CD40 agonist development for cancer

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Targeting CD40 for cancer therapy

• Member of the TNF receptor superfamily

• Broadly expressed by APC and normal cells, including endothelium and platelets

• No intrinsic kinase or other signal transduction activity
Physiology of CD40

• Binds to CD40-ligand expressed primarily by T cells
  – Activates APC
  – Provides a key component of T cell help
  – Enhances anti-tumor cellular immunity

• Over-expressed by >50% of carcinomas and melanomas, and nearly 100% of hematological B cell malignancies
  – Mediates direct cytotoxicity of tumor cells via apoptosis

• Plays a role in vascular inflammation and coagulation
CD40 agonists for cancer therapy

Proposed rationale

Resting antigen presenting cell

Activation

MHC class I
MHC class II
Costim. molecules
Adhes. molecules

Induce anti-tumor T cells
Substitute for T cell help

Tumor death

CD40 agonist

CD40 agonist

CD40+ tumor

Tumor Ags

Tumor death
CP-870,893: agonist anti-CD40 mAb (Pfizer)

- Fully human monoclonal antibody
  - Potent and selective agonist of the CD40 receptor
- IgG2
  - For minimal activation of complement and poor FcR binding
- Exhibits anti-tumor activity in xenograft models
- Activates human monocyte-derived dendritic cells \textit{in vitro}

\textit{Gladue et al, ASCO 2006; Bedian et al, ASCO 2006; Hunter et al, Scand J Imm, 2007}
Phase 1, dose-escalation, first-in-human study of the CD40 agonist mAb CP-870,893

- **Primary Objectives**
  - Safety, tolerability and MTD of a single infusion of CP-870,893 in adult patients with advanced solid tumors

- **Inclusion criteria**
  - Patients with solid tumors relapsed or refractory to standard therapy or for whom no effective therapy exists (hematological malignancies not allowed)
  - Signed, written informed consent

- **Exclusion criteria**
  - No concomitant anti-cancer, anti-coagulation, or immunosuppressive therapy
  - History of autoimmune disorders

Vonderheide et al, J Clin Onc, 2007
Enrollment, toxicities, and MTD

- **29 patients at 2 clinical sites (UPenn and Moffitt)**
  - Melanoma (n=15), NSCLC (n=5), sarcoma (n=3), cholangioCa (n=2), thyroid, breast, mesothelioma, unknown primary

- **Six doses explored**
  - 0.01 (n=3), 0.03 (n=3), 0.06 (n=3), 0.1 (n=4), 0.2 (n=9), 0.3 (n=7) mg/kg
  - Dose escalation based on toxicity

- **Dose limiting toxicities**
  - 0.3 mg/kg: grade 3 headache (n=1), and pulmonary embolism (n=1)
  - 0.2 mg/kg: transient grade 3 AST and ALT elevations (n=1)
  - Single dose MTD estimated as 0.2 mg/kg

*Vonderheide et al, J Clin Onc, 2007*
Clinical response from single infusion

- 29 patients evaluated by RECIST
  - 4 Partial Responses
  - 7 Stable Disease

- All partial responses were in patients with melanoma
  - Regression of lesions in liver, skin, lymph nodes, lung, muscle
  - All PRs at MTD or higher

- 7 patients with SD or PR were retreated with CP-870,893
  - Interval between doses was 2-4 months
  - One melanoma patient (at 0.2 mg/kg) had a near CR for 18 mo, then isolated LN recurrence, underwent surgery, now NED for 12+ add’l mo
Combining CD40 agonists with tumor vaccines

Points and questions to consider

• Numerous models in mice; are we (finally) ready for the first test in humans?
  – New agents clearly hit the target without major toxicity
  – PD and PK of CD40 agonists likely to differ between humans than mice

• Rationale is clear but are the nuances understood sufficiently?
  – Effects of CD40 on Treg, MDSC, platelets, endothelium, other?
  – How do CD40 agonists really work?

• Dosing an agonist, not an antagonist
  – What is the optimal schedule, interval, sequence for CP-870,893?

• Combination with vaccines
  – Which vaccine? Which PD endpoints?
  – Does it have to be a vaccine for CD40 agonists to augment anti-tumor immunity?
# Combination therapy with CD40 agonists

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<th>CD40 agonist plus…</th>
<th>Rationale</th>
<th>Mouse model</th>
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<td>Radiation</td>
<td>Induce tumor death while stimulating immune system</td>
<td>Honeychurch et al, Blood, 2003</td>
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<tr>
<td>FDA-approved mAb</td>
<td>Induce tumor death while stimulating immune system, without treatment immunosuppression</td>
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<td>Anti-CTLA4 blocking mAb</td>
<td>Inhibit negative immune regulation while triggering immune activation</td>
<td>Ito et al, JI, 2000</td>
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<td>TLR agonists</td>
<td>Synergistic activation of both innate and acquired immunity</td>
<td>Ahonen et al, JEM, 2004; Ahonen et al, Blood, 2008</td>
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<td>DR5 and CD137 agonist mAb</td>
<td>Induce apoptosis while fully stimulating immune system</td>
<td>Uno et al, Nat Med, 2006</td>
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Systemic CD40 agonists: Too much of a ‘good’ thing?

- Cytokine release syndrome following infusion
- Activation of coagulation system
- Induction of autoimmunity?
  Ichikawa et al, JI, 2002; Roth et al, JI, 2002
- Promotion of angiogenesis during carcinogenesis?
  Chiodoni et al, JEM, 2006
- Abolishment of long-term T cell responses against tumor or viral antigens?
Summary: the CD40 agonist case study

- Physiologic consequences of CD40 signaling are multifaceted, even biologically opposed, depending on the type of cell expressing CD40 and the microenvironment in which the CD40 signal is provided.

- Working hypothesis is that CD40 agonists including CP-870,893 mediate tumor regression through both indirect effect of immune activation and direct cytotoxic effect on the tumor (“two-for-one effect”).

- Immunomodulatory effects of agonist CD40 mAb include cytokine release syndrome and pharmacodynamic changes in peripheral B cells.

- Objective clinical responses have been reported in the first-in-human studies of every CD40 reagent tested so far.

- Next challenge is to deploy CD40 agonists in combination with standard therapy or experimental therapy.
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