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OX40 Immunotherapy in Cancer Patients: Immunological Observations and Implications for T Cell Immunotherapy

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Disclosures

- Earle A. Chiles Research Institute accepted grants from BMS, MedImmune, Prometheus and Merck to cover costs of clinical trials.
- I am neither employed nor do I have equity interests in any company or entity whose products/drugs will be discussed today.
- Research Support: NIH, Prostate Cancer Foundation, Safeway Foundation, Kuni Foundation, Prometheus Pharmaceuticals
- Speakers Bureau: Prometheus
- Unpaid Consultant: Agonox

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Overview

- Selective summary of preclinical OX40 data
- Summary of phase I immunological and clinical monitoring from anti-OX40 phase I trial
- OX40-based combinations entering the clinic

OX40 Background: Expression

A) OX40 is a T cell activation protein that is expressed upon TCR engagement (a TNF-receptor family member).

1) Primarily on activated $CD4^+$ and $CD8^+$ T cells
2) Engaging CD28 increases OX40 expression
3) Also expressed on Tregs, PMNs, and monocytes/DCs

B) OX40 expression is transient, peaking 24-48 hr after TCR engagement and down-regulated 72-96 hr later.

C) The OX40 ligand is transiently expressed on activated APC.

1) B cells, macrophage, endothelial cells, and dendritic cells
2) Engaging CD40 or TNF up-regulates OX40 ligand expression
3) Low OX40L in vivo limits OX40 enhancement of T cell function

OX40 Background: Costimulation

A) Engagement of OX40 costimulates activated T cells.

1) OX40 ligand expressed on APC or soluble OX40L:Ig and antibodies to OX40 are all costimulatory.

B) Engagement of OX40 will costimulate both TH1 and TH2 cells and increase cytokine production and proliferation.

1) Enhances Ag-specific Ab production

C) OX40 costimulation during primary immunization leads to increased survival of memory T cells through inhibition of activation-induced cell death.

Human Tumors with OX40+ TIL

- Breast Cancer
- Colon Cancer
- Melanoma
- Head and Neck Cancer
- Prostate Cancer
- Bladder Cancer
- Lung Cancer
- Ovarian Cancer

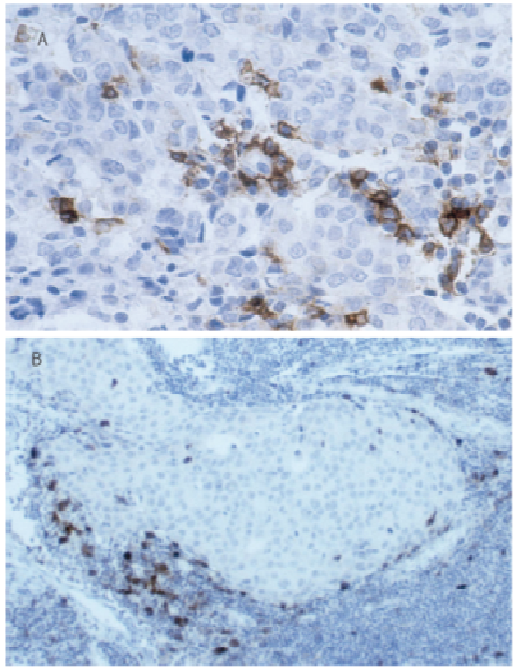

Figure 2. Immunohistochemistry of breast cancer tissue and regional lymph node with breast cancer involvement. OX40-expressing cells are seen mostly around tumor cells. A) Primary tumor., B) Tumor infiltrated lymph node.

Ramstad et al.,
Am J Surg 179:400, 2000

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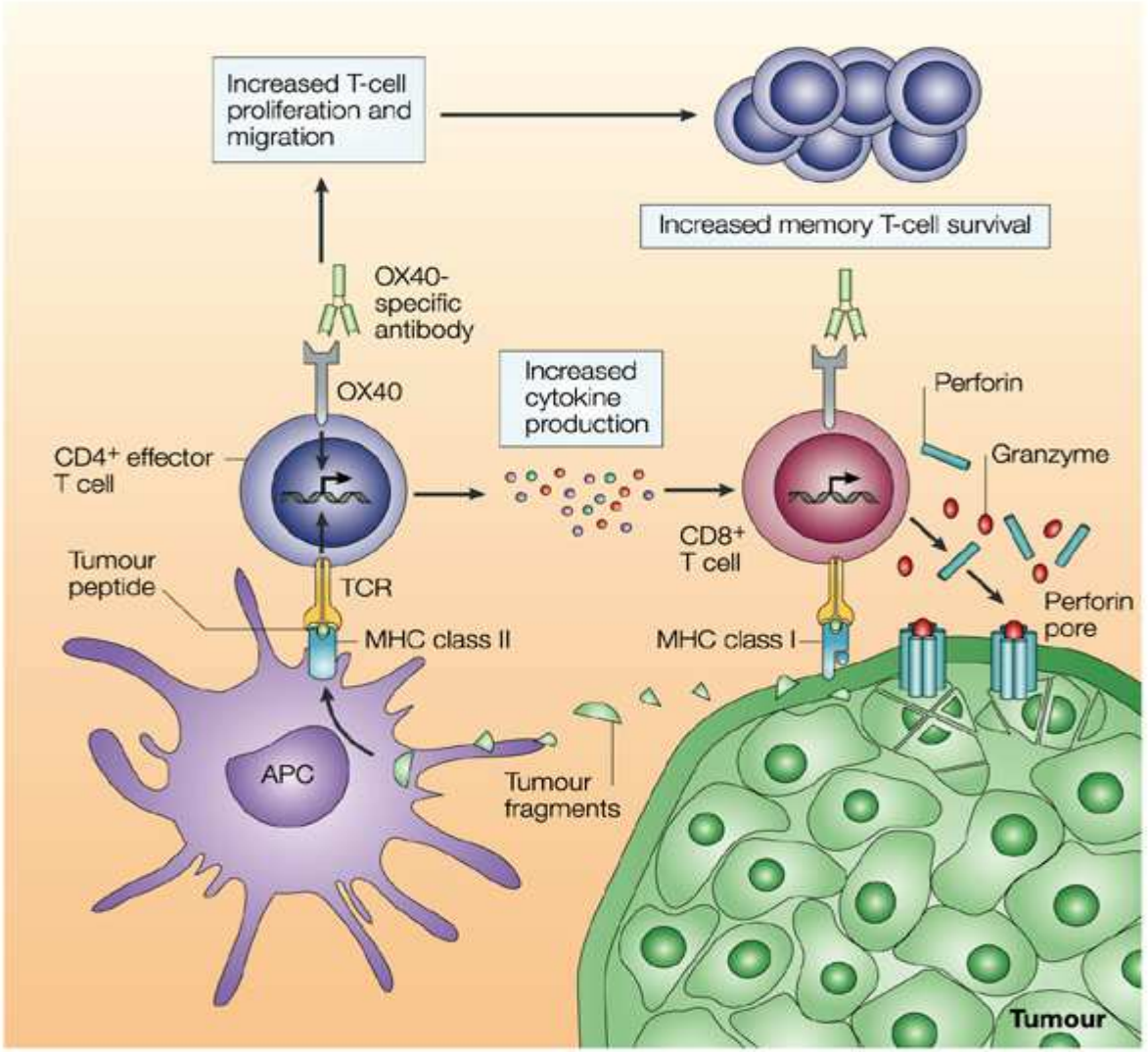
Pre-clinical Models Showing Anti-Tumor Activity of OX40 Agonists

- Breast (4T1, SM1, EMT-6)
- Sarcoma (MCA 303, 205, 203)
- Colon (CT-26)
- Glioma (GL261)
- Melanoma (B16/F10)
- Prostate (TRAMP-C1)
- Lung (Lewis lung)

Summary of OX40 Immunological Effects:

Tumor Immunity



Nature Reviews | Immunology

Microenvironment and Immunology

Cancer Research

OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients

Brendan D. Curti[1], Magdalena Kovacsovics-Bankowski[1], Nicholas Morris[1], Edwin Walker[1], Lana Chisholm[1], Kevin Floyd[1], Joshua Walker[2], Iliana Gonzalez[1], Tanisha Meeuwsen[1], Bernard A. Fox[1], Tarsem Moudgil[1], William Miller[1], Daniel Haley[1], Todd Coffey[1], Brenda Fisher[1], Laurie Delanty-Miller[1], Nicole Rymarchyk[1], Tracy Kelly[1], Todd Crocenzi[1], Eric Bernstein[1], Rachel Sanborn[1], Walter J. Urba[1], and Andrew D. Weinberg[1]

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OX40 Dose Levels

- 0.1 mg/kg, 0.4 mg/kg, 2 mg/kg
- Consecutive enrollment to cohorts
- 10 patients per cohort (random assignment to arms A and B)
- KLH and tetanus used as reporter antigens
    - Arm A
        - Anti-OX40 on days 1, 3 and 5
        - KLH on day 1
        - Tetanus on day 29
    - Arm B
        - Anti-OX40 on days 1, 3 and 5
        - Tetanus on day 1
        - KLH on day 29

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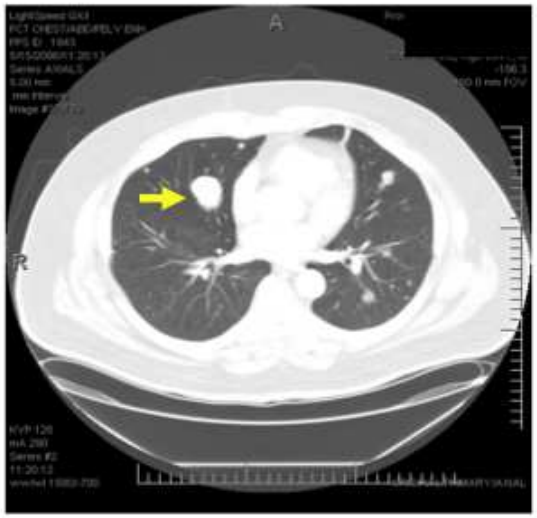
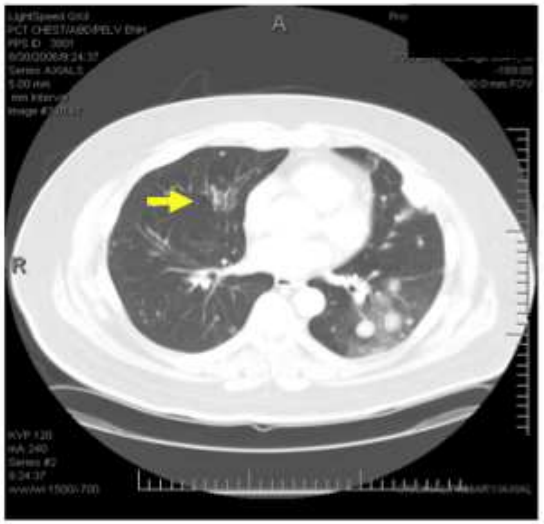
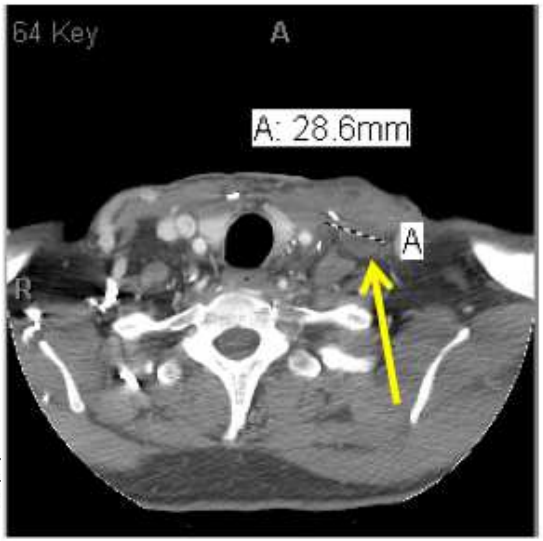
Toxicity Related to Anti-OX40

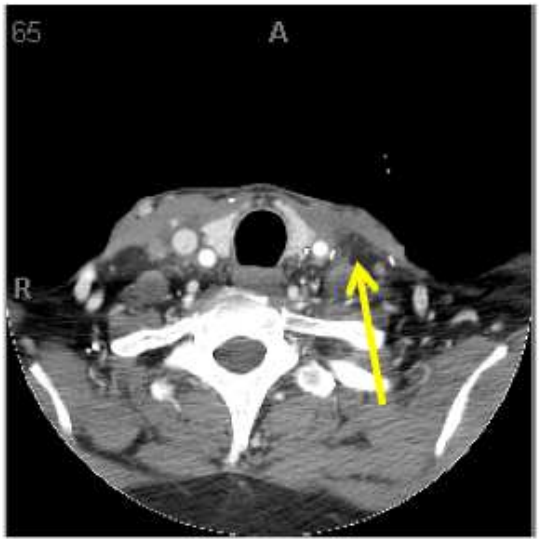
Adverse events				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Lymphopenia	3	10	6	1
Fatigue	7	12		
Rash/Skin Changes	4	6		
Pruritis	5	1		
Fever/Chills	11	2		
Splenomegaly	7			
Arthralgias/Myalgias	5	5		
Nausea/Vomiting	4	3		
Increased AST, ALT or alkaline phosphatase	2	1		
Anemia	1	8		

Tumor Response Illustrations









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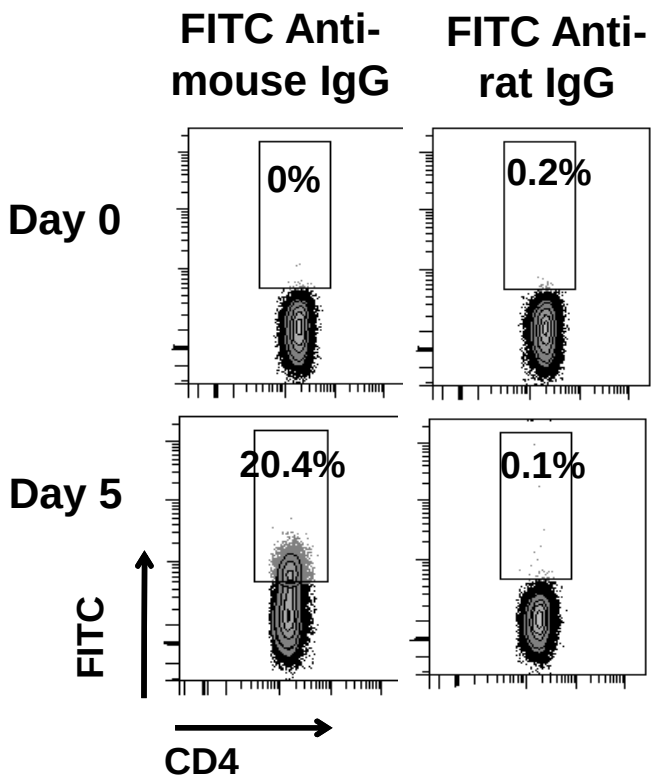
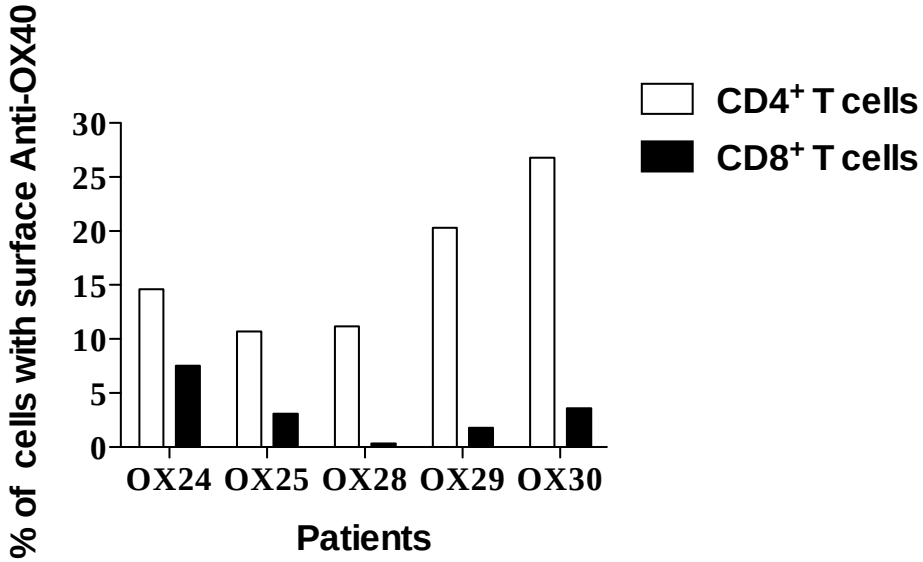
Anti-OX40 on PBMC





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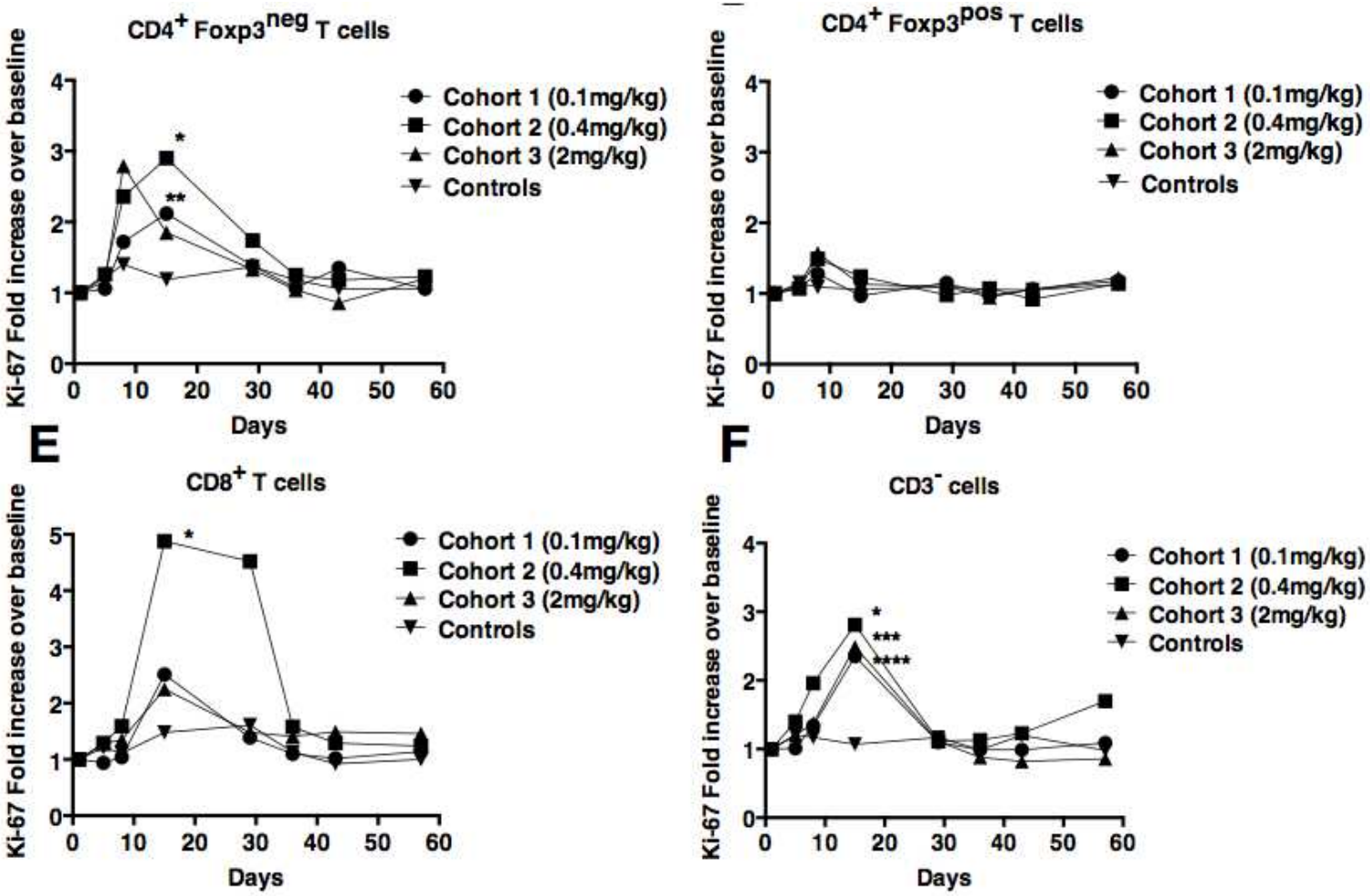
T-Cell Proliferation



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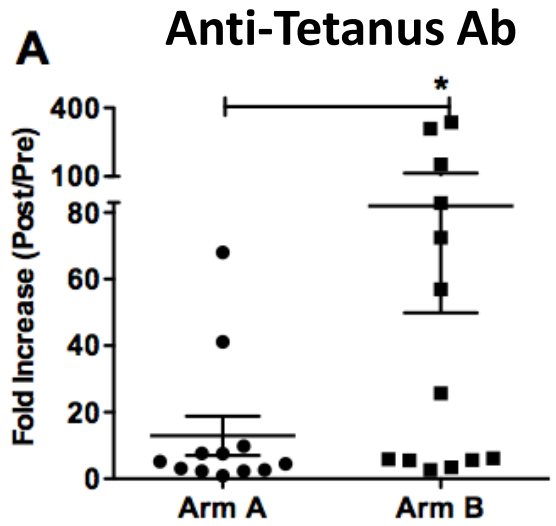
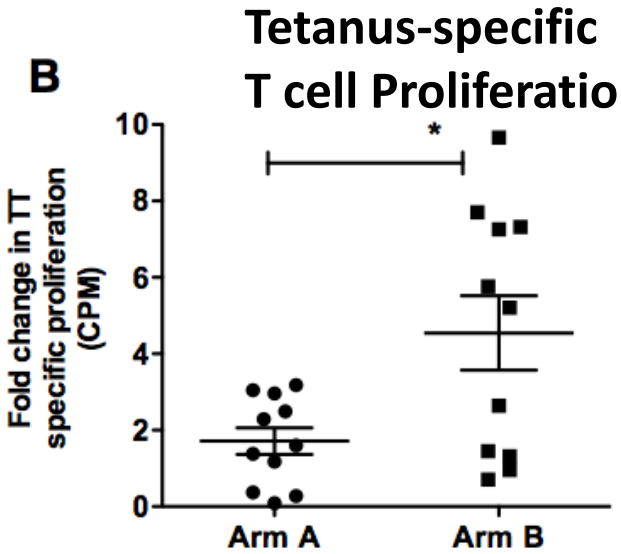
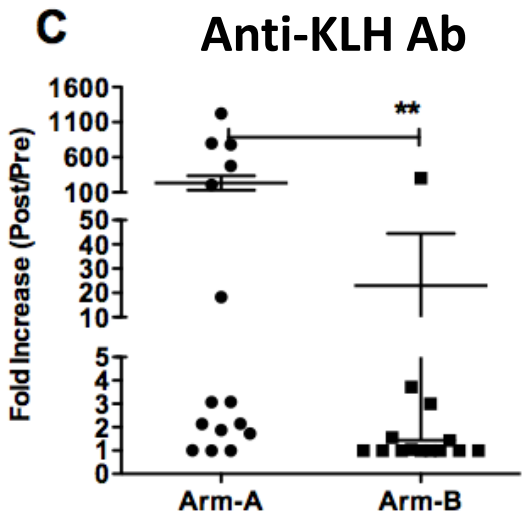
Reporter Antigen Responses







- Arm A
  - Anti-OX40 on days 1, 3 and 5
  - KLH on day 1
  - Tetanus on day 29
- Arm B
  - Anti-OX40 on days 1, 3 and 5
  - Tetanus on day 1
  - KLH on day 29

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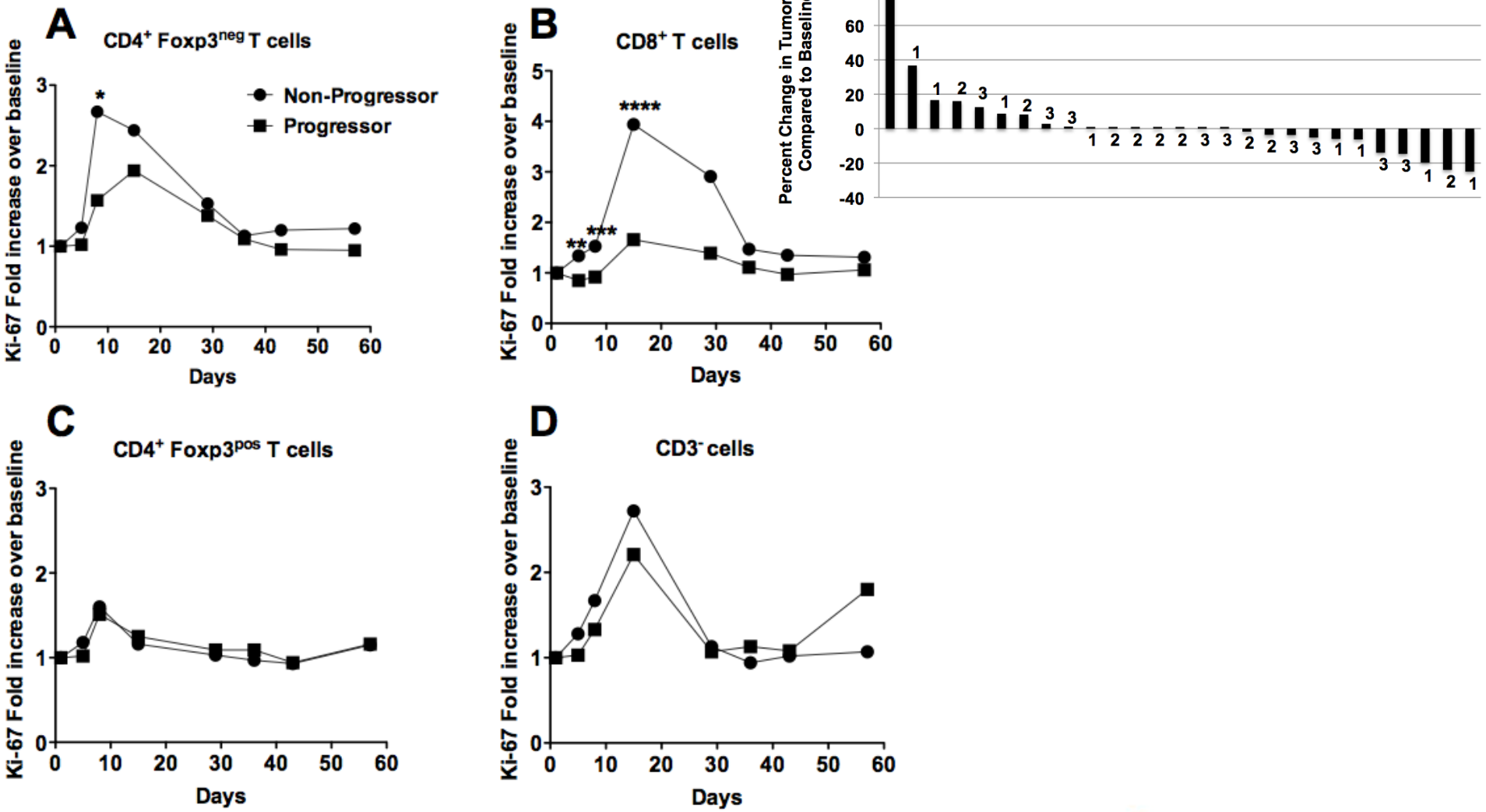
T-Cell Proliferation by "Response"



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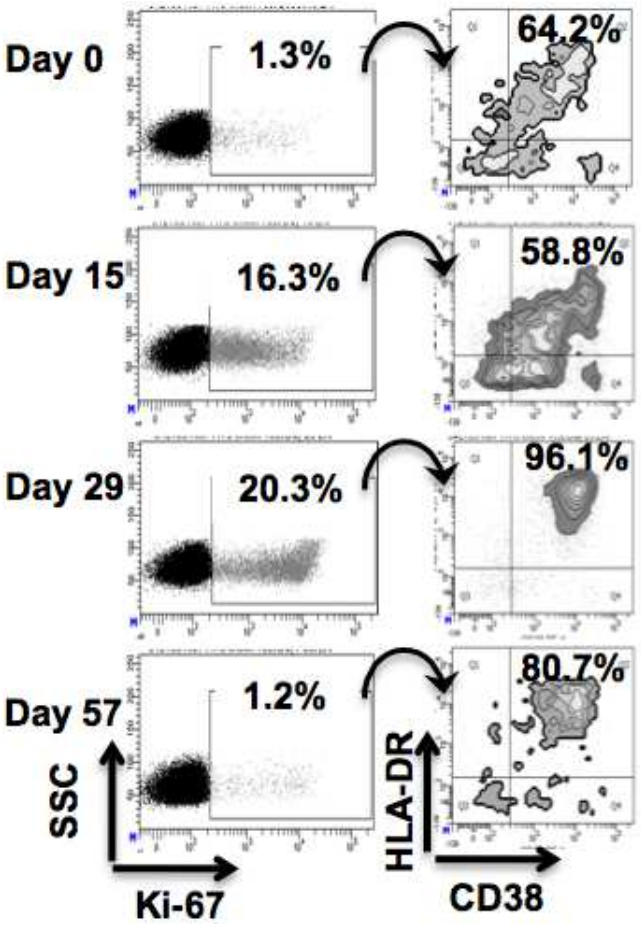
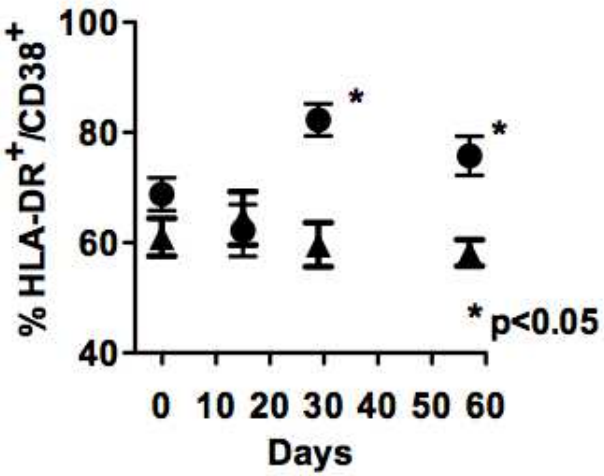
Antigen-Exposed T-Cell Proliferation





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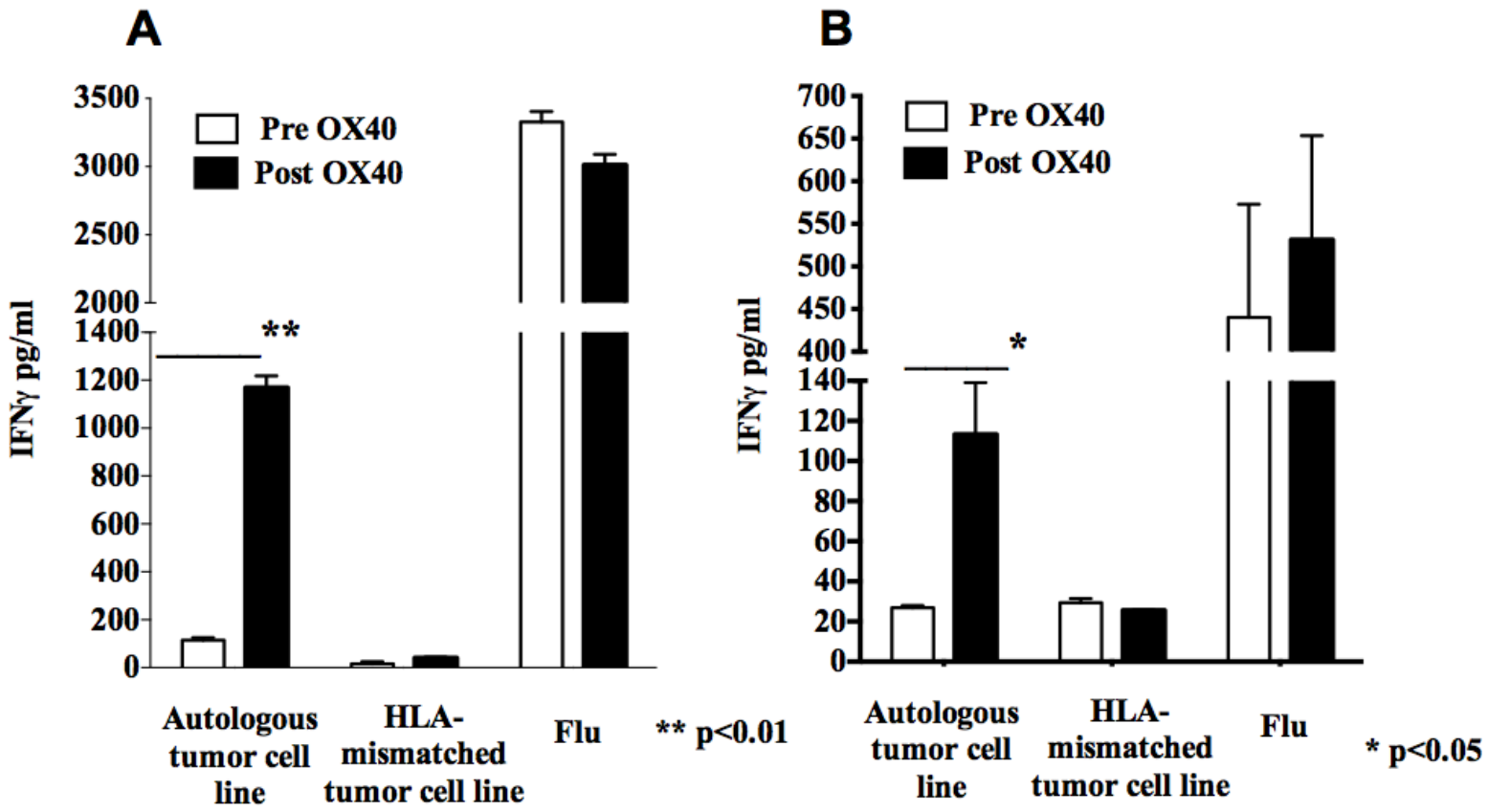
Tumor-Specific Immune Response



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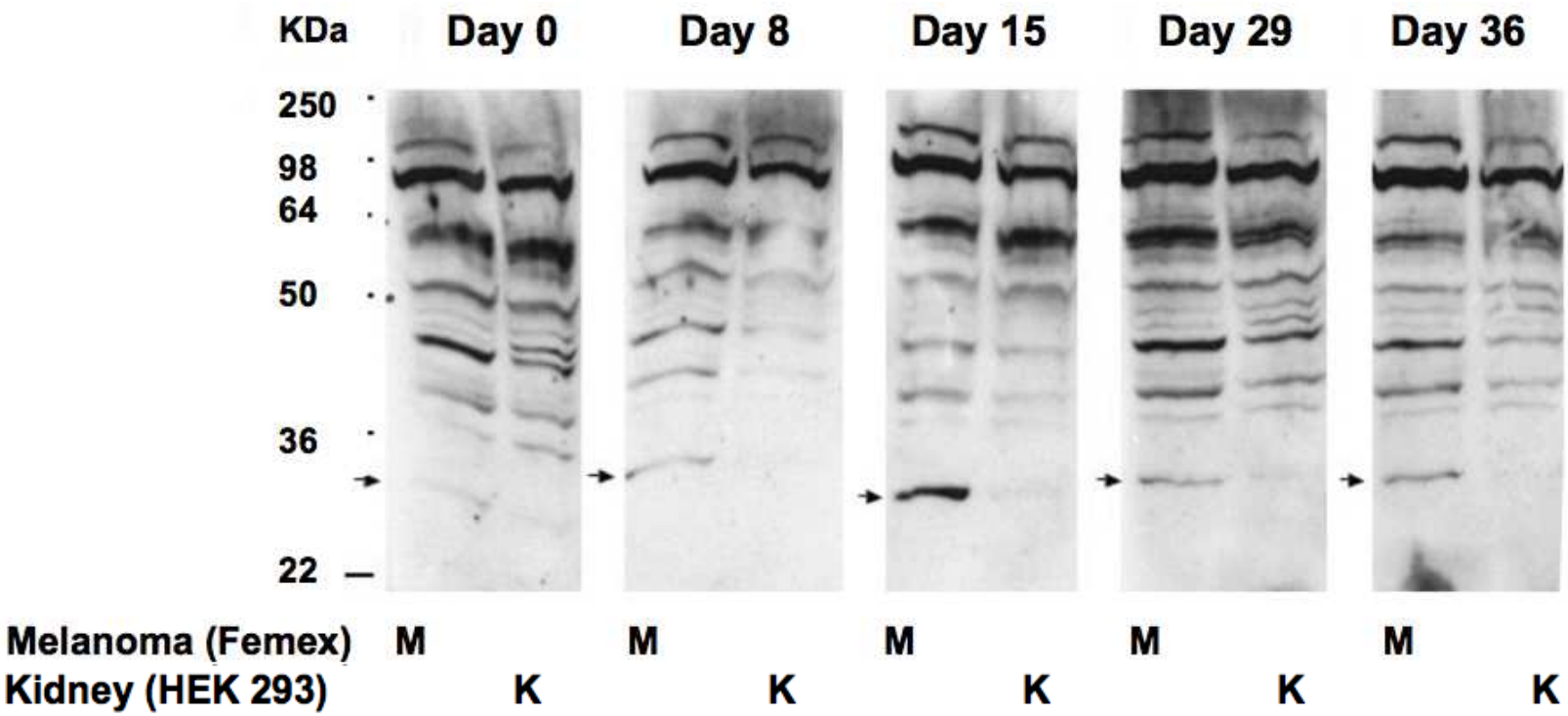
Tumor-Specific Antibody Response



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Summary: Anti-OX40 Clinical and Immunological Effects

- Anti-OX40 was well tolerated.
- Humoral and cellular immune responses to reporter antigens were enhanced by anti-OX40.
- Peripheral blood $CD4^+$ and $CD8^+$ T cells with effector and memory phenotypes proliferated after anti-OX40 without T_{reg} proliferation.
- We saw these immunological changes with a *mouse* monoclonal antibody that we gave for only one cycle.

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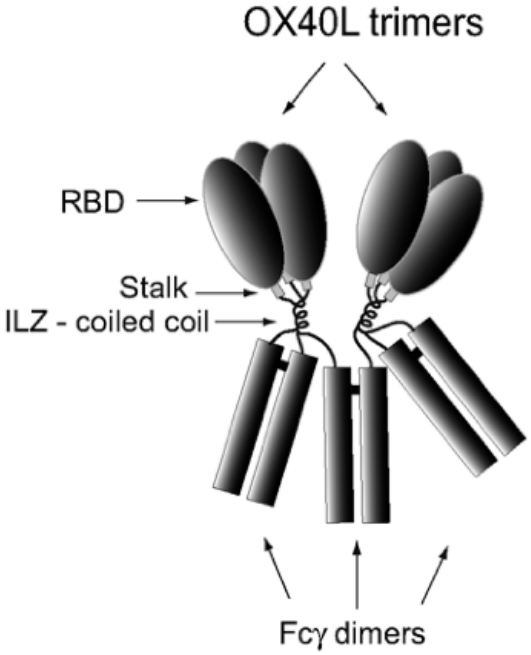
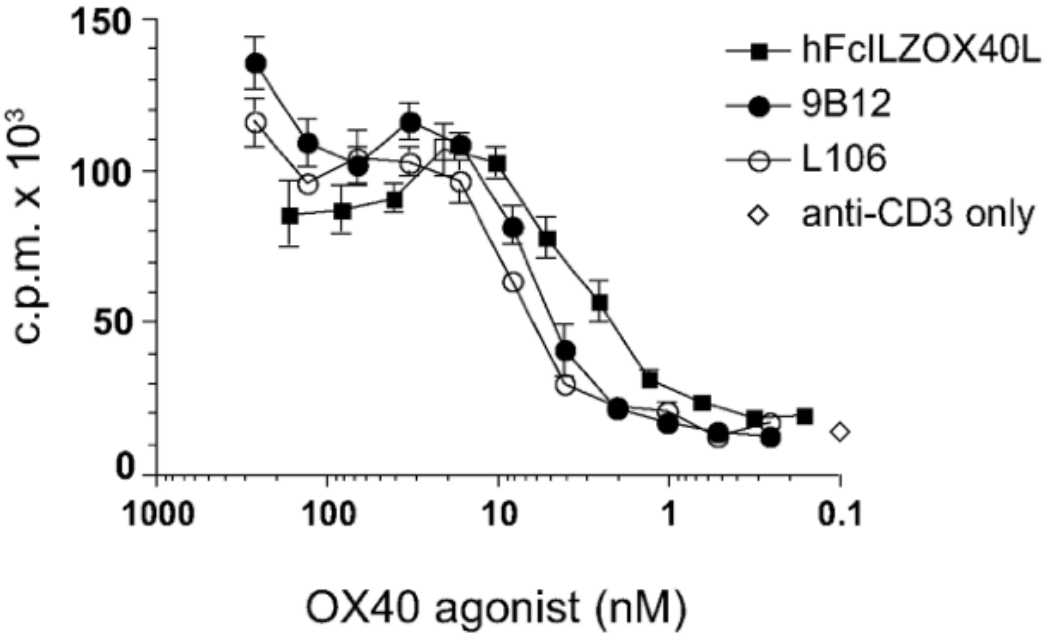
Human OX40 Agonist

Published in final edited form as:
Mol Immunol. 2007 May ; 44(12): 3112–3121.

Development and Characterization of Recombinant Human Fc:OX40L fusion protein linked via a coiled-coil trimerization domain

Nicholas P. Morris, **Carmen Peters**, **Ryan Montler**, **Hong-Ming Hu**, **Brendan D. Curti**, **Walter J. Urba**, and **Andrew D. Weinberg***
Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Portland Medical Center, 4805 N.E. Glisan Street, Portland OR, 97213





A Phase I Study of MEDI6383 in Adult Subjects with Select Advanced Solid Tumors

- Opened September 2014
- Metastatic bladder, colorectal, non-small cell lung or squamous cell head and neck cancer with disease progression after standard therapy.
  - Restrictions on prior anti-CTLA-4, anti-PD-1, anti-PDL1, anti-4-1BB, GITR, OX40 and CD27
- Phase I dose escalation and dose expansion
- MEDI6383 dosing every 2 weeks for 6 months

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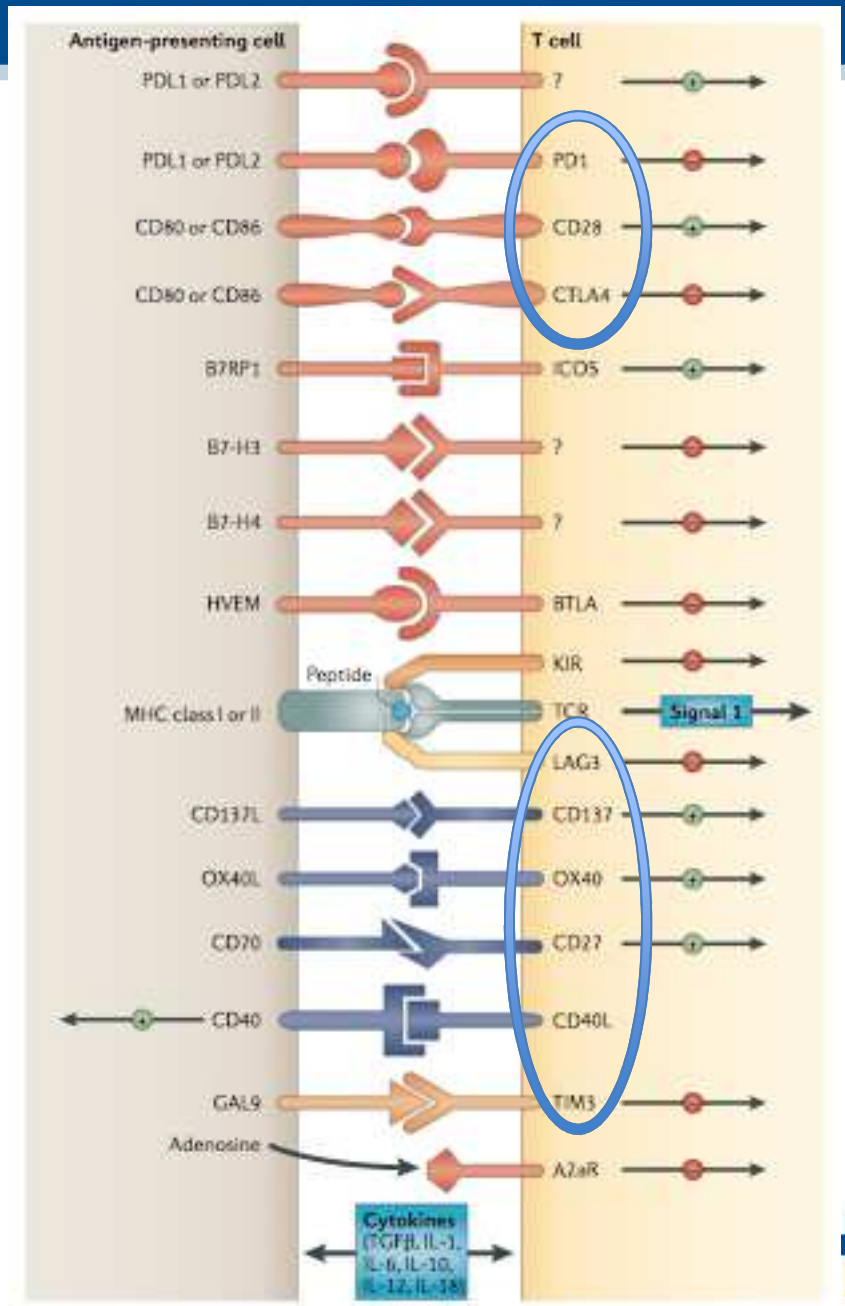
OX40 Combinations



= -1?

= +1?

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Pardoll, Nature April 2012

Combinatorial Arithmetic Applied to Immunotherapy

- Modest Hypothesis:
  - $-(-1) + 1 = 2$
- Hopeful Hypothesis:
  - $(-(-1) + 1)^2 = 4$
- Hypothesis of Maximum Hope:
  - $(-(-1) + 1)^n$ = Cure

Selected Published Pre-Clinical Anti-OX40

- Anti-OX40 + anti-CTLA4
  - Marabelle et al., J Clin Invest 123:2447, 2013
  - Redmond et al. Cancer Immunol Res 2:142, 2014
- Anti-OX40 + anti-PD1
  - Guo et al., PLOSone 9:e89350, 2014
- Anti-OX40 + antiPDL-1 + anti-41BB
  - Morales-Kastresana et al., Clin Cancer Res 19:6151, 2013
- Anti-OX40 + TGF beta inhibition
  - Garrison et al., Cancer Immunol Immunother 61: 511, 2012

Clinical Trials Investigating OX40 Combinations

- Phase 1b/2 Safety and Tolerability of MEDI6469 in Combination with Therapeutic Immune Agents or Monoclonal Antibodies
  - Tremelimumab
  - MEDI4736 (anti-PDL1)
  - Rituximab
- Stereotactic Body Radiation and Monoclonal Antibody to OX40 in Breast Cancer Patients with Metastatic Lesions

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