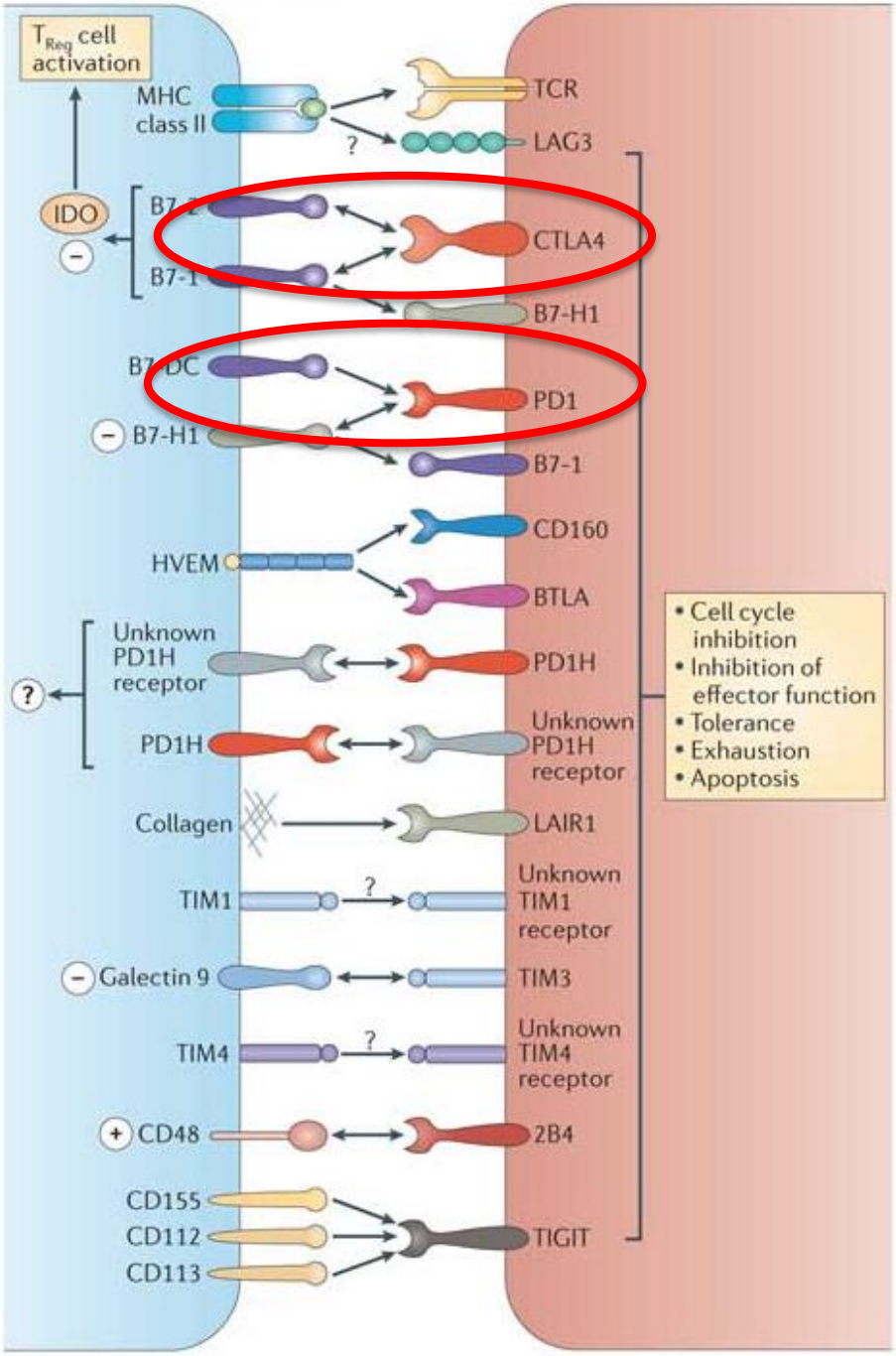
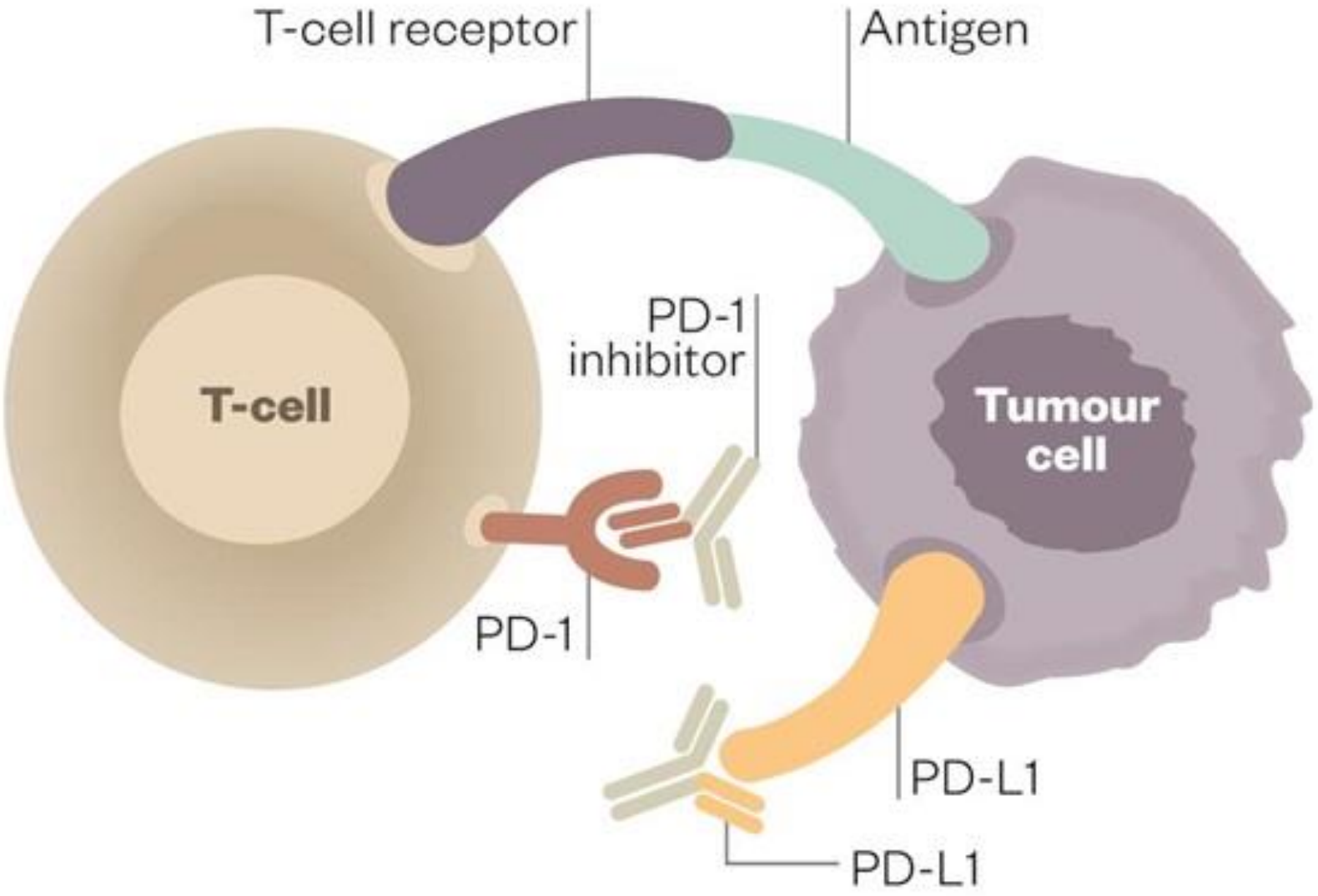
Resistance to anti-PD1 and selecting combination

Samir N. Khleif

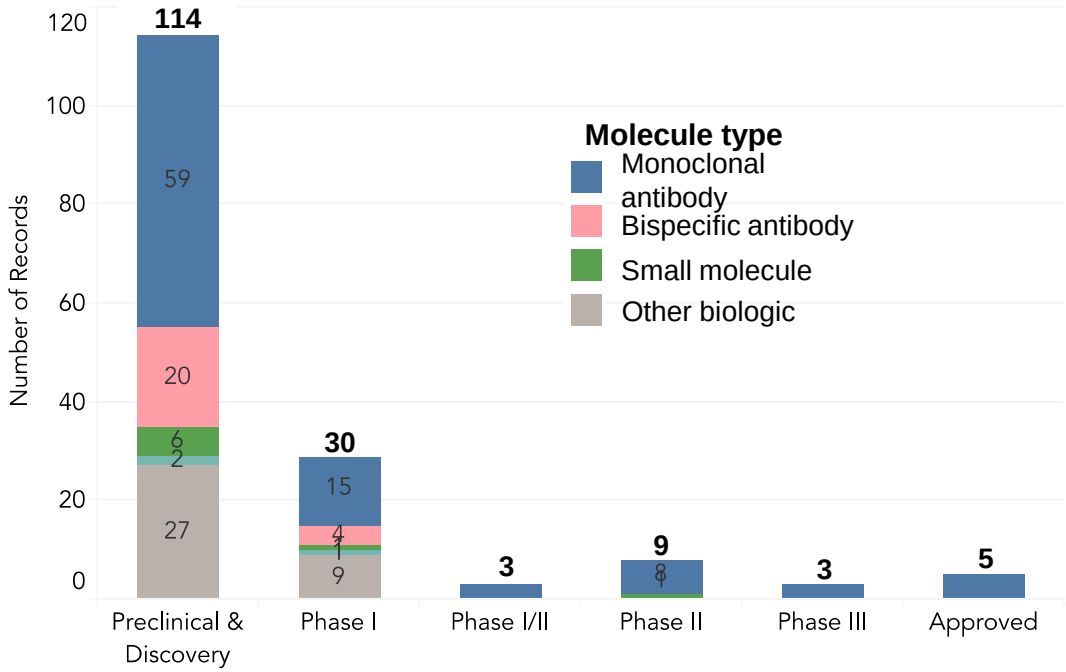
Co-inhibitory Molecules



PD1 : PD-L1 interaction renders the cells non-responsive



164 PD-1/L1-TARGETED AGENTS, 50 IN CLINICAL DEVELOPMENT



Studies

- **164 Agents (clinical+ preclinical)**
- **PD-1/L1: Clinical Trials: 1,502**
- **PD-1/L1 Combos: 1,105**
- **50 in clinical phase**
- **34 MoAb Clinical Development**

Tang, Shalabi, Lucey (Annual Oncology 2017)

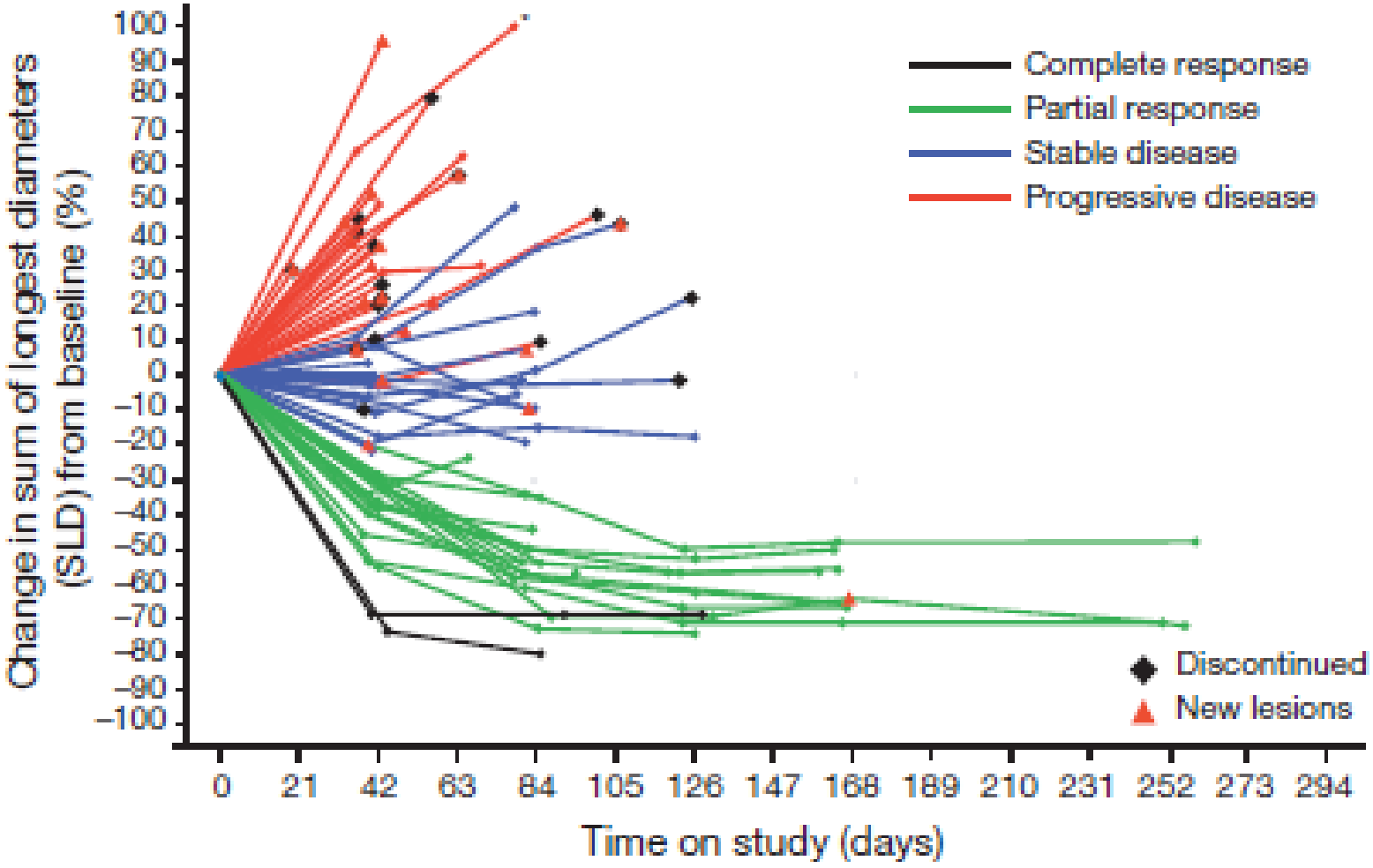
Email: *ClinicalAcceleratorIO@cancerresearch.org*

Combinational Immunotherapy

- PD1 Clinical trials 1,502
- PD1 Combination clinical trials 1,105
- PD1/PDL1 agents
  - 164 agents
  - 50 in clinical phase
  - 34 are in clinical development

Tang, Shalabi, Lucey (Annual Oncology 2017)

MPDL3280A (anti-PD-L1) in metastatic bladder cancer



Powles T et al. *Nature* 515(7528), 558-562 (2014)

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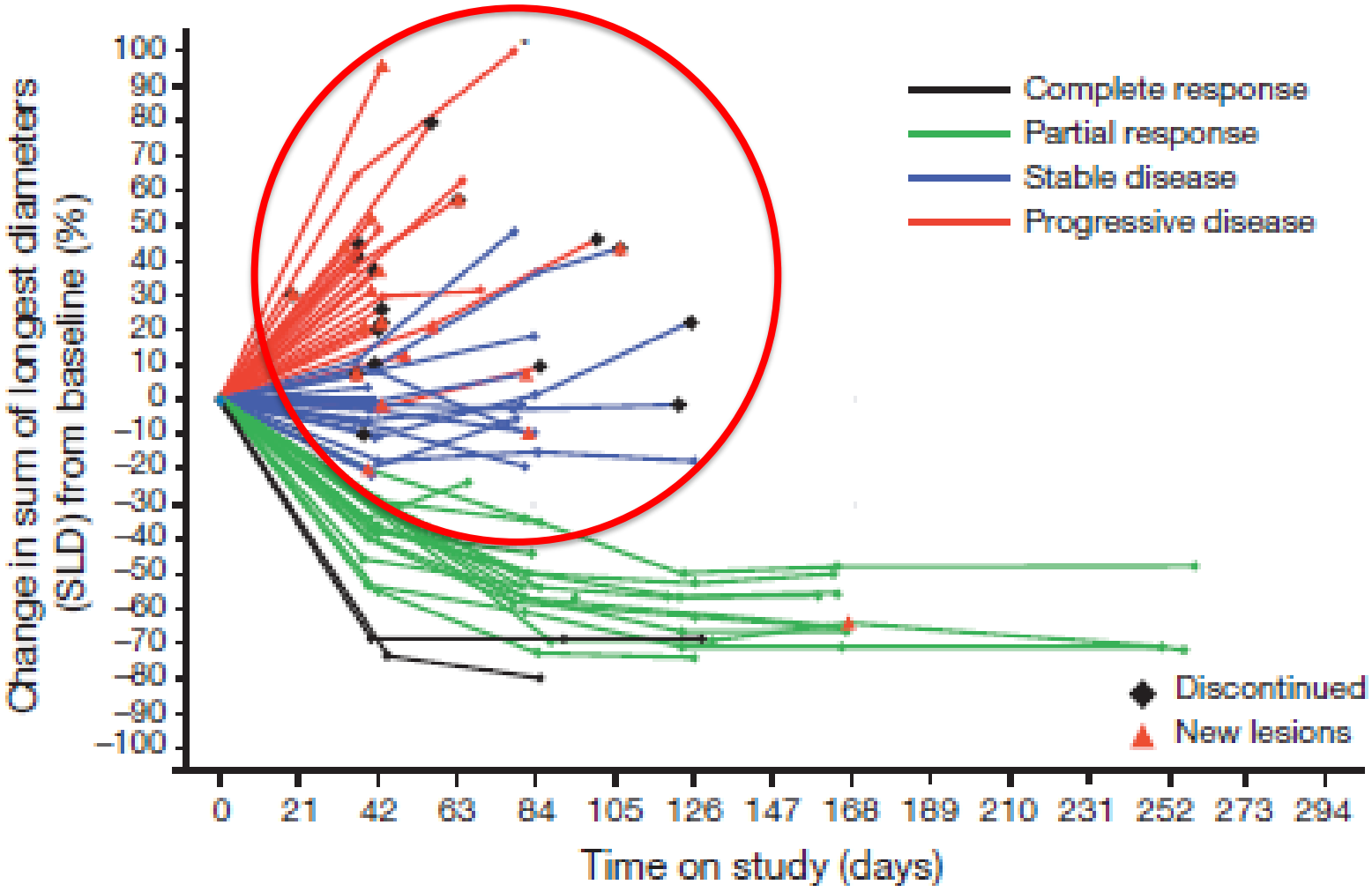

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Immuno-therapy Resistance

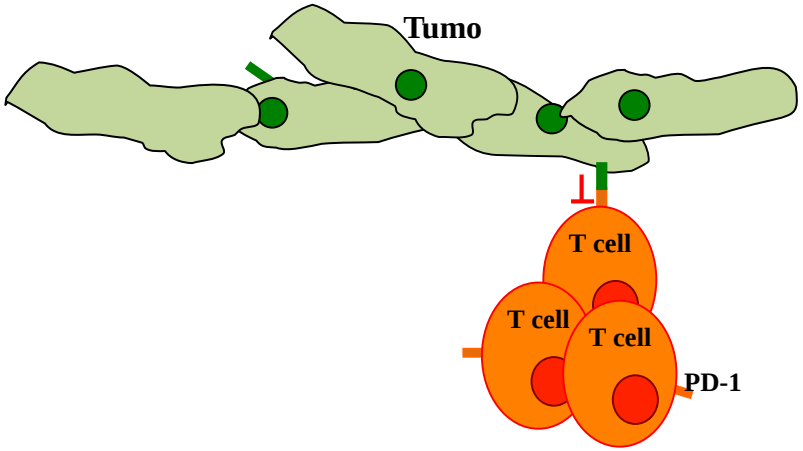
Immuno-therapy Resistance

- Primary resistance

- Secondary resistance

Immuno-therapy Resistance

- General mechanisms
  - Intrinsic Tumor biology



Immuno-therapy Resistance

- General mechanisms
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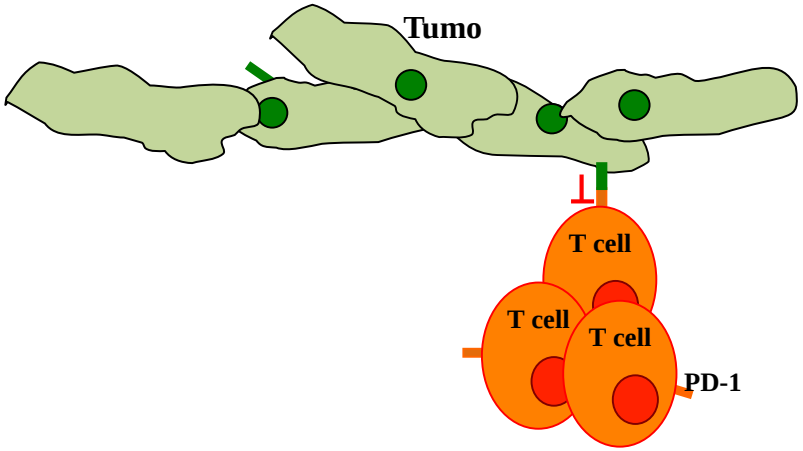
    - Lack of antigen presentation
      - Lack of antigen expression
      - Lack of antigen processing and presentation (TAP, MHC, B2M)



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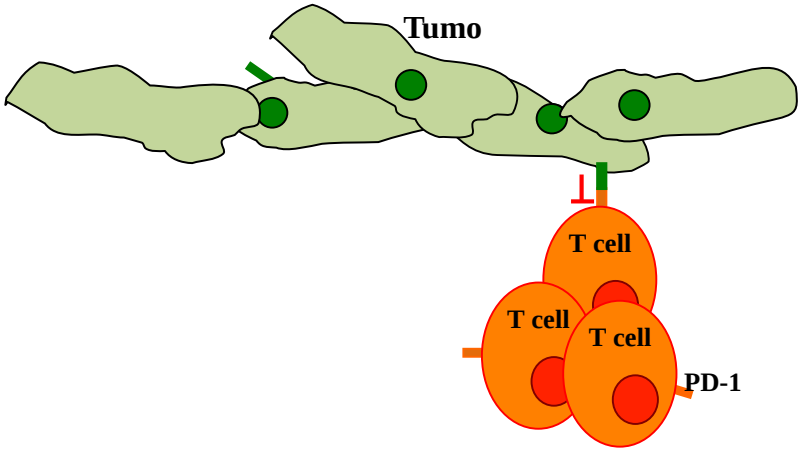

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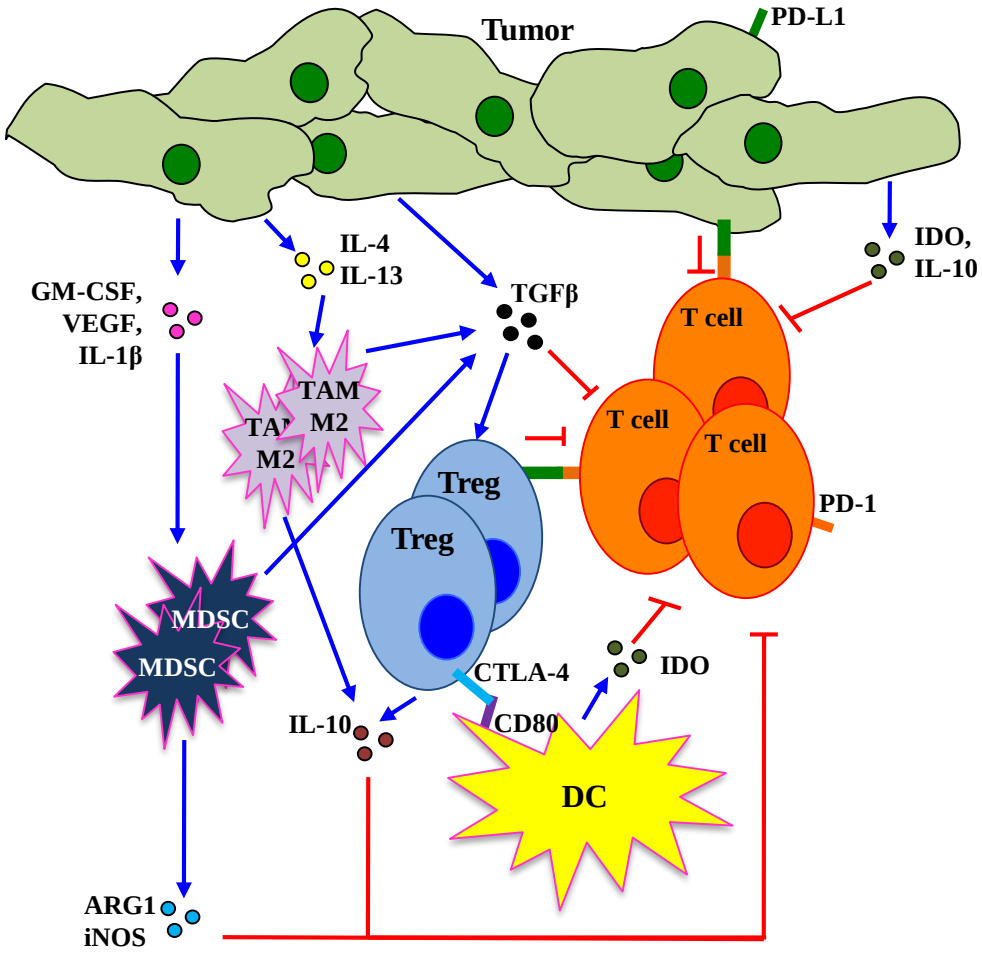
Tumor-Immune Interaction



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- Treatment Specific mechanisms
  - Low PDL1 expression
  - JAK2 mutation
- Immuno-Combination incompatibility
- Immunotherapy biologic incompatibility

Combinational Immunotherapy

Combinational Immunotherapy

- Vaccines
- Immune Modulators
  - Immune Agonists
    - Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
    - Co-stimulatory molecules (OX-40, GITR, 4-1BB)
  - Immune inhibitors
    - Check point inhibitors (CTLA4, PD1/PDL1, LAG3, TIM3, iDO)
    - Inhibitory cytokines/factors (IL-10, TGFb)
- Standard Therapy
  - Chemotherapy
  - Radiation Therapy
- Small Molecules
- CARS

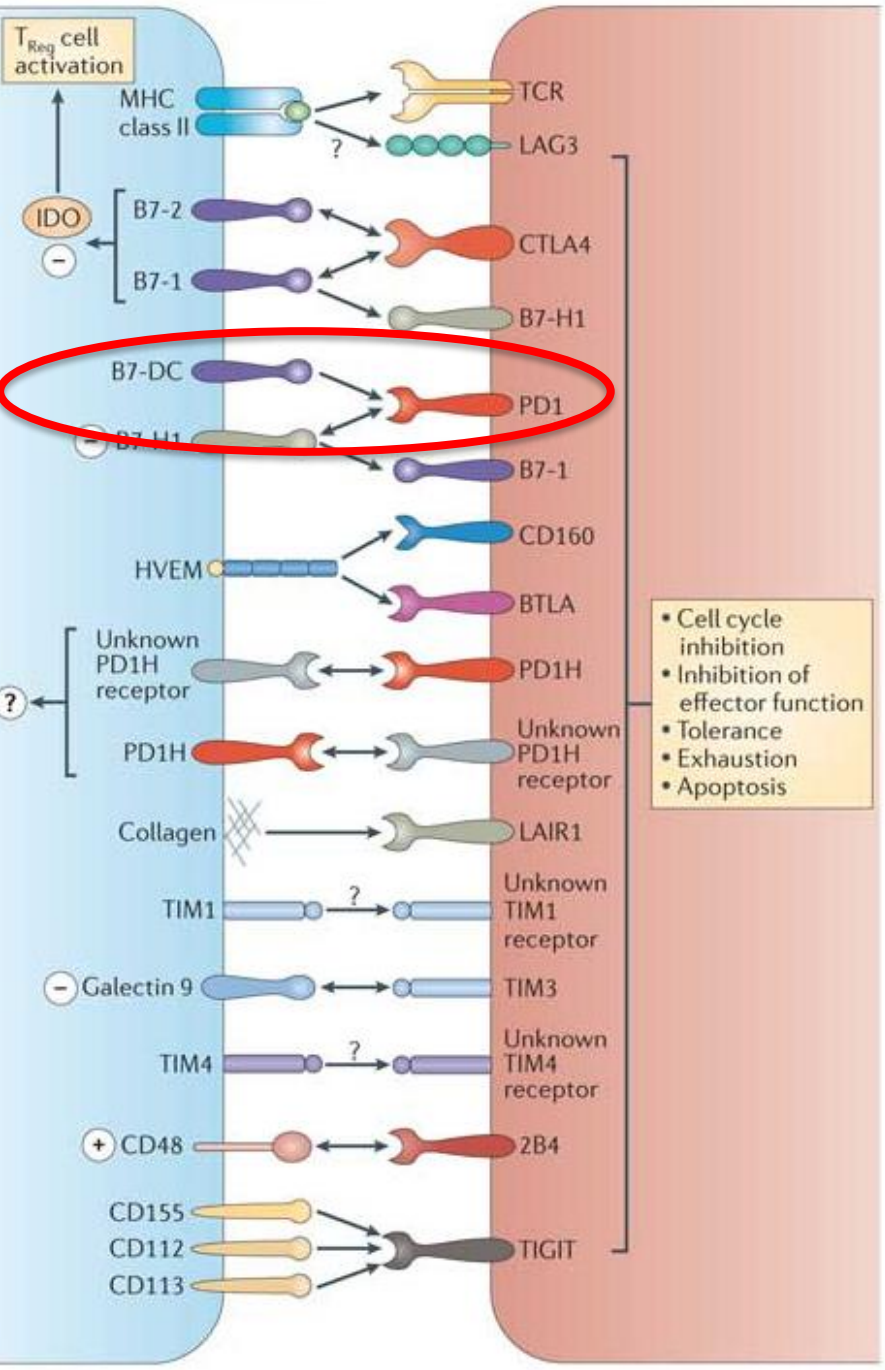
Combinational Immunotherapy

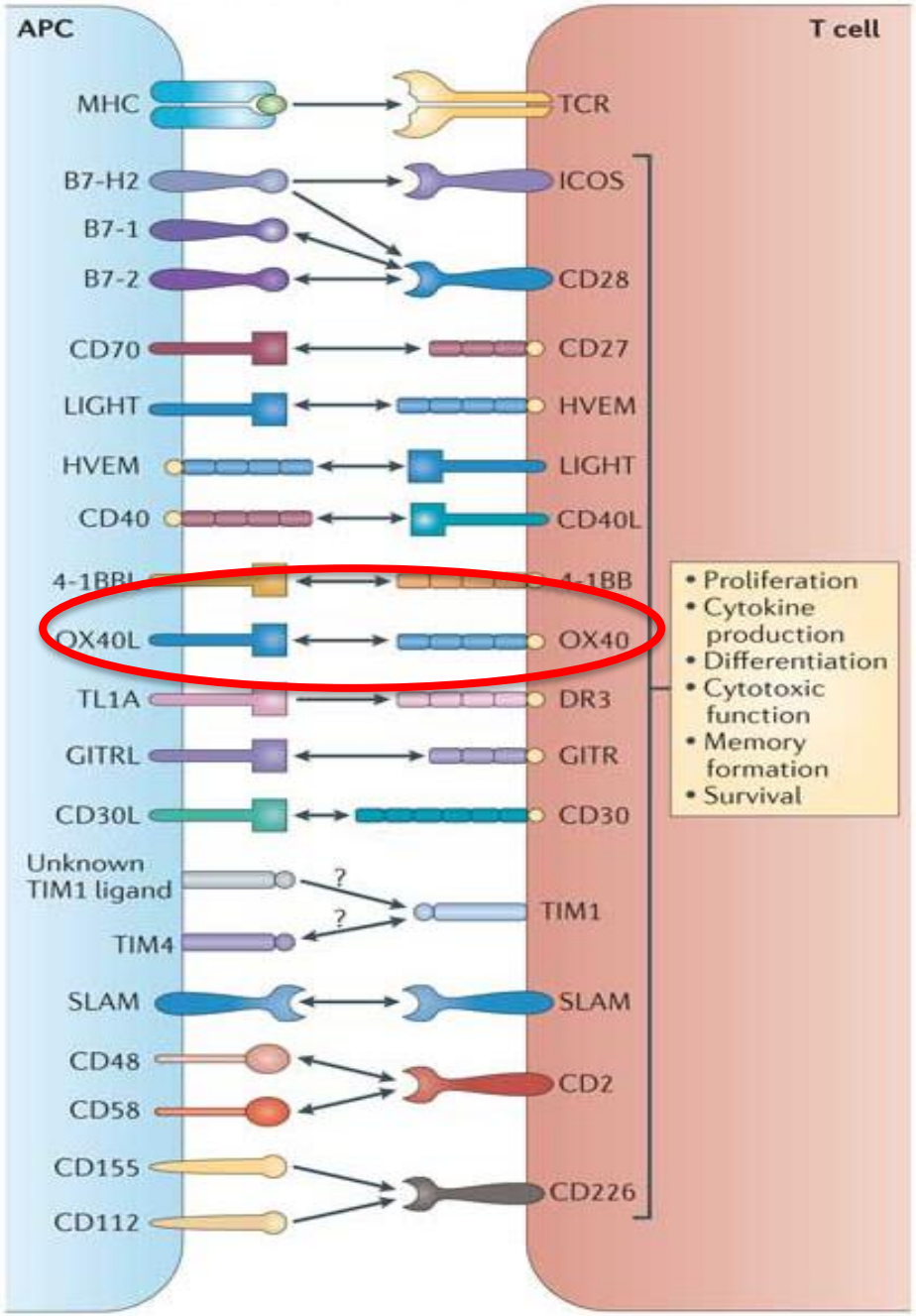
940 different IO agents in clinical stage

Source: Aman Shalabi CIR

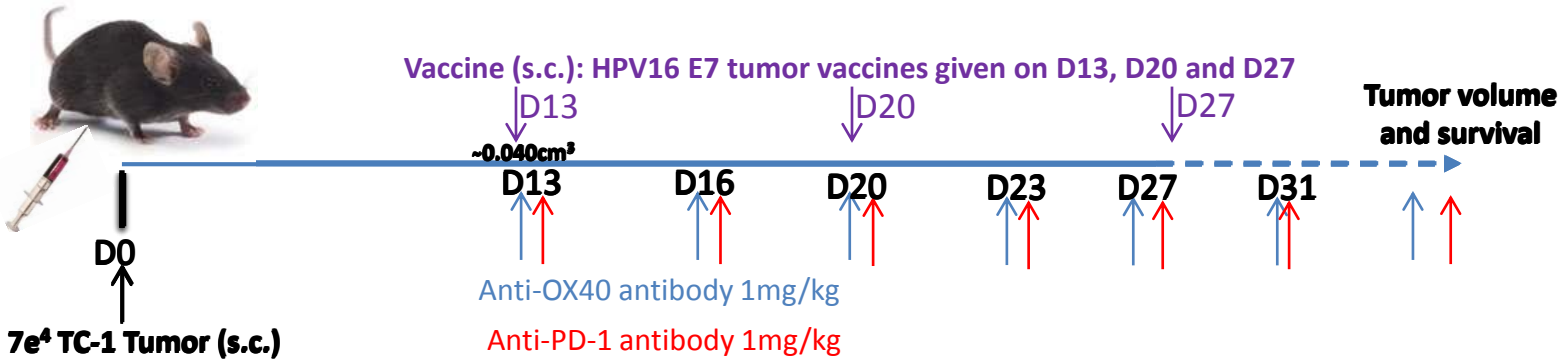
Combination of Anti-PD-1 with immune-priming agent

vaccine
radiation therapy
chemotherapy
insitu therapy


T_{Reg} cell activation
MHC class II
TCR
?
LAG3
IDO
B7-2
B7-1
CTLA4
B7-H1
B7-DC
PD1
B7-H1
B7-1
CD160
HVEM
BTLA
Unknown PD1H receptor
PD1H
?
PD1H
Unknown PD1H receptor
Collagen
LAIR1
TIM1
?
Unknown TIM1 receptor
Galectin 9
TIM3
TIM4
?
Unknown TIM4 receptor
CD48
2B4
CD155
CD112
CD113
TIGIT
• Cell cycle inhibition
• Inhibition of effector function
• Tolerance
• Exhaustion
• Apoptosis


APC
T cell
MHC
TCR
B7-H2
ICOS
B7-1
B7-2
CD28
CD70
CD27
LIGHT
HVEM
HVEM
LIGHT
CD40
CD40L
4-1BBL
4-1BB
OX40L
OX40
TL1A
DR3
GITRL
GITR
CD30L
CD30
Unknown TIM1 ligand
?
?
TIM1
TIM4
SLAM
SLAM
CD48
CD2
CD58
CD155
CD226
CD112
• Proliferation
• Cytokine production
• Differentiation
• Cytotoxic function
• Memory formation
• Survival

Adding α-PD1 to α-OX40 and E7 vaccine negates the effect of α-OX40 and Vaccine combination



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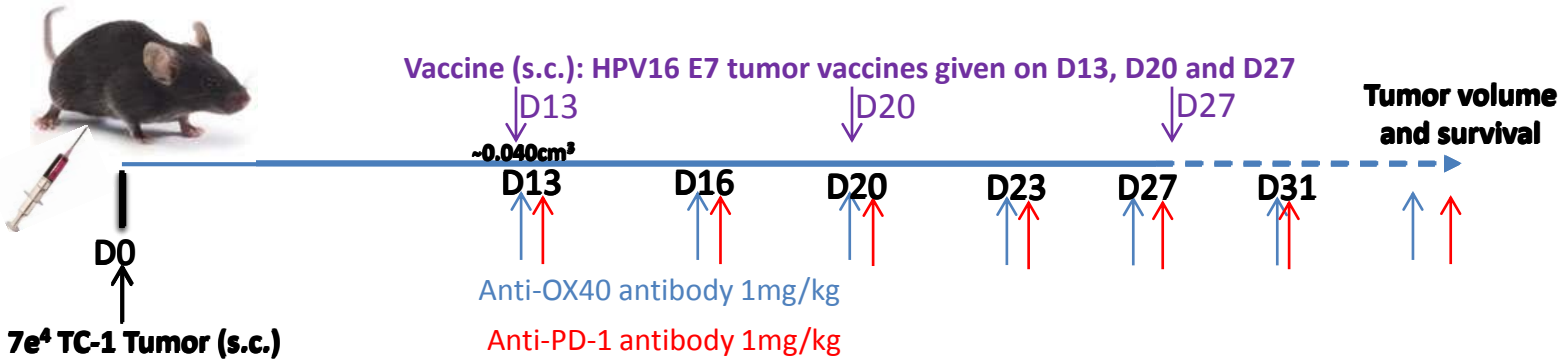

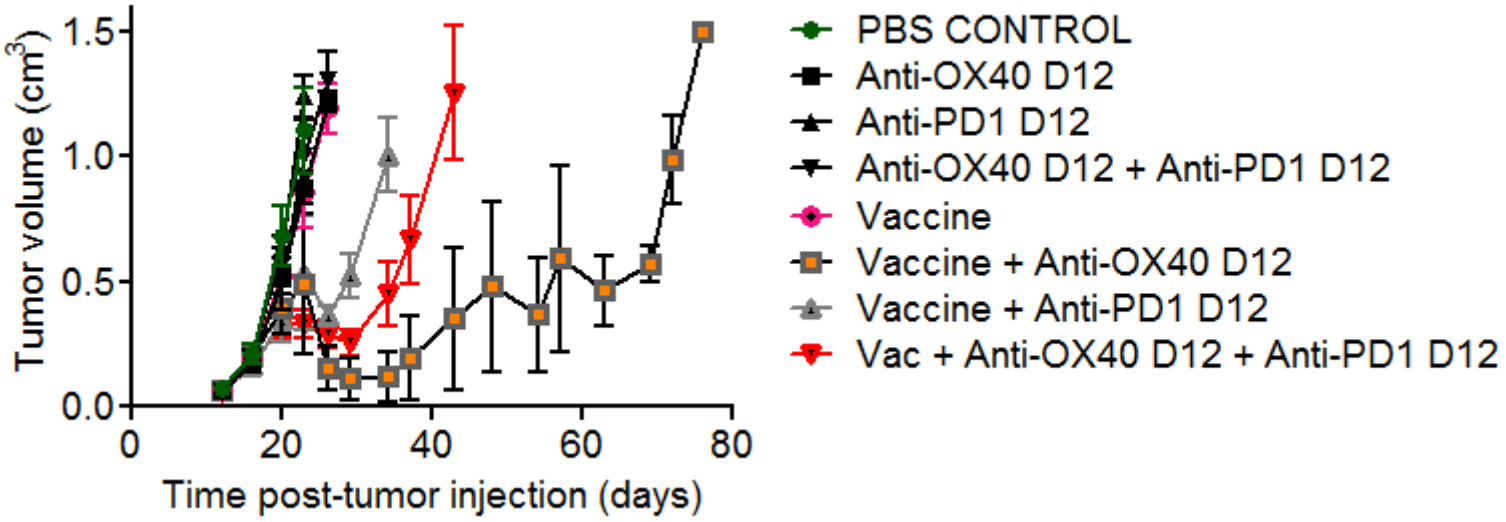

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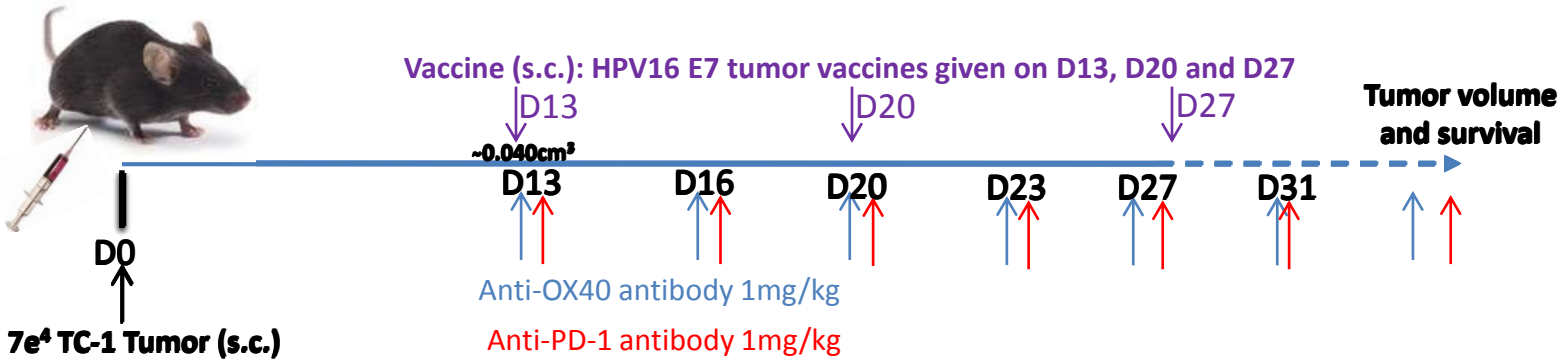

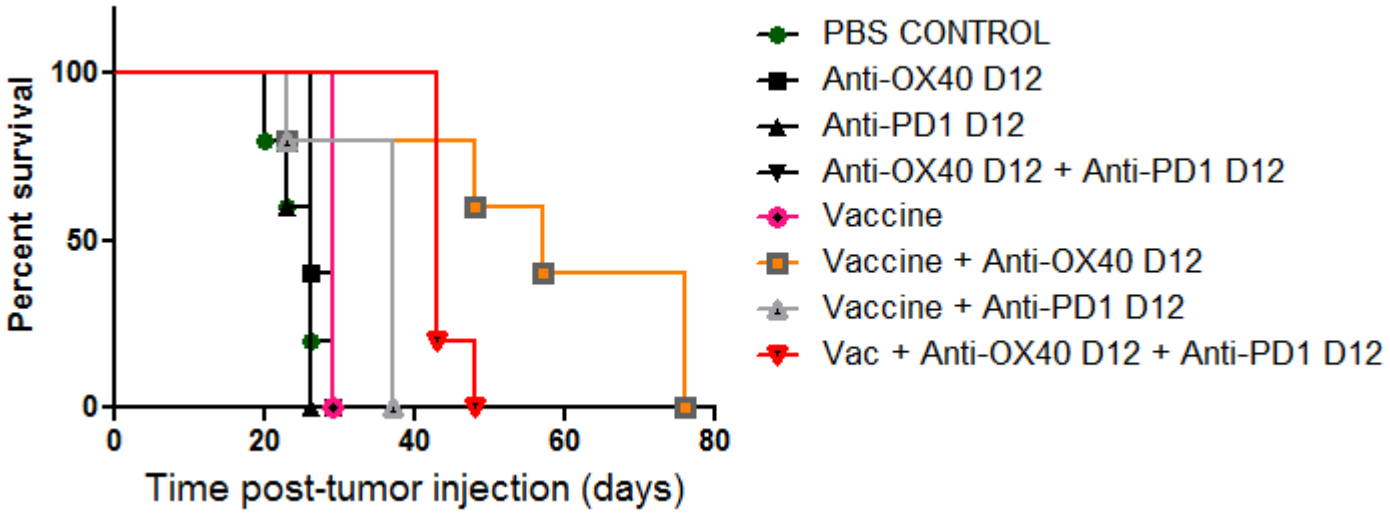

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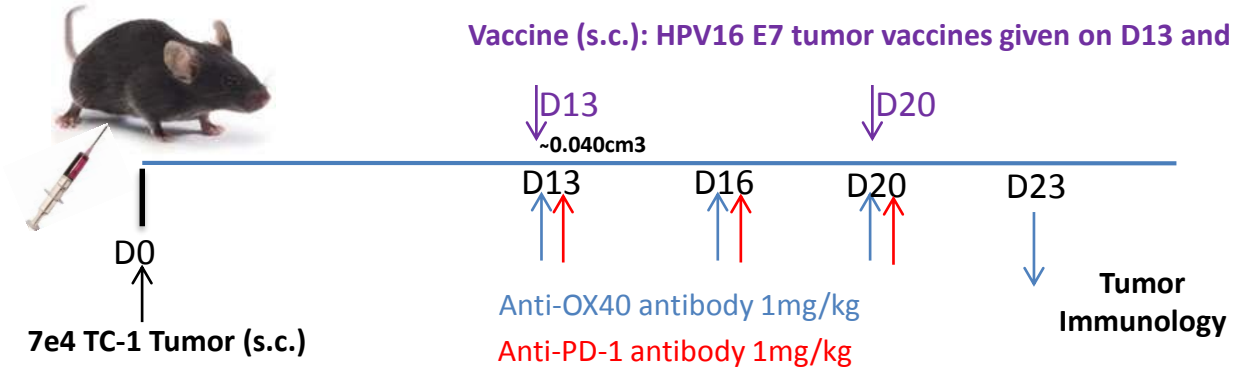
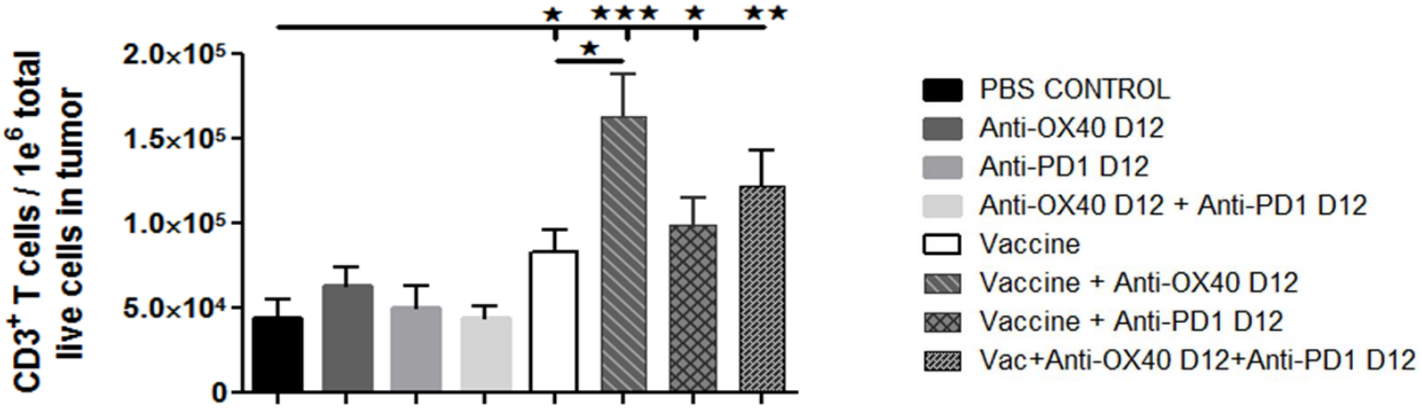
Tumor Infiltration of T cells





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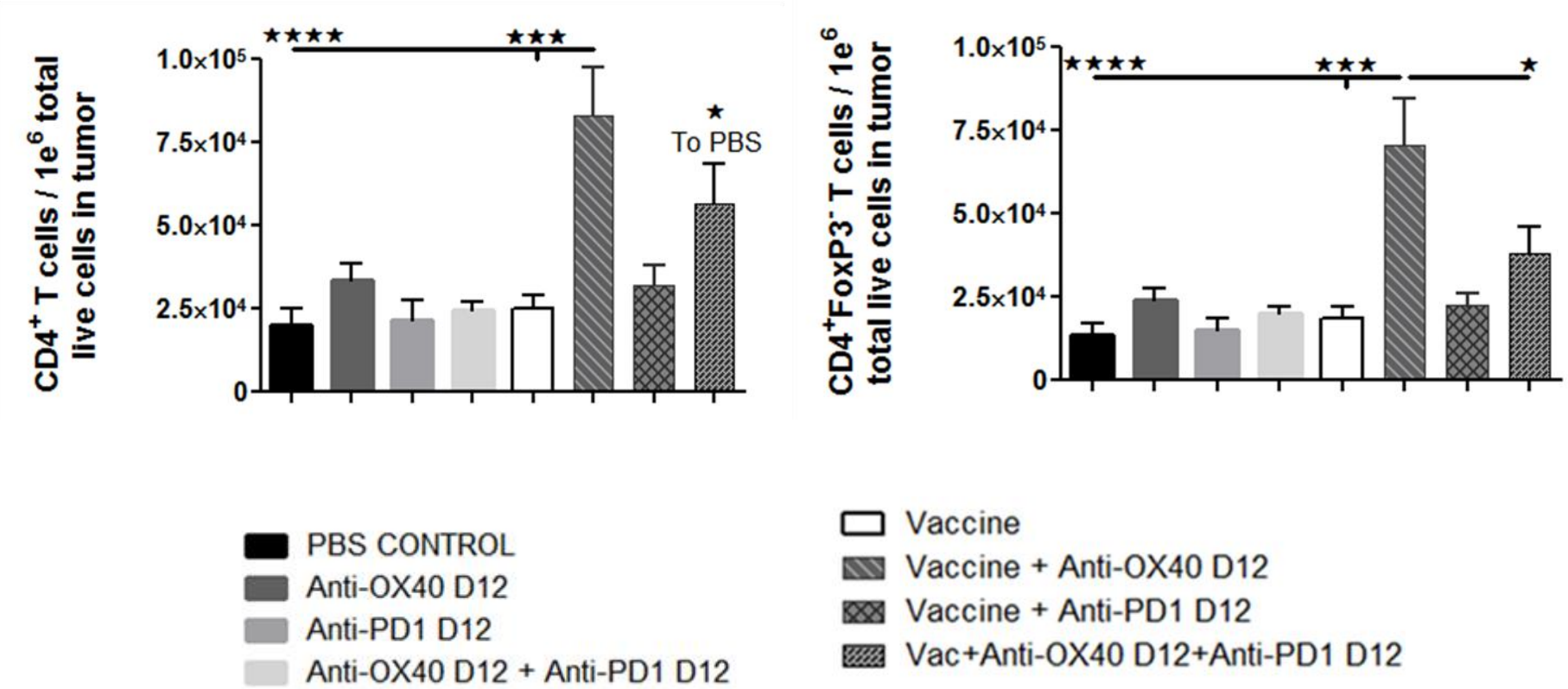
Tumor Infiltration of CD4+ T cells



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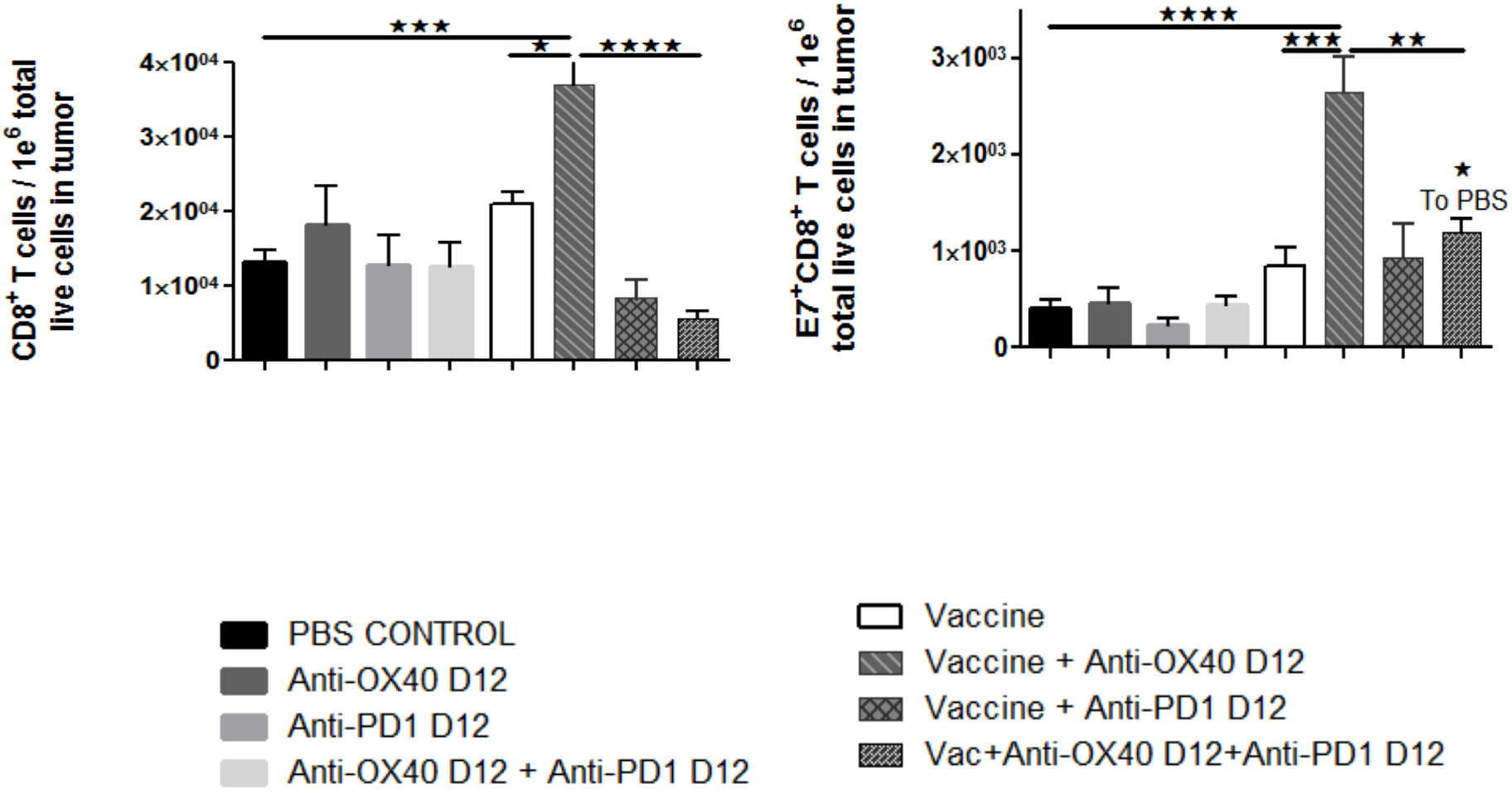
Tumor infiltration of CD8+ T cells and antigen specific CD8+ T cells



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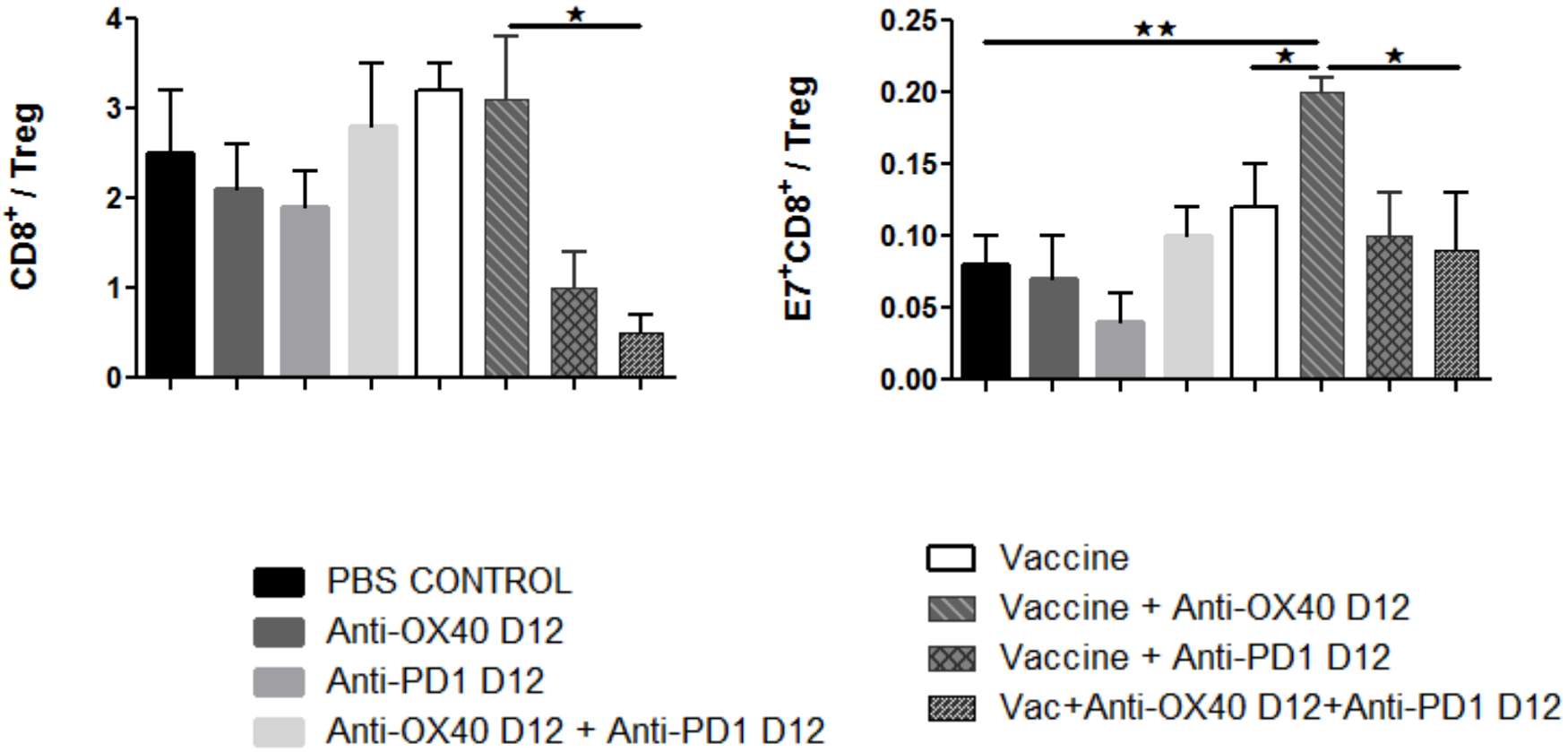
Therapeutic Ratio in Tumor Microenvironment



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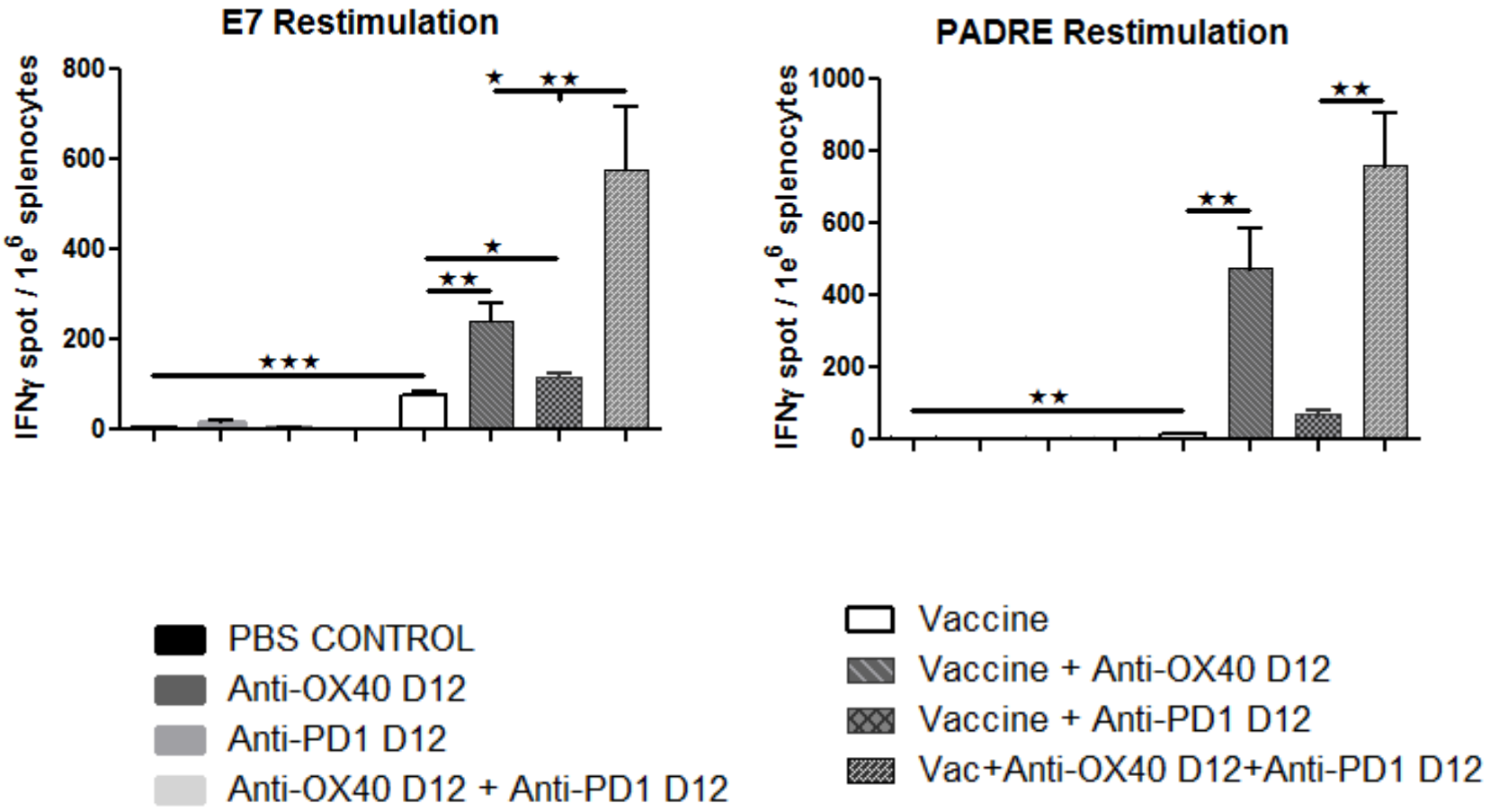
IFNγ responses- ELISPOT



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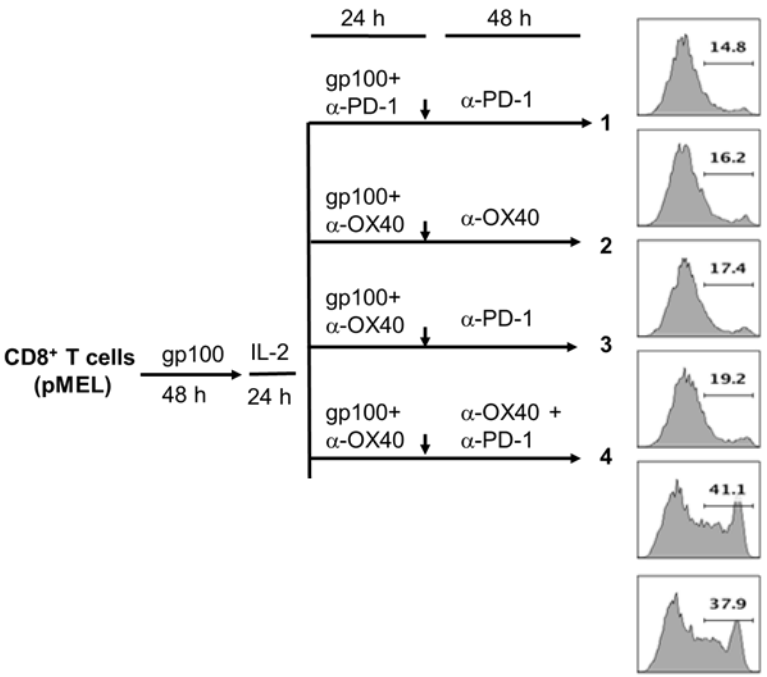
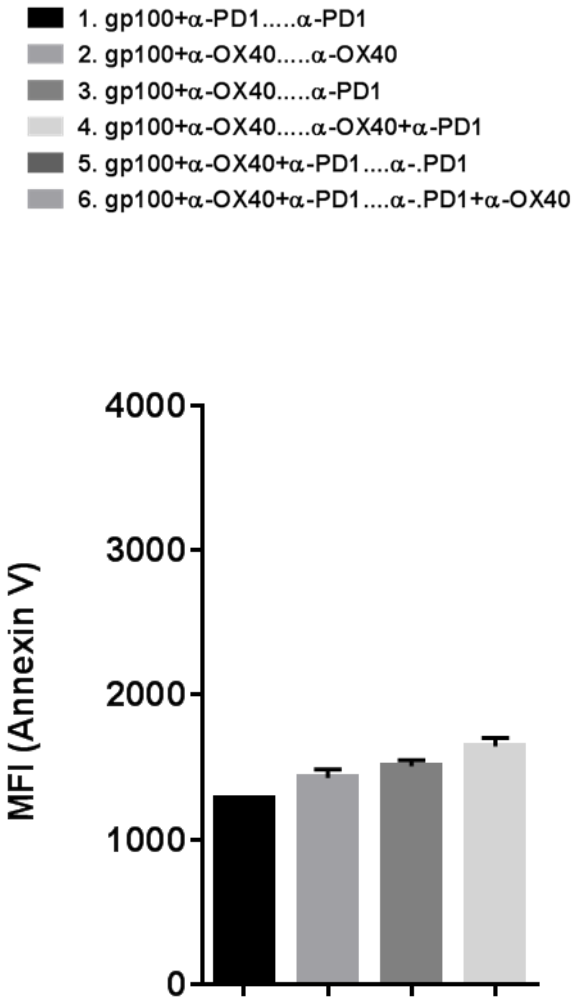
Adding α-PD1 to α-OX40 in antigen primed cells induces apoptosis in vitro





Shrimali, et al. 2017

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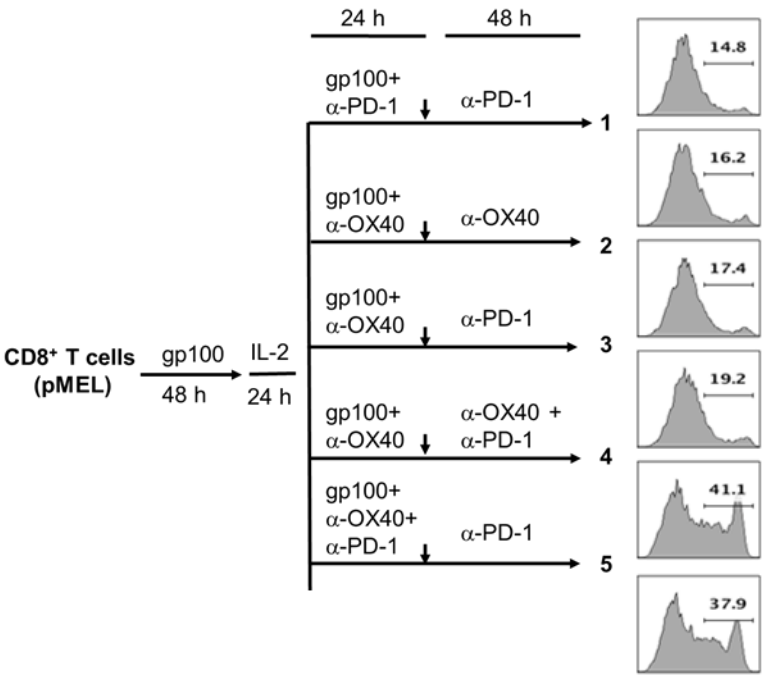

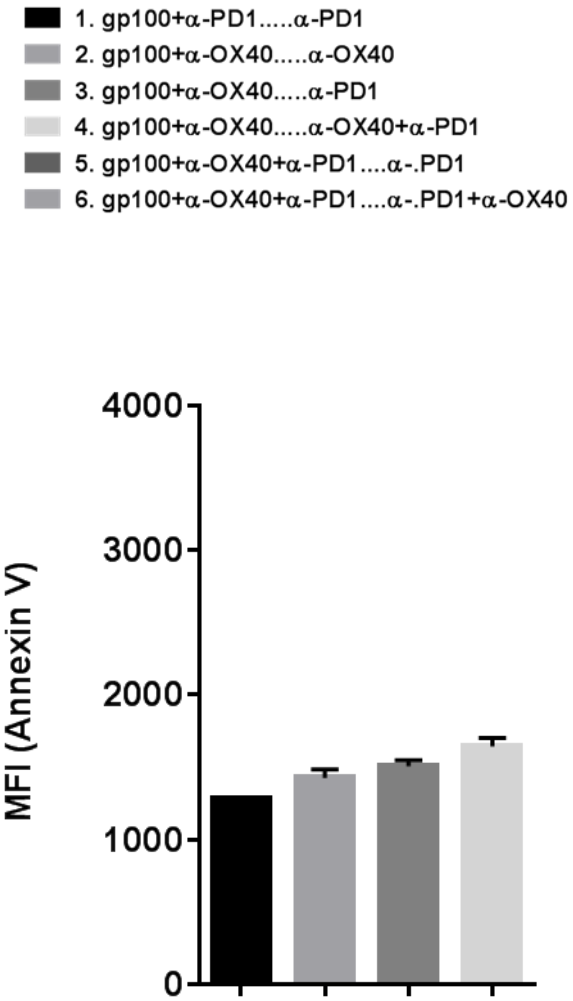

Shrimali, et al. 2017

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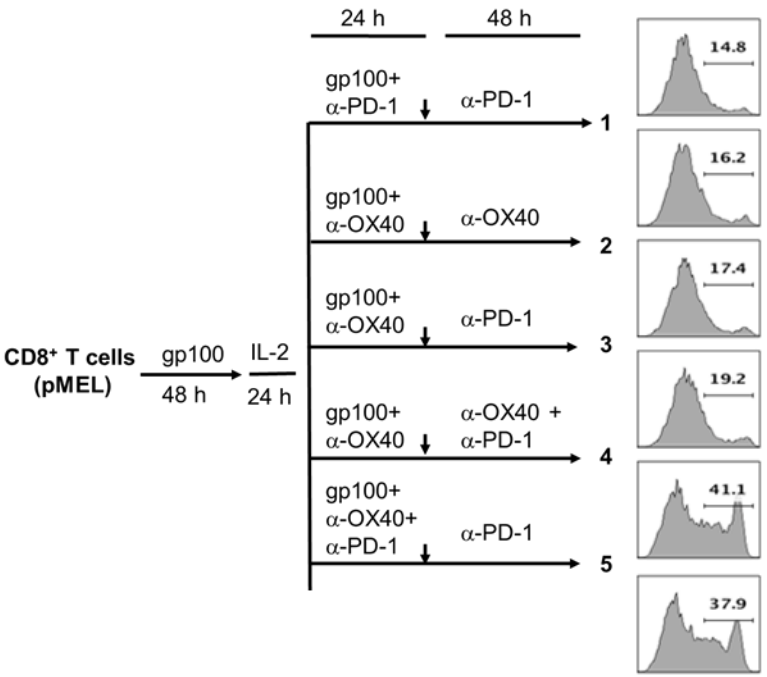

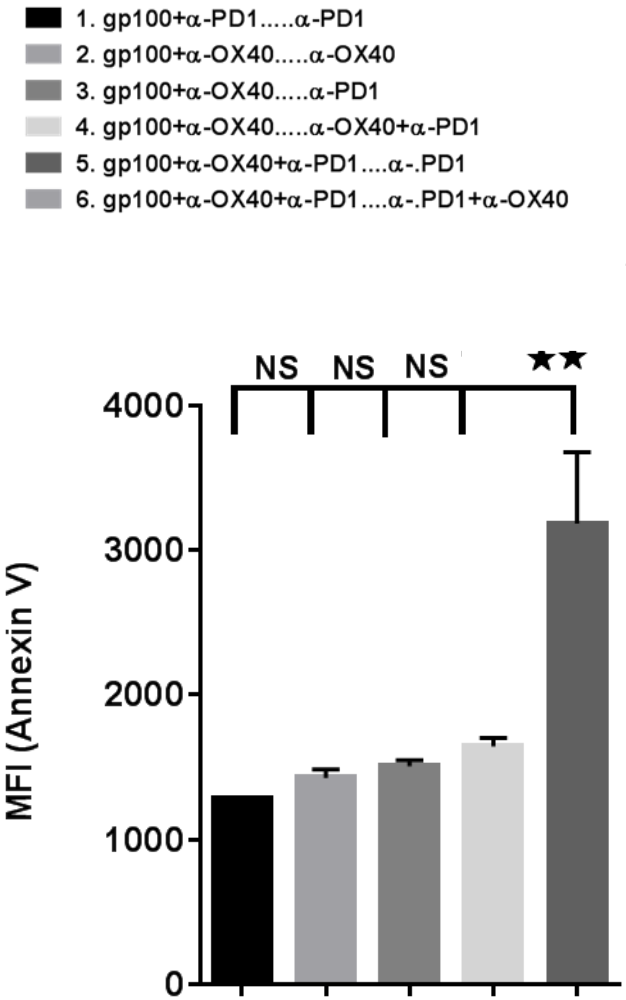

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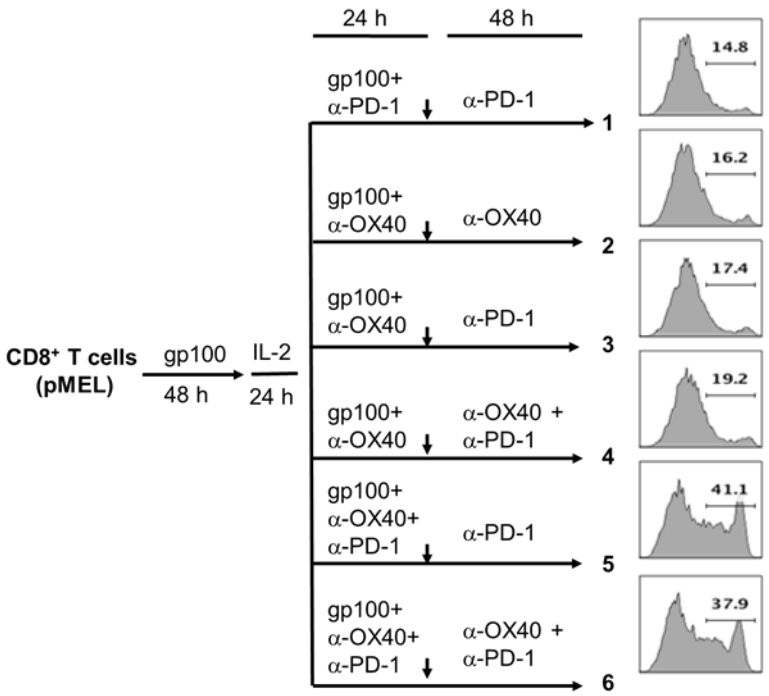

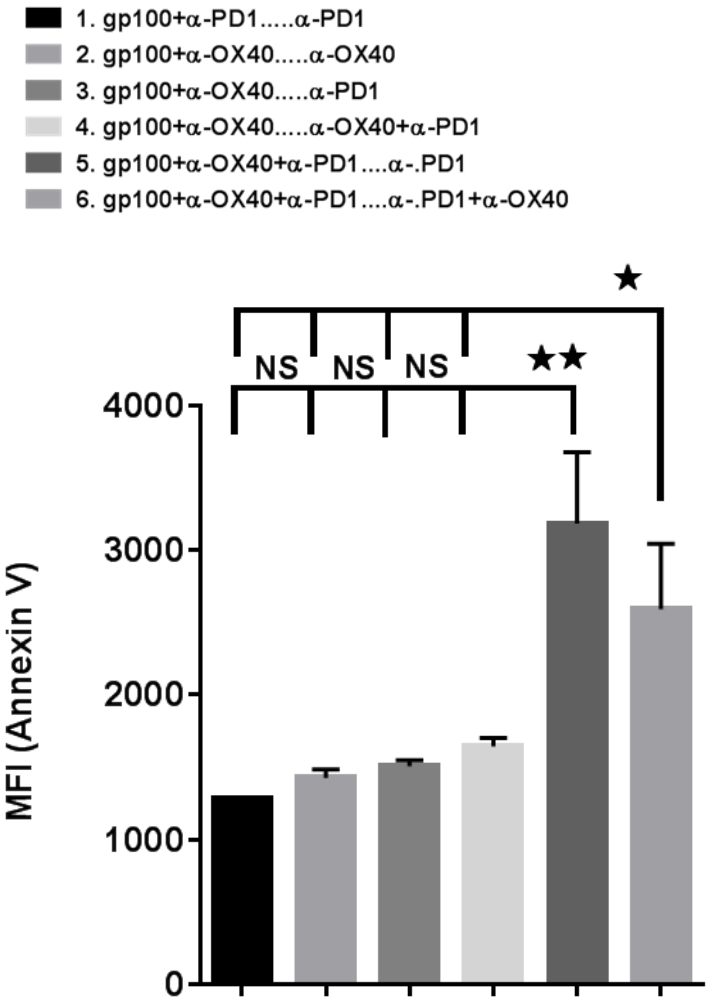

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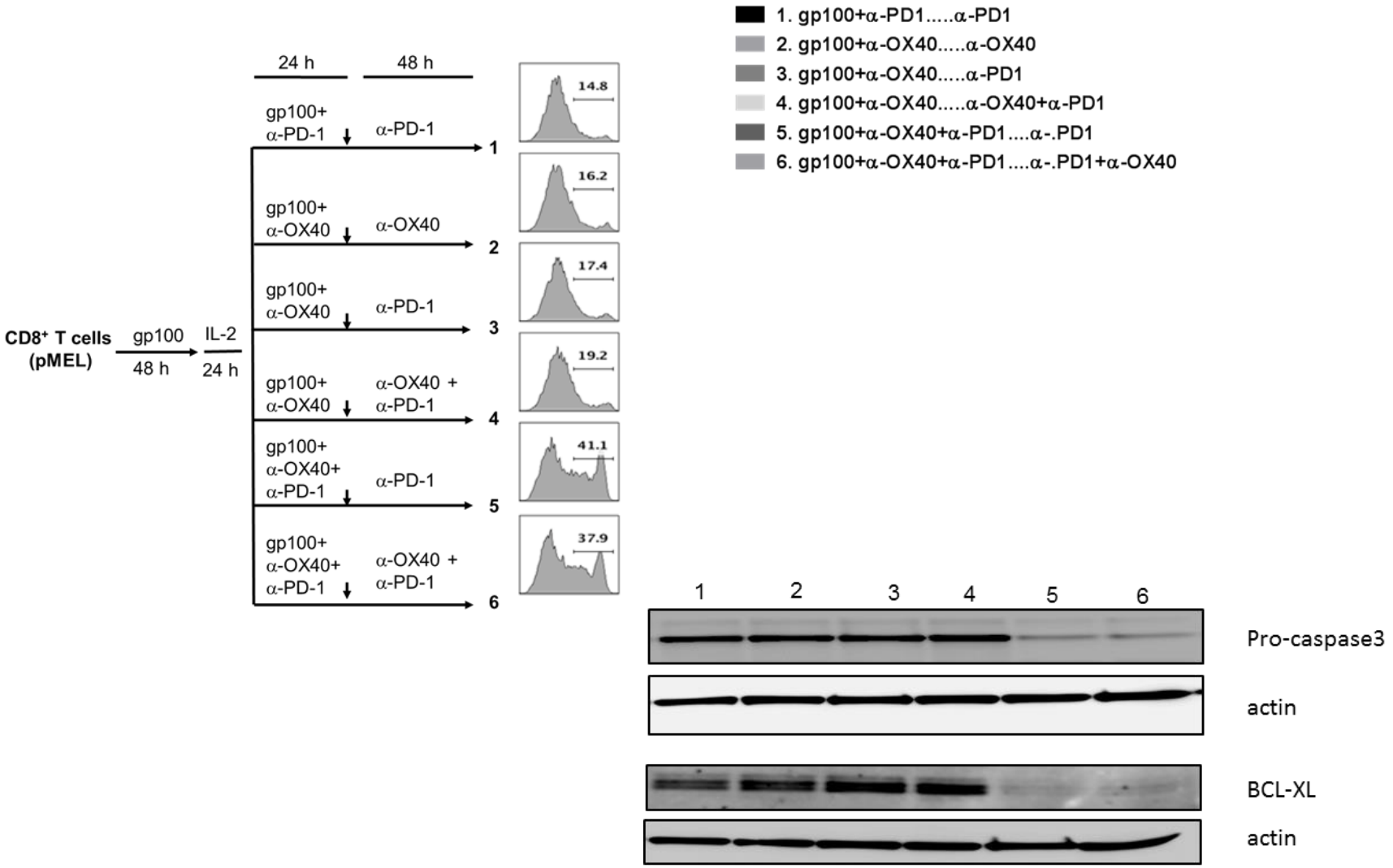

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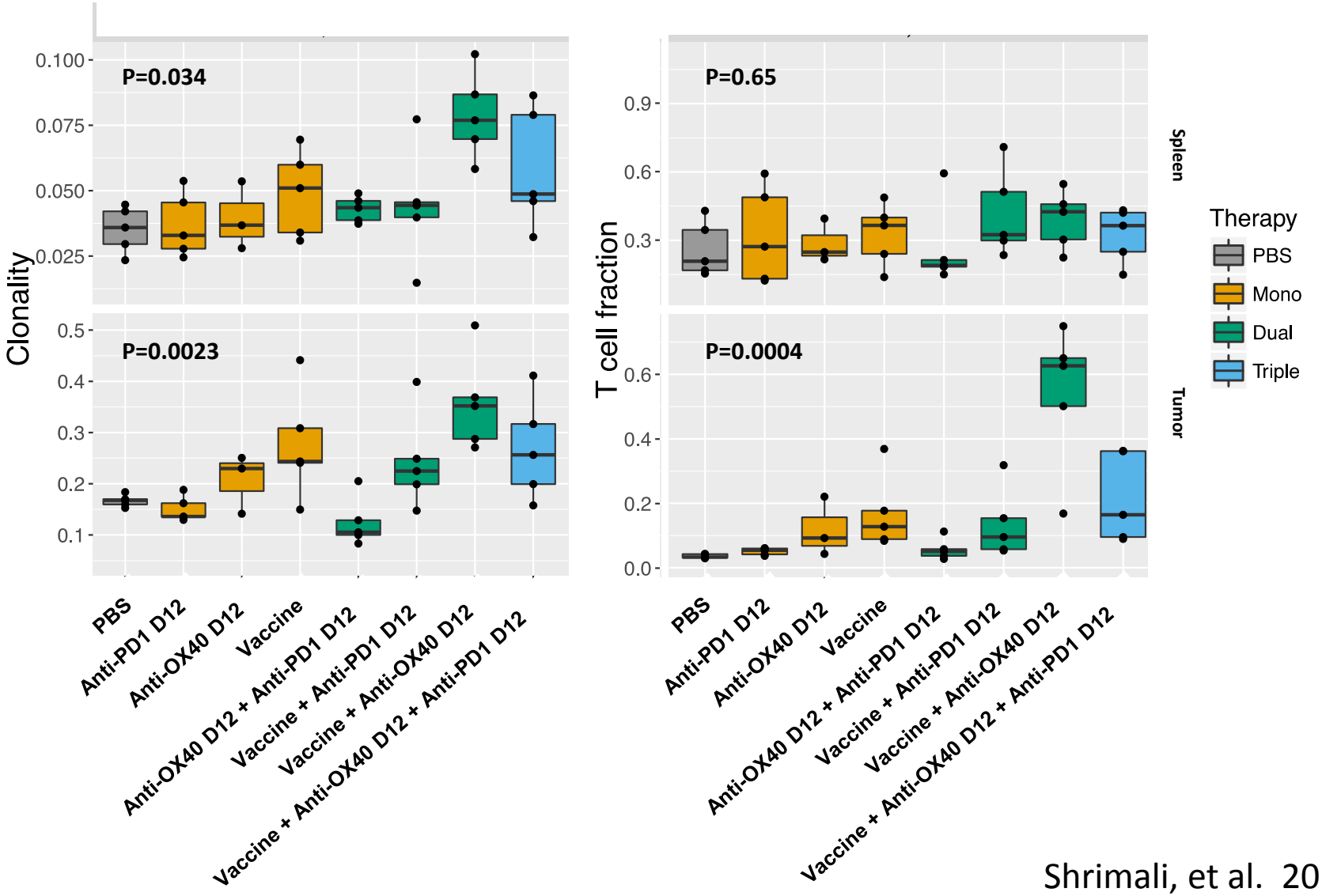
Adding α-PD1 to α-OX40 and E7 vaccine reduces clonality and T cell fraction



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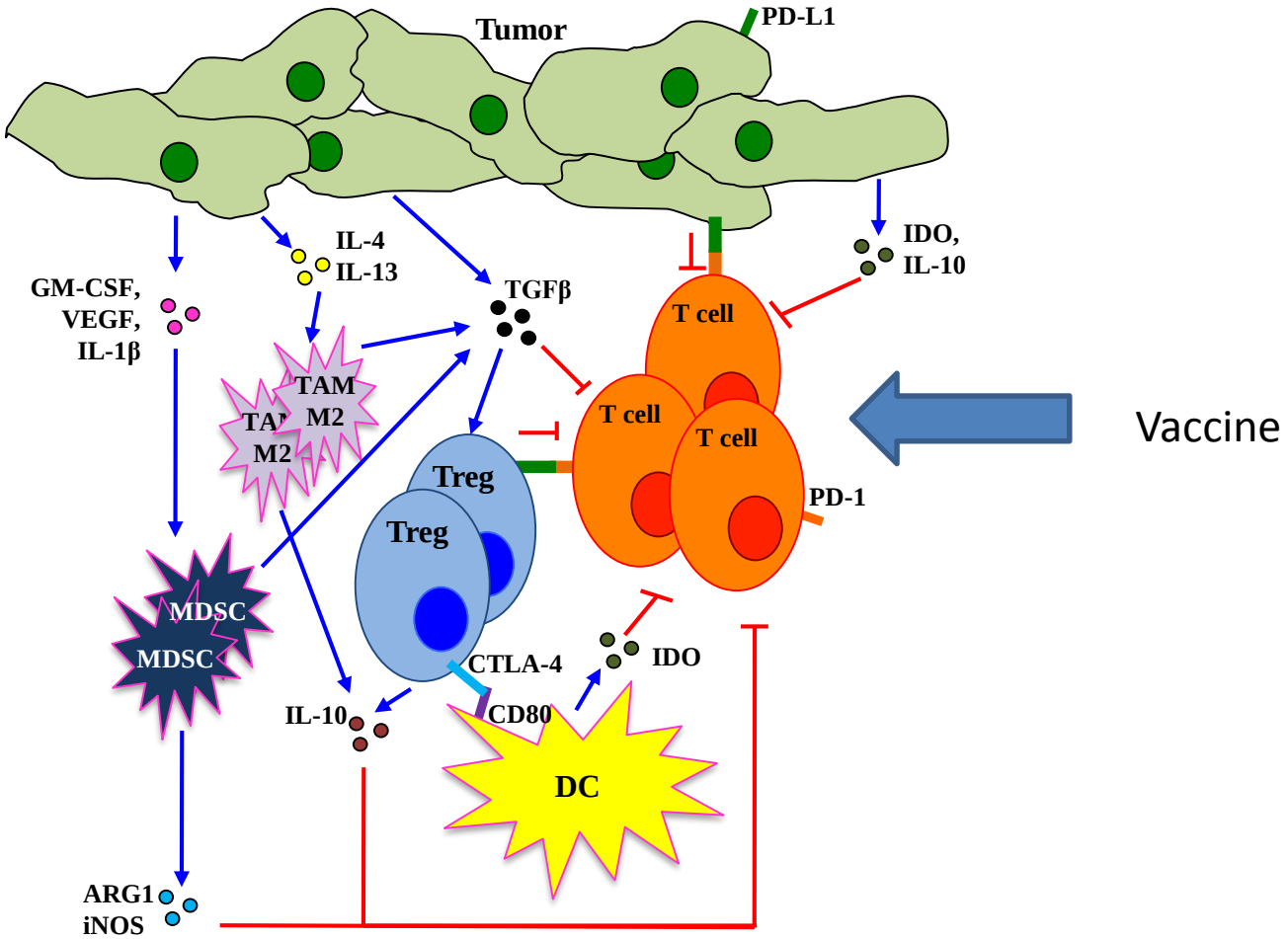
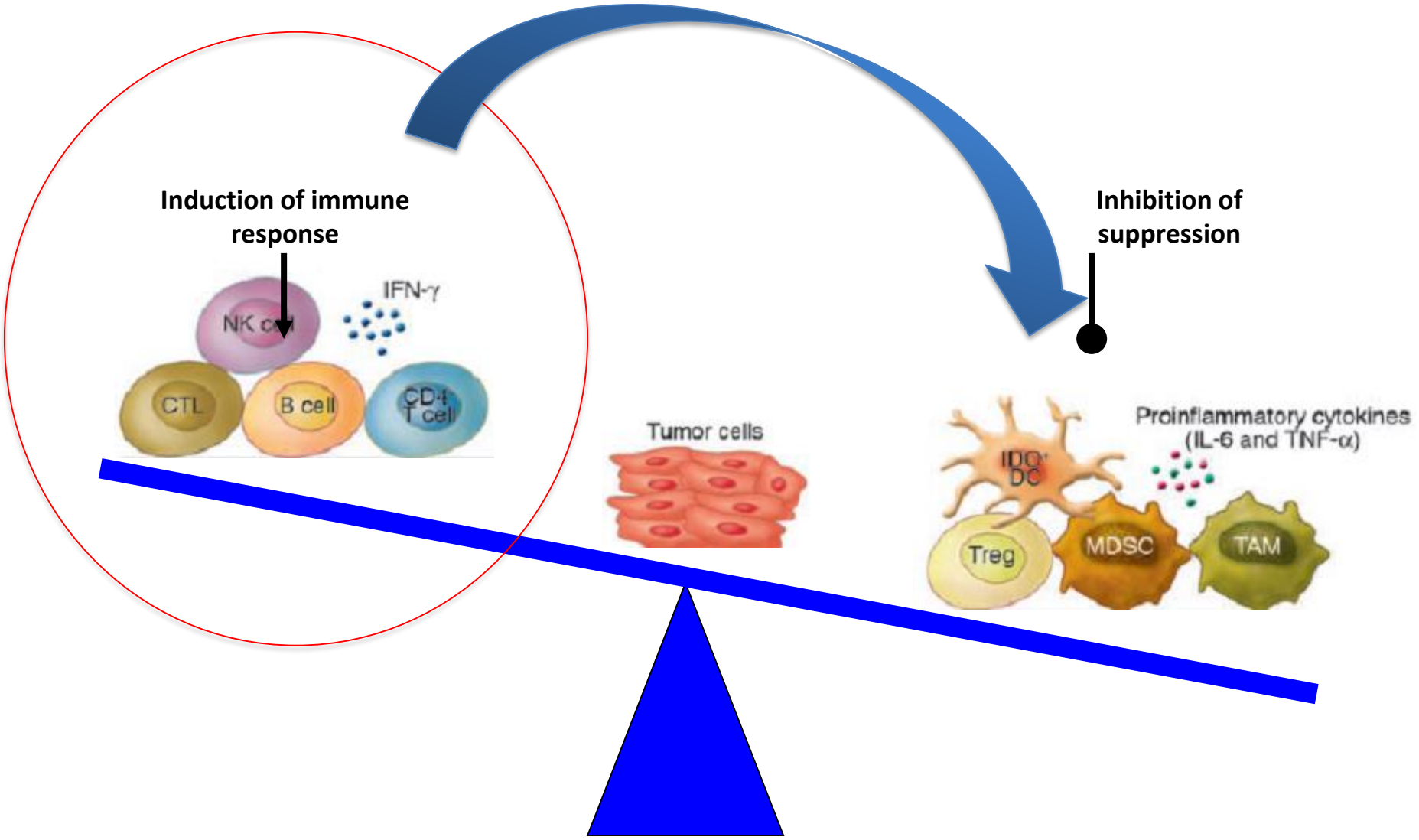
Combination of Anti-PD-1 with anti-OX40 has not shown good outcome

Combination of Anti-PD-1 with immune-priming agent

Combinational Immunotherapy



Effective Therapeutic immunebalance



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  - Jeane Silva