Does Antibody Therapy Induce 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)
Retreatment with Rituximab in Non-Hodgkin’s Lymphoma

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

Dhodapkar et al. PNAS 99: 13009, 2002
Enhanced T cell Immunity after Immune Complex Mediated Antigen Presentation
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)
Selective blockade of inhibitory Fcγ receptor leads to DC maturation in the presence of normal human plasma

Dhodapkar et al. PNAS 2005
Enhanced Generation of Anti-Tumor Immunity After Blockade of Inhibitory Fcγ receptors on human DCs

Dhodapkar et al, PNAS 2005
Effect of activating FcγR polymorphisms on survival of Rituxan treated patients

## Preliminary Evidence for Induction of T cell immunity In Patients Treated With Anti-tumor mAbs

<table>
<thead>
<tr>
<th>mAb</th>
<th>Investigator</th>
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<tbody>
<tr>
<td>Rituxan (Anti-CD20)</td>
<td>Wong &amp; Levy</td>
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<td>2B1 (HER2-neu-RIII bispecific)</td>
<td>Weiner et al.</td>
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<tr>
<td>Anti-MUC1</td>
<td>DeBono et al.</td>
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INDUCTION OF ADAPTIVE ANTI-HER2/neu IMMUNE RESPONSES BY ANTIBODY THERAPY

Phase IB/II Trial of 2B1 Antibody in HER2/neu (+) Breast Cancer

ECOG Trial E3194

Alpaugh, Borghaei, Clark, Weiner
2B1 Treatment-induced T-Cell Responses

Anti-HER2/neu x anti-FcγRIII bispecific antibody treatment is associated with the induction of host immune responses against HER2/neu in a manner that suggests antigen presentation.

Intracellular cytokine flow cytometry analysis of antibody therapy-induced anti-HER2/neu CD4 and CD8 T cell responses
Induction of T cell immunity after injection of anti-MUC1 mAb

<table>
<thead>
<tr>
<th>Dose level</th>
<th># Pts with MUC1 sp T cell responses</th>
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<tr>
<td>2 mg</td>
<td>3/5 patients</td>
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<tr>
<td>4 mg</td>
<td>2/4 patients</td>
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</tbody>
</table>

deBono JS et al. Ann Oncol 2004
Induction of T cell immunity by mAbs: Some questions

- Nature of T cell response
  - How frequent, antigenic targets, effector function, tissues.

- Underlying biology
  - What is special about FcR mediated signals and cross-presentation

- Variables that impact induction
  - Host related (e.g. FcR polymorphism)
  - mAb related (e.g. Fc engineering, target antigen)

- Clinical Significance / opportunities
  - Impact on durability of responses, immune escape.
  - Combination with other vaccines.
Conclusion

- Anti-tumor mAbs can lead to the induction of adaptive immunity against cancer.

- Harnessing the ability of these mAbs to elicit adaptive immunity may enhance the anti-tumor effects of mAbs in the clinic.
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All patients;
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