New mechanistic insights from TME reconditioning by an Fc engineered anti-CTLA-4 antibody

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Sylvia Vincent, PhD
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Full-time employee at:

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How do we “raise the tail” on CTLA-4 therapies?

Jim Allison’s notebook (“Raise the tail”)

Canavan, N. A Cure Within: Scientists Unleashing the Immune System to Kill Cancer
Anti-CTLA-4 antibodies engage multiple mechanisms-of-action to promote T cell-mediated immunity

**MoA 1: Ligand-Blockade**
- **Lymph node**
- **Signal 1**
- **T cell**
- **APC**
- **CD80/CD86**
- **TCR**
- **MHC**
- **CTLA-4**
- **anti-CTLA-4**
- **FcγR-independent**

**MoA 2: Treg Depletion via ADCC/P**
- **TME**
- **Tumor**
- **ADCC**
- **ADCP**

**MoA 3: Priming**
- **Lymph node**
- **Signal 1**
- **T cell**
- **APC**
- **CD80/CD86**
- **TCR**
- **MHC**
- **FcγR-dependent**
Ipilimumab clinical data highlight importance of Fc-FcγR interactions for anti-CTLA-4 immunotherapy

Better clinical outcome in melanoma patients with high-affinity FcγRIIIA polymorphism

Better clinical outcome in melanoma patients with more circulating non-classical FcγR⁺ myeloid subset

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Sources: Adapted from Vargas et al., Cancer Cell 2018; Adapted from Romano et al. PNAS 2015
FcγR co-engagement is required for T cell responses to anti-CTLA-4

Superantigen Stimulation Assay

Reduced cytokine secretion using hlgG1 Fc silent (N297A)

FcγRIIIA blockade attenuates T cell responses

Source: Waight et al., Cancer Cell 2018
Fc-engineered anti-CTLA-4 antibody improved binding to low- and high-affinity FcγRIIIA alleles

FcγRIIIA-enhanced: S239D/A330L/I332E

FcγRIIA/B-enhanced: S267E/L328F

Antibody binding to FcγRIIIA-expressing CHO cells

Source: Waight et al., Cancer Cell 2018
FcγRIIIA is the critical receptor for mediating T cell responses to anti-CTLA-4 immunotherapy.

*Source*: Waight et al., *Cancer Cell* 2018
Fc-enhanced antibody enhances T cell responses in FcγRIIIA low-affinity and high-affinity donors

**In vitro** PBMC superantigen stimulation

V/V 158
High-affinity receptor

F/F 158
Low-affinity receptor
~35% of population

Source: Agenus data
Fc-enhanced anti-CTLA-4 demonstrates increased potency in CT26 syngeneic tumor model

Titration of parental or Fc-enhanced CTLA-4 monoclonal antibody induces tumor control

1x10^5 CT26 cells s.c.
Single dose at 50-75 mm^3
Antibody administered at study day 8

Source: Agenus data
Fc-enhanced anti-CTLA-4 exhibits increased and selective intratumoral Treg depletion

Enhanced selective depletion of intratumoral Treg cells

Increased CD8 T effector ratio to Treg in the tumor

Source: Agenus data
Fc-enhanced anti-CTLA-4 antagonist exhibits dose-dependent tumor control in late-treatment model

Increased anti-tumor activity of Fc-enhanced anti-CTLA-4 antibody

Reduced potency of Fc-enhanced anti-CTLA-4 antibody with decreased dose

Source: Agenus data
Treg-independent MoA for tumor control

Selective depletion of regulatory T cells in the tumor

Source: Agenus data
TCR signaling correlates with FcγR affinity

Increased TCR signaling

Source: Waight et al., Cancer Cell 2018
Fc-enhanced anti-CTLA-4 increases T cell responses independent of antibody-mediated Treg depletion

**In vivo antigen stimulation model**

C57BL/6

Co-administration of SEB peptide and anti-CTLA-4 antibody

**Anti-CTLA-4 increases T cell responses to SEB in Treg-depleted mice**

Source: Waight et al., Cancer Cell 2018
Fc-enhanced anti-CTLA-4 increases T cell responsiveness after SEB stimulation

Enhanced SEB-specific T cell response

Increased functionality of SEB-specific T cells

Source: Agenus data
Fc-enhanced CTLA-4 expands memory T cells

**non tumor-bearing model**

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non tumor-bearing model

CS7Bl/6

SEB + mAb

MPECs

% of TCR+ CD8 T cells

0 10 20 30 40

* isotype

Anti-CTLA-4

parental

Fc-enhanced

Increased memory-precursor effector cells

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**tumor bearing-model**

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tumor bearing-model

1x10^6 CT26

Increased memory T cells in the periphery

% CD45+ CD62L+ of CD8 T cells

0 5 10 15

* isotype control

Anti-CTLA-4

parental

anti-CTLA-4

Fc-enhanced

200 ug parental

200 ug anti-CTLA-4

100 ug anti-CTLA-4

50 ug anti-CTLA-4

Increased memory T cells in the periphery

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Source: Agenus data
Summary: Two FcγR-dependent mechanisms contribute to therapeutic effect of Fc-enhanced anti-CTLA-4 immunotherapy.
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