SITC – 2014

T Cell Costimulation in Cancer Immunotherapy Through Agonist Agents: OX40

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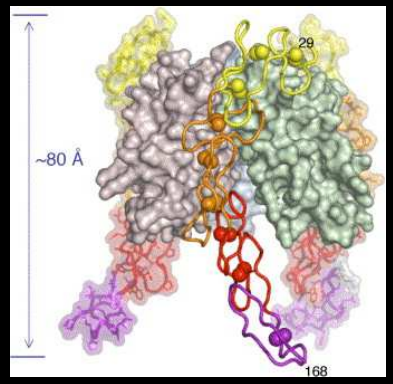
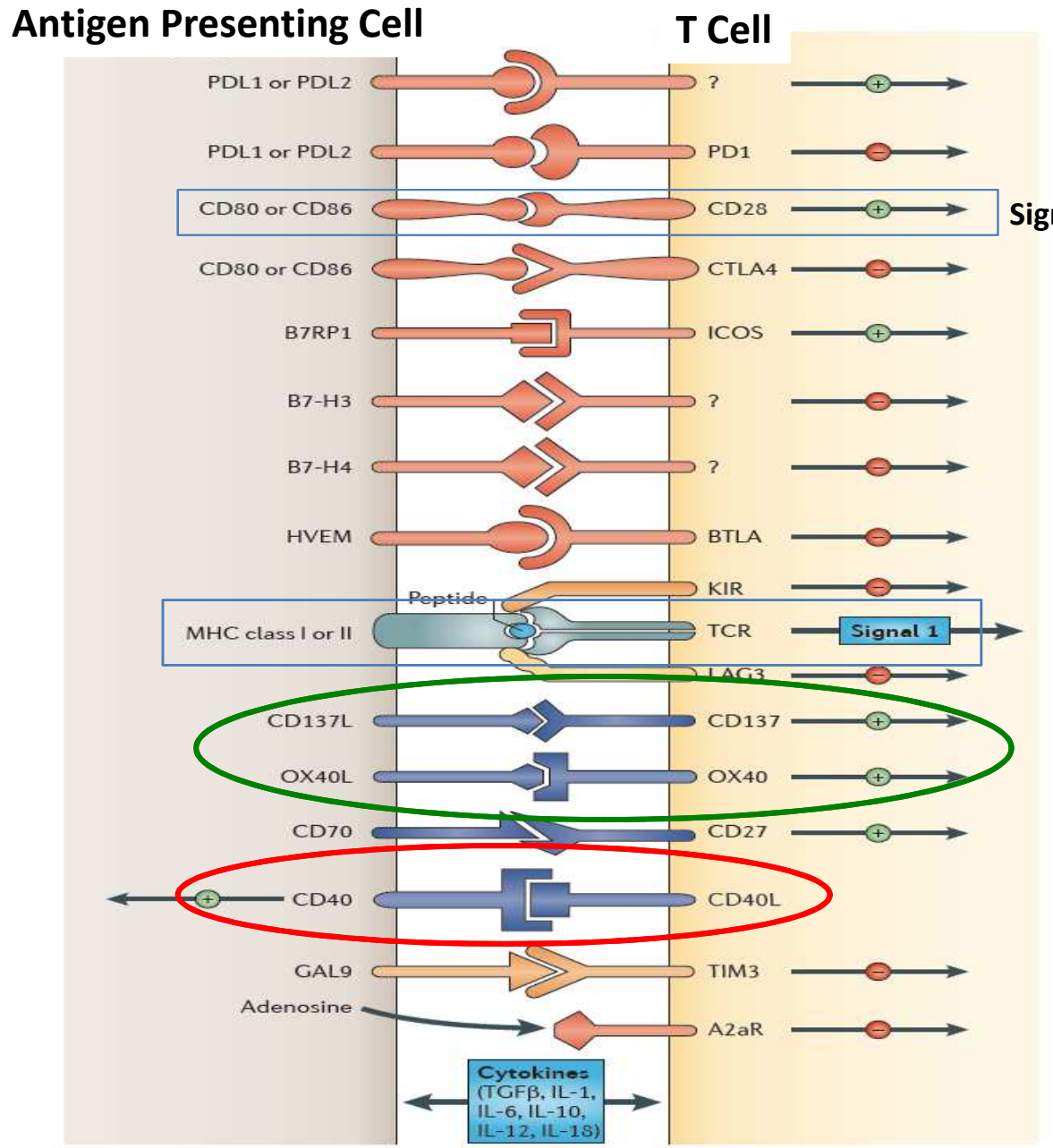


- Introduction of TNF-Rs in Immunotherapy: OX40, 4-1BB, CD40
- T Cell Costimulation: History – CD28
- OX40 Costimulation – In Vitro and In Vivo
- OX40 Agonist Therapy Preclinical Models
- OX40 Agonist Therapy in the Clinic
- OX40 Agonist Combinations

Disclosures

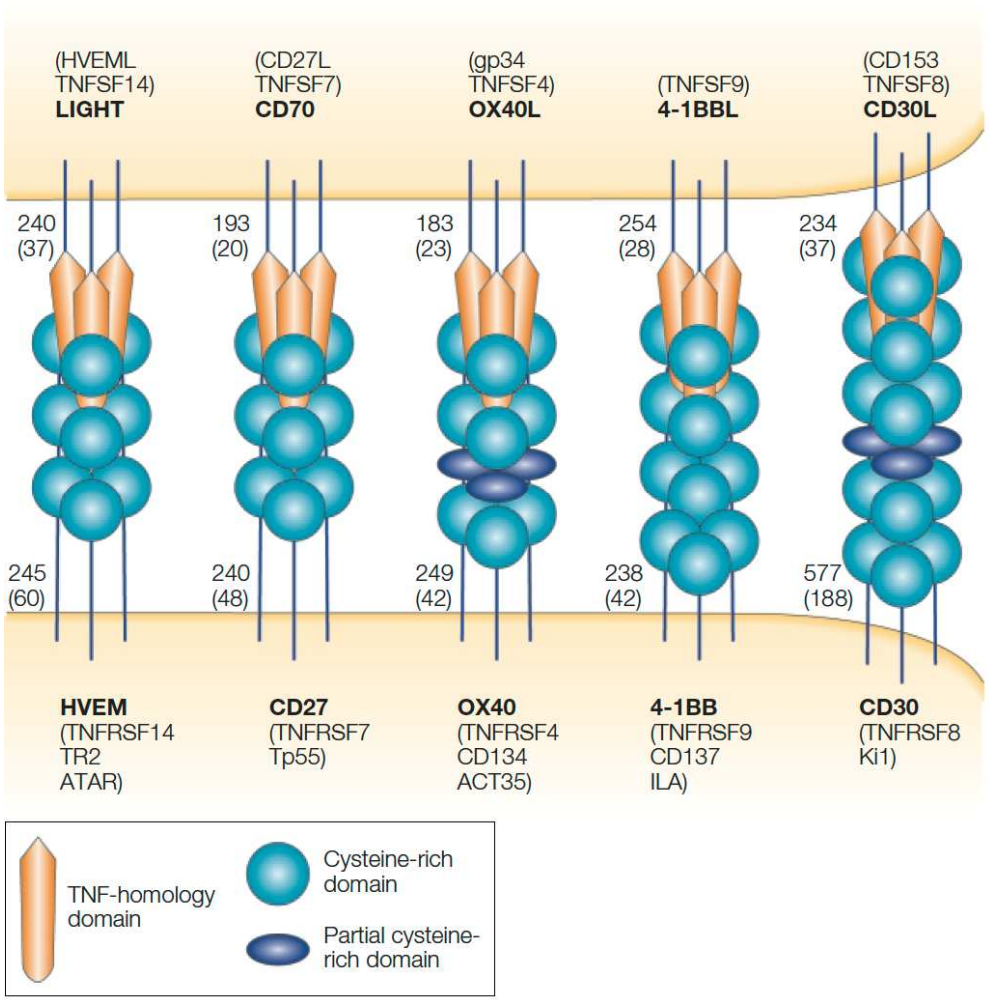
- Have issued patents pertaining to OX40 Agonists for use in Cancer Patients
- Receive OX40 Agonist Research Funding from MedImmune
- President and CSO of Agonox, Inc

Multiple co-stimulatory and inhibitory interactions regulate T cell responses



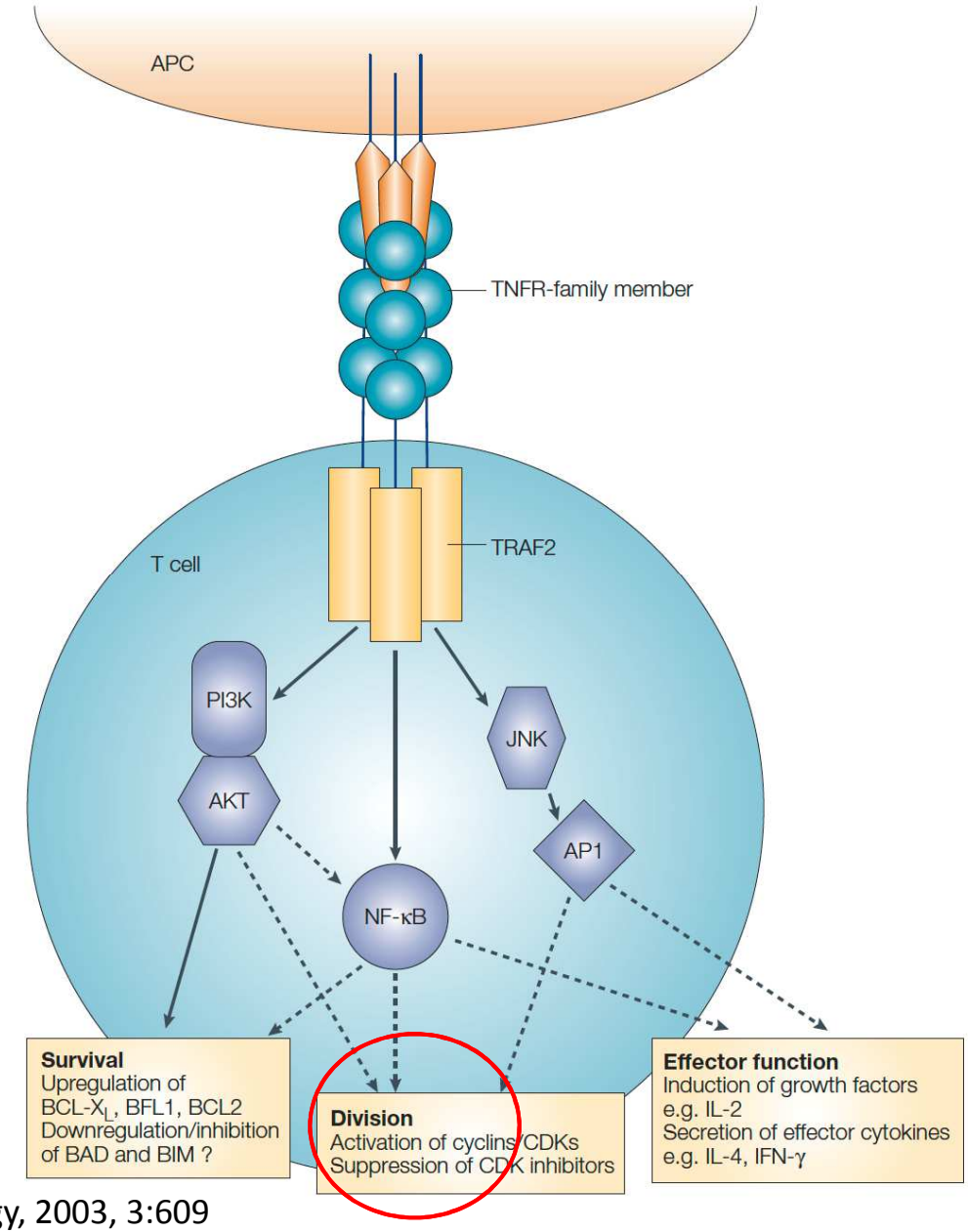
Pardoll: Nature Rev Cancer 12: 254, 2012

Biochemical Structure of the TNF/TNF-receptor Family Members



Croft M., Nature Reviews Immunology, 2003, 3:609

Overview of TNF-R Signaling



Croft M., Nature Reviews Immunology, 2003, 3:609

The Genesis of T Cell Costimulation

The Journal of Immunology

Pillars Article: Antigen Presentation by Chemically Modified Splenocytes Induces Antigen-Specific T Cell Unresponsiveness In Vitro and In Vivo. *J. Exp. Med.* 1987. 165: 302–319

Marc K. Jenkins and Ronald H. Schwartz

ECDI-APC/splenocytes with Ag or w/o Ag

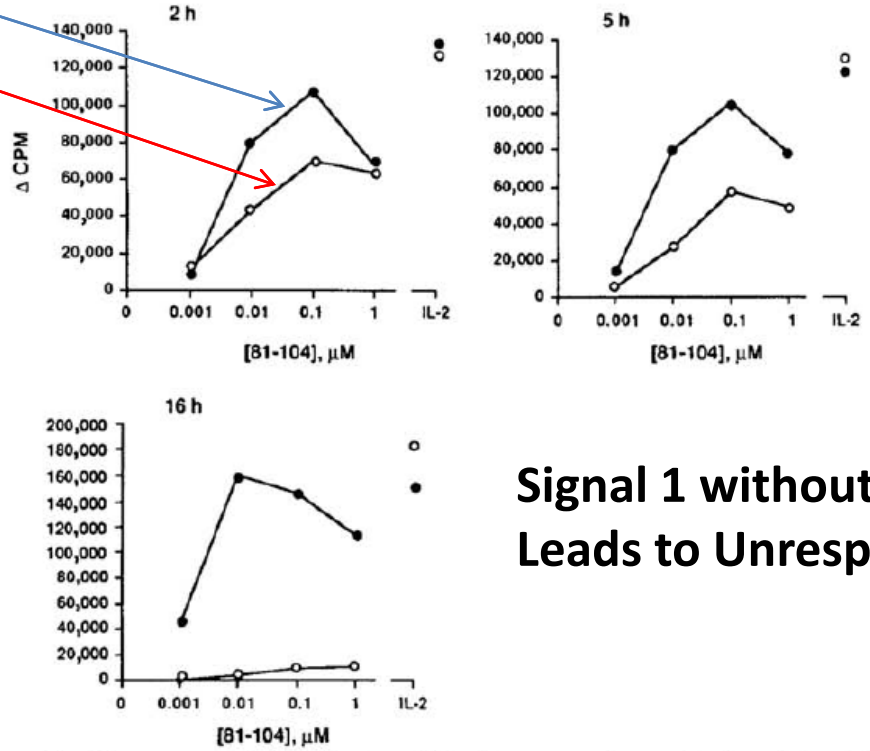


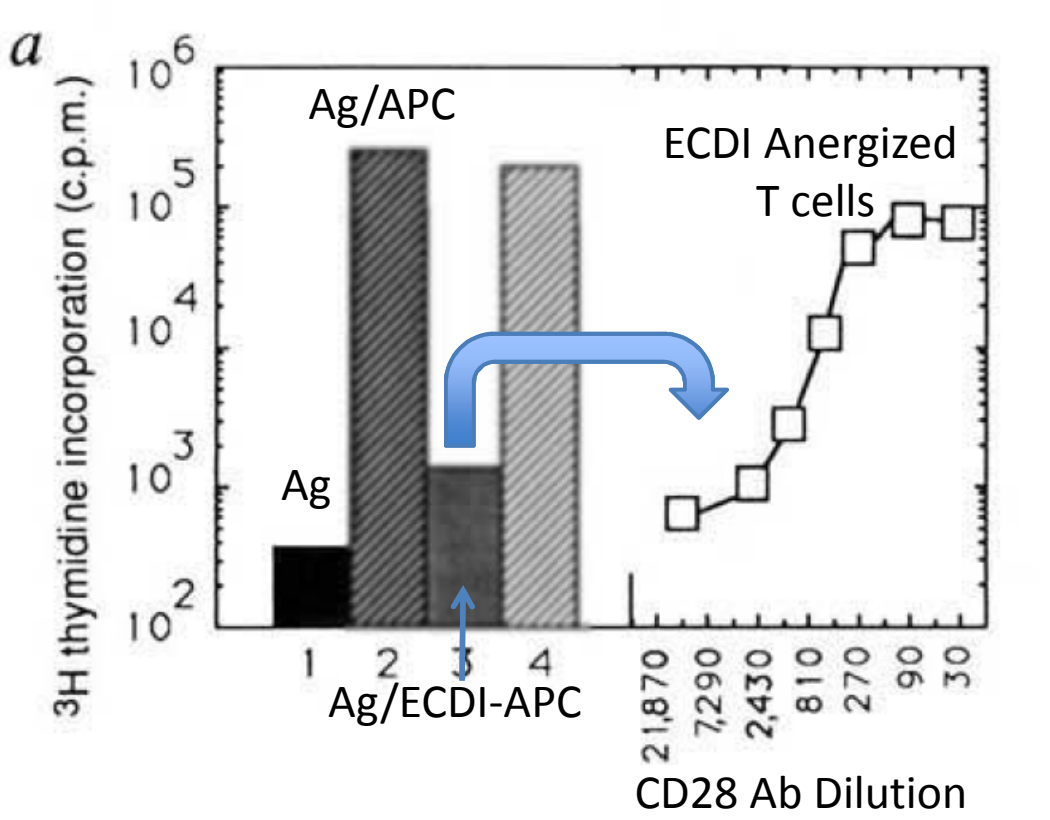
FIGURE 6. Time course of the induction of T cell unresponsiveness in vitro. T cell clone A.E7 (5×10^5) was preincubated with 5×10^6 ECDI-treated B10.A splenocytes with (*open circles*) or without (*filled circles*) 5 μM pigeon fragment 81-104 for the indicated times, after which the T cells were reisolated and restimulated as described in the legend to Fig. 2. The results are expressed as Δ cpm.

Signal 1 without Signal 2 Leads to Unresponsive T Cells

CD28-mediated signalling co-stimulates murine T cells and prevents induction of anergy in T-cell clones

Fiona A. Harding*†, James G. McArthur*†,
Jane A. Gross‡, David H. Raulet* & James P. Allison*§

NATURE · VOL 356 · 16 APRIL 1992

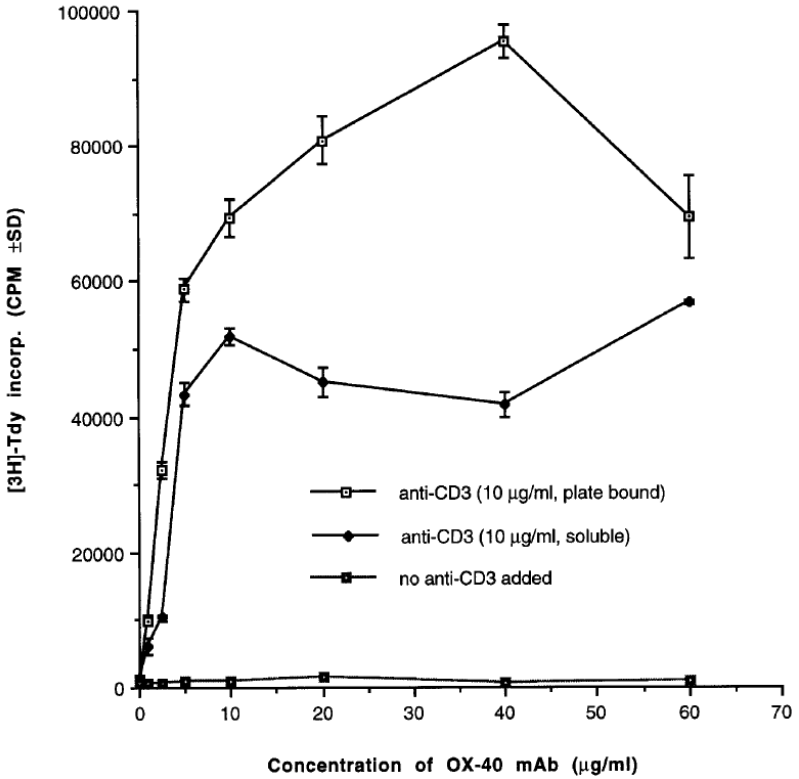


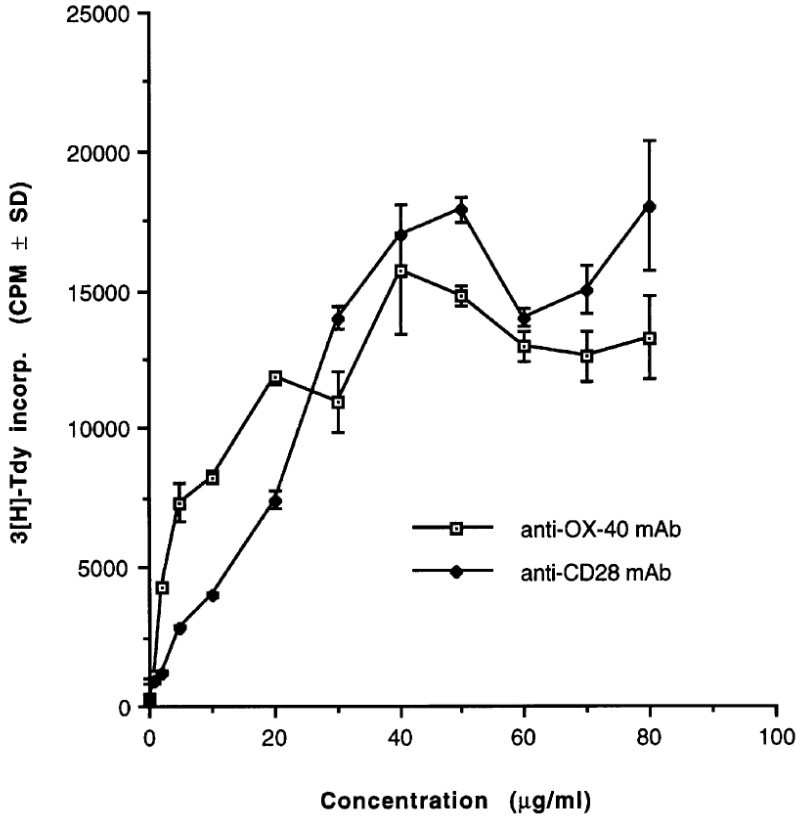
OX40 Abs Costimulate T cells In Vitro

International Immunology, Vol. 10, No. 4, pp. 453–461 1998

J. A. R. Kaleeba[1], H. Offner[2,3], A. A. Vandenbark[1–3], A. Lublinski[4] and **A. D. Weinberg[1,4]**

Co-stimulation of CD4$^+$ T cells through OX-40





OX40 Costimulates Effector T Cells

OX40 Abs Costimulate In Vivo Leading to Enhanced T Cell Survival

The Journal of Immunology, 2000, 164: 107–112.

Joseph R. Maxwell,[2]* Andrew Weinberg,[2†] Rodney A. Prell,[†] and Anthony T. Vella[3]*

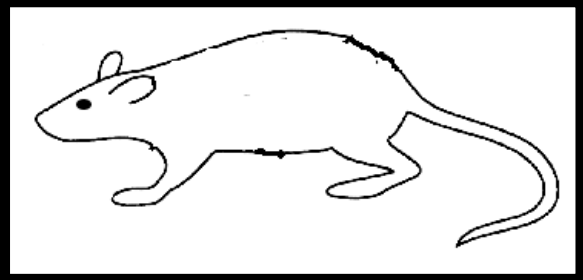
Table II. *Optimal long-term memory T cell survival of Ag-activated $CD4^+$ T cells is obtained when OX40 engagement occurs in a proinflammatory environment*[a]

Treatment	Spleen Cells[b]	LN[b]
No OVA	2.62 ± 0.91	1.76 ± 0.17
OVA/IgG	3.21 ± 1.54	1.26 ± 0.59
OVA/anti-OX40	39.63 ± 20.25	7.63 ± 4.67
OVA/LPS/IgG	5.24 ± 0.19	1.88 ± 0.11
OVA/LPS/anti-OX40	191.85 ± 30.92	12.06 ± 2.23

60 Days Post-Immunization

EFFECT of mOX40L:Ig or anti-OX40 Solid Tumor Growth In Vivo

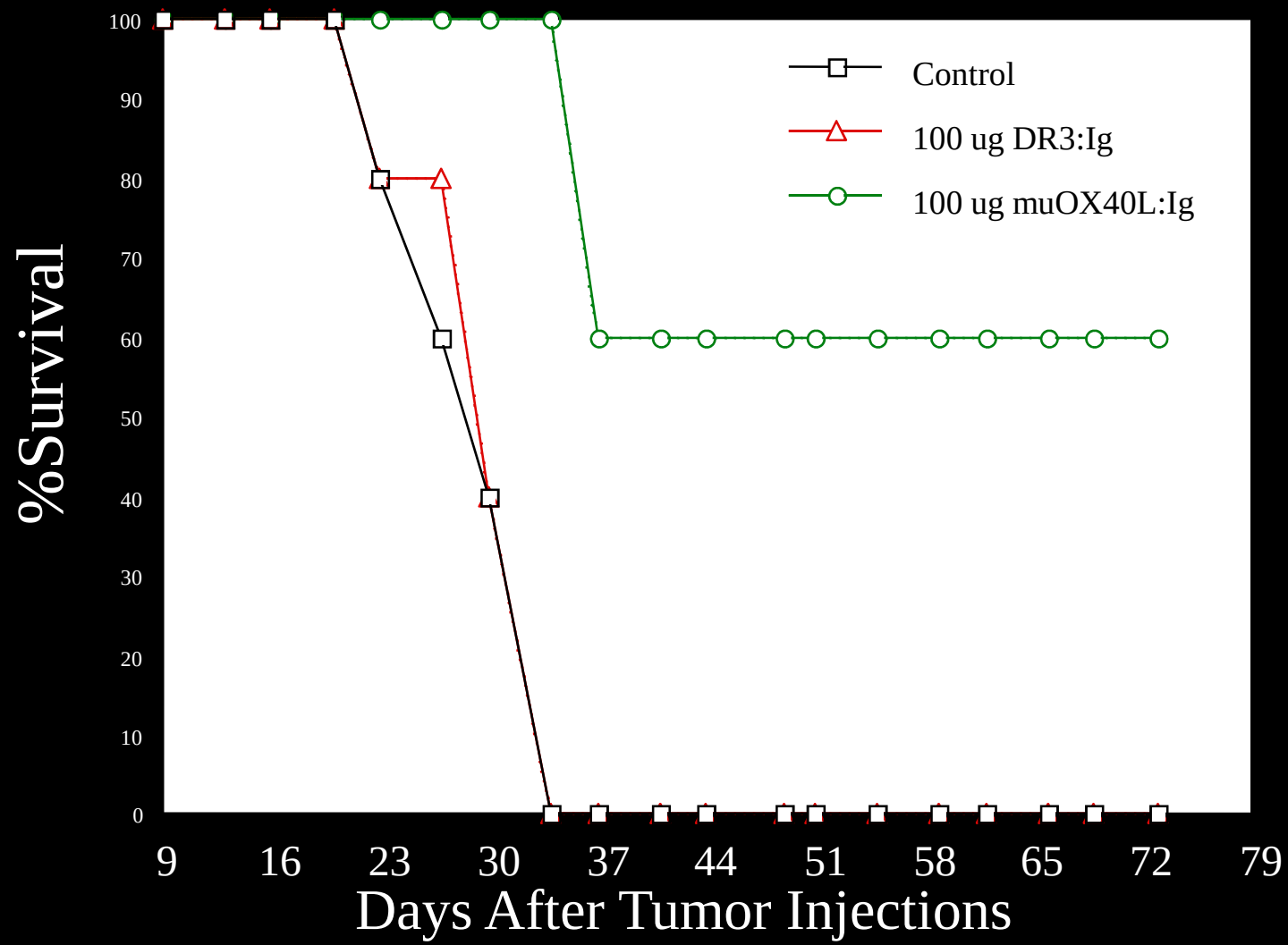
Solid Tumor
Administered s.c.



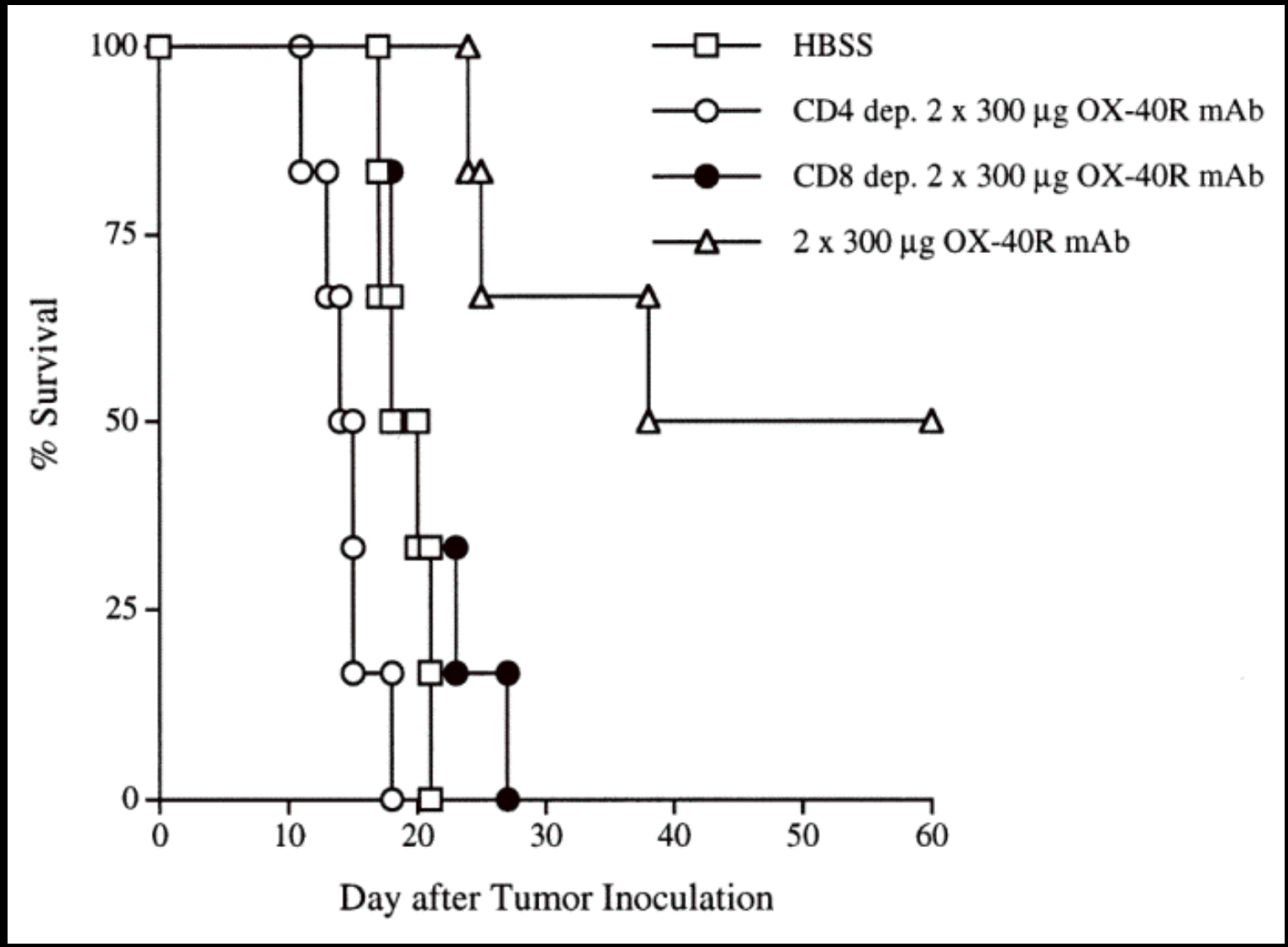
Days 3 and 7 after tumor injection

- Control
- 150 μg Sol. mu OX40L
- 150 μg anti-OX40
- Control

OX40L:Ig Treatment of MCA 303



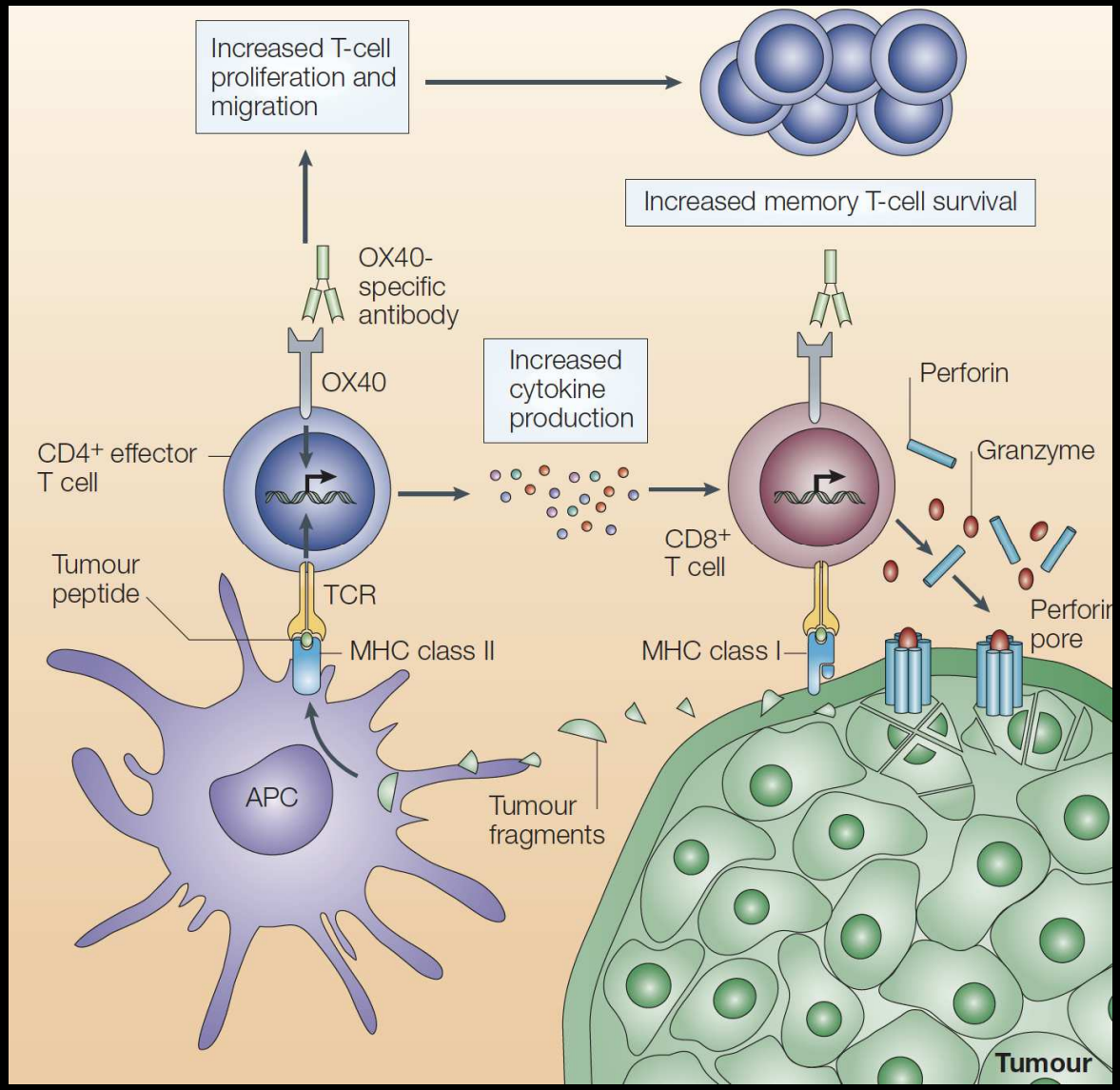
CD4 and CD8 T cells Roles in anti-OX40 Enhanced Tumor Immunity (Glioma Model)



Tumor Models Successfully Treated with OX40 Engagement

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

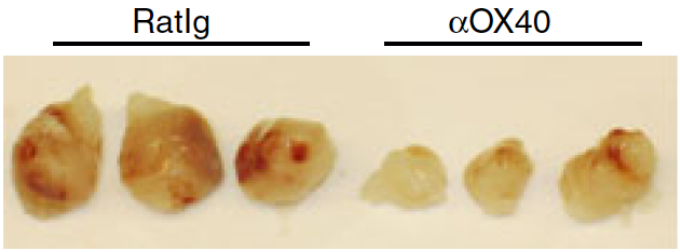
Schematic Representation of OX40-enhanced Tumor Immunity



OX40 Agonists Impact the Immune Environment within the Tumor

Gough et al., Cancer Research. 2008, 68:5206

(a)



(b)

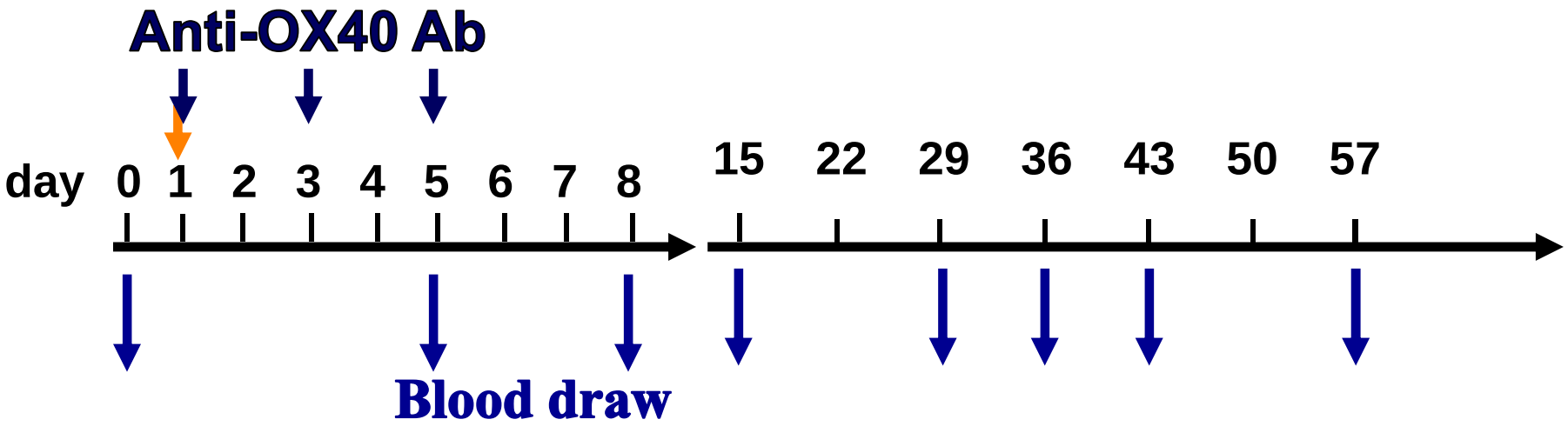
	% positive						*P* value
$CD11b^{+}\ Gr1^{hi}$	12	25	14	2	3	4	*
$CD11b^{+}$	33	46	40	11	17	17	**
$CD8^{+}$	20	16	18	45	44	33	**

Taking OX40 Agonists to the Clinic

- Treated patients with all solid malignancies
- Anti-OX40 was well-tolerated.
- The maximum tolerated dose was not reached.
- All patients made HAMA
- No CRs or PRs; however,
  - 12 patients had regression of at least one tumor nodule
  - 17/30 had SD by RECIST criteria for 56 days
  - Median survival 392 days after receiving anti-OX40

Curti et. al., Cancer Research, 2013. 73(24):7189 – 7198.

Anti-OX40 Phase I Clinical Trial Time Course



Immune function tests

Did we observe an increased in T cell proliferation in the patients treated with anti-OX40?

Flow Cytometry Panel

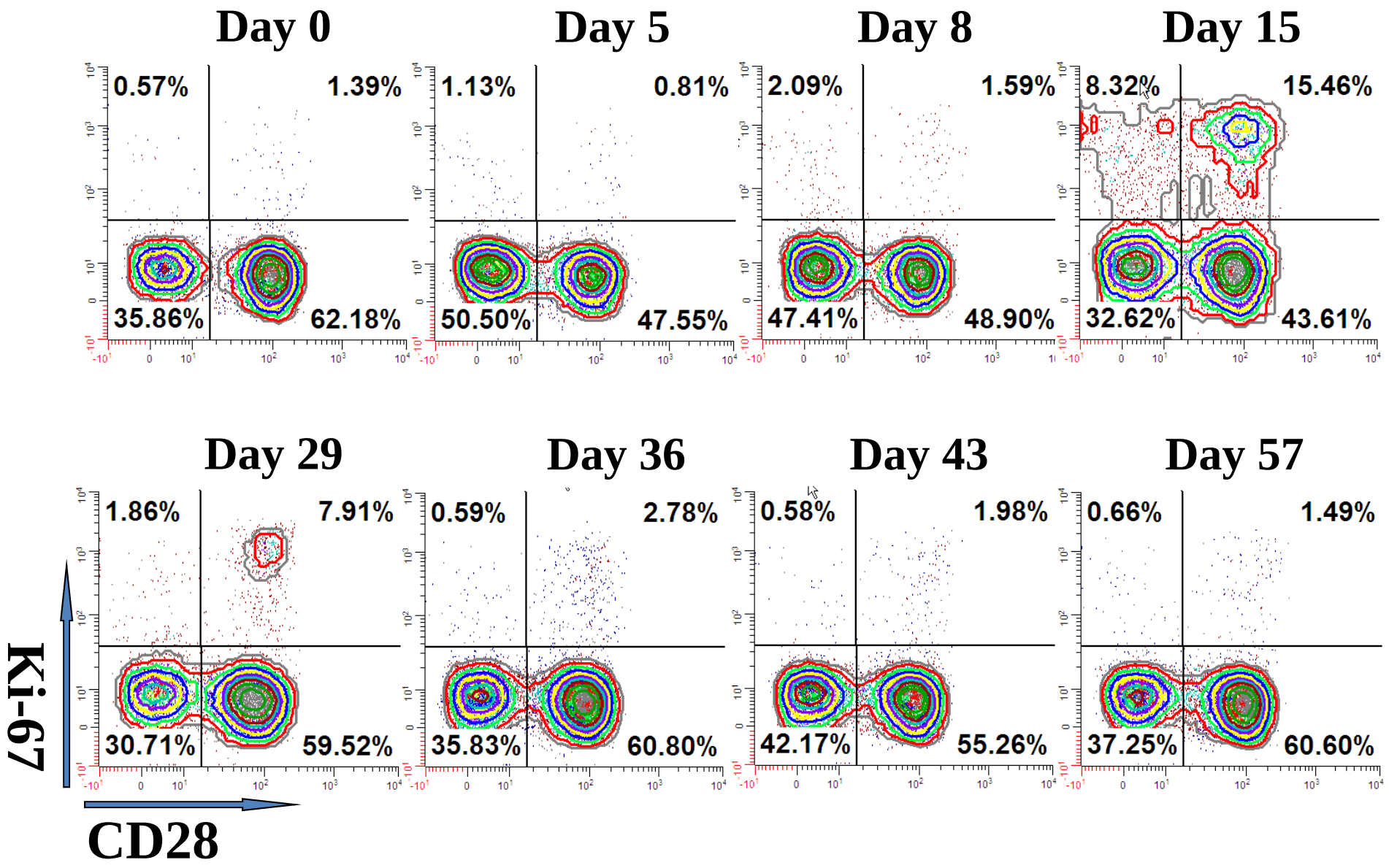
CD3
CD4
CD8
CD95
CD25
FoxP3
CD28
CCR7
CD127
Ki-67 (proliferation)

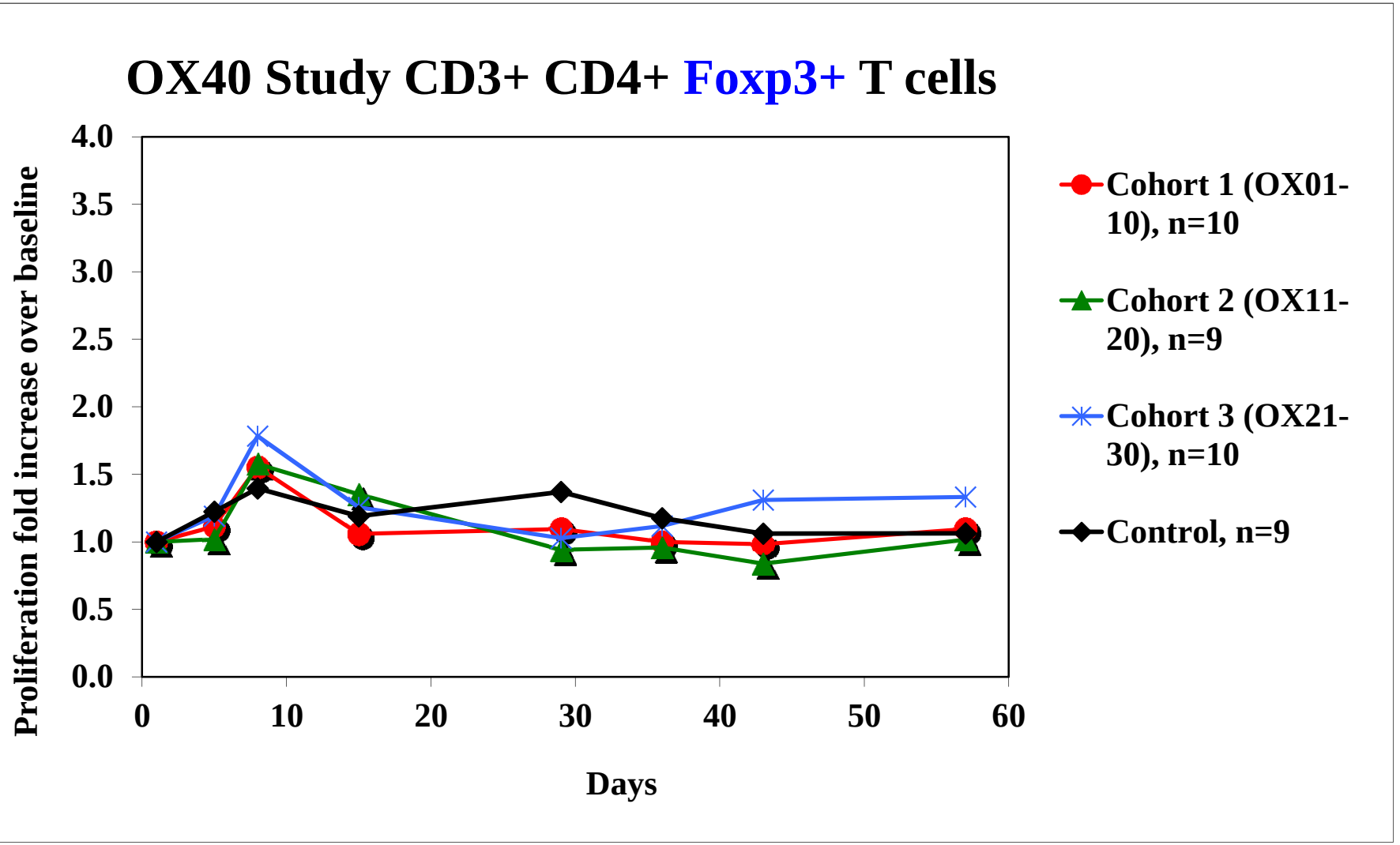
Strategy adapted from Louis Picker (SIV monkey studies)

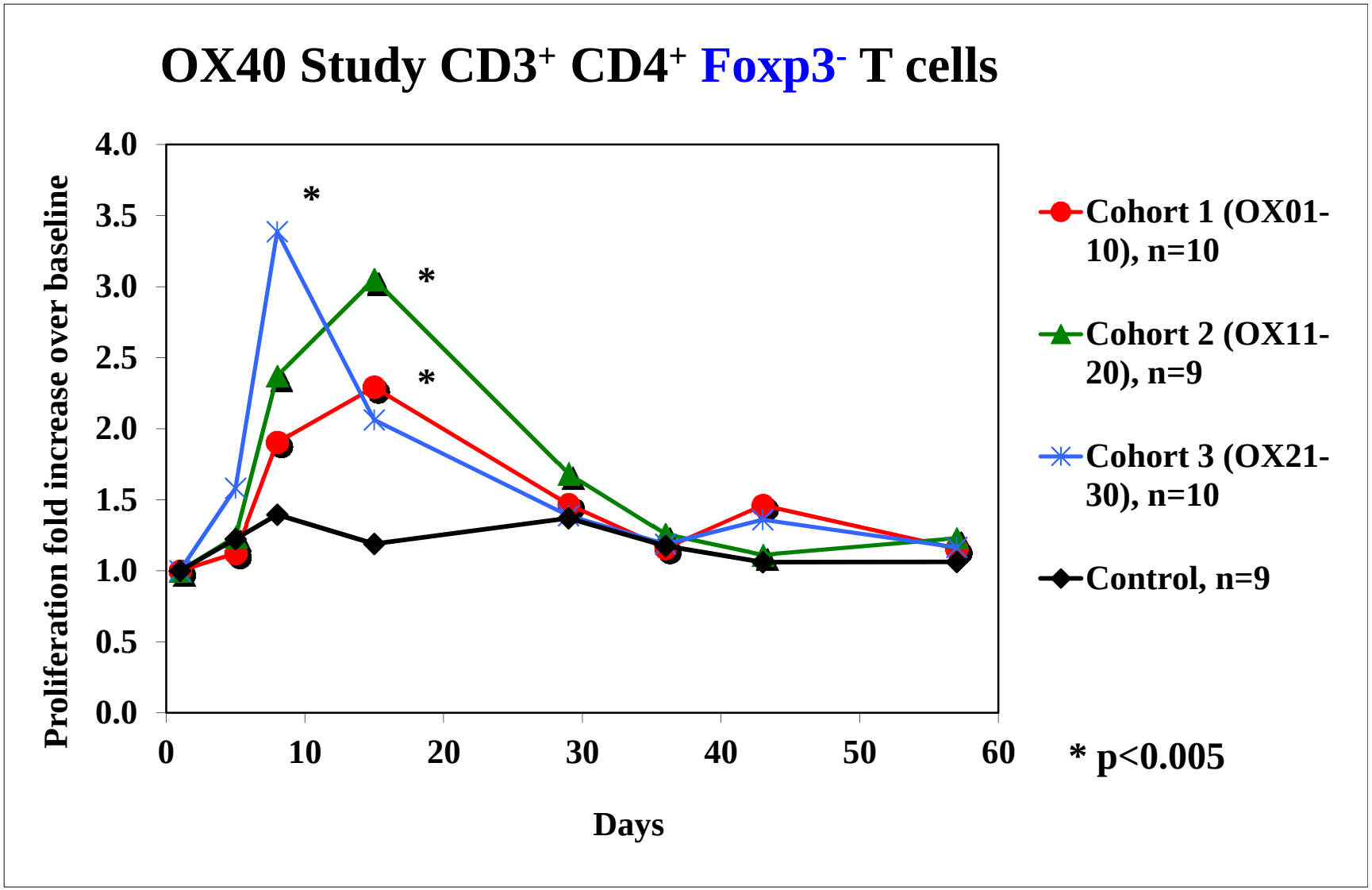
J Immunol, 2002, 168:29.
J Exp Med, 2004, 200:1299.
J Clin Invest, 2006, 116:1514.

Patient #14

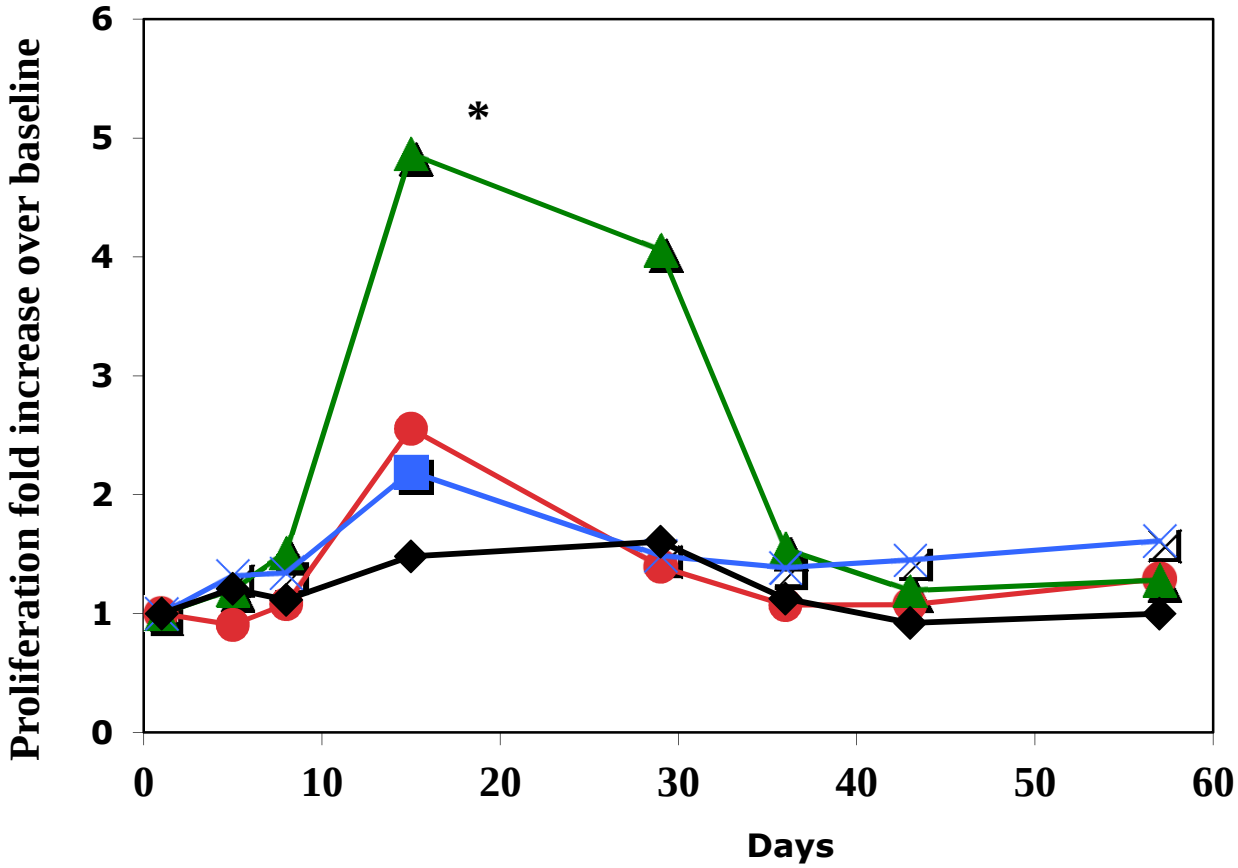
$CD8^+CD95^+$ T cell




OX40 Study CD3+ CD4+ Foxp3+ T cells
Proliferation fold increase over baseline
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
Days
Cohort 1 (OX01-10), n=10
Cohort 2 (OX11-20), n=9
Cohort 3 (OX21-30), n=10
Control, n=9

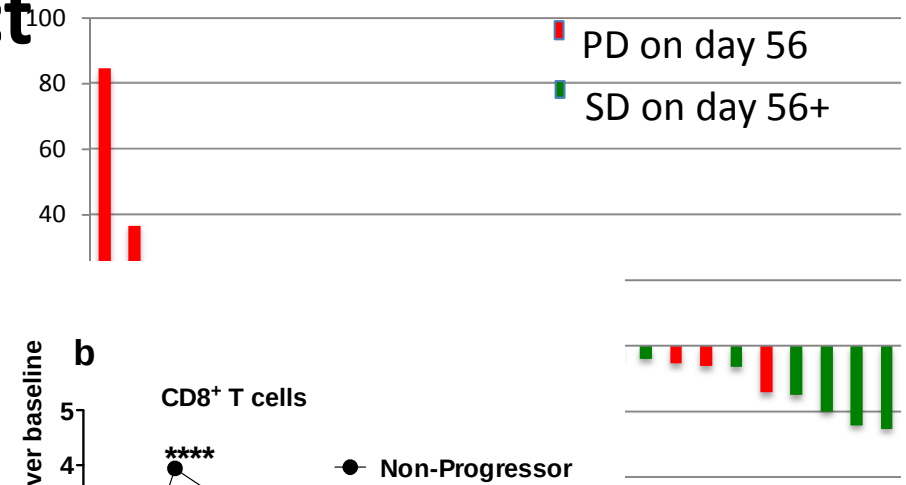

OX40 Study CD3+ CD4+ Foxp3- T cells
Proliferation fold increase over baseline
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
Days
*
*
*
Cohort 1 (OX01-10), n=10
Cohort 2 (OX11-20), n=9
Cohort 3 (OX21-30), n=10
Control, n=9
* p<0.005

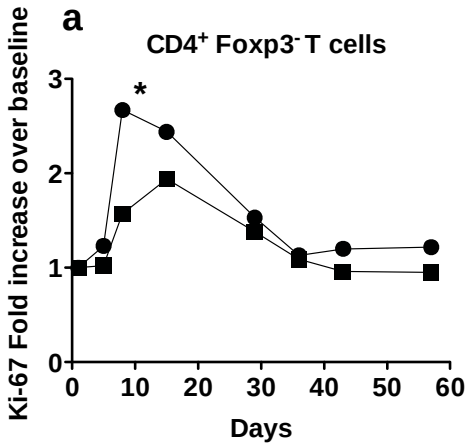
$CD3^+$ $CD8^+$ T cells

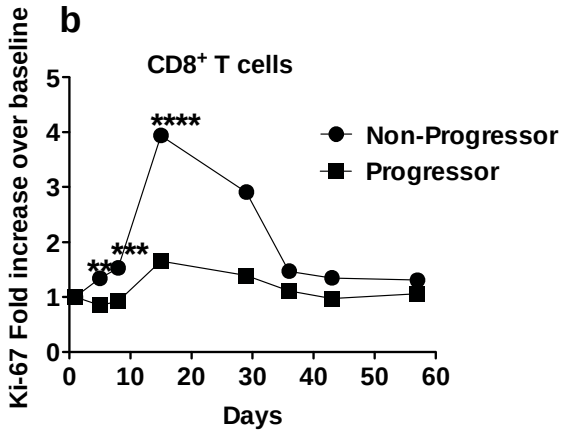


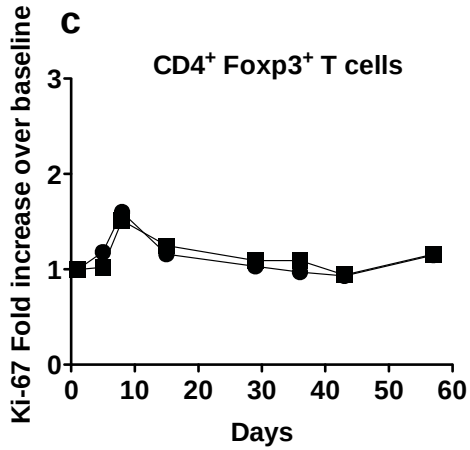
* P < 0.05

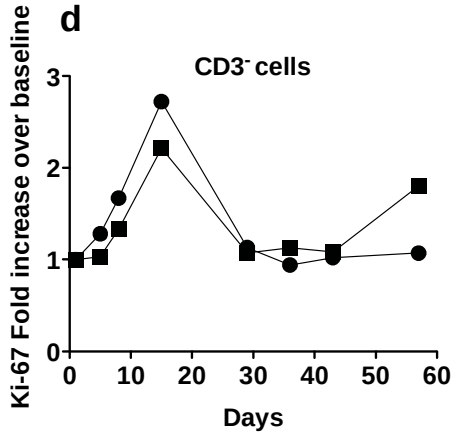
Do increases in Ki-67 predict clinical outcome?





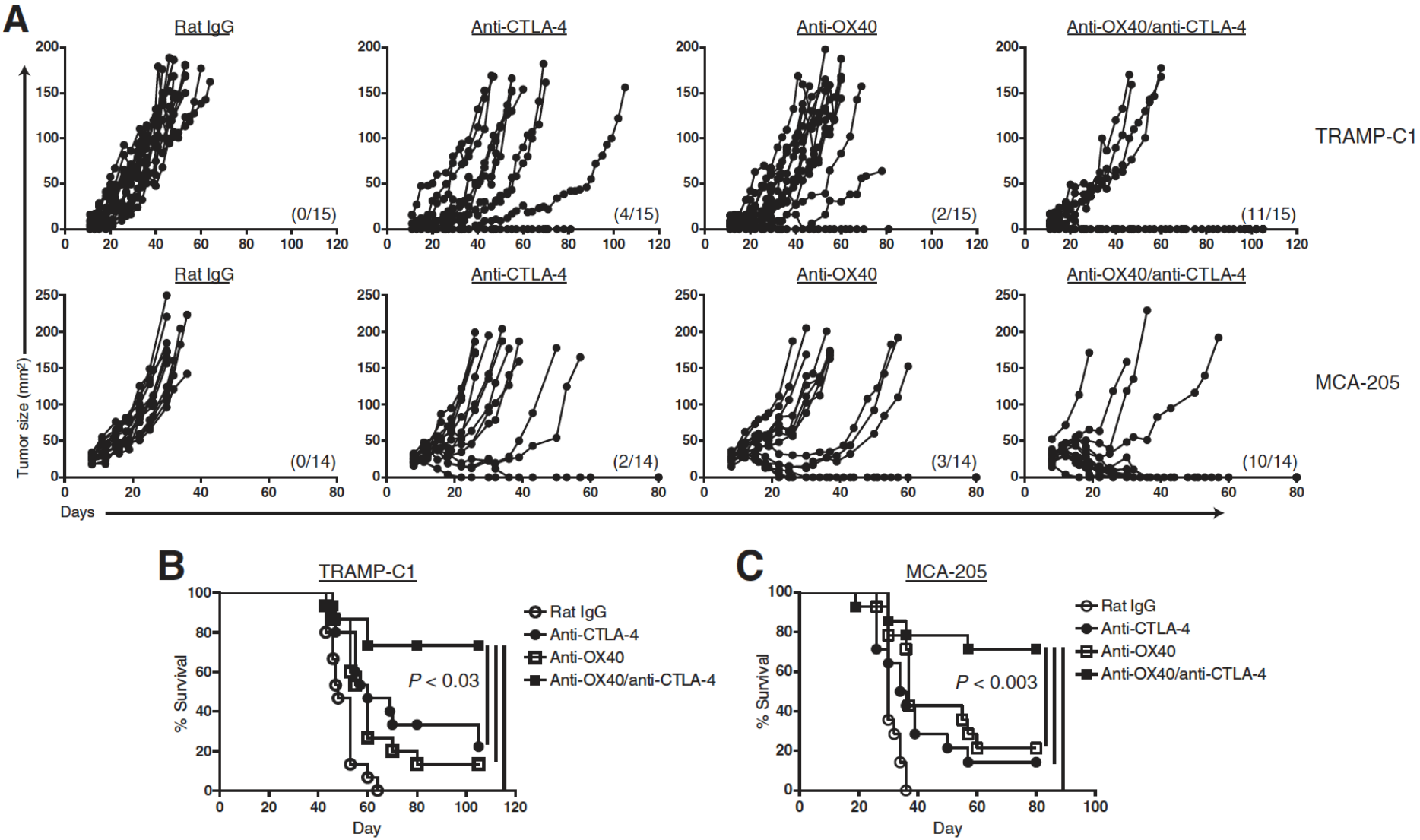






Combination Immunotherapy

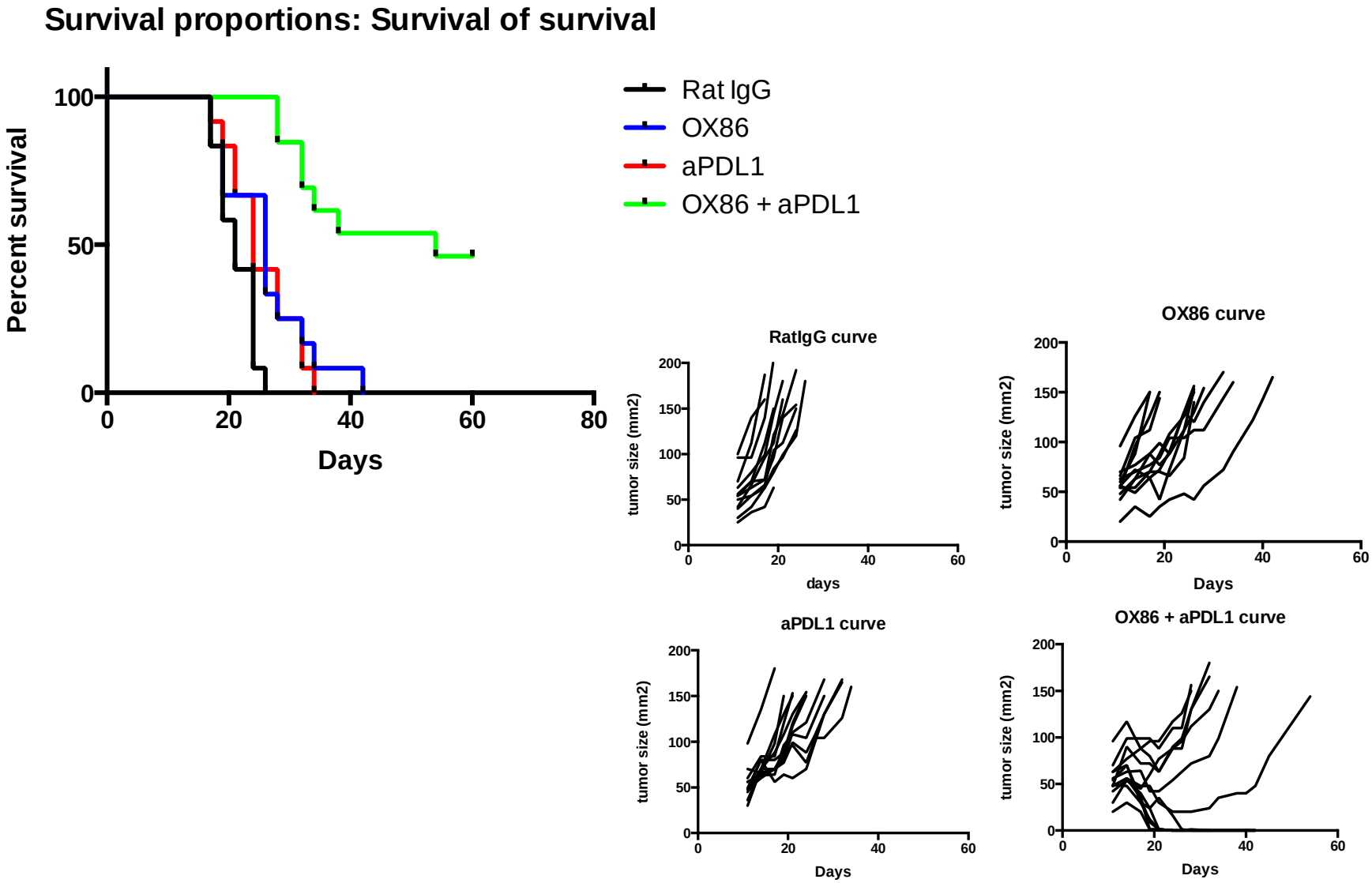
Checkpoint Blockade with TNF-R Agonists
anti-OX40 and anti-CTLA-4



Redmond, W. et al., Cancer Immunology Research, 2013, 2(2):1

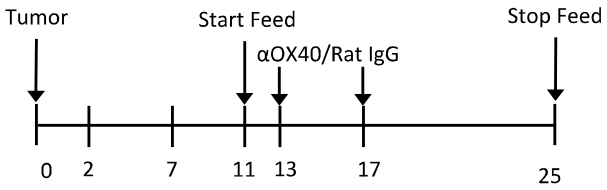
Anti-OX40/PDL1 Combo in MCA205 Tumor Model

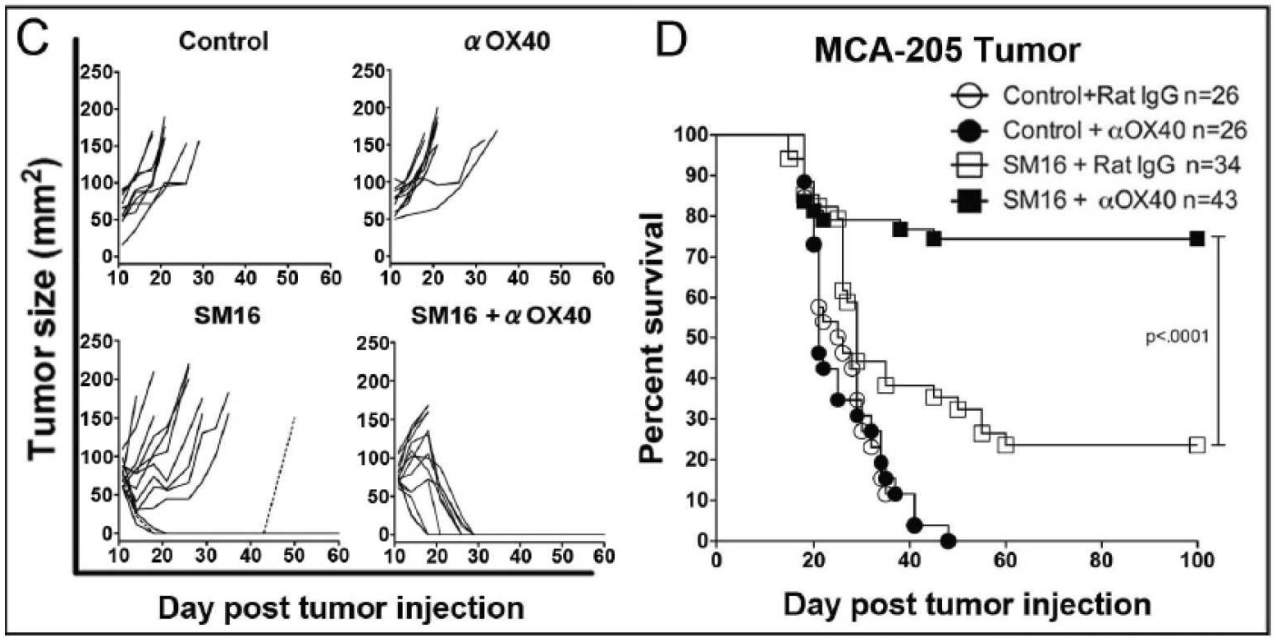
α-PDL1 (clone 10F9-G2) injections (200ug) on day 11, 14, 17 and 20.
α-OX40 or RatIgG injections (250ug) on day 11 and 15

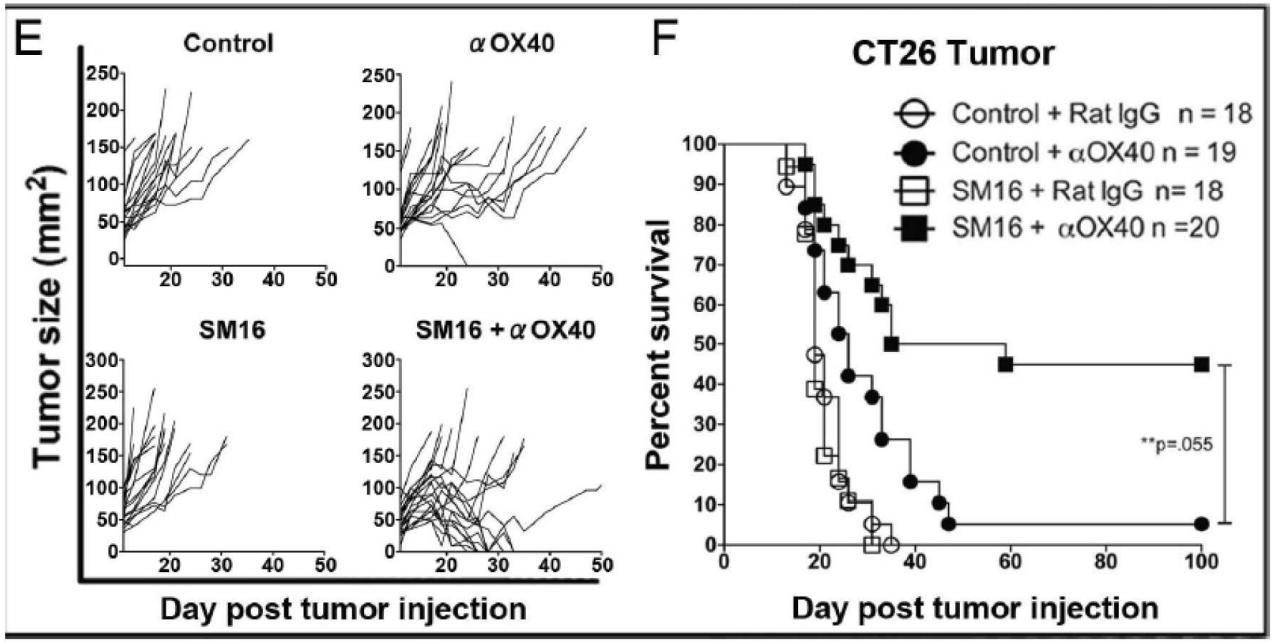


TNF-R Agonist with Cytokine Blockade

Anti-OX40 and TGF β-receptor inhibitor (SM16)







Providence Cancer Center
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Patients

Healthy volunteers

Patient Coordinators