CD40 agonist development for cancer

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Targeting CD40 for cancer therapy

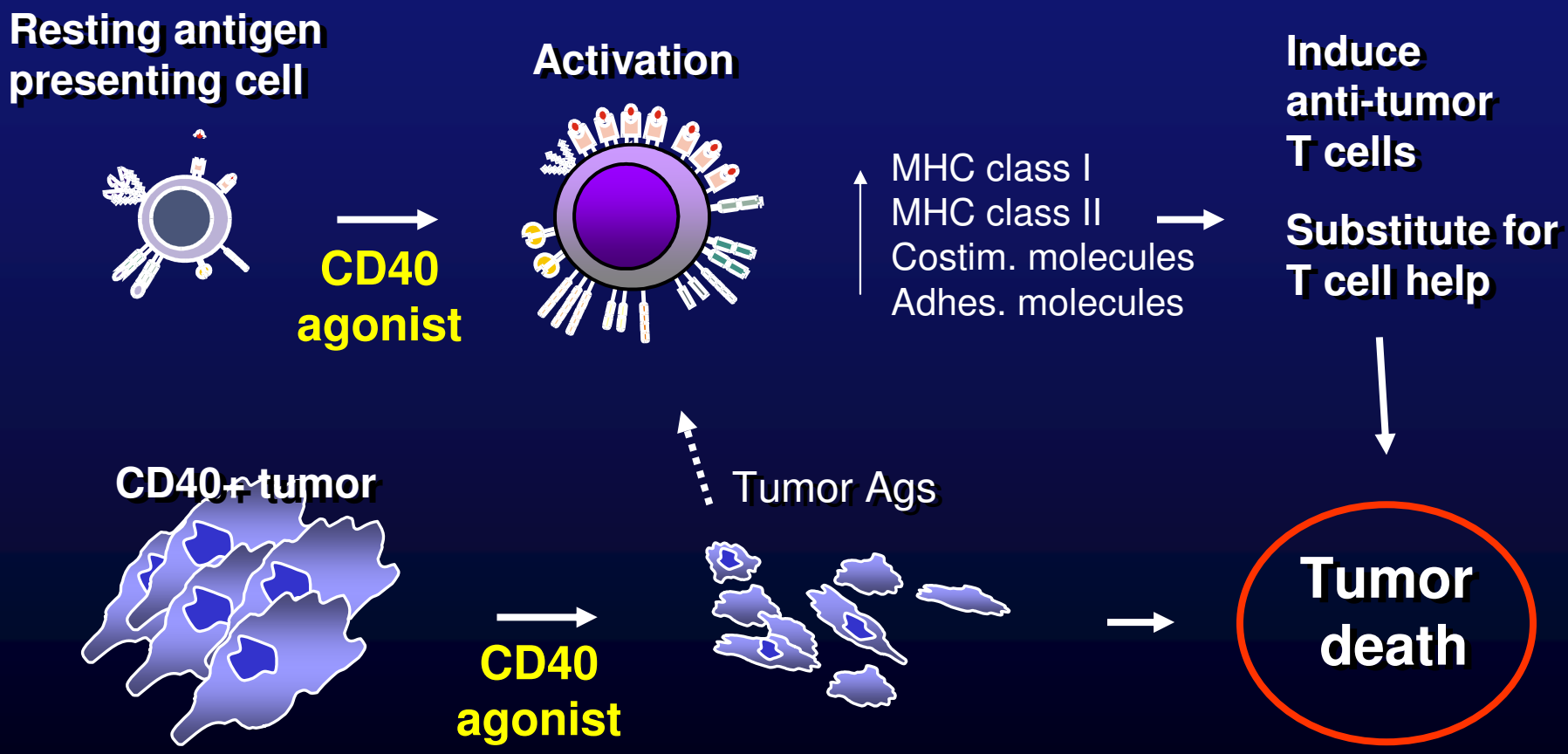
- Member of the TNF receptor superfamily
- Broadly expressed by APC and normal cells, including endothelium and platelets
- No intrinsic kinase or other signal transduction activity

Physiology of CD40

- **Binds to CD40-ligand expressed primarily by T cells**
  - Activates APC
  - Provides a key component of T cell help
    Schoenberger et al, Nature, 1998; Bennett et al, Nature, 1998; Ridge et al, Nature, 1998
  - Enhances anti-tumor cellular immunity
    Sotomayor et al, Nat Med, 1999; Diehl et al, Nat Med, 1999; French et al, Nat Med, 1999
- **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



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 *in vitro***

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

CD40 agonist plus…	Rationale	Mouse model
Cancer vaccine	Reverse T cell tolerance Substitute for T cell help	Sotomayor et al, Nat Med, 1999; Diehl et al, Nat Med, 1999
Chemotherapy	Induce tumor death while stimulating immune system	Tong et al, Clin Can Res, 2001; Nowak et al, Can Res, 2003
Radiation	Induce tumor death while stimulating immune system	Honeychurch et al, Blood, 2003
FDA-approved mAb	Induce tumor death while stimulating immune system, without treatment immunosuppression	
Anti-CTLA4 blocking mAb	Inhibit negative immune regulation while triggering immune activation	Ito et al, JI, 2000
TLR agonists	Synergistic activation of both innate and acquired immunity	Ahonen et al, JEM, 2004 Ahonen et al, Blood, 2008
DR5 and CD137 agonist mAb	Induce apoptosis while fully stimulating immune system	Uno et al, Nat Med, 2006

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?**
  Mauri et al, Nat Med, 2000; Kedl et al; PNAS, 2001; Bartholdy, JI, 2007; Berner et al, Nat Med, 2007

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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