-ICOS mAbs on Jurkat ICOS-Reporter Assay:**

- Anti-ICOS antibody displays agonist activity in Jurkat cell reporter assay with GFP readout.
- A published antagonist anti-ICOS has no agonist activity.

PMA in all wells except unstimulated.

- Anti-ICOS antibody displays agonist activity in Jurkat cell reporter assay with GFP readout.
- A published antagonist anti-ICOS has no agonist activity.
Anti-ICOS Displays Agonist but NOT Super-Agonist Activity

**Anti-ICOS is Agonistic**

On Anti-CD3-Activated CD4+ T Cells

- Ab in solid-phase, in presence of sub-optimal anti-CD3

**Anti-ICOS is NOT Super-Agonistic**

on CD4+ T Cells

- No anti-CD3 in this assay

- ICOS Ab induces proliferation of primary human T cells in a co-stimulation assay (requires initial “1st” signal)

- CD28 super-agonist antibody induces T cell proliferation in soluble format in absence of anti-CD3 co-stimulation

- ICOS Ab does not induce T cell proliferation in absence of signal 1.

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Select Anti-ICOS mAbs are Efficacious in a Syngeneic Tumor Model

**Experimental Design:**
- Implant Tumor: Day 0
- Treatment: Days 7, 10, 14, 17
- Measure tumor growth

**Average Tumor Volume Over Time:**

<table>
<thead>
<tr>
<th>Days after tumor challenge</th>
<th>Tumor volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isotype 0/10</td>
</tr>
<tr>
<td></td>
<td>Ab 1 5/10</td>
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<td></td>
<td>Ab 2 8/10</td>
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<td>Ab 3 8/10</td>
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<tr>
<td></td>
<td>Ab 4 8/10</td>
</tr>
<tr>
<td></td>
<td>Ab 5 6/10</td>
</tr>
</tbody>
</table>

# tumor free
- Isotype 0/10
- Ab 1 5/10
- Ab 2 8/10
- Ab 3 8/10
- Ab 4 8/10
- Ab 5 6/10
ICOS Antibodies Create Durable Effects

Animals cured of tumors are immune to tumor re-challenge

First dose

Tumor volume (mm$^3$)

Days after tumor challenge

Tumor volume (mm$^3$)

Days after tumor re-challenge

# tumor free

Control Ig (0/10)

ICOS Ab 1 (8/10)

Naïve mice

Mice previously cured by anti-ICOS Ab 1

0 10 20 30
Mechanisms of Jounce Anti-ICOS Antibodies

Primary mechanism

Agonism of ICOS

Secondary mechanism

Depletion or re-programming of Tregs
Treatment with Anti-ICOS Antibodies Results in Reduction in FoxP3+ Tregs in Tumors

- Treatment with anti-ICOS mAbs reduces tumor-associated Tregs, but not Teffs
- CD8:Treg ratio is increased following anti-ICOS treatment
- No change in T cell subsets or ratios observed in spleen, lymph nodes, or peripheral blood (data not shown)
Anti-ICOS mAbs Selectively Reduce Tregs vs Teffs

Selective reduction of Tregs in vitro:

- Anti-ICOS antibody selectively depletes Tregs from IL-2 activated PBMCs
- Under these conditions, Tregs and Teffs express similar levels of ICOS
Potential Combination Approaches

Chen and Mellman, Immunity (2013)
ICOS and PD-1 Antibody Combination is Highly Effective

**Syngeneic tumor model in immunocompetent Mice**

- **Isotype**: (0/10)
- **Ab 2**: (2/10)
- **Anti-PD1**: (6/10)
- **Anti-PD1+ Ab 2**: (9/10)

Tumor Volume (mm$^3$) vs. Days after Tumor Challenge

N=10 / group
Positioning ICOS Therapeutics

Monotherapy

Tumors naturally high in ICOS density on T cells

ICOS mAb

Agonize Teff & reduce Tregs

Combo Therapy

(Agent that induce ICOS Expression)

- Anti-PD-1/L1
- Anti-CTLA-4
- Novel Combos

Induction of ICOS on T cells
Hypothesis: ICOS CD4 T cells are Essential for Response to Anti-ICOS Therapy
Quantitative Evaluation of ICOS Across Human Tumor Types

100-200 tumors per indication or subtype

ICOS High
ICOS Medium
ICOS Low

ICOS Density (Cells/mm²)

HNSCC  NSCLC  BrCa  TNBC
ICOS Density in Individual Patients in NSCLC and HNSCC

- **NSCLC**
- **HNSCC**
Summary

• Anti-ICOS antibodies were generated with dual function:
  – Agonistic activity on Teff cells
  – Capacity to selectively deplete Tregs
• Anti-ICOS antibodies are efficacious in syngeneic tumor models and induce durable protective immunity
• Anti-ICOS antibodies may be effectively combined with other immunotherapeutics, such as anti-PD1
• Immunohistochemical analysis of clinical samples has identified key indications for our lead ICOS therapeutic
  – Allows for patient enrichment and hypothesis testing in early clinical trials
Acknowledgements

**MD Anderson**
- Jim Allison
- Pam Sharma
- Ignacio Wistuba

**University of Chicago**
- Tanguy Seiwart

**Jounce Therapeutics**
- Jennifer Michaelson
- Kutlu Elpek
- Christopher Harvey
- Ellen Duong
- Tyler Simpson
- Jenny Shu
- Tong Zi
- Amit Deshpande
- Lindsey Shallberg
- Matt Wallace
- Sriram Sathy
- Robert Mabry
- Debbie Law