Harnessing Antibodies To Stimulate Antigen-specific Immune Responses

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Mechanisms of Anti-tumor Effects of MoAbs

MoAb
- Direct effect
- Innate effectors
  - ADCC
  - Complement
- ???
  - Adaptive immunity
  - T cell immunity
Why Harness MoAbs to Elicit Adaptive Immunity

- May provide a mechanism for durable responses.
- Immunologic memory: booster effect with repeat administration.
- Targeting antigen negative tumor cells (epitope spread)
Opsonizing tumor cells with moAbs enhances dendritic cell mediated cross-presentation of cellular antigens

FcγR dependent
Not simply increased uptake

Expansion of tumor reactive T cells in patients with progressive myeloma after stimulation with tumor cell loaded DCs

APC to Expand T cells
DC(-)  Iso-Tum  mAb-Tum  DC (Tumor)
APC to detect T cells
Non-tumor  Tumor

PNAS 99: 13009, 2002
Extending FcγR targeting on DCs to clinical grade MoAbs

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Isotype</th>
<th>Target</th>
<th>Tumor</th>
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<tbody>
<tr>
<td>Rituxan</td>
<td>IgG1</td>
<td>CD20</td>
<td>Lymphoma</td>
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<td>Macroglobulinemia</td>
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<tr>
<td>Cetuximab</td>
<td>IgG1</td>
<td>EGF-R</td>
<td>Epithelial tumors</td>
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<td>Glioma</td>
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Generation of Anti-Lymphoma T Cells using Autologous Tumor Cells Coated With Anti-CD20 MoAb (Rituxan)

Interferon-γ producers/10^5 cells

Antigen on DCs to expand T cells

Targets

Tumor (CD19+)

Non-Tumor (CD19-CD138-)

(-) (IsoTum) (-) (mAbTum) (-) (Iso-Tum) (-) (mAbTum)
Coating Human Glioma Cells With Anti-EGFR mAb Enhances The Induction Of Anti-Glioma Immunity
Targeting tumor antigens to Fcγ receptors on dendritic cells via anti-tumor mAb enhances anti-tumor immunity.
Fc receptor system as a balance of activating and inhibitory receptors

Ravetch JR. Ann Rev Imm 2001
Human Fc Receptors

FcγRI
CD64

FcγRIIA
CD32

FcγRIIB
CD32

FcγRIIIA
CD16

FcγRIIIB
CD16

FcεRI

FcαRI
CD89
Hypothesis

Selective blockade of inhibitory Fcγ receptors using new antibodies that selectively bind these receptors will enhance DC function and presentation of tumor antigens by human DCs.
Expression of FcγRII receptors on myeloid and plasmacytoid DCs

Myeloid DCs
Lin-, HLA DR+, CD11c+

Plasmacytoid DCs
Lin-, HLA-DR+, CD123+

→ FcγRIIB

→ FcγRIIA
Both Immature and Mature Monocyte Derived DCs Express Both Activating and Inhibitory forms of FcγRII
Selective blockade of inhibitory Fcγ receptor leads to DC maturation in the presence of normal human plasma
Isotype Chimeric 2B6 Aglycosylated 2B6

RPMI + 1% Ig depleted plasma

RPMI + 1% plasma

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<th>Chimeric 2B6</th>
<th>Aglycosylated 2B6</th>
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<tbody>
<tr>
<td>RPMI + 1% Ig depleted plasma</td>
<td>1.4%</td>
<td>3.2%</td>
<td>3.5%</td>
</tr>
<tr>
<td>RPMI + 1% plasma</td>
<td>2.5%</td>
<td>10.1%</td>
<td>8.3%</td>
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</table>
Selective blockade of inhibitory Fcγ receptor on purified DCs Leads to Induction of IL-12p70 production
Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fcγ receptors on Human DCs
Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fcγ receptors on DCs
Blockade of FcγRIIB leads to induction of anti-glioma immunity without the need for exogenous maturation stimulus.
DC Function Is Modulated by a Balance Between Activating and Inhibitory Fc Receptors
Balance Of Effector Versus Tregs As A Determinant Of Vaccine Efficacy

- Effector and Memory T cells
- Regulatory T cells (Tregs)

Tumor Antigen presenting DC
Efficiency of DCs for expansion of Human FOXP3+ Tregs
Effect Of FcR Mediated DC Maturation On The Ability of DCs To Induce FOXP3+ Tregs

Expansion of FOXP3+ Tregs after stimulation with tumor loaded DCs
Conclusions

• Selective engagement of activating FcRs leads to DC maturation and boosts the generation of anti-tumor immunity by human DCs
  – More anti-tumor effector T cells
  – Fewer concurrent FoxP3+ Tregs.

• Alteration of activating / inhibitory FcR balance may impact the ability of DCs to induce adaptive immunity in vivo in mAb treated patients
  – FcR polymorphisms
  – Fc engineering

• Further studies are needed to directly characterize the nature of T cell response in patients treated with anti-tumor MoAbs, and understand the mechanism of FcγR mediated enhancement of dendritic cell function.
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