Anti-CD40 Agonist Antibody-

The Ideal Combination Partner for Cancer Immunotherapy

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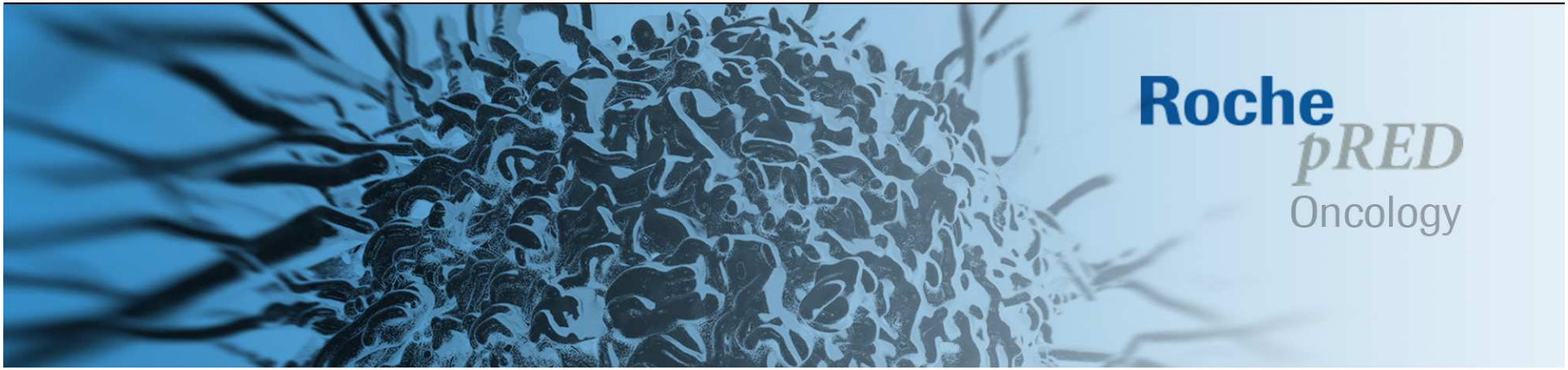
Roche Pharma Research and Early Development, Oncology

November 9, 2014

SITC- Hot Topic Symposium, Accelerating Tumor Immunity with Agonist Antibodies



Presenter Disclosure Information

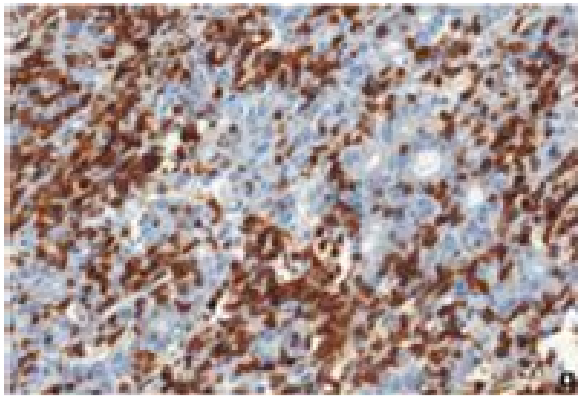
Hy Levitsky

The following relationships exist related to this presentation:

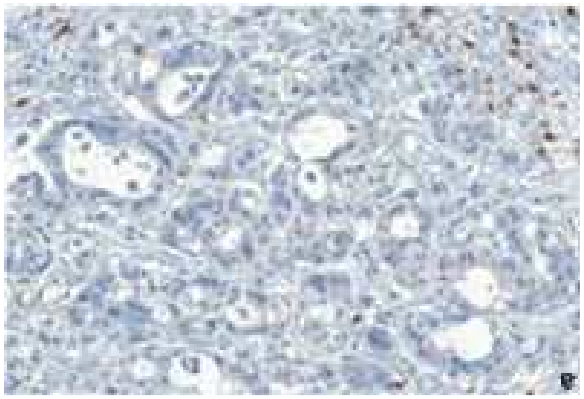
Hoffmann La Roche, Inc., Salary and Equity, Employee

Rationale for immune activating agonist antibodies

Inflamed



Non-inflamed



Tumor phenotype by T cell staining

PA{3

20-30% patients

- T cells present in tumor
- Chemokines present (attract leukocytes)
- Other immuno-regulatory factors (PD-L1, IDO, FoxP3)

Often responsive to single agent immunotherapies

70-80% patients

- Lack lymphocytic infiltrates

Rarely responsive to single agent

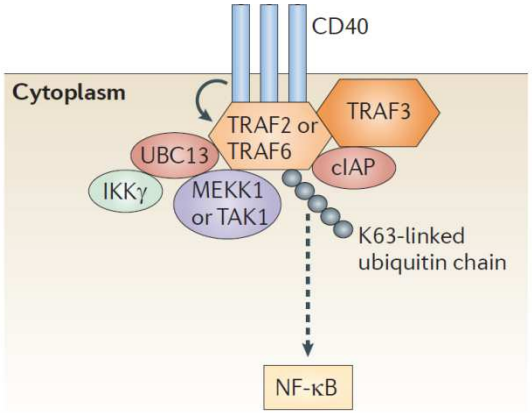
Slide 3

PA{3 any data on this?

Passioukov, Alexandre {POTM~Schlieren}, 10/2/2014

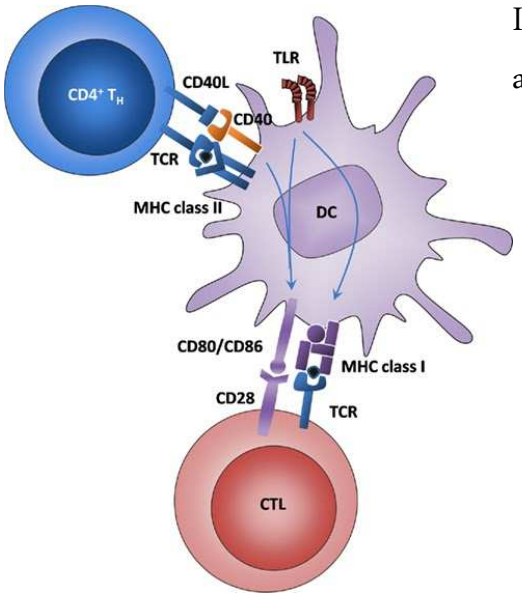
CD40 biology

Expression pattern and biological function



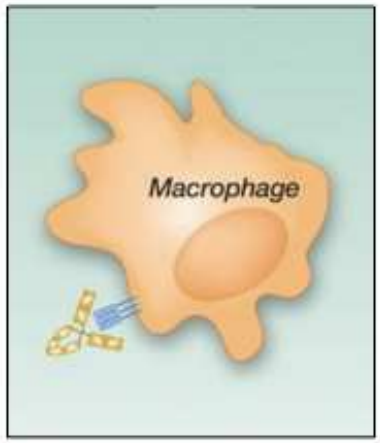
Member of the TNF-receptor superfamily

Expressed on APC (B-cells, macrophages, dendritic cells), endothelial cells, platelets, and on many tumors



Interacts with CD40L (CD154) on activated CD4 T-cells, to activate APC and prime CD8 T-cells

Augments macrophage tumoricidal activity including antibody dependent cellular phagocytosis (ADCP)



Häcker, Nat Rev Imm, 2011, Bishop, Nat Rev Imm, 2004

nature medicine
NATURE MEDICINE • VOLUME 5 • NUMBER 7 • JULY 1999

ARTICLES

Conversion of tumor-specific CD4+ T-cell tolerance to T-cell priming through *in vivo* ligation of CD40

EDUARDO M. SOTOMAYOR[1], IVAN BORRELLO[1], EREV TUBB[1], FRÉDÉRIQUE-MARIE RATTIS[1], HAROLD BIEN[1], ZHENGBIN LU[1], STEVE FEIN[1], STEPHEN SCHOENBERGER[2] & HYAM I. LEVITSKY[1]

ARTICLES

CD40 activation *in vivo* overcomes peptide-induced peripheral cytotoxic T-lymphocyte tolerance and augments anti-tumor vaccine efficacy

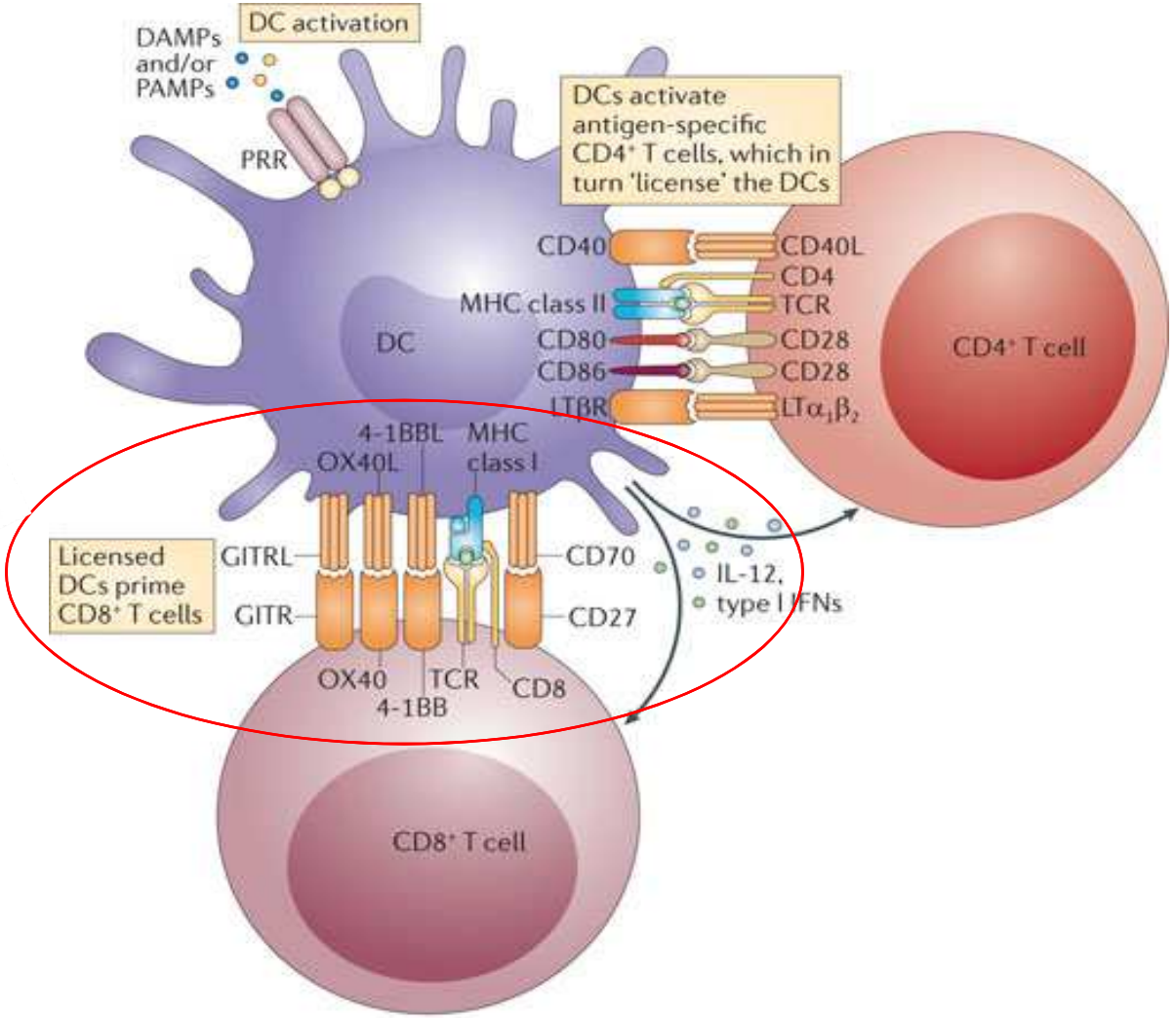
LINDA DIEHL[1], ANNEMIEKE TH. DEN BOER[1], STEPHEN P. SCHOENBERGER[2], ELLEN I.H. VAN DER VOORT[1], TON N.M. SCHUMACHER[3], CORNELIS J.M. MELIEF[1], RIENK OFFRINGA[1] & RENE E. M. TOES[1,4]

ARTICLES

CD40 antibody evokes a cytotoxic T-cell response that eradicates lymphoma and bypasses T-cell help

RUTH R. FRENCH, H.T. CLAUDE CHAN, ALISON L. TUTT & MARTIN J. GLENNIE

CD40 agonistic antibody promotes T cell priming via APC activation

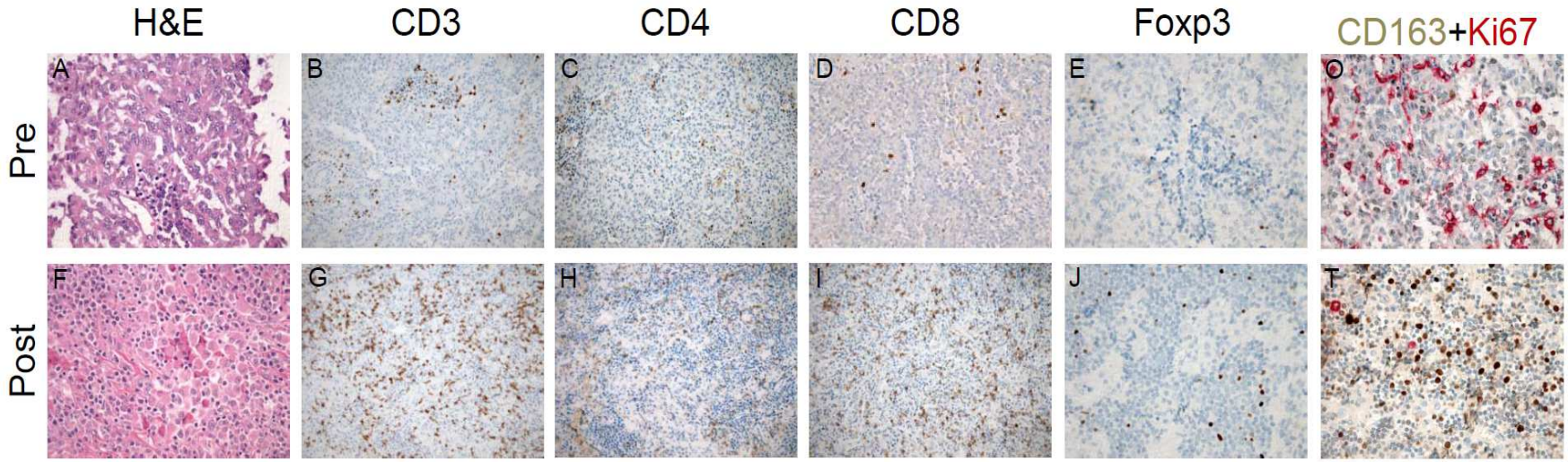


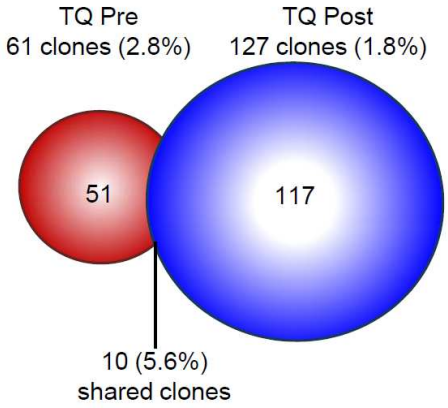
deLuca and Gommerman, 2012

Nature Reviews | Immunology

Long-lasting response to single agent αCD40 agonist

Dramatic change in tumor cellular infiltrate





TQ = top quartile clones, i.e. most frequent clones that make up 25% of the repertoire

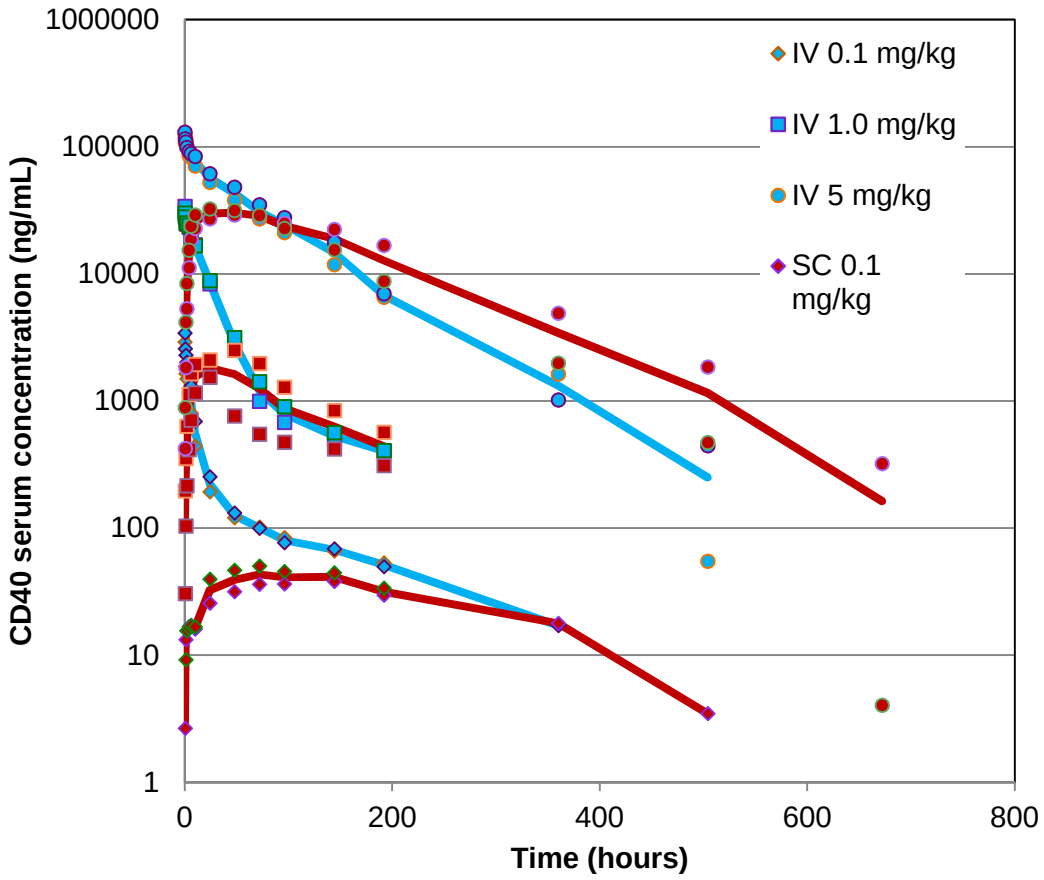
Bajor et al, Cancer Immunology Research, 2014

α-CD40 Agonist mAb (RO7009789)

- Produced by Abgenix (1997) and licensed to Pfizer
- Modest activity as s.a. and in combination with chemo, and suggested synergy in combination with tremelimumab (Pfizer, 2004-2010)
- Licensed by Roche for use in combination immunotherapy (2013)
- Fully agonistic, human IgG2 (low/no ADCC activity)
- Does not require FcR cross-linking (in contrast to murine surrogates)
- High affinity (Kd 0.4nM, 200-fold higher than murine surrogates)

Single dose PK profiles in cyno

Lower Cmax in s.c. vs i.v.

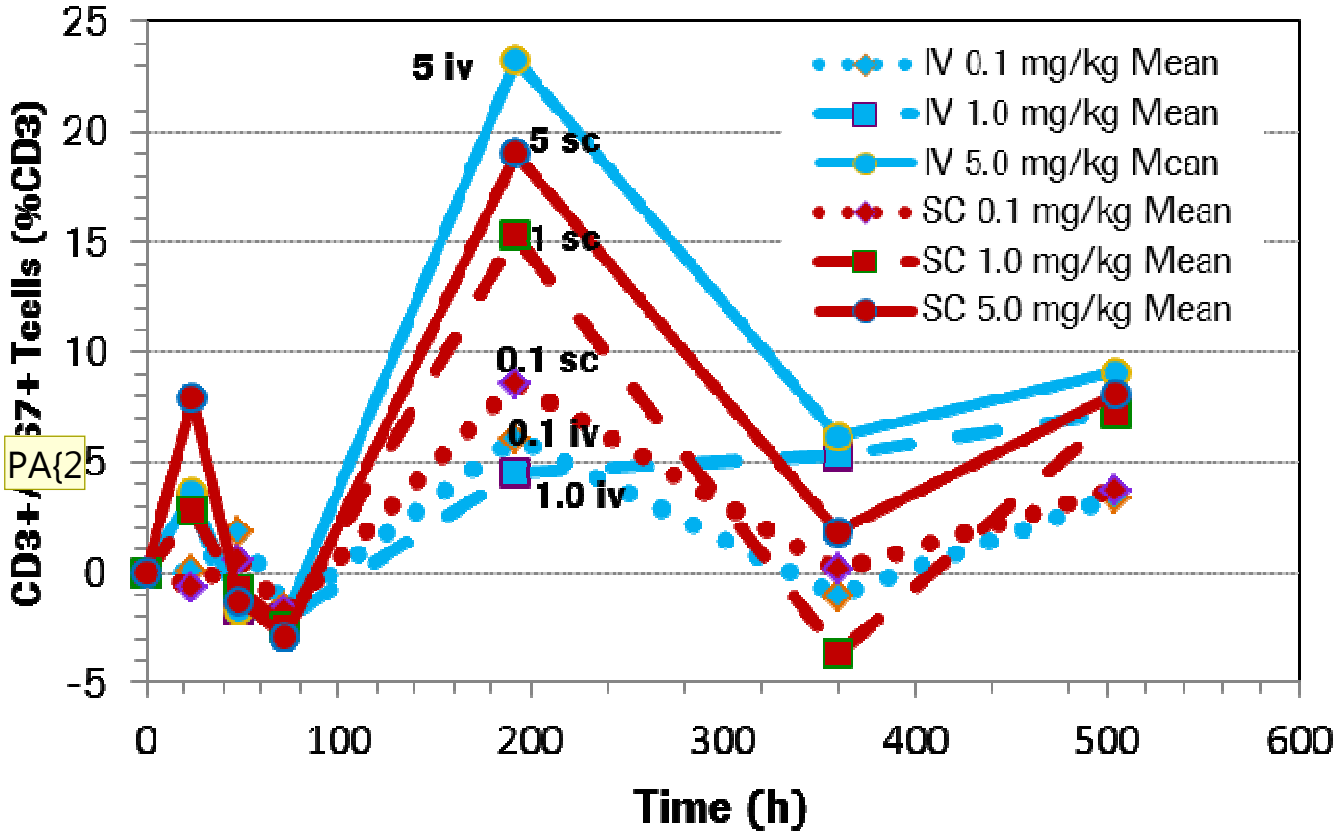


Non linear bioavailability:

- ~100% bioavailability at high dose
- ~30% bioavailability at mid and low dose suggesting a *saturable first-pass effect*

Immuno PD profile in single dose PK Cyno

Similar PD effects i.v. & s.c.



Dose dependent induction of T cell proliferation on day 8

Slide 10

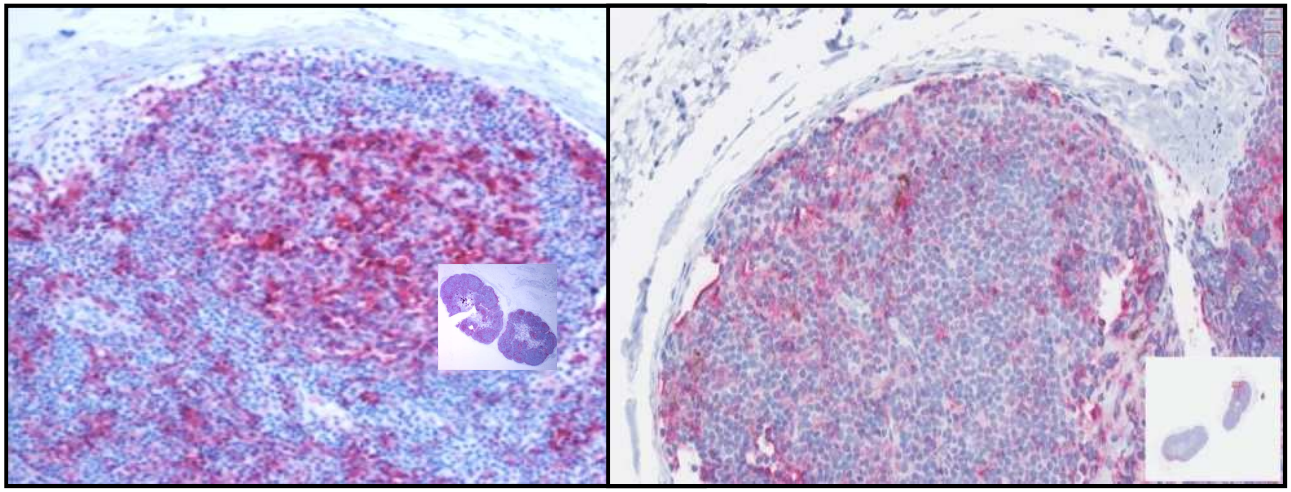
PA{2 I'd rather suggest 'increase of proliferating T cells in circulation'

Passioukov, Alexandre {POTM~Schlieren}, 10/2/2014

CD40 NHP study – Lymph node IHC data

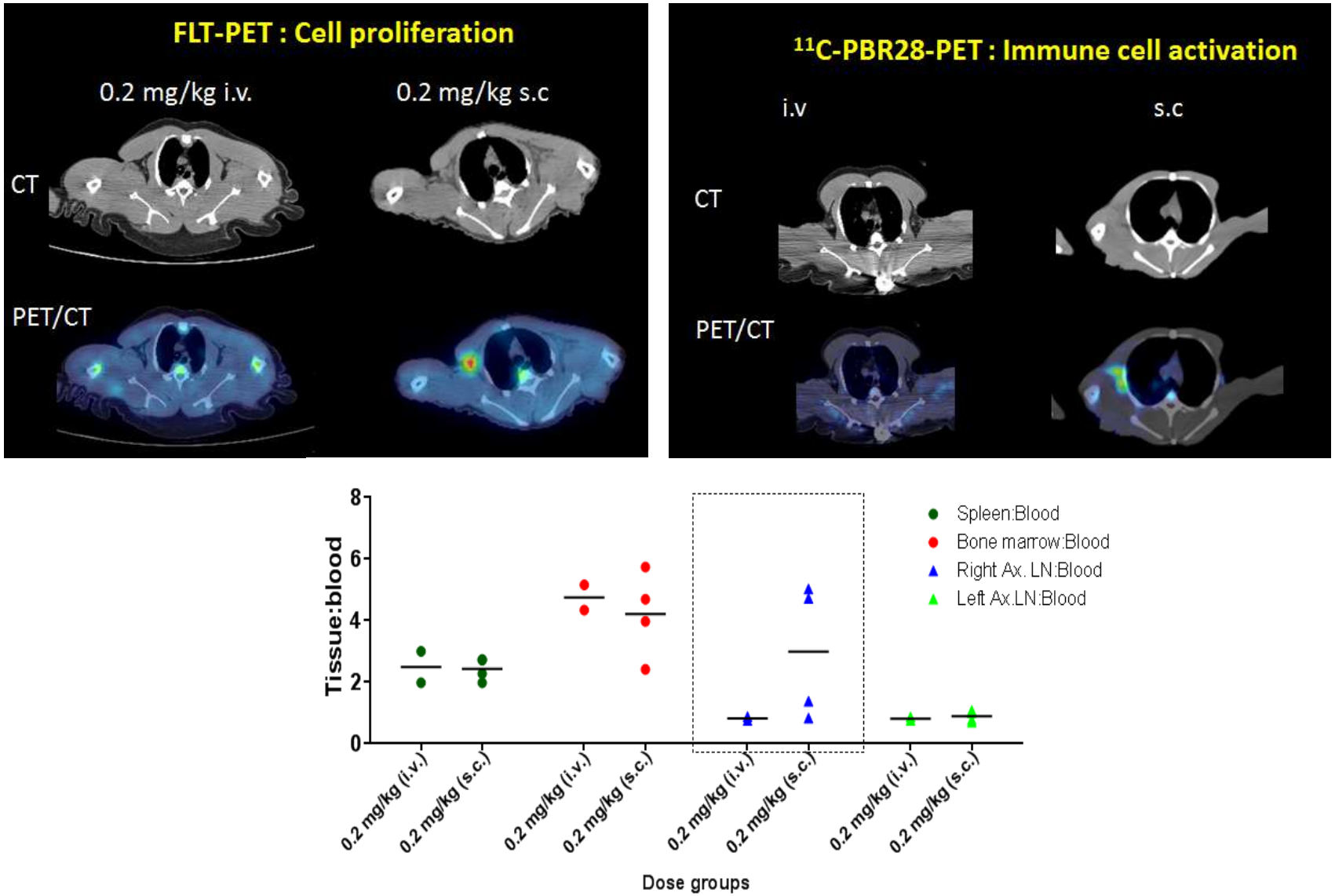
Increase of CD11c+ DCs after single dose CD40 imAb

Lymph node CD11c staining (day 8 after s.c. 0.25mg/kg *vs.* control)



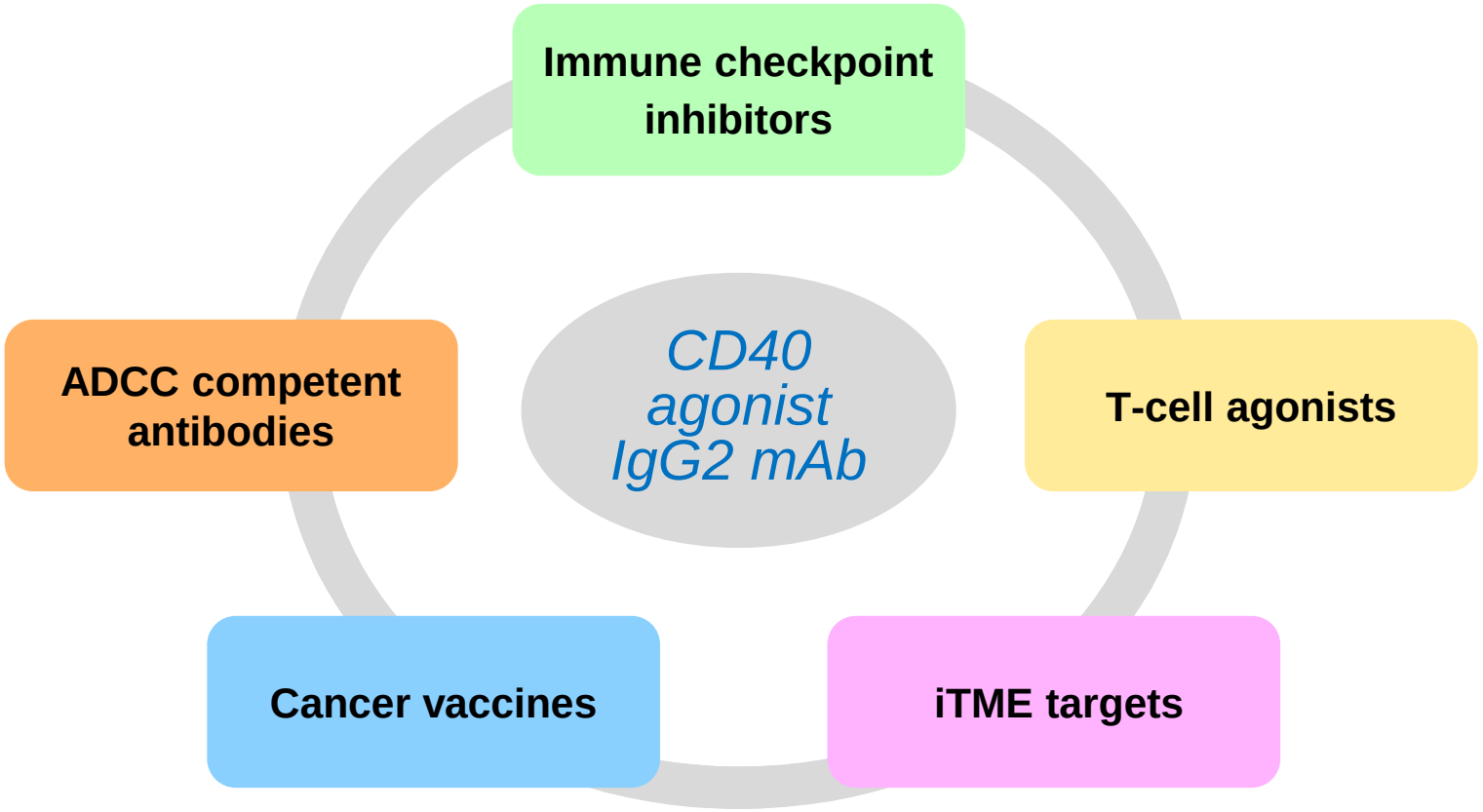
CD40 Saline

PET-based Detection of CD40 Mediated Immune Cell Activation



Activating Antigen Presenting cells to Jumpstart Adaptive Immunity

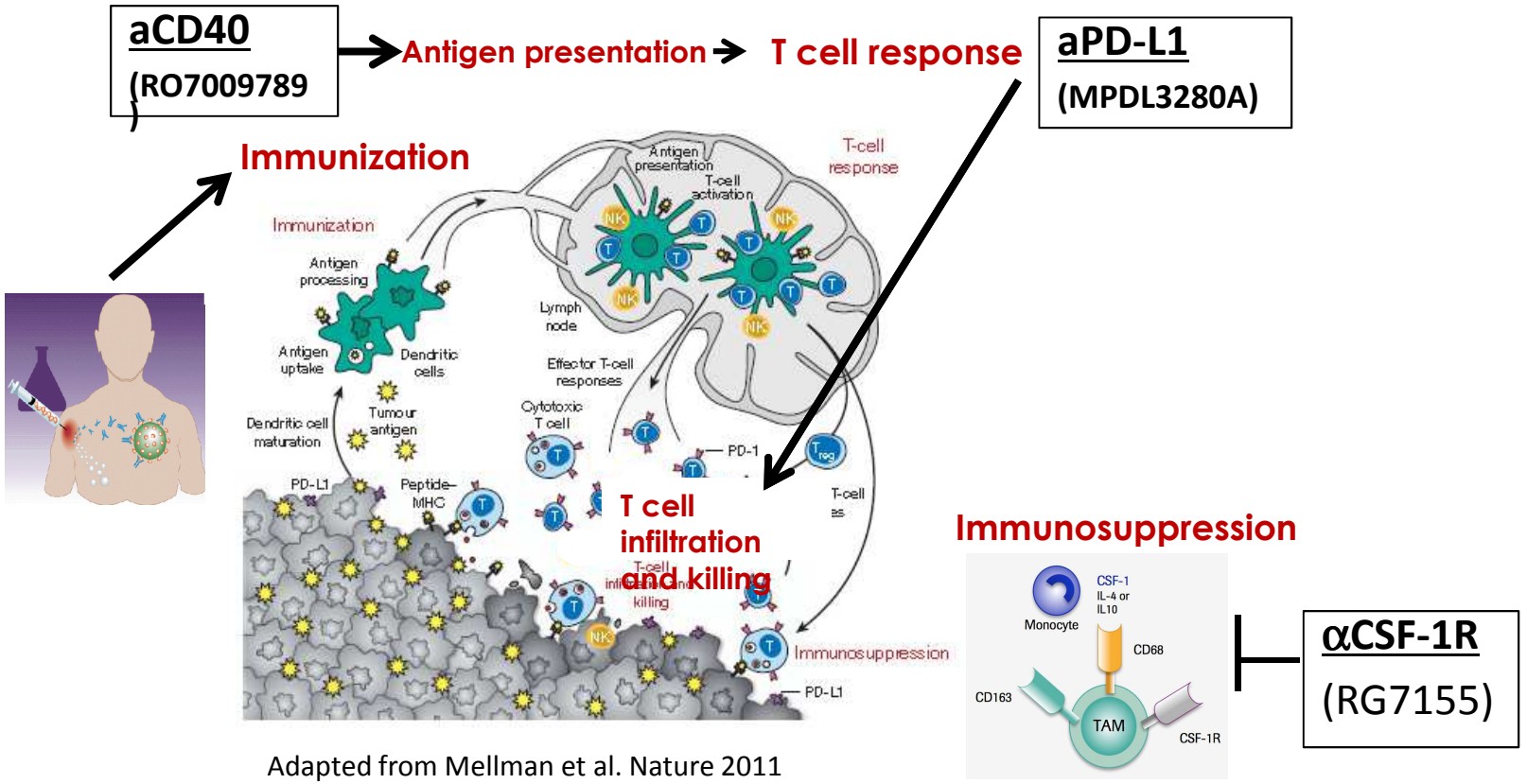
Anti-CD40 agonistic IgG2 mAb



Multiple immune doublet opportunities

Biological rationale for CD40 combination therapy

- ***α-CSF1R*** *relieves local immunosuppression which hampers T cell responses induced by CD40 mediated APC activation*
- ***α-PD-L1*** *blocks interferon dependent adaptive resistance in response to T cell effector response*
- ***Vaccination-*** *α-CD40 licenses antigen presenting cells to promote T cell priming in response to vaccination*



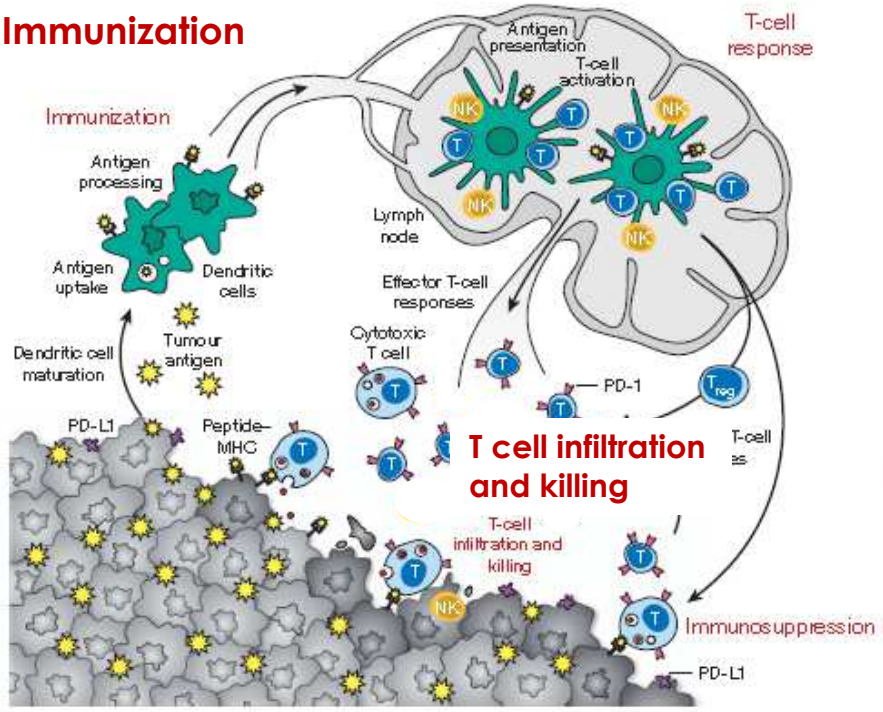
Adapted from Mellman et al. Nature 2011

Biological rationale for CD40 combination therapy

- ***α-CSF1R*** *relieves local immunosuppression which hampers T cell responses induced by CD40 mediated APC activation*

aCD40
(RO7009789) → **Antigen presentation** → **T cell response**

Immunization

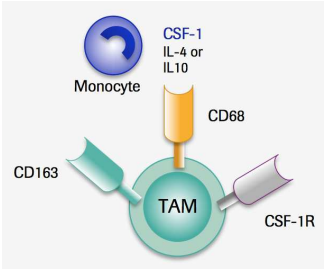


Adapted from Mellman et al. Nature 2011

α-CSF-1R (RG7155) depletes suppressive macrophages which:

- secrete suppressive cytokines e.g. IL-10
- affect T cell metabolism
  - reduce T cell proliferation
  - impair T cell signaling

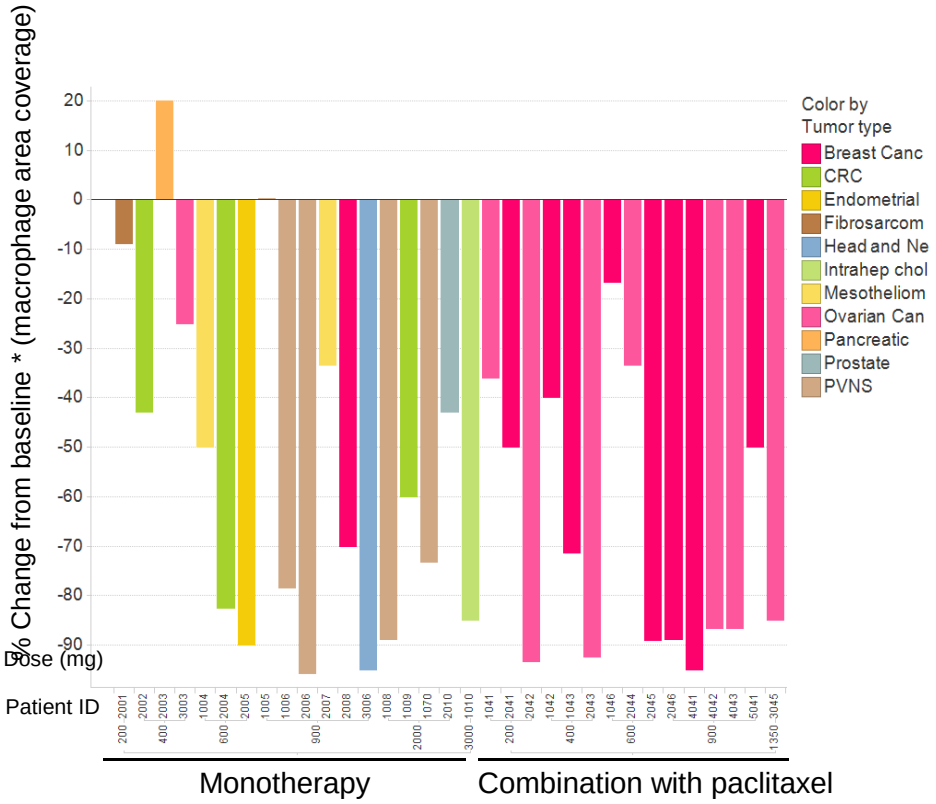
Immunosuppression

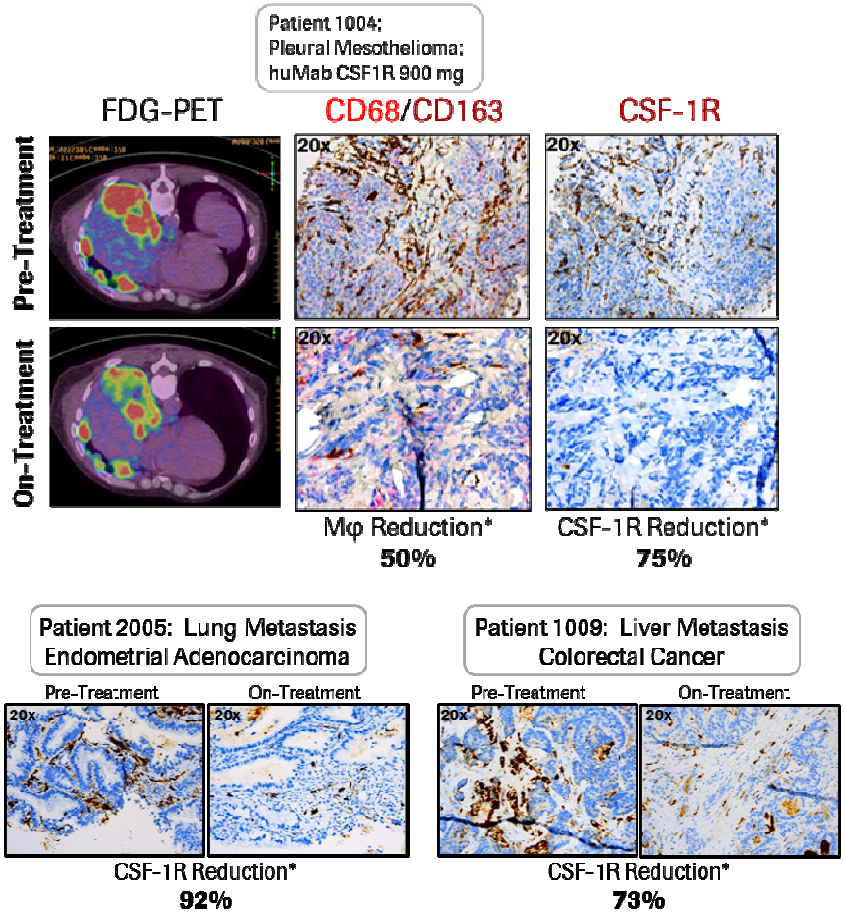


αCSF-1R
(RG7155)

Anti-CSF1R mAb RG7155 Proof-of-Mechanism: Phase 1 clinical trial

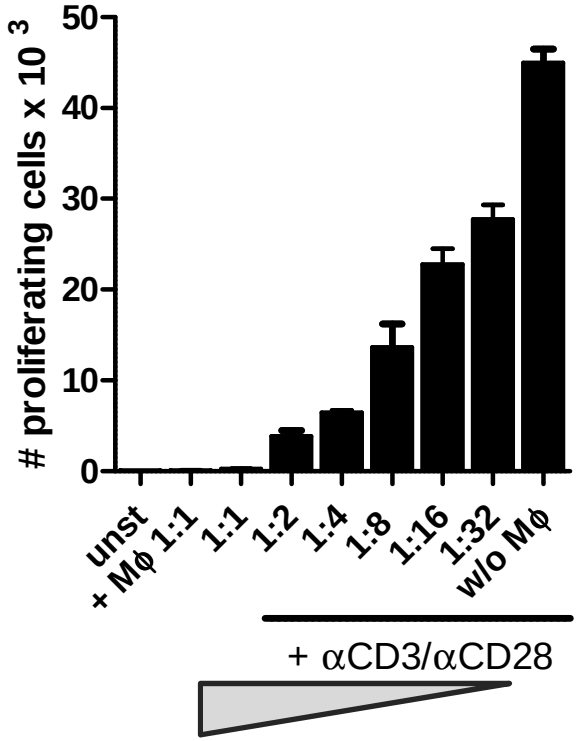
Significant Mφ reduction in various solid malignancies

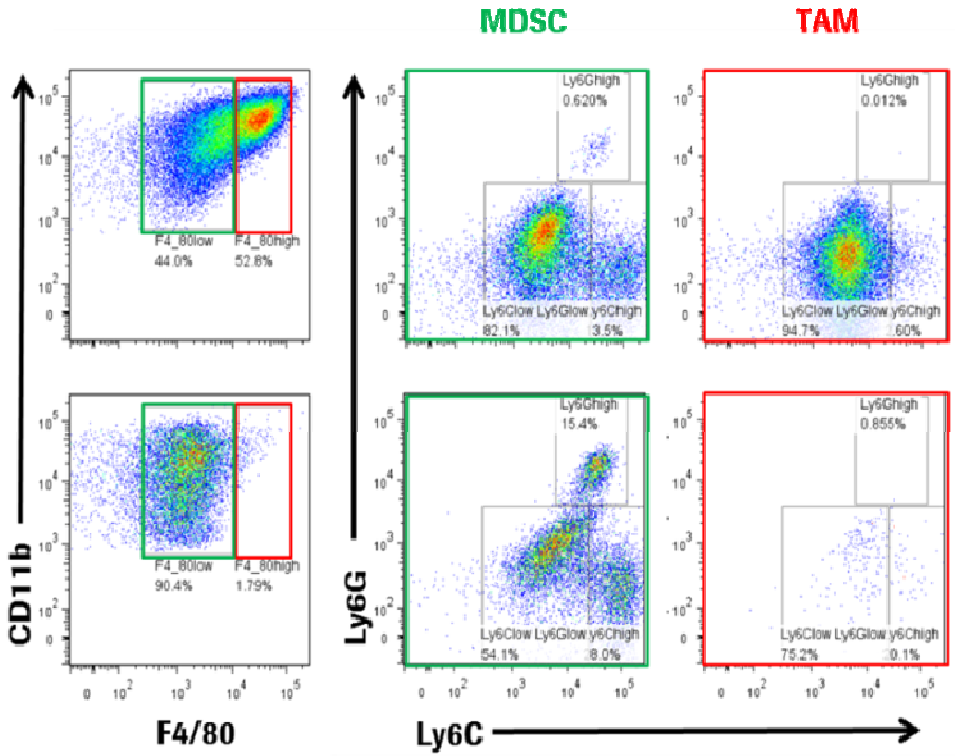




*pre- vs on-treatment tumor biopsies at 4 weeks, i.e. two cycles of treatment

TAMs are potent suppressors of T cell activation and are depleted by α-CSF-1R therapy





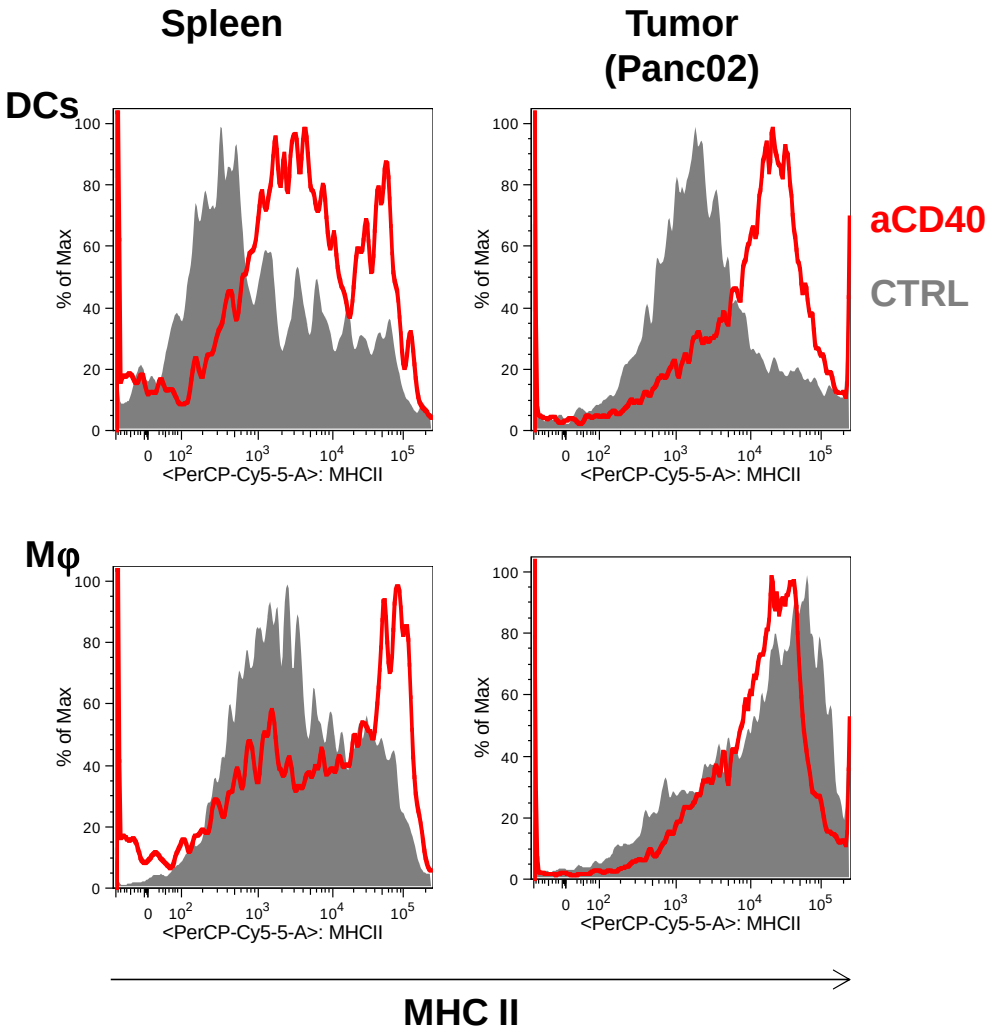
TAM suppression assay:
(sorted CD11b+Ly6G-Ly6Clo TAMs from PyMT tumor)

MC38 tumors:

- Efficient elimination of TAM by CSF-1R

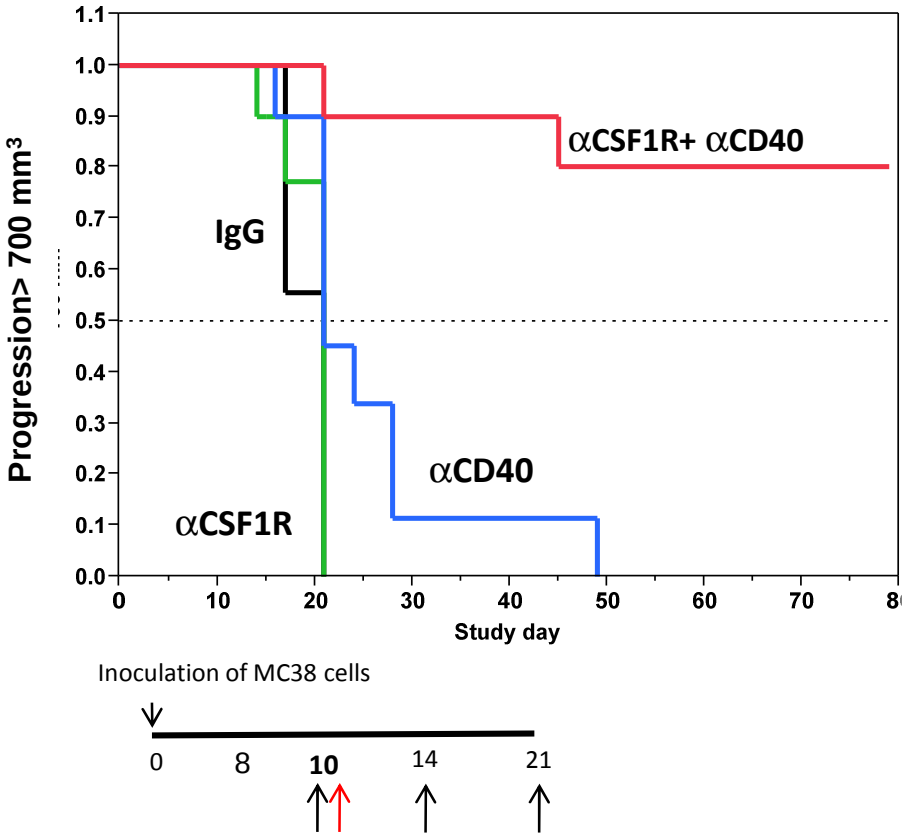
Data: B. Threm, Ries lab, Sabine Hoves Discovery Oncology Penzberg

αCD40 activates Dendritic Cells and Macrophages in Tumor Bearing Mice

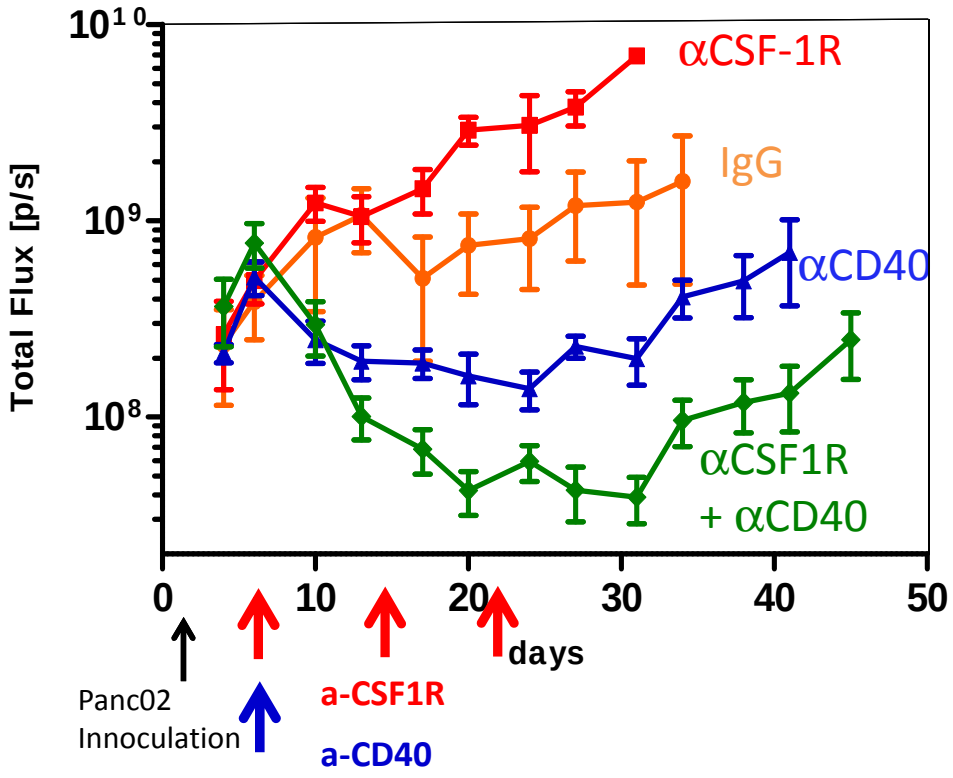


Evaluation of αCD40 + αCSF-1R in two syngeneic tumor models (MC38 SC and Panc02-fluc intra-pancreatic)

MC38 SC



Panc02 orthotopic

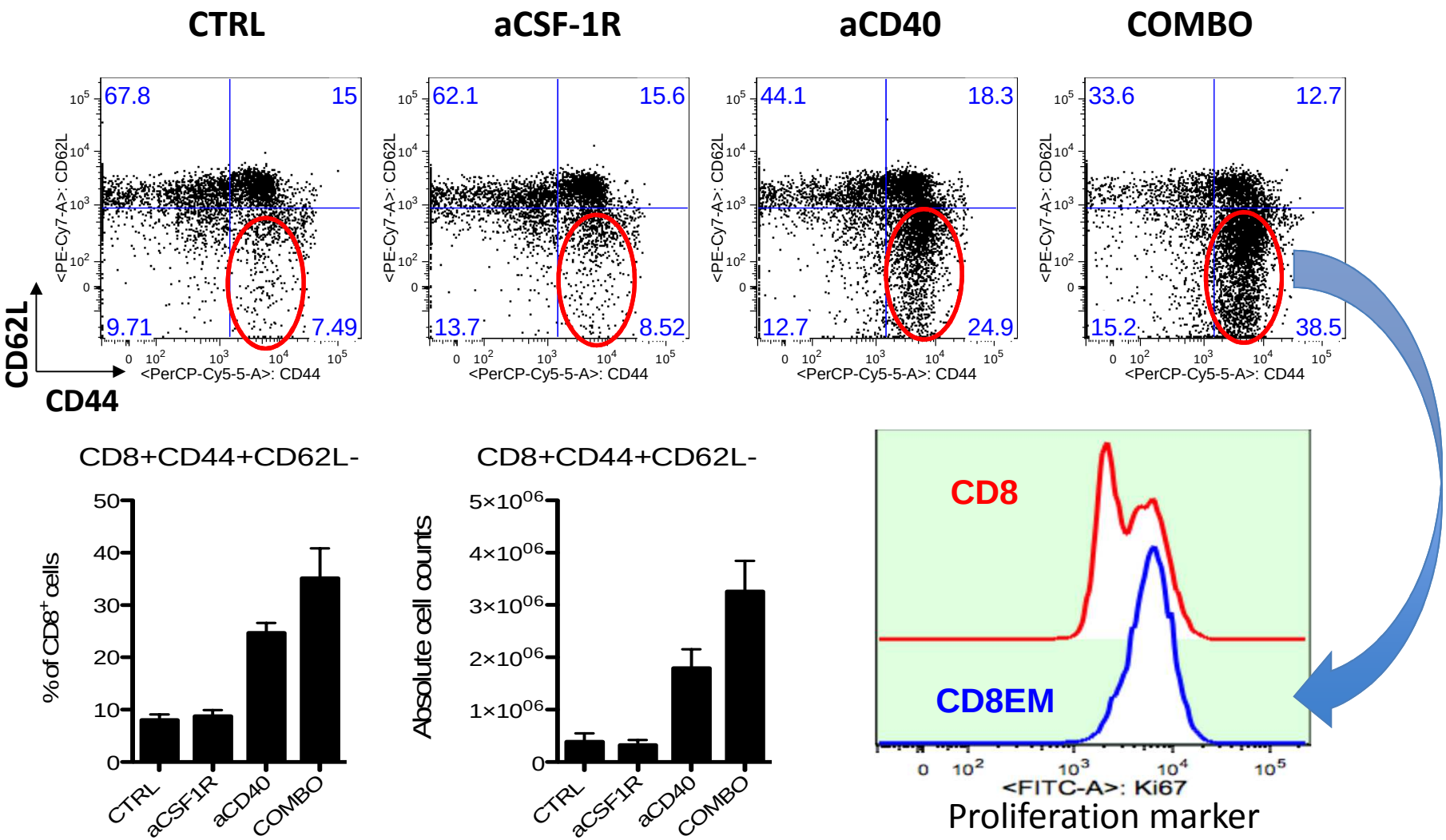


C. Wolter, K. Wartha, S. Hoves, C. Ries, Roche Innovation Center Penzberg

Marine Le Clech, Olivier Freytag, Christian Gerdes, Roche Innovation Center Zurich

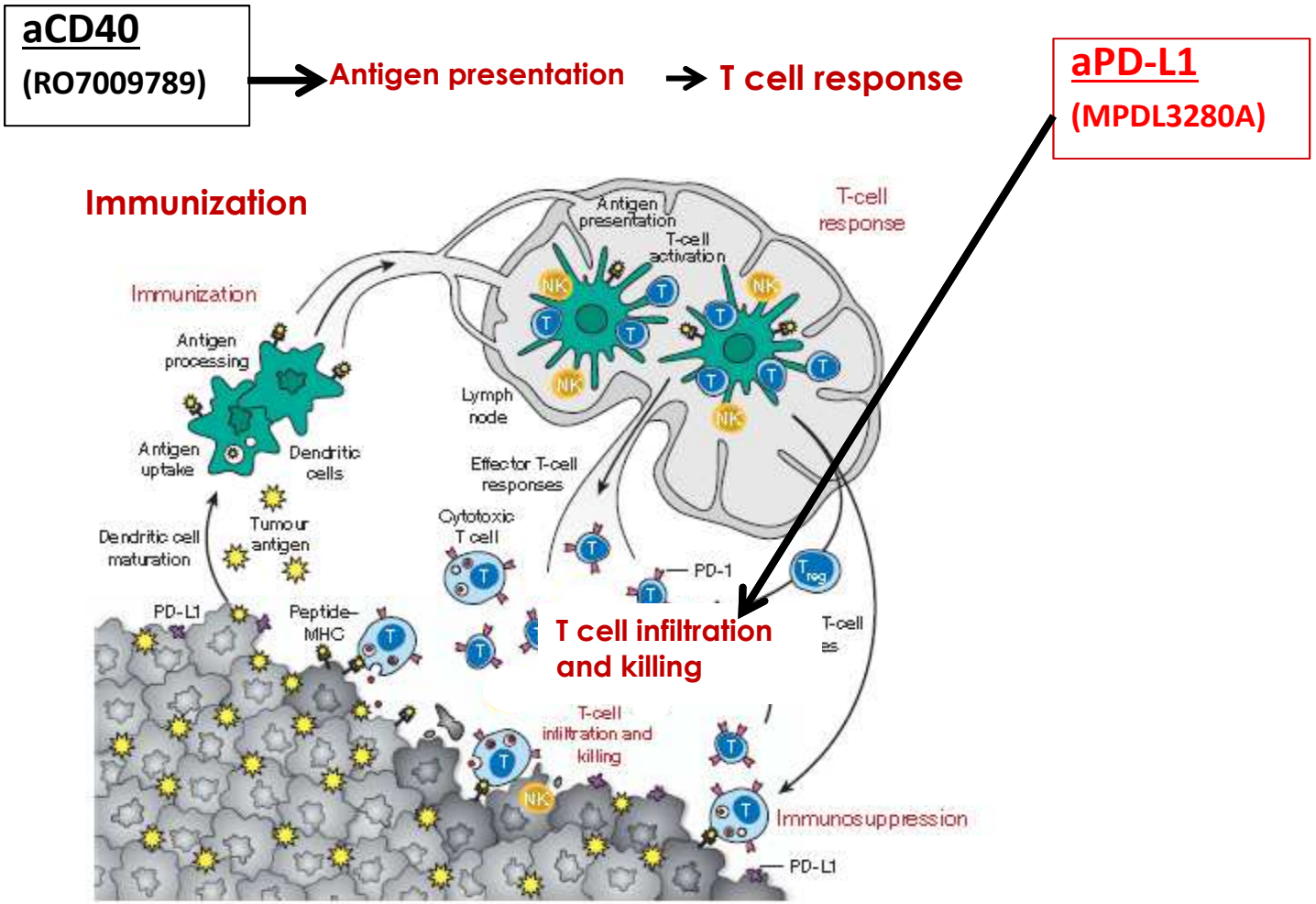
α-CD40 and α-CSF-1R synergize to expand effector memory CD8 T cells

(gaited on CD8+ splenocytes from Panc02 bearing mice)



Biological rationale for CD40 combination therapy

- ***α-PD-L1*** *blocks interferon dependent adaptive resistance in response to T cell effector response*



Adapted from Mellman et al. Nature 2011

Overcoming Adaptive Resistance with PD-L1 Blockade

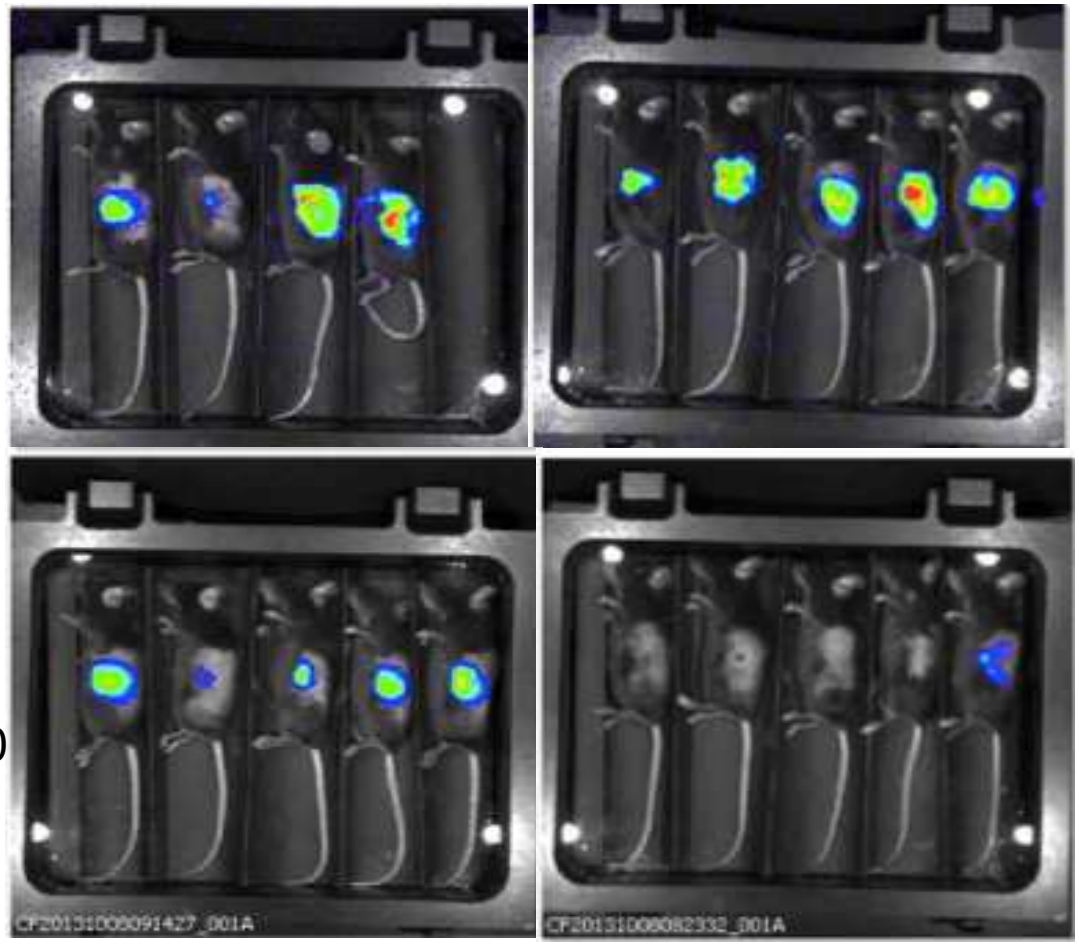
αCD40 Converts an αPD-L1 Unresponsive Tumor into an αPD-L1 Responsive Tumor:

Vehicle

Anti-PDL1

Anti-CD40

Anti-PDL1 +
Anti-CD40

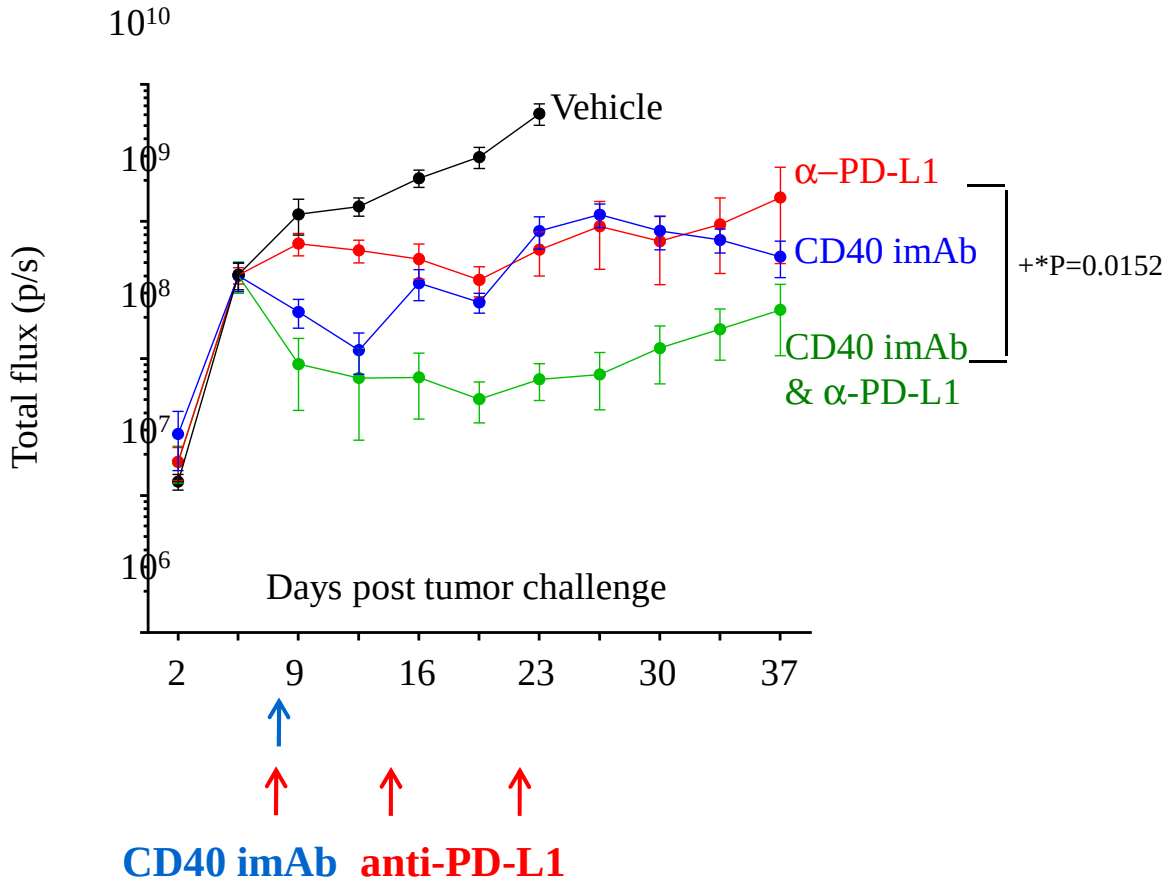


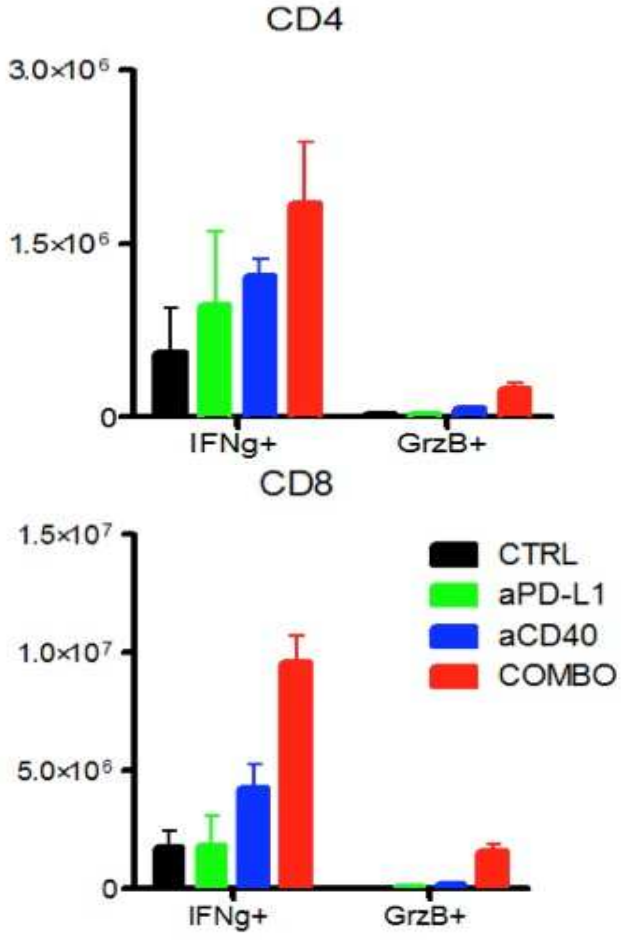
Orthotopic (intrapancreatic) tumor growth inhibition of Panc02-luciferase

Synergy of anti-CD40 + anti-PDL1

Strong tumor growth inhibition, and induction of effector T-cells

PancO2/Fluc orthotopic model





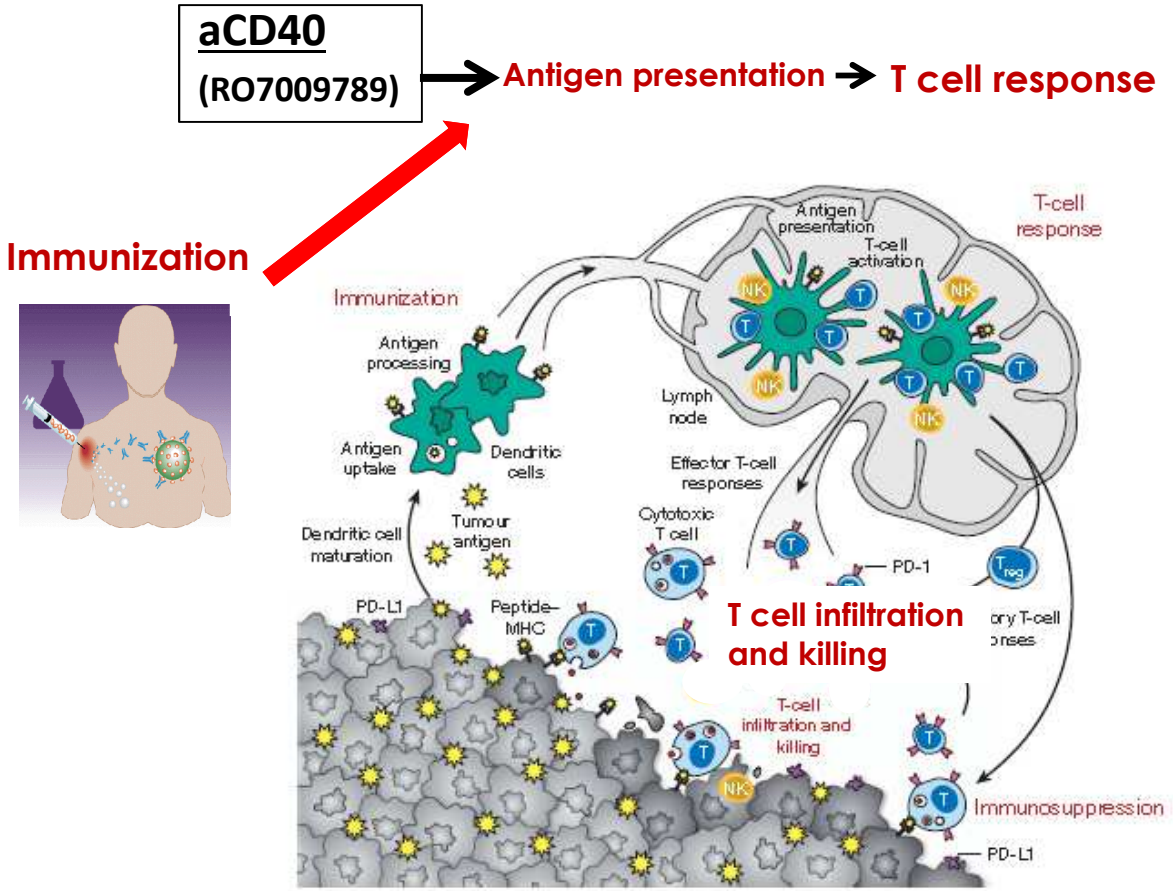
Day 21

Christine Fischer, Marine Le Clech, Esther Bommer

Wei Xu, Karoline Rommel, Marine Le Clech, Esther Bommer

Biological rationale for CD40 combination therapy

- ***α-CD40 licenses antigen presenting cells to promote T cell priming in response to vaccination***

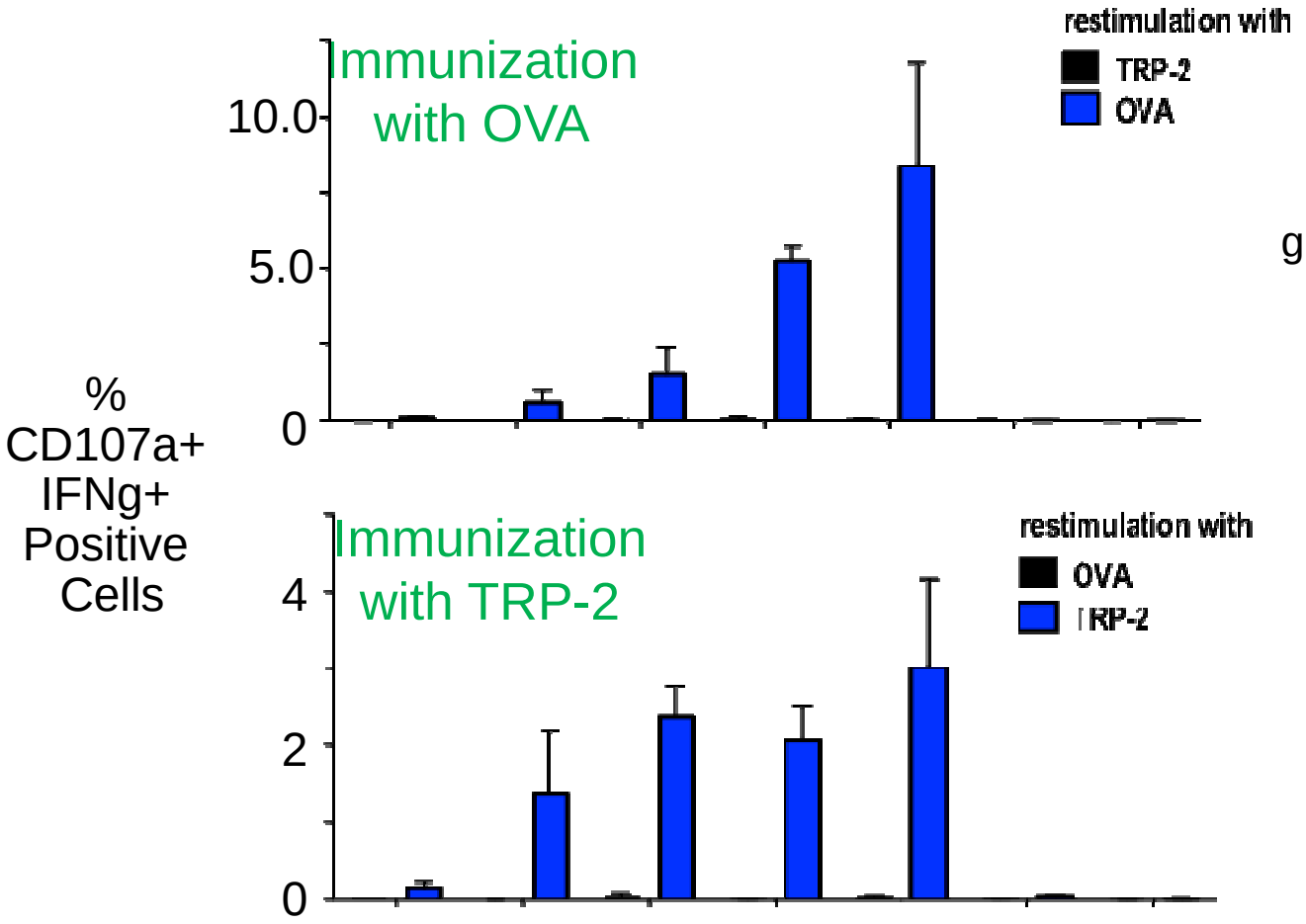


Adapted from Mellman et al. Nature 2011

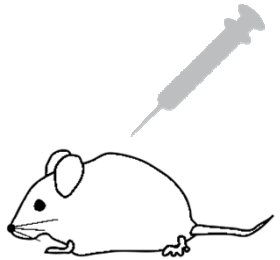
TC{3

Impact of anti-CD40 on immune response to vaccine

Anti-CD40 improves T cell response against peptide + poly ICLC vaccine



OVA or TRP-2/ pICLC @d0 + diff.doses of anti-CD40 @ d0 given subcutaneously



Read out @d7 In the spleen

Anti-CD40 (mg/kg)	0	0.05	0.25	1.25	6.25	1.25	0
pICLC (50 µg/mouse)	+	+	+	+	+	+	-
Peptide (100 µg/mouse)	+	+	+	+	+	-	-

Gated on live CD3+CD8+ cells (3 mice/group)

Slide 25

TC{3 from oRRC presentation

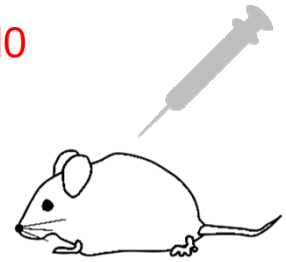
Trumpfheller, Christine {POHB~Schlieren}, 10/31/2014

TC{7

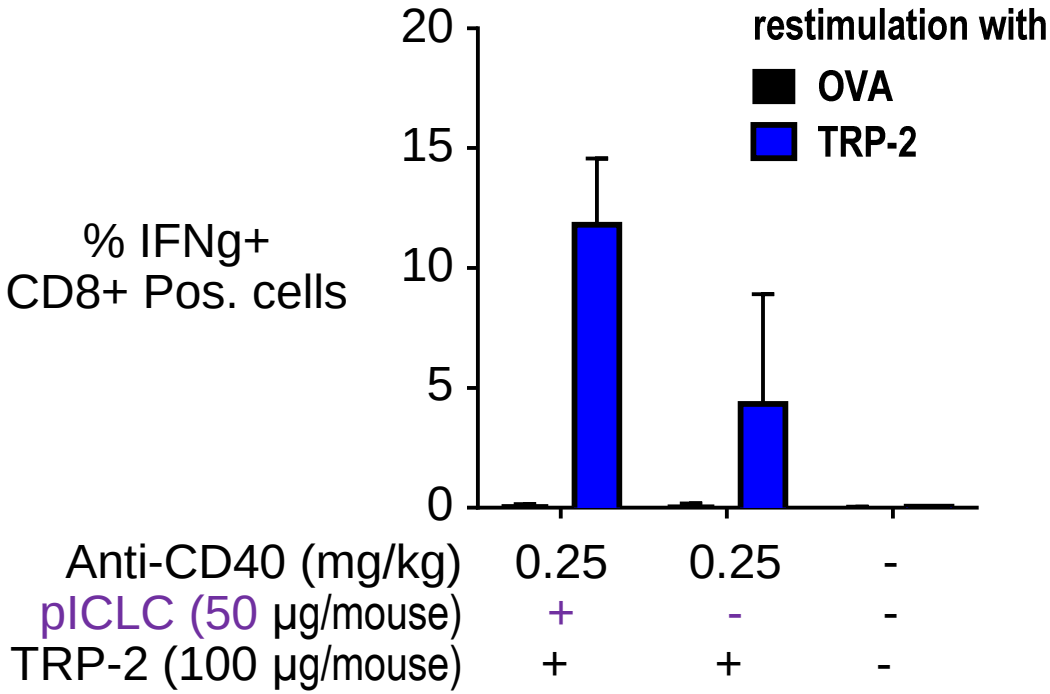
Impact of poly ICLC on immune response

All 3 components are required for an optimal immune response

TRP-2/ anti-CD40 @ d0
+/- pICLC @d0
given subcutaneously



Read out
@d7
In the spleen



Gated on live
CD3+CD8+ cells
(3 mice/ group)

TC{7 from oRRC presentation

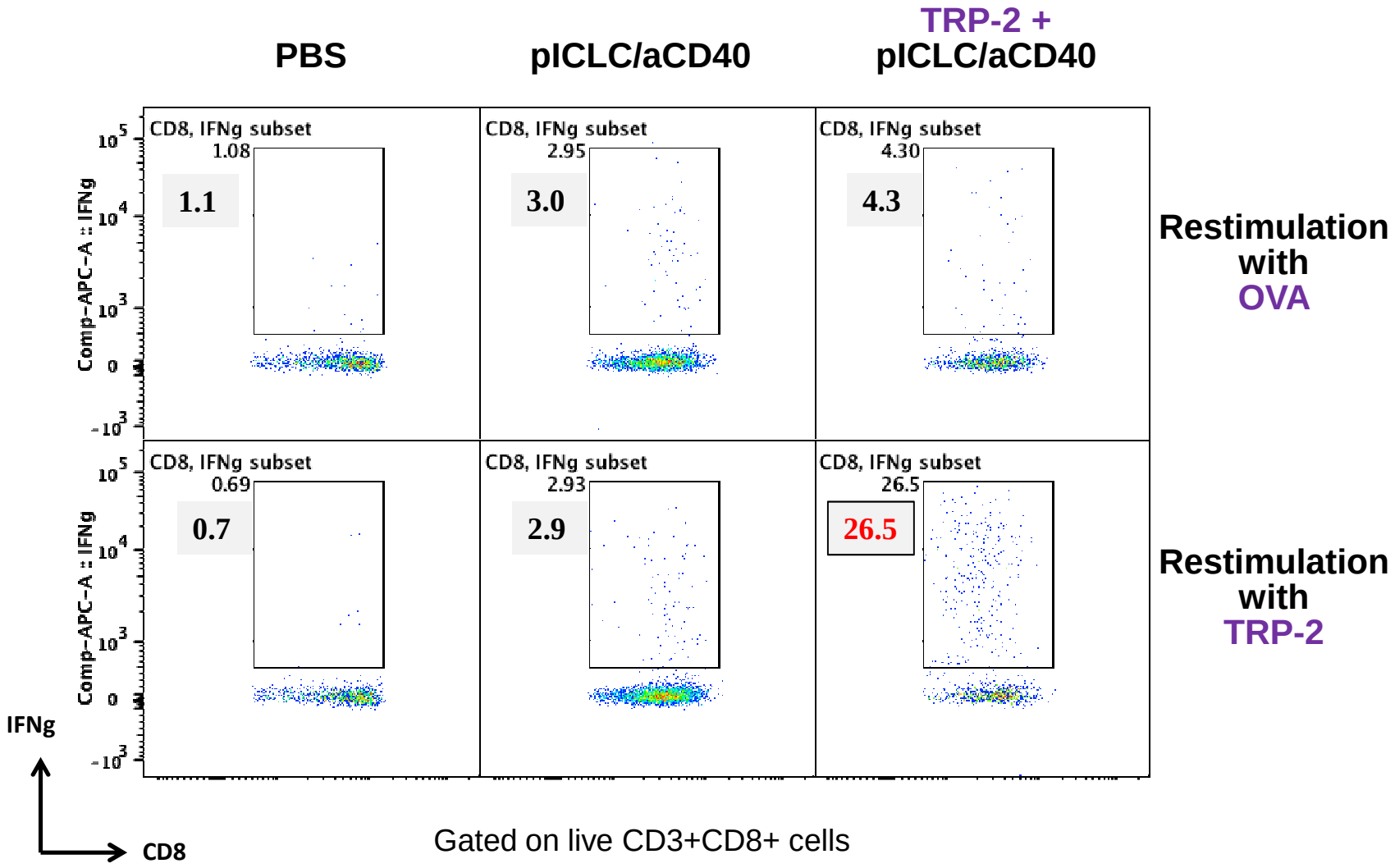
Trumpfheller, Christine {POHB~Schlieren}, 10/31/2014

TC{1

RF{1

B16F10 tumor challenge

A single vaccination with TRP-2/anti-CD40/poly ICLC drives tumor antigen-specific T cells into the Tumor



Gated on live CD3+CD8+ cells
(one mouse per group is shown)

Slide 27

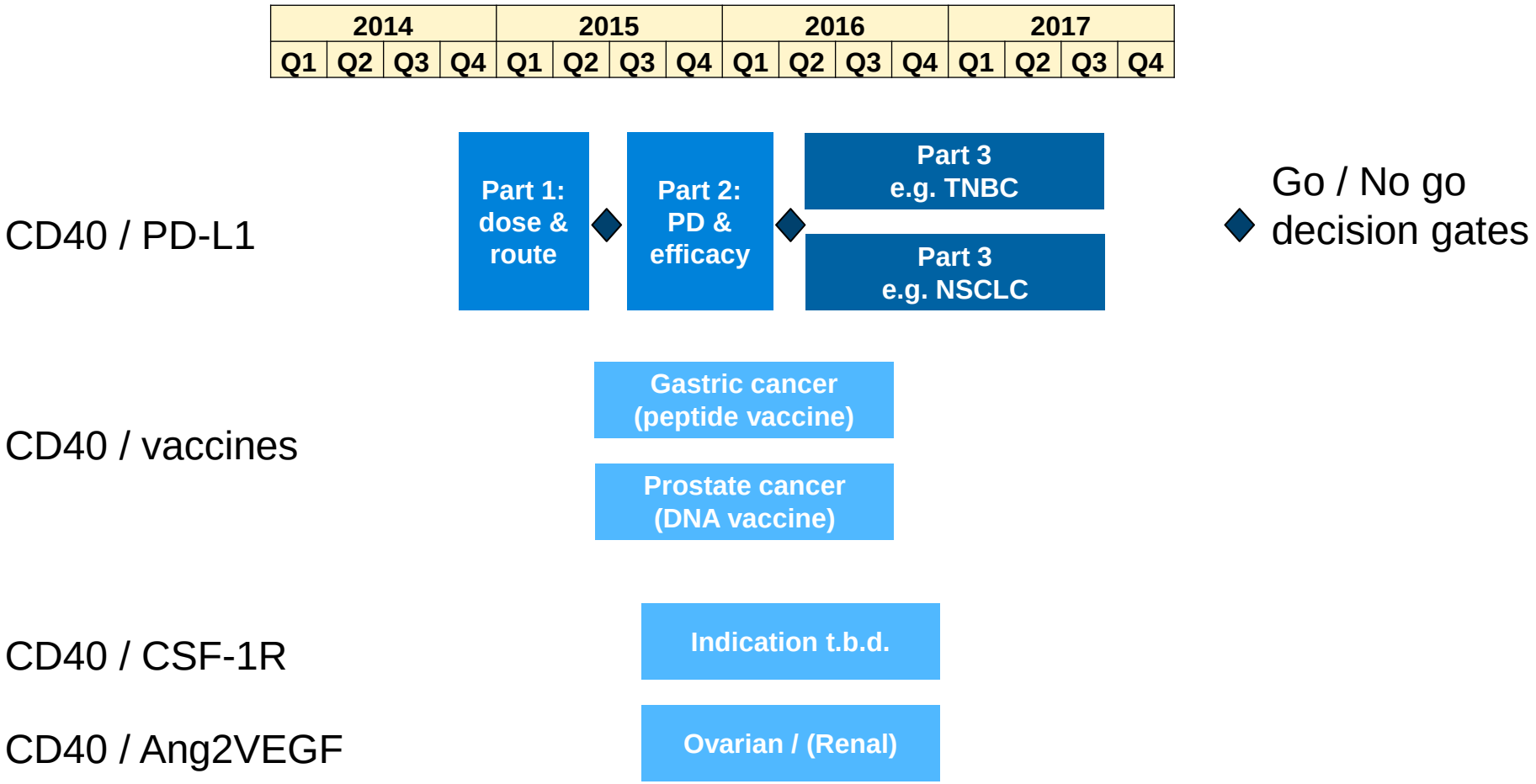
TC{1 some more raw data - FACS plot from one mouse per group - cells isolated from tumor are either restimulated with OVA or cognate TRP-2 peptide

Trumpfheller, Christine {POHB~Schlieren}, 10/31/2014

RF{1 Do you need this slide? Next slide summarizes the results nicely

Regenass, Franziska {PNPP~Basel}, 11/2/2014

Staggered development



Lessons and Take Home Messages

- Key points:

  CD40 is centrally positioned to initiate and amplify adaptive immunity through the induction of multiple co-stimulatory pathways.

- Potential impact on the field:

  The mechanism of action of agonist anti-CD40 antibody complements multiple other immunomodulators in the clinic making it an excellent combination partner for cancer immunotherapy.

- Lessons learned:

  Unless a car is parked on a hill, it takes more than removing the breaks to make it go.

Many thanks to all contributors

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Joel Freiman
Merlind Muecke
Helen Norman
Olaf Kuhlmann
Zuzana Lindberg
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