

# **CD40 agonist development for cancer**

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# Targeting CD40 for cancer therapy

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- **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

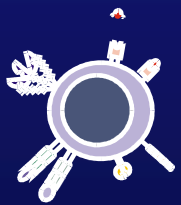
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- **Binds to CD40-ligand expressed primarily by T cells**
  - Activates APC
  - Provides a key component of T cell help  
Schoenberger et al, Nature, 1998; Bennett et al, Nature, 1998; Ridge et al, Nature, 1998
  - Enhances anti-tumor cellular immunity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

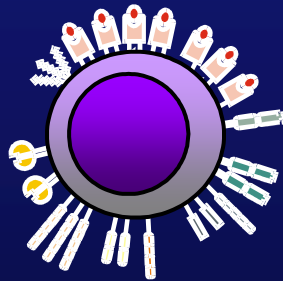
## *Proposed rationale*

Resting antigen presenting cell



CD40 agonist

Activation



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

Induce anti-tumor T cells

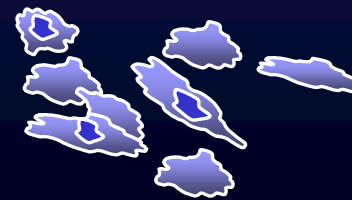
Substitute for T cell help

CD40+ tumor



CD40 agonist

Tumor Ags



Tumor death



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

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- **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

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- **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

# Enrollment, toxicities, and MTD

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- **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

# Clinical response from single infusion

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- **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*

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- **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?***

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- **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

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- 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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