SESSION 2

Current Challenges and Opportunities: Selection of Experimental Agents in Combinations

NATIONAL ACADEMIES Sciences Engineering Medicine

MODERATORS

Gideon Blumenthal, Merck

Marc Theoret, Oncology Center of Excellence, Food and Drug Administration

SPEAKERS

Samir Khleif, Georgetown University Medical Center

Jane Healy, Merck

Jason Luke, University of Pittsburgh Medical Center

George Weiner, Holden Comprehensive Cancer Center

NATIONAL CANCER POLICY FORUM

Forum on DRUG DISCOVERY, DEVELOPMENT, and TRANSLATION

Understanding Immune Therapy Efficacy, Preclinical Models & Combination Resistance

Samir N. Khleif, MD
Georgetown University

KHLEIFGroup

Disclosure

- Advisory Board/Board Member: Northwest Bio, Bethesda, MD; UbiVac, LLC Providence, OR; LLC, Syndax Pharmaceuticals, Waltham, MA; PDS Biotechnology, North Brunswick Township, NJ; KAHR, Israel; AratingaBio INC, San Mateo, CA; IO Biotechnology, Copenhagen, Denmark; CanImGuide Therapeutics, Malmo, Sweden; Bioline Therapeutics, Israel; McKinsey Cancer Center, McKinsey and Company; Incyte, Alapocas, Delaware; Israel Biotech Fund GP Partners, L.P., Israel; Cancer Panel, LLC Advaxis Immunotherapeutics; Incyte
- KOL/Consultant: J&J, AstraZenica, Lycera, Berringer Engelheim
- Unrestricted preclinical Research funding: AstraZeneca, Bioline Therapeutics, Lycera, IO Biotech, Syndax, Biotechnologies, HeatBio/Pelican, BMS

Immuno-therapy Resistance

- Primary resistance
- Secondary resistance

Immuno-therapy Resistance

- General mechanisms
  - Intrinsic Tumor biology
    - Lack of antigen presentation
      - Lack of antigen expression
      - Lack of antigen processing and presentation (TAP, MHC, B2M)
    - T cell deprived environment (b-Catenin, MAPK, etc..)
  - Suppressive micro- environment

- Treatment Specific mechanisms
  - Low PDL1 expression
  - JAK2 mutation

Immuno-therapy Resistance

- Immuno-Combination incompatibility
- Immunotherapy biologic incompatibility
- Adaptive resistance

Immuno-therapy Resistance

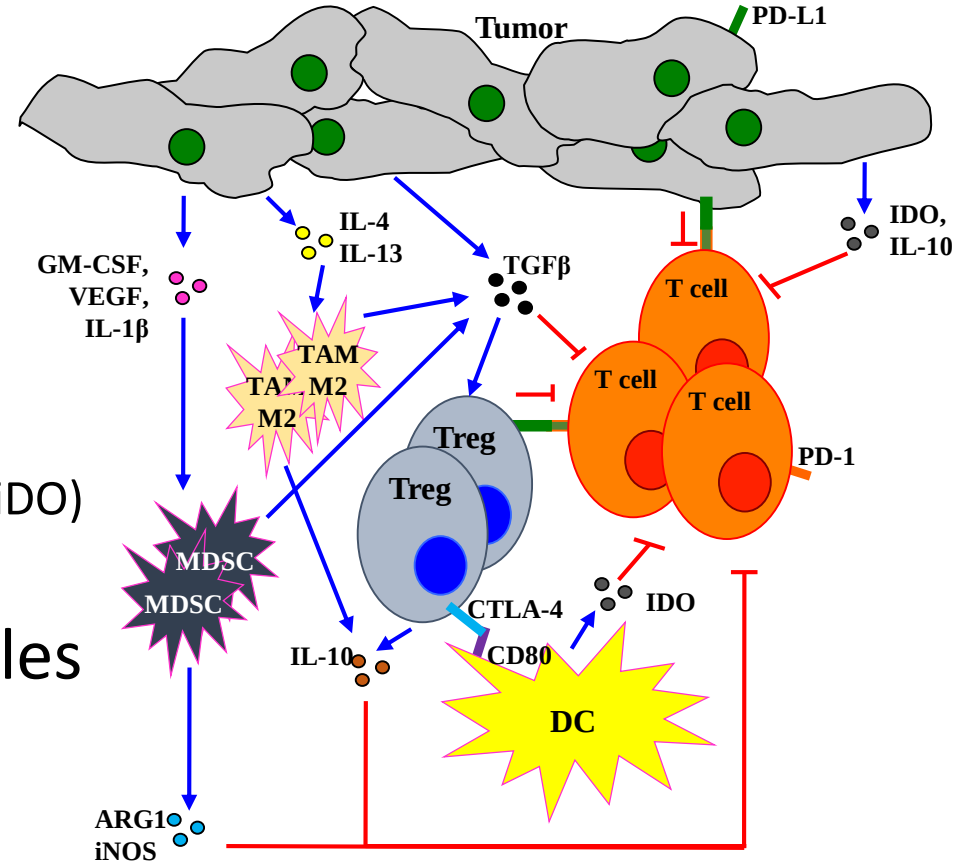
- Immunotherapy biologic incompatibility
- Immuno-Combination incompatibility
- Adaptive resistance

Iatrogenic Resistance

Immunotherapy Combination

Immunotherapy Combination

- Priming agents e.g. 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)
- Reprogramming therapy; Small Molecules
- Oncolytic Viruses
- T cell therapy, including CARS
- Standard Therapy



The Concept of:

X + Y = ??

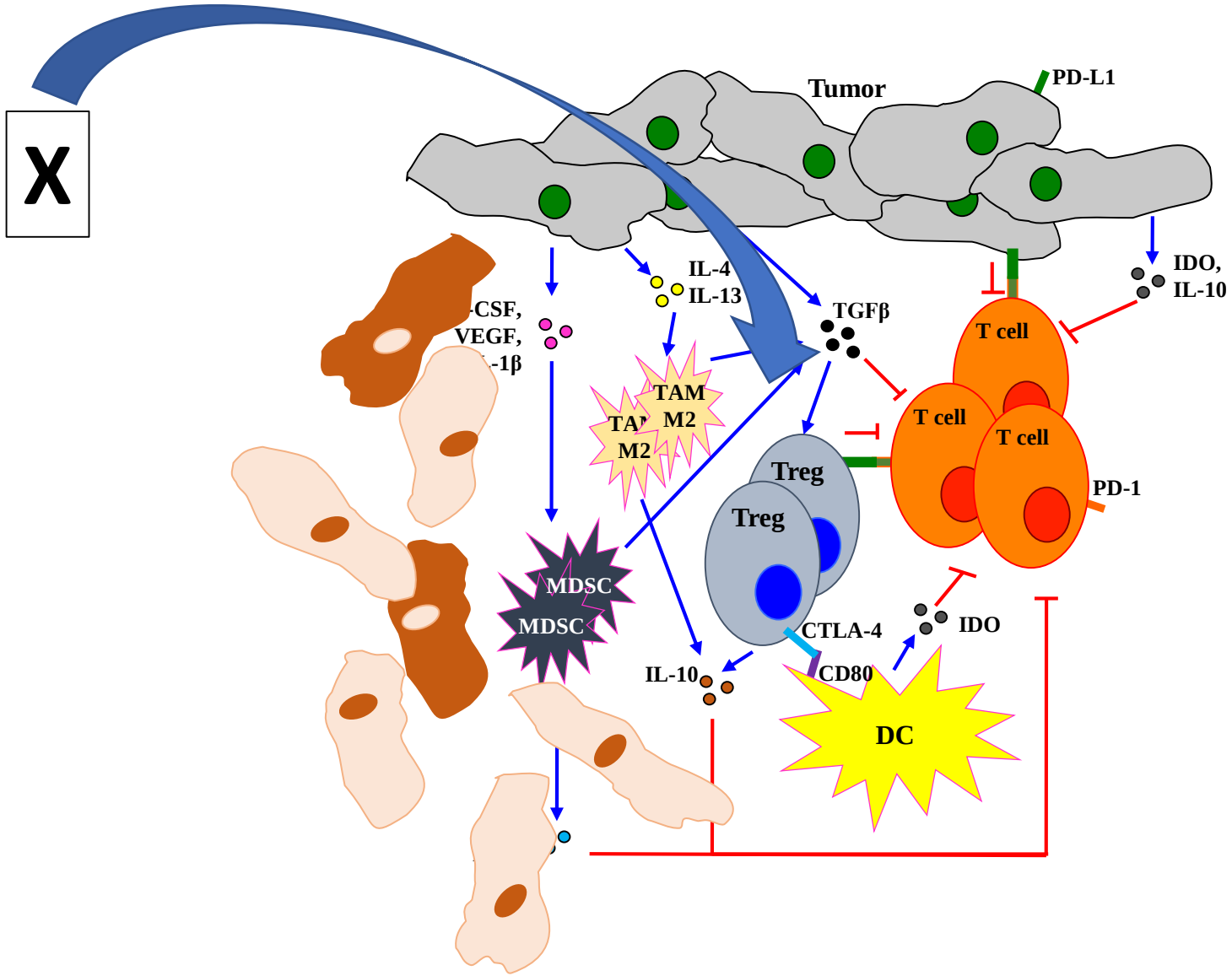
The Concept of:

$$X + Y = A$$

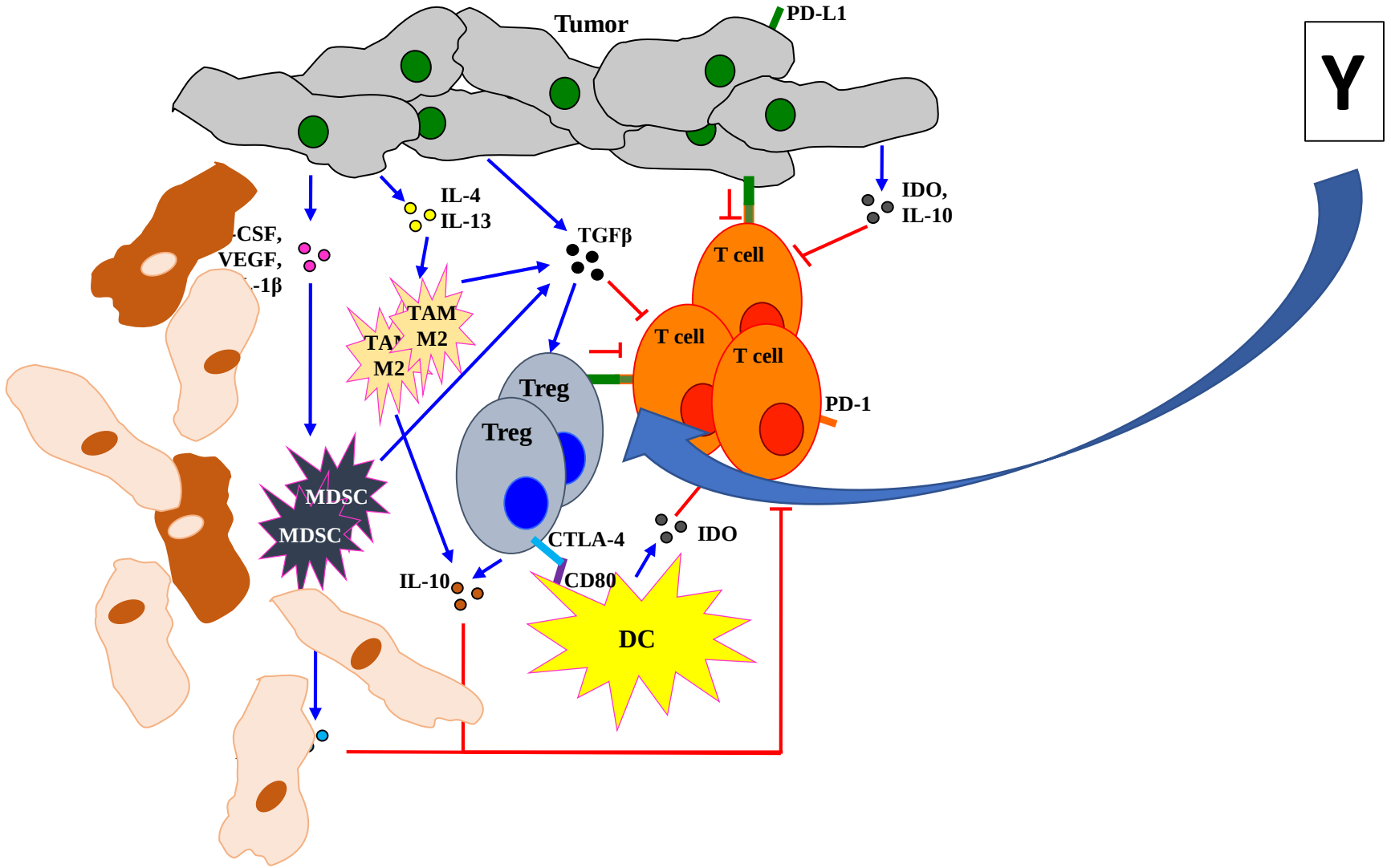
$$X > Y = B$$

$$Y > X = C$$

Tumor-Immune Interaction



Tumor-Immune Interaction



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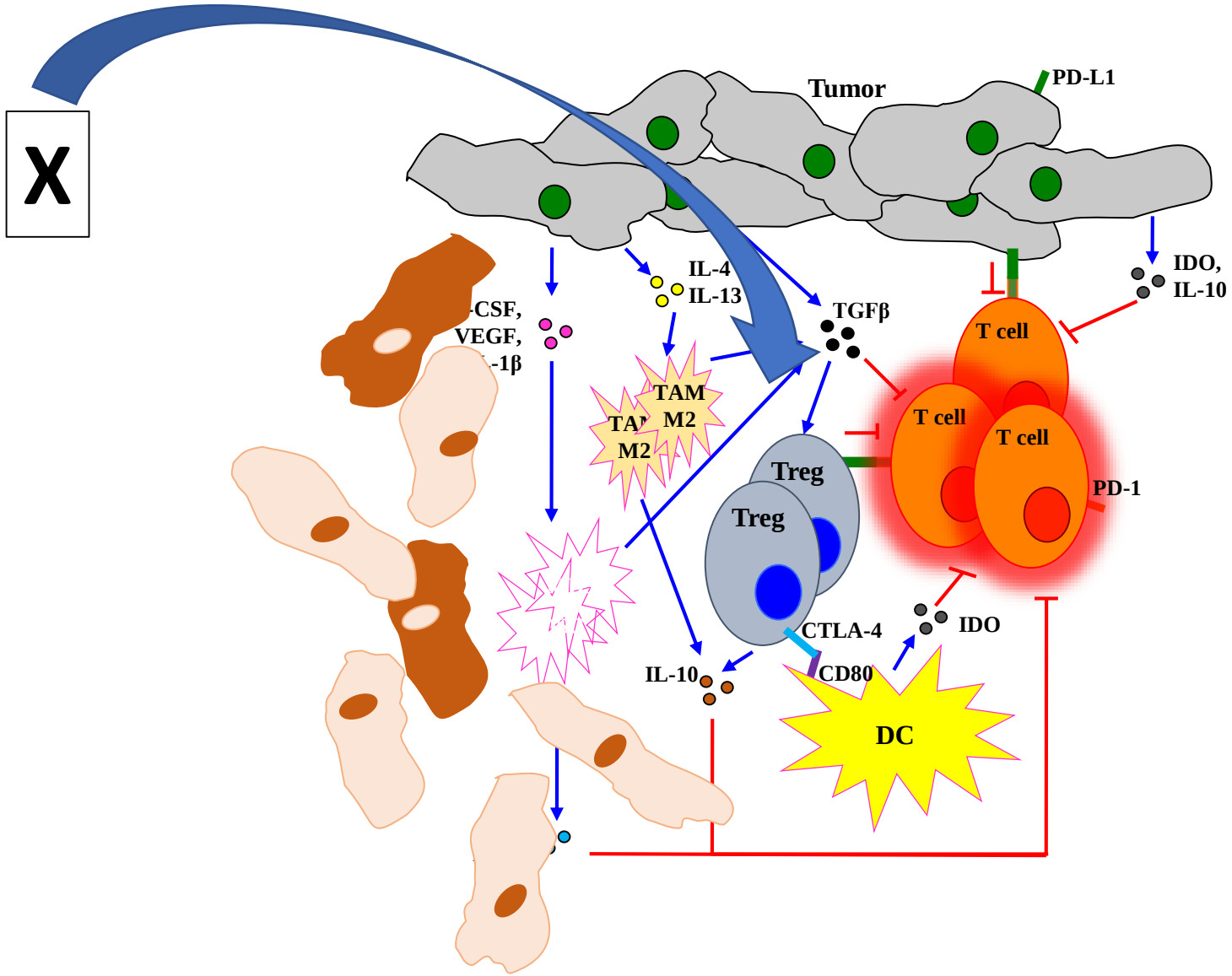

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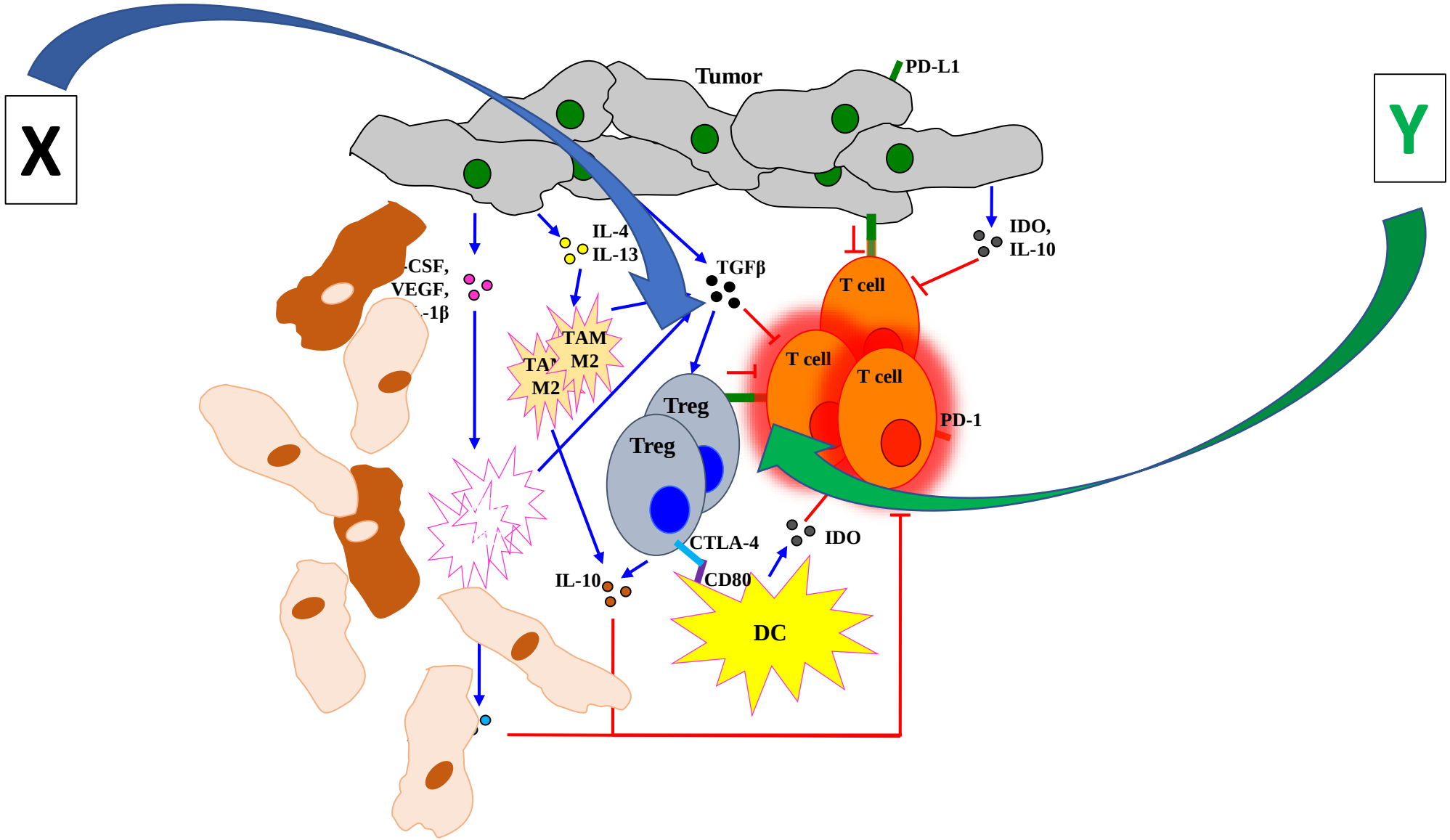

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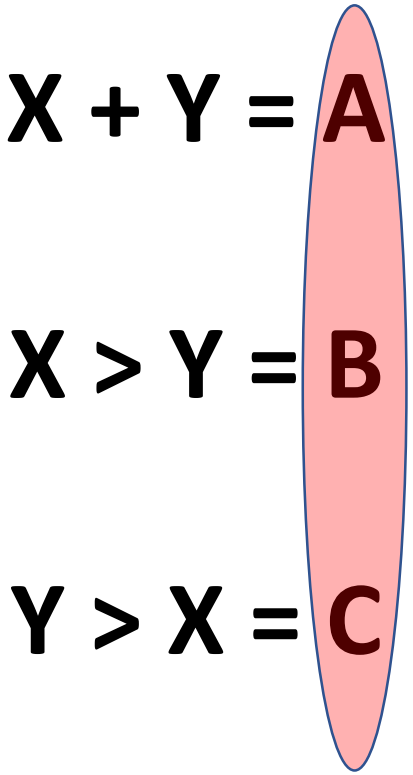


The Concept of:

1 + 1 = 2

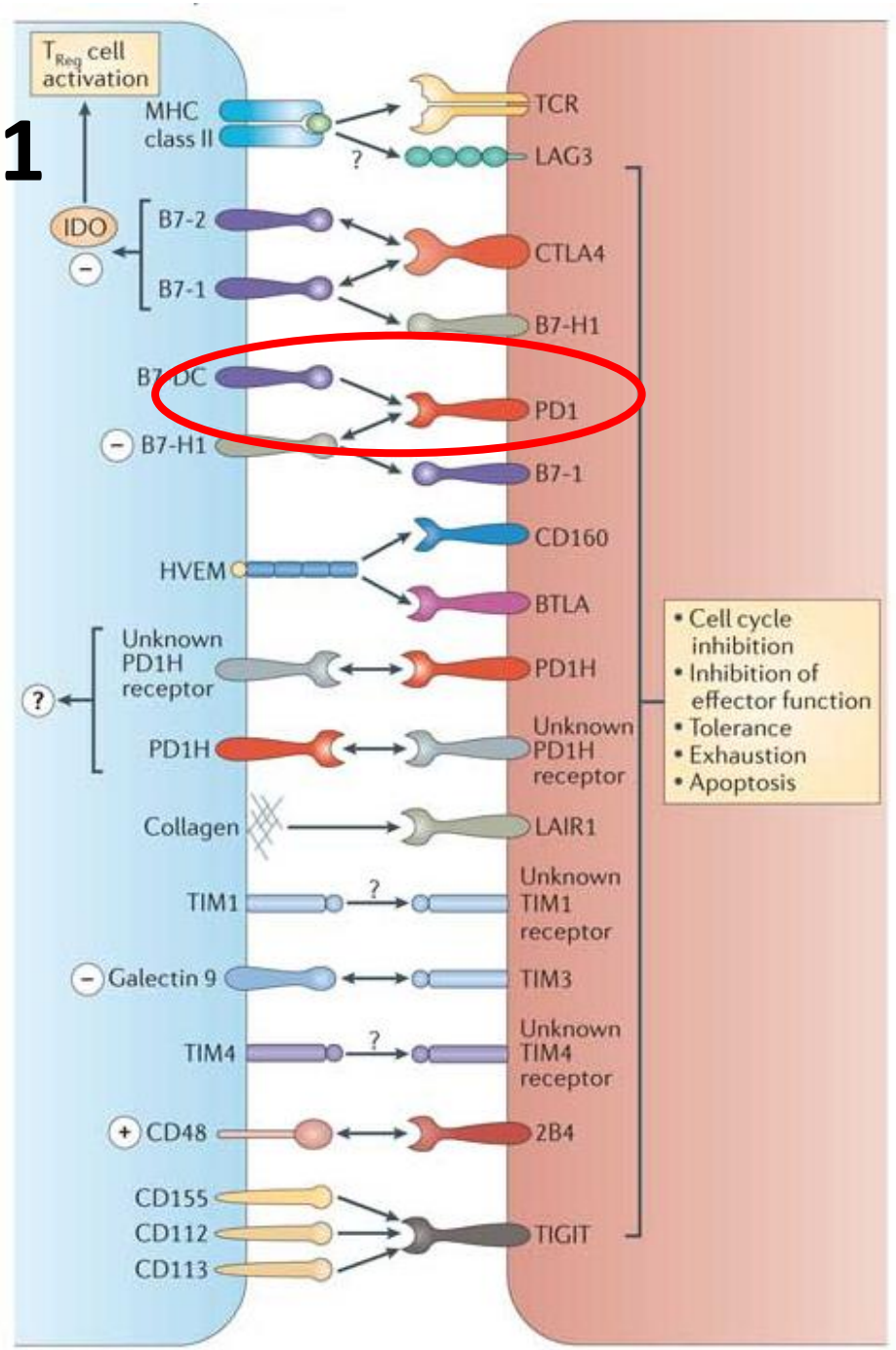
The Concept of:

1 + 1 = 2,3,4,5

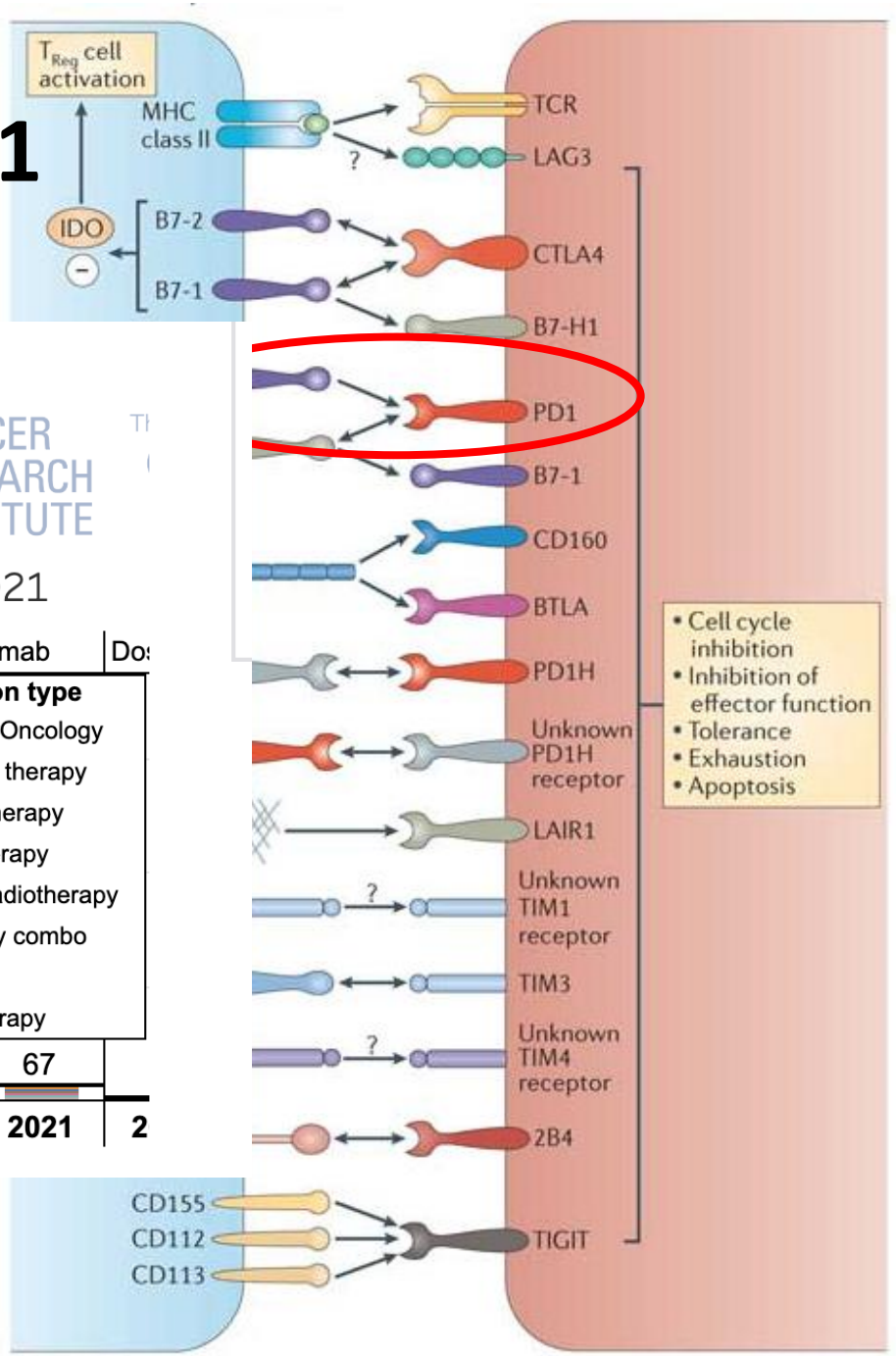
The Concept of:

1 + 1 = 0

Anti-PD1


T_{Reg} cell activation
MHC class II
TCR
LAG3
IDO
B7-2
CTLA4
B7-1
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

Anti-PD1



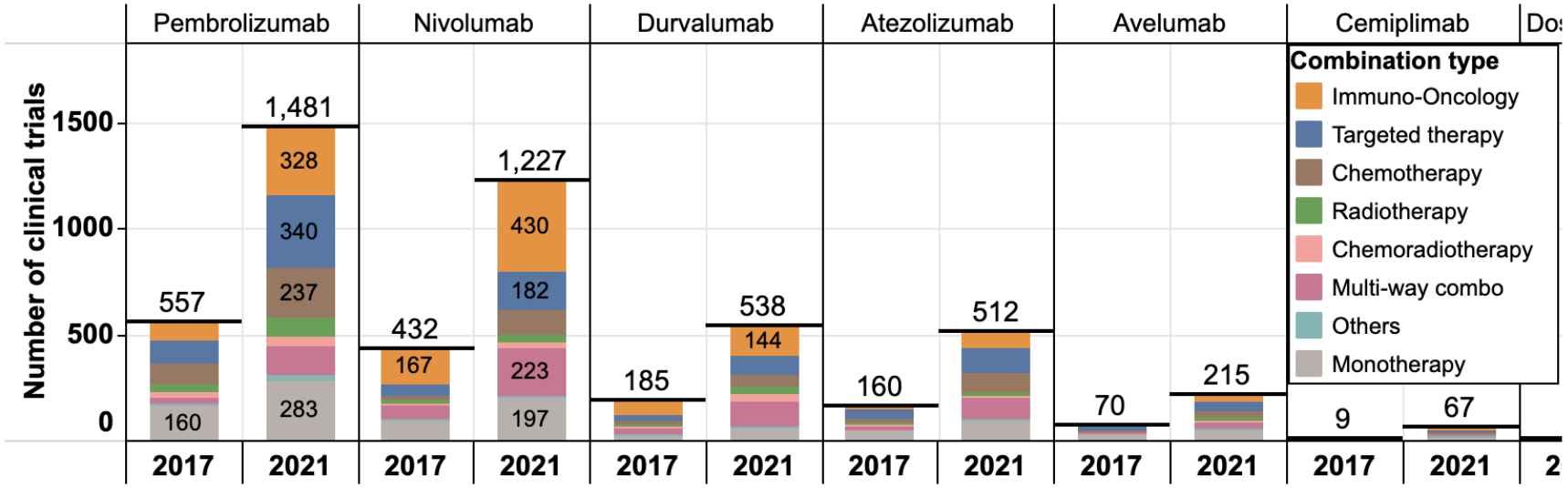
PD-1/L1 mAb Clinical Trial Landscape

Published on February 10, 2022

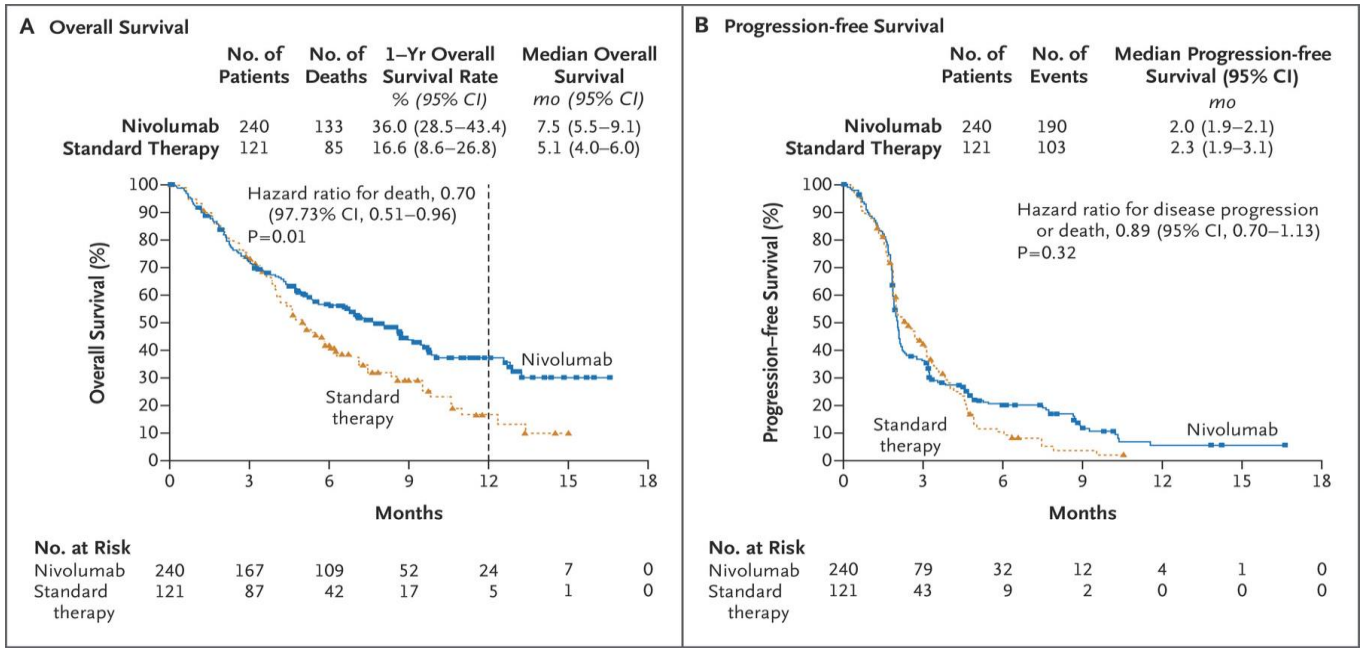
Sources: CRI, CRI Analytics, and Clinicaltrials.gov

CANCER RESEARCH INSTITUTE

Total 5,683 interventional trials as of December, 2021

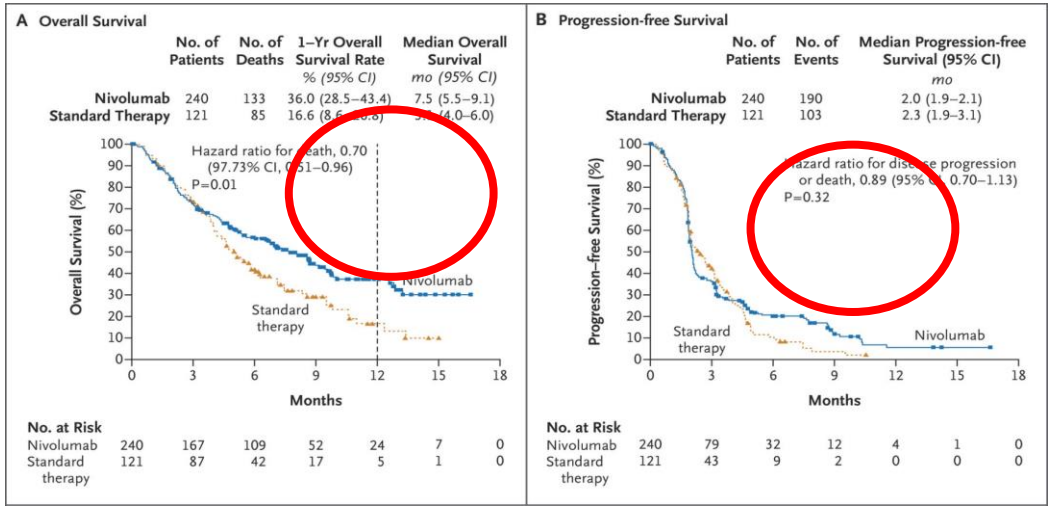


85% 0f patients do not response to anti-PD1 therapy



Who respond to anti-PD1 therapy

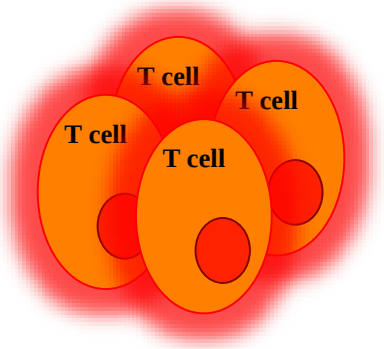
- Patients with immune high T cell infiltration “Hot”
- Patients with high TMB



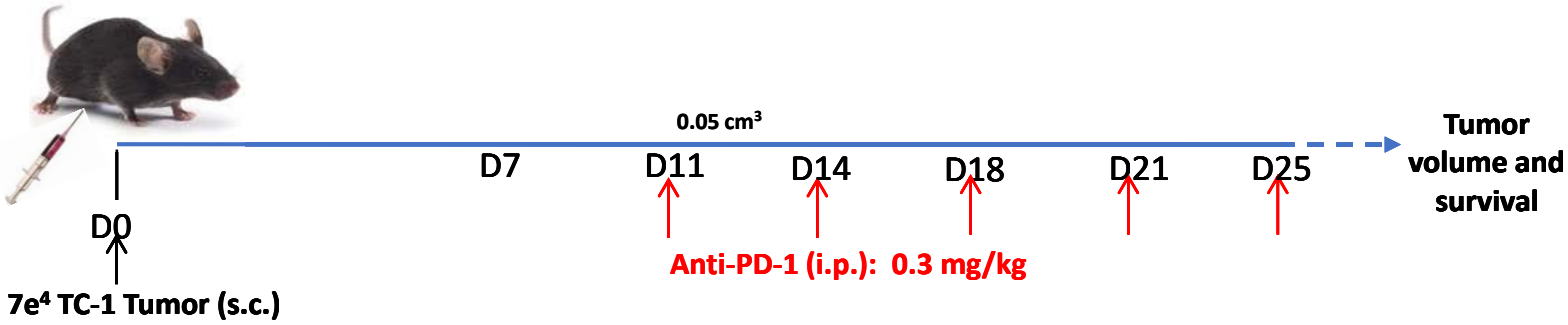
Who respond to anti-PD1 therapy

- Patients with immune high T cell infiltration “Hot”
- Patients with high TMB

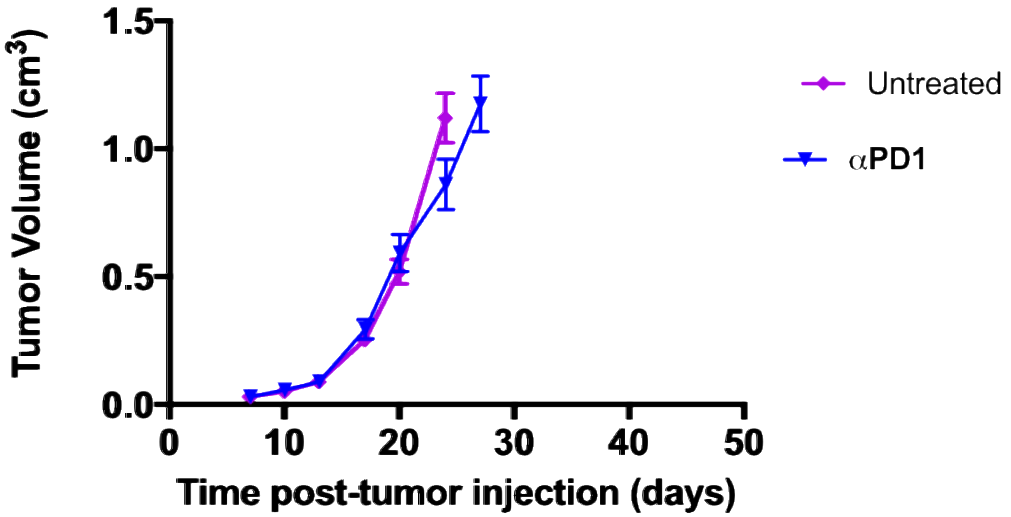
Patients with properly primed or activated CD8 T cells

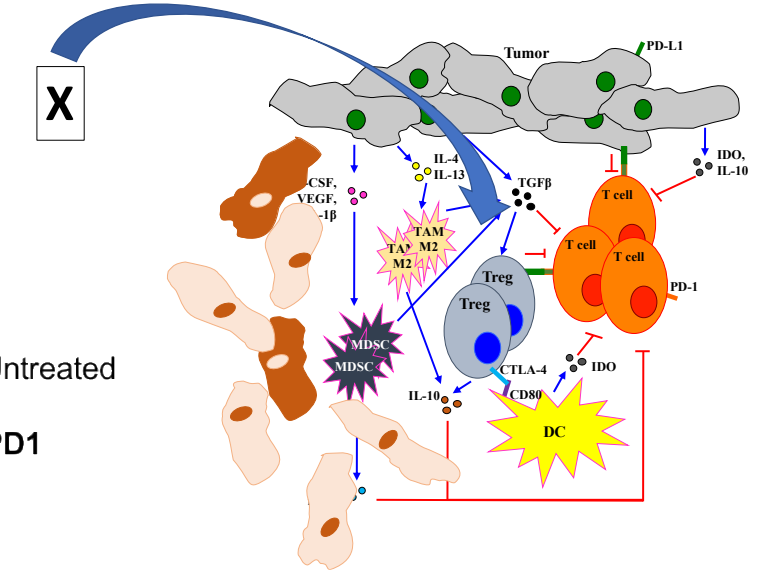


PD-1 blockade prior to antigen priming with cancer vaccine abrogates the anti-tumor immune effects



Anti-PD-1 administered QOW

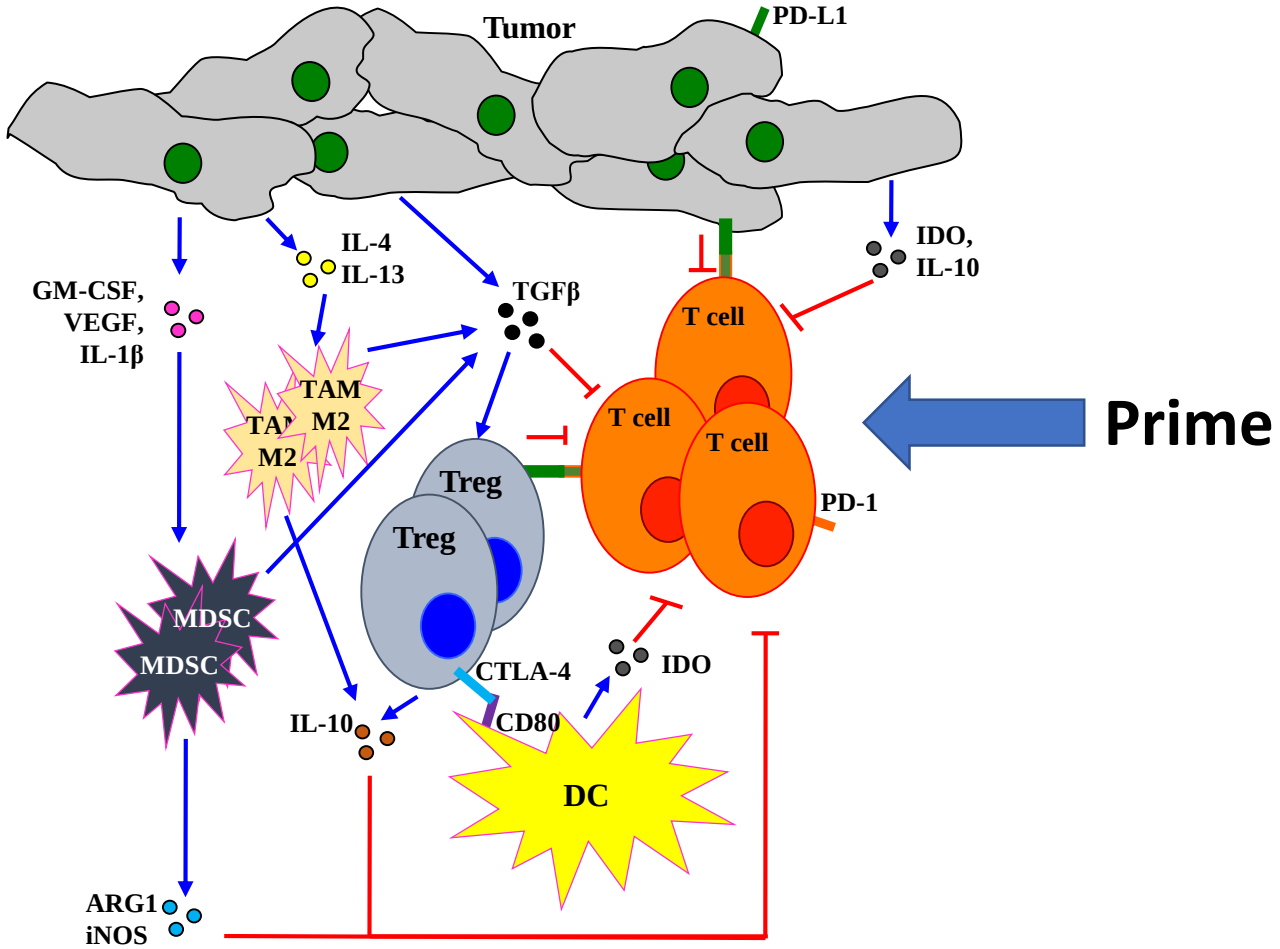




Could activation of T cell enhance anti-PD1 response?

Mika Mkrtichyan

Rajeev Shrimali



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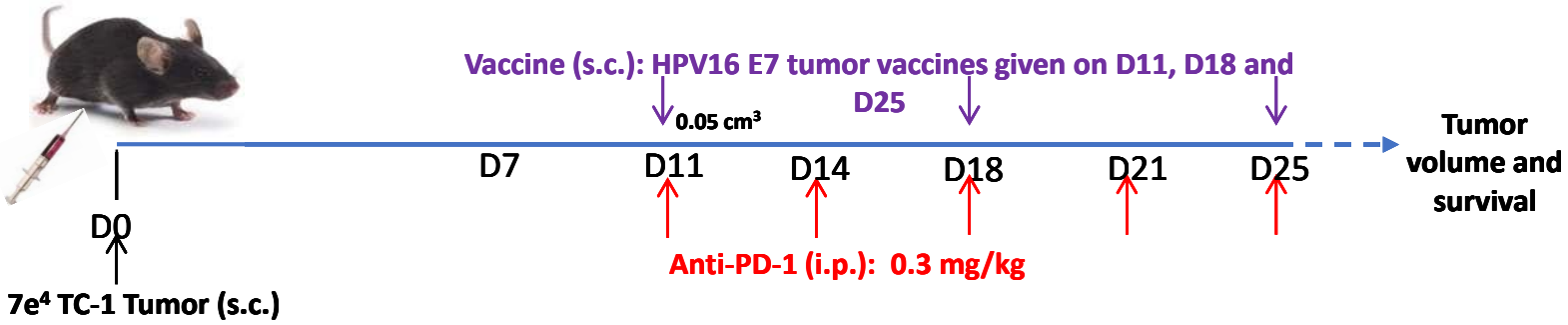
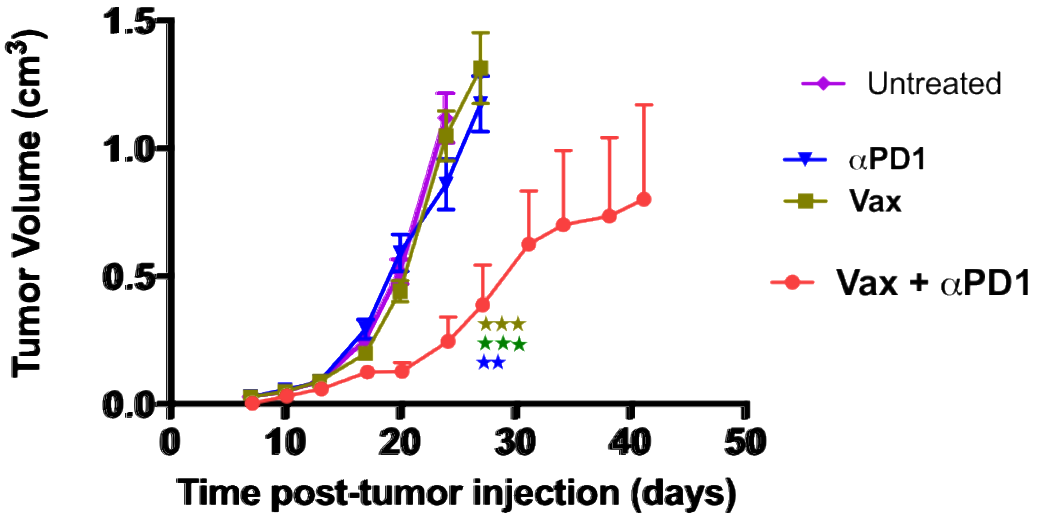


Anti-PD-1 starts either on Day 7 or Day 11 and vaccine starts on Day 11



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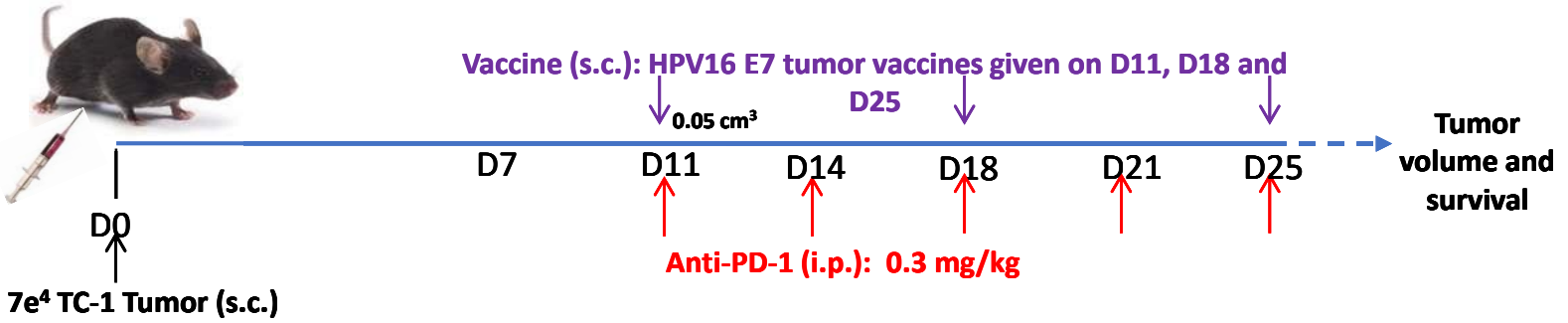

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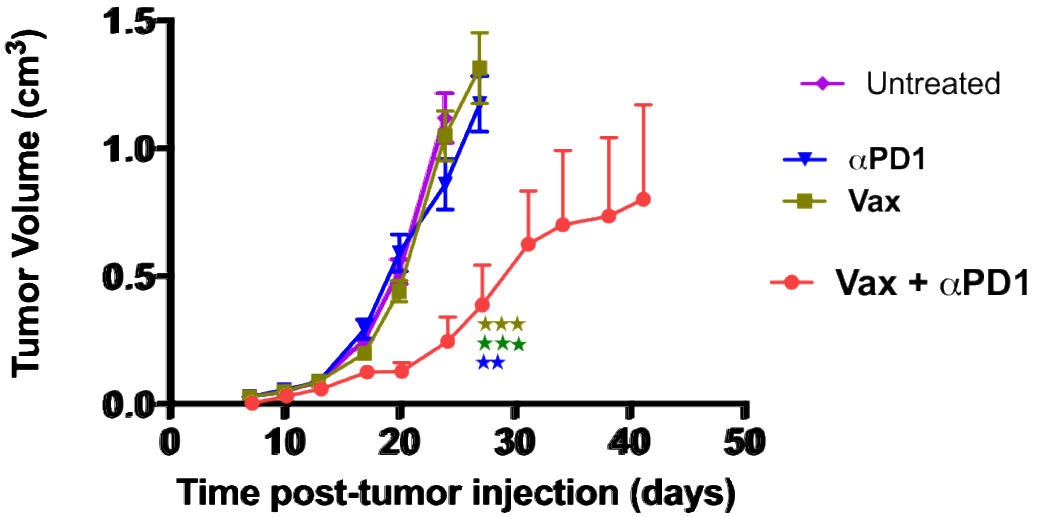
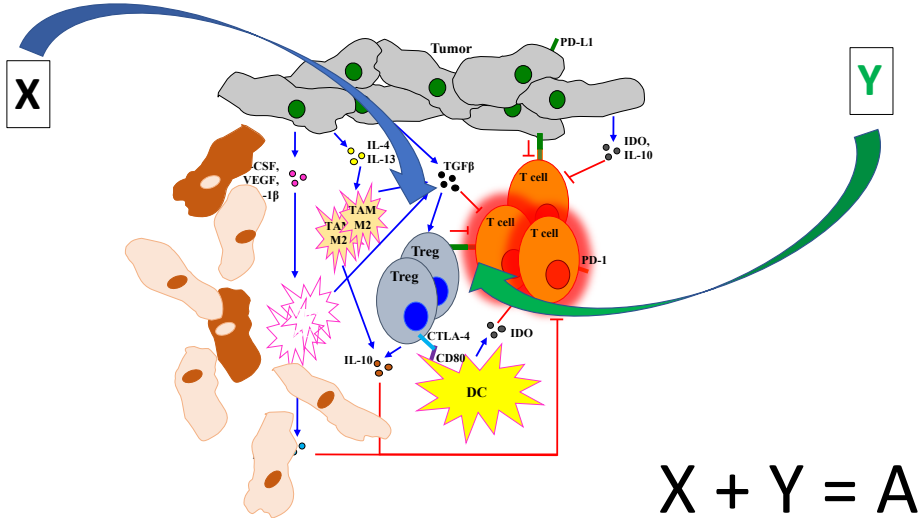
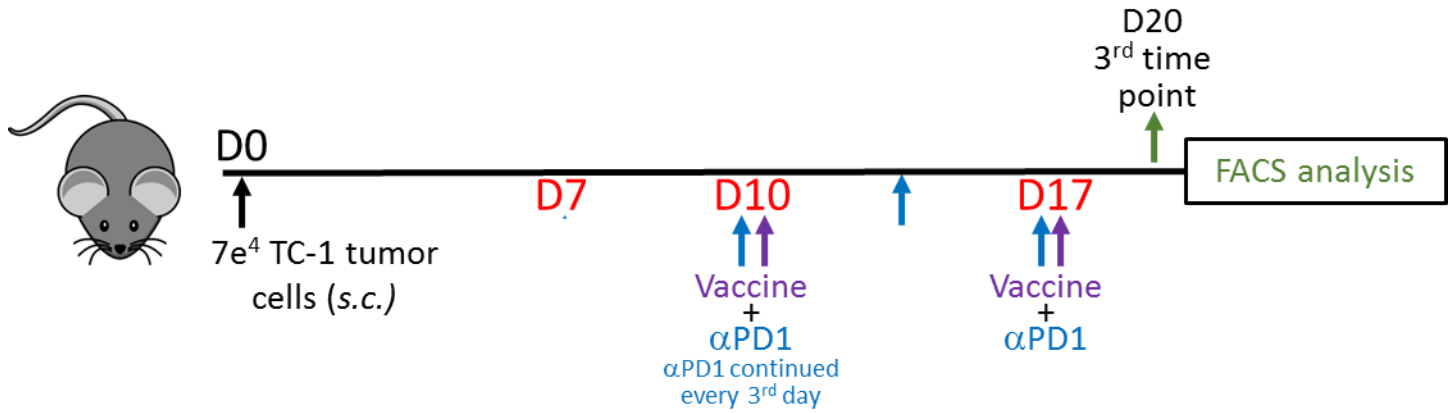
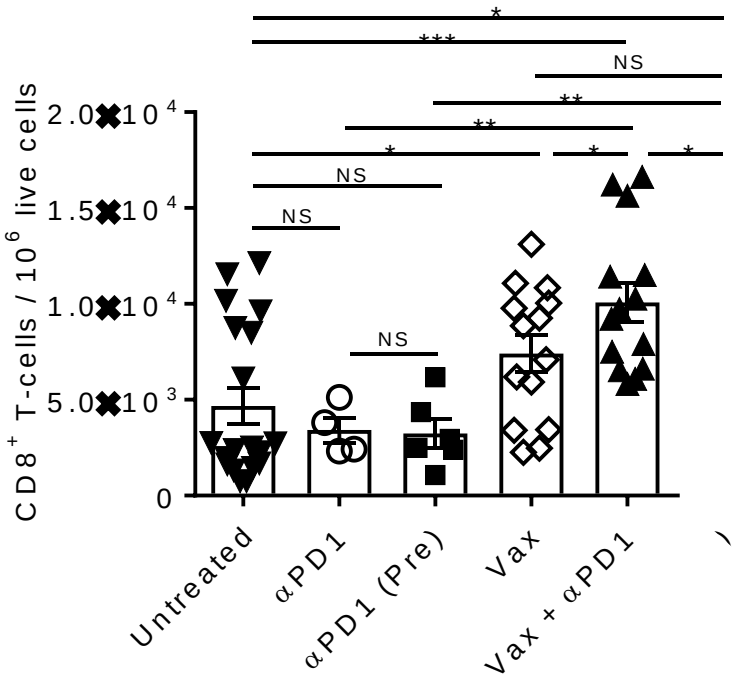




X + Y = A

PD-1 blockade prior to antigen priming with cancer vaccine results in impaired antigen-specific CD8+ T cells tumor-infiltration





D20

Verma, et al, ***Nature Immunol***

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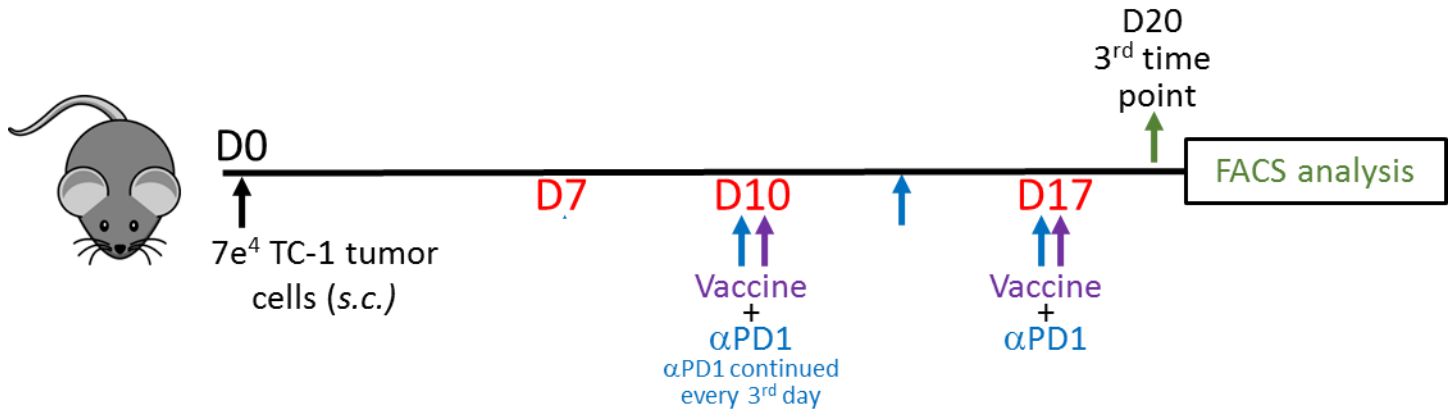

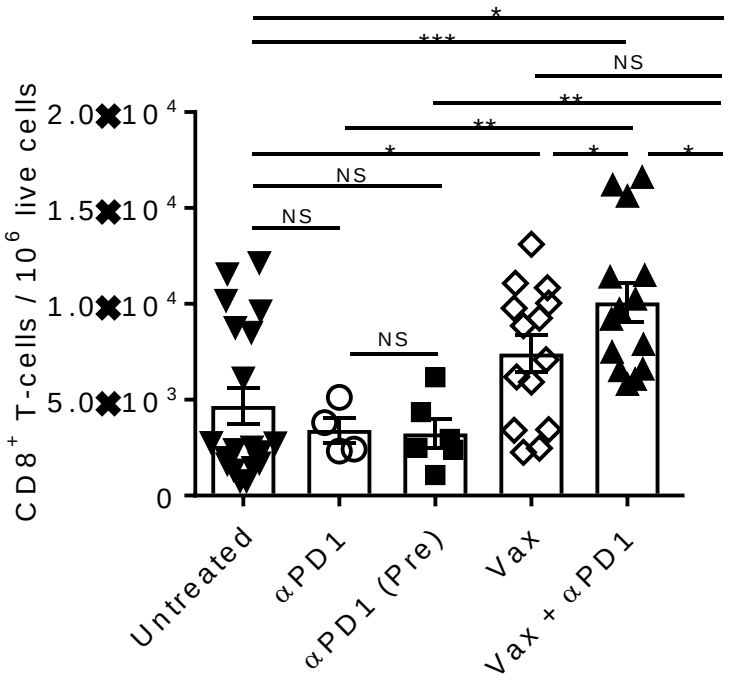

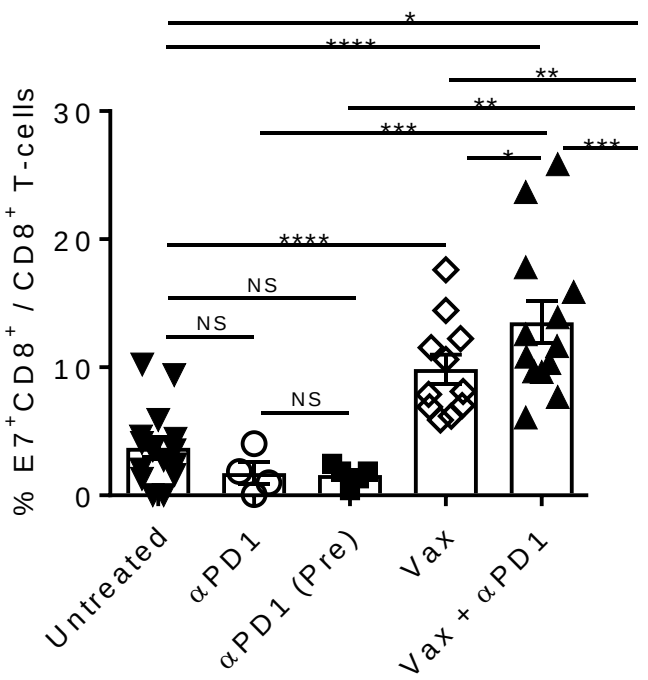

D20

Verma, et al, *Nature Immunol*

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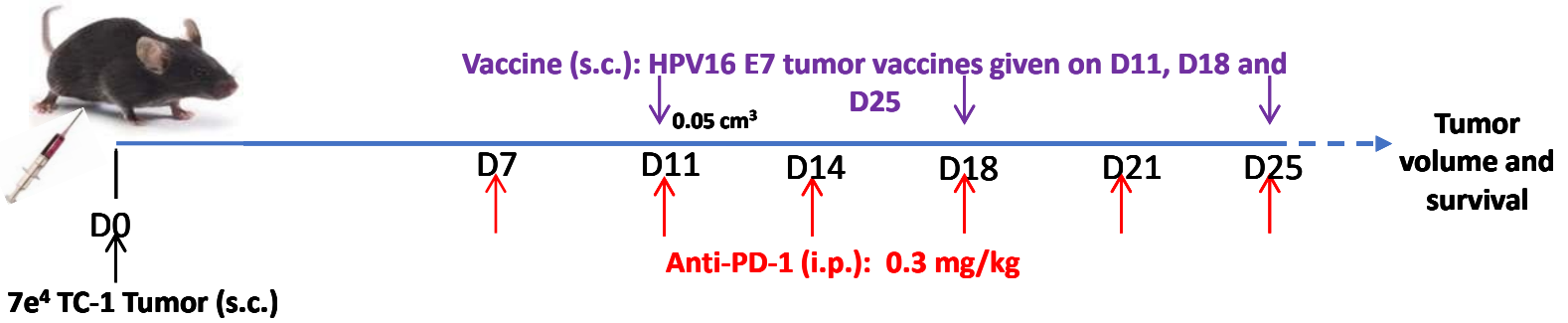
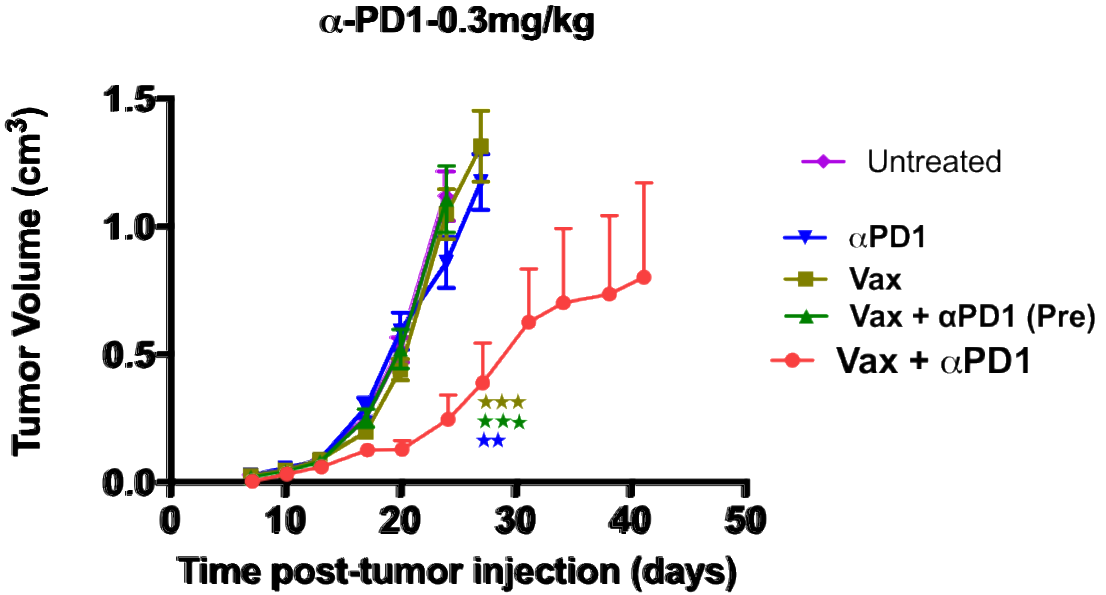


When

Anti-PD-1 starts either on Day 7 or Day 11 and vaccine starts on Day 11



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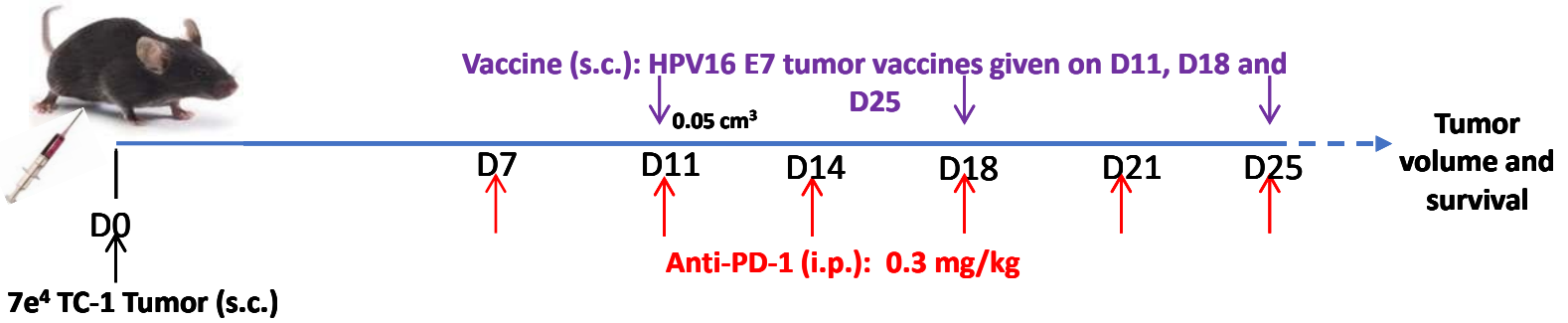

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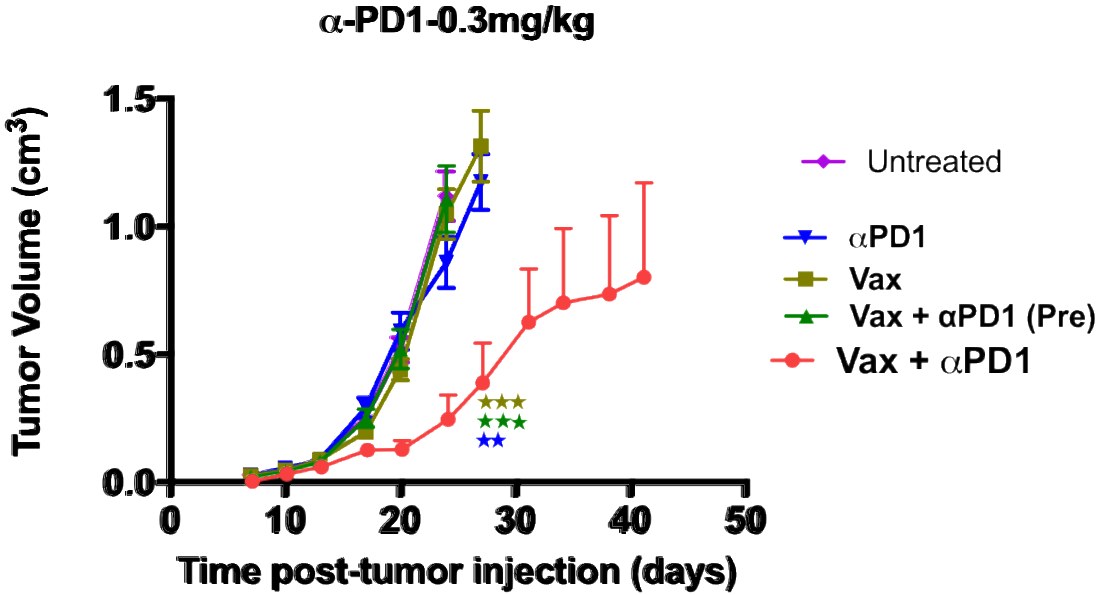
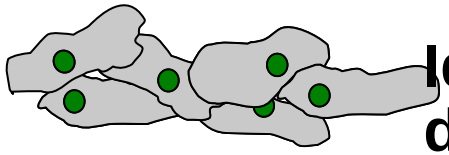
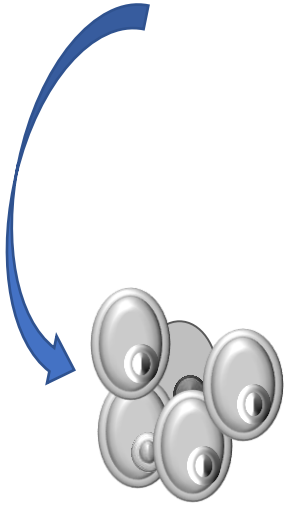




Identified a New mechanism for why patients do not respond to immunotherapy



nature immunology

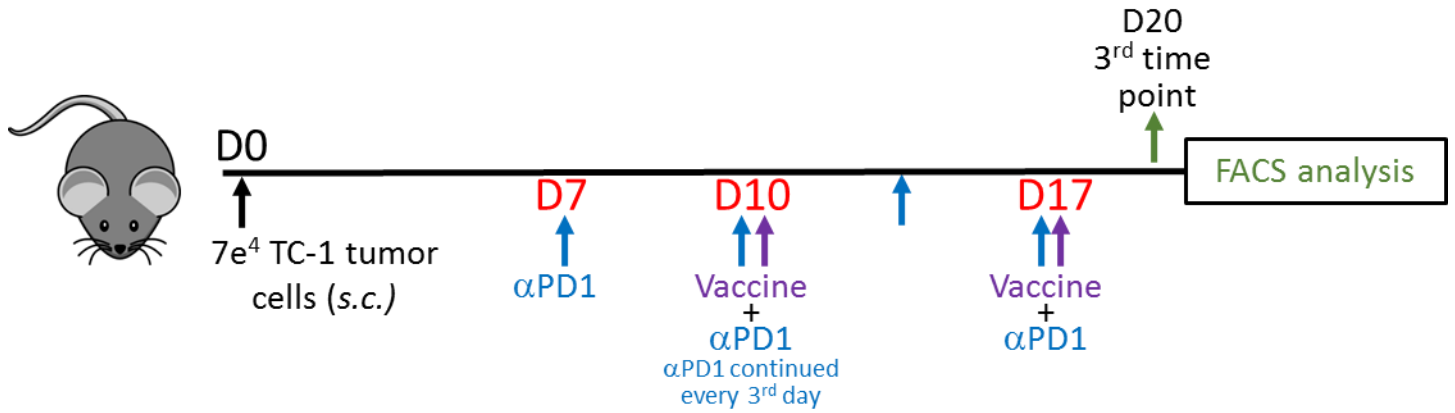
ARTICLES

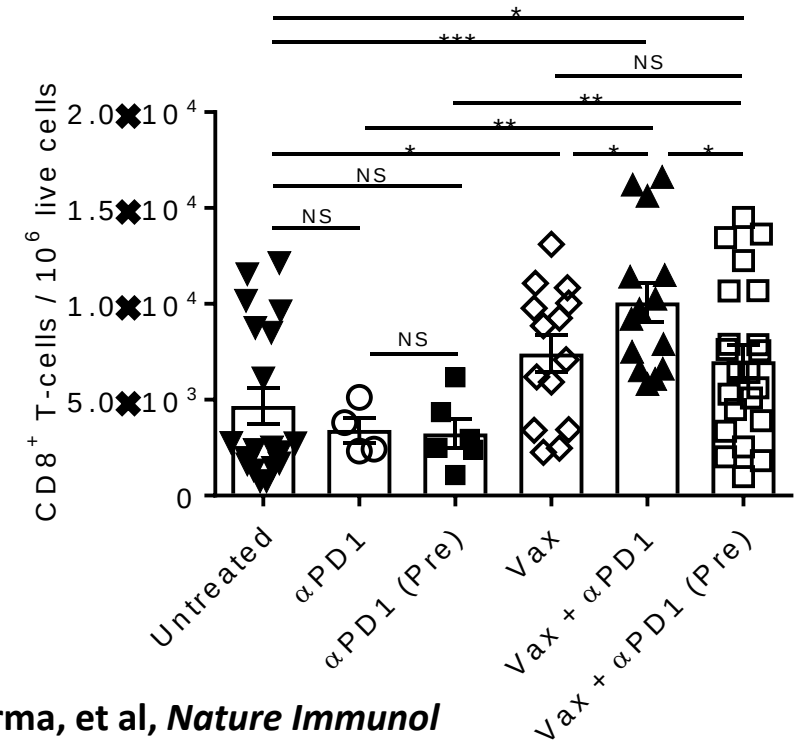
https://doi.org/10.1038/s41590-019-0441-y

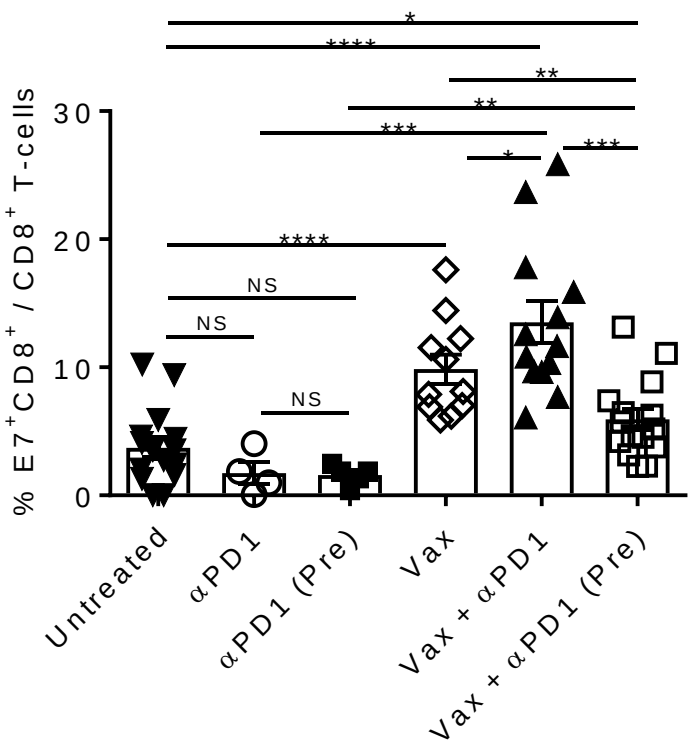
PD-1 blockade in subprimed CD8 cells induces dysfunctional PD-1^{+}CD38^{hi} cells and anti-PD-1 resistance

Vivek Verma[1,11], Rajeev K Shrimali[1,12], Shamim Ahmad[1,13], Winjie Dai[1], Hua Wang[1], Sumin Lu[1], Rahul Nandre[1,11], Pankaj Gaur[1,11], Jose Lopez[11], Moshe Sade-Feldman[2,3], Keren Yizhak[3], Stacey L. Bjorgaard[2,3], Keith T. Flaherty[2], Jennifer A. Wargo[4], Genevieve M. Boland[5], Ryan J. Sullivan[2], Gad Getz[2,3,6], Scott A. Hammond[7], Ming Tan[8], Jingjing Qi[9], Phillip Wong[9], Taha Merghoub[9,10], Jedd Wolchok[9,10], Nir Hacohen[2,3], John E. Janik[1,14], Mikayel Mkrtichyan[1,11,15], Seema Gupta[1,11] and Samir N. Khleif[1,11]*

PD-1 blockade prior to antigen priming with cancer vaccine results in impaired antigen-specific CD8+ T cells tumor-infiltration







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Verma, et al, ***Nature Immunol***

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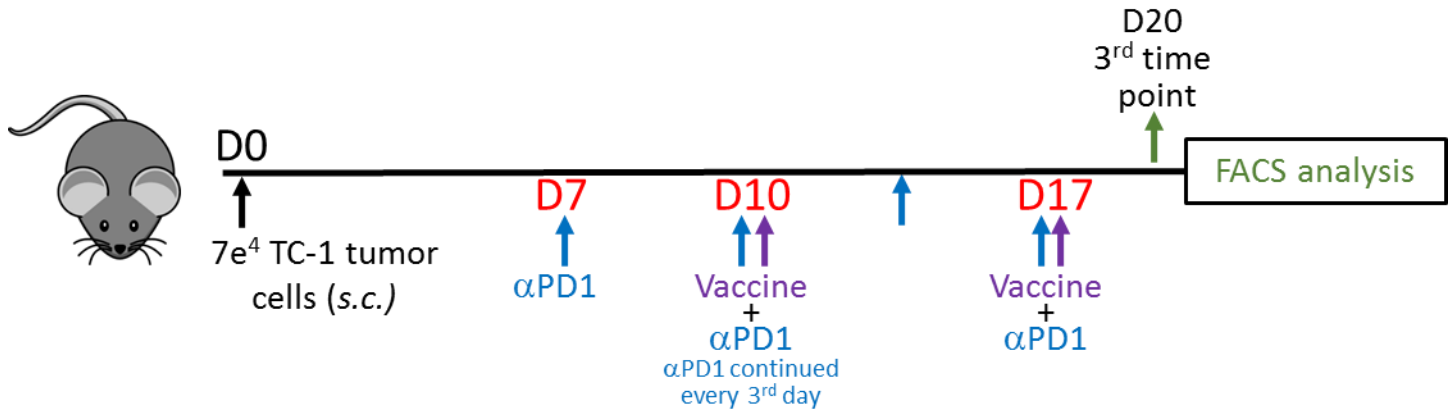

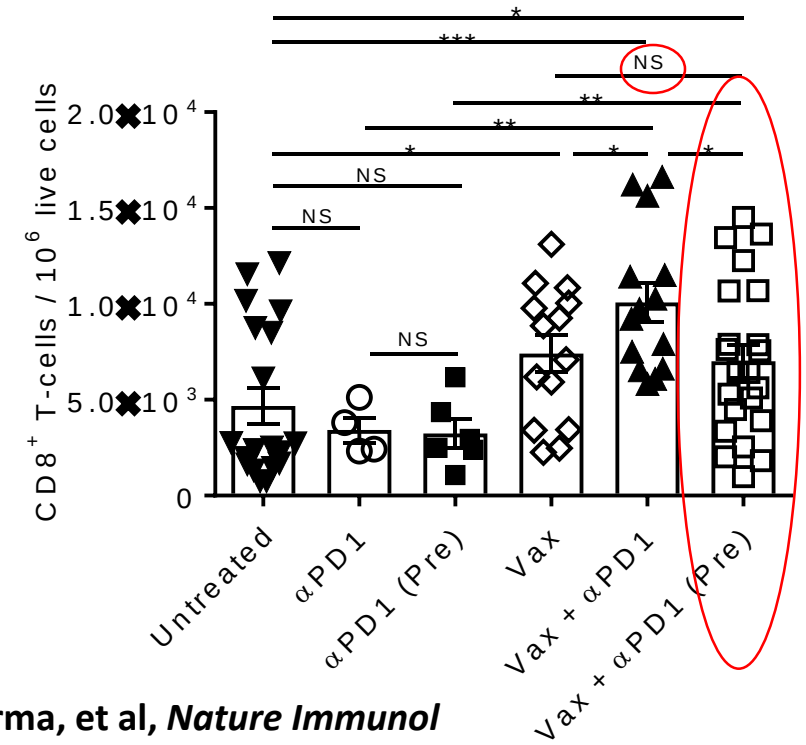

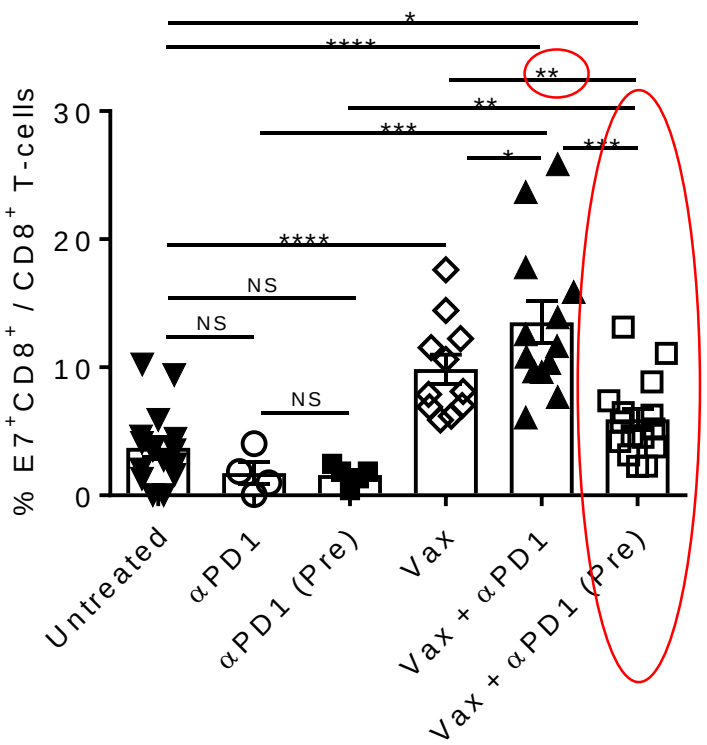

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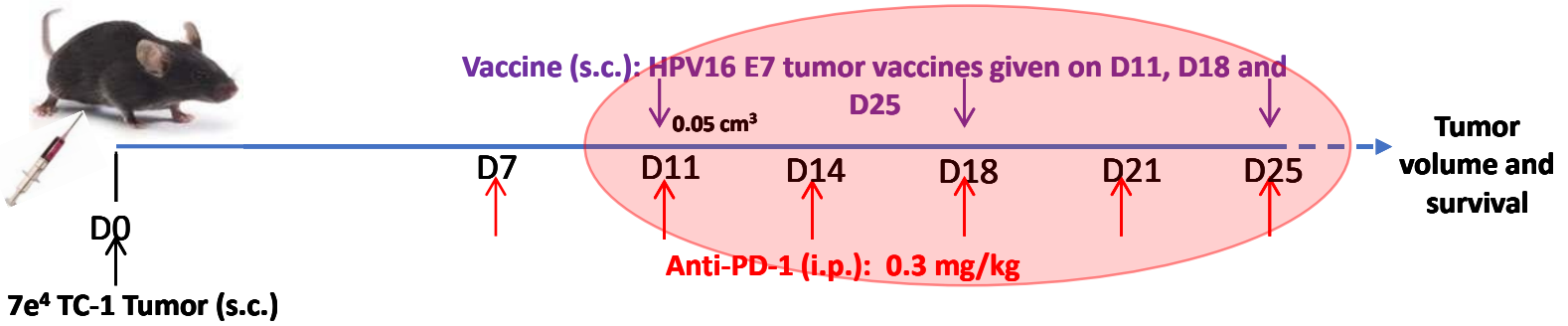

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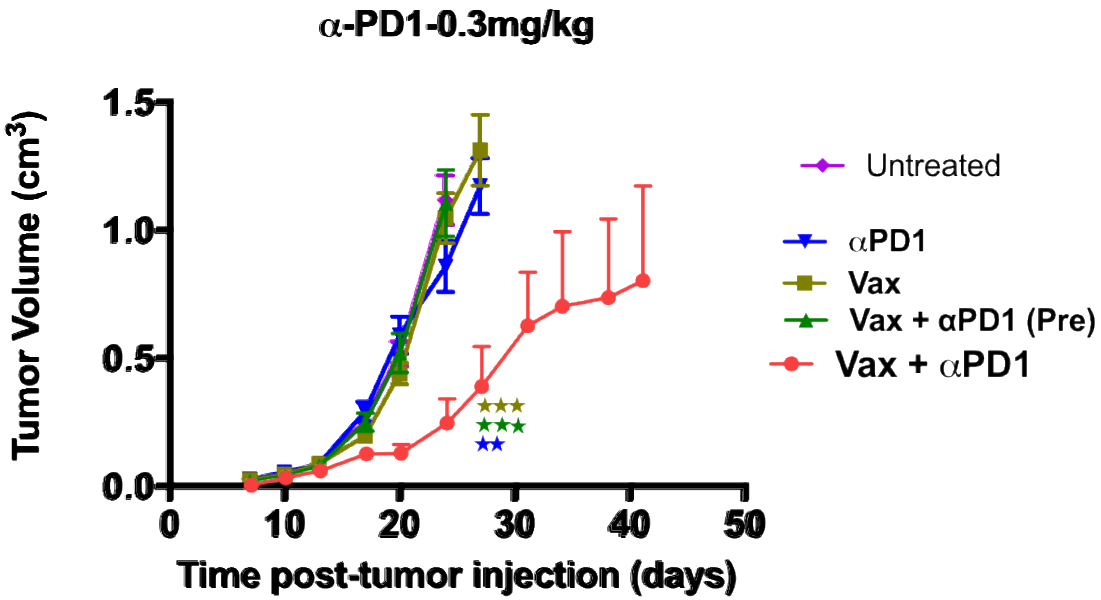
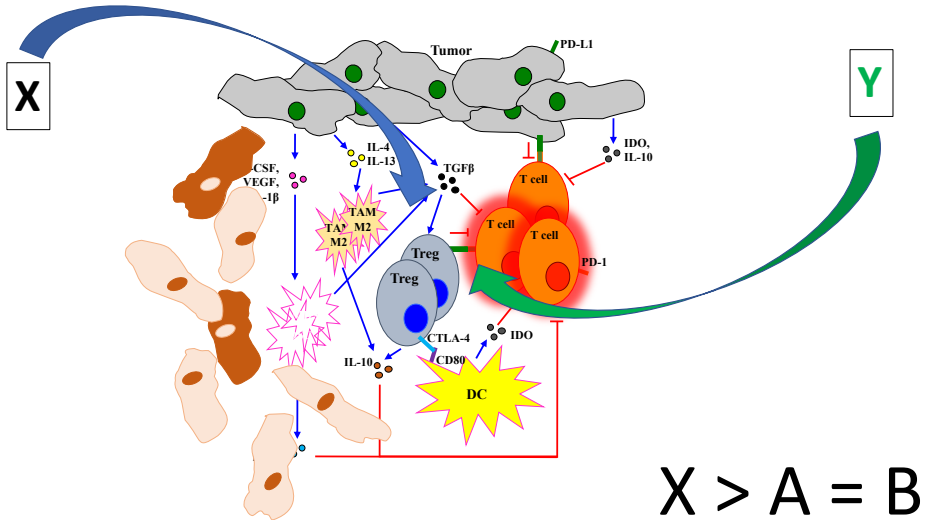
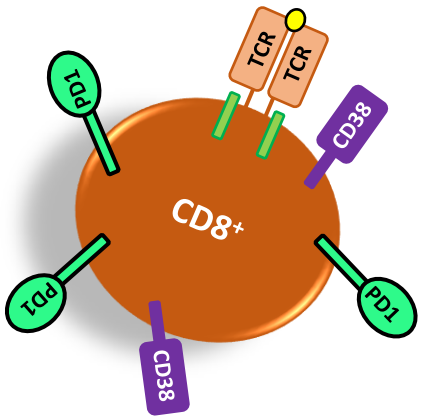
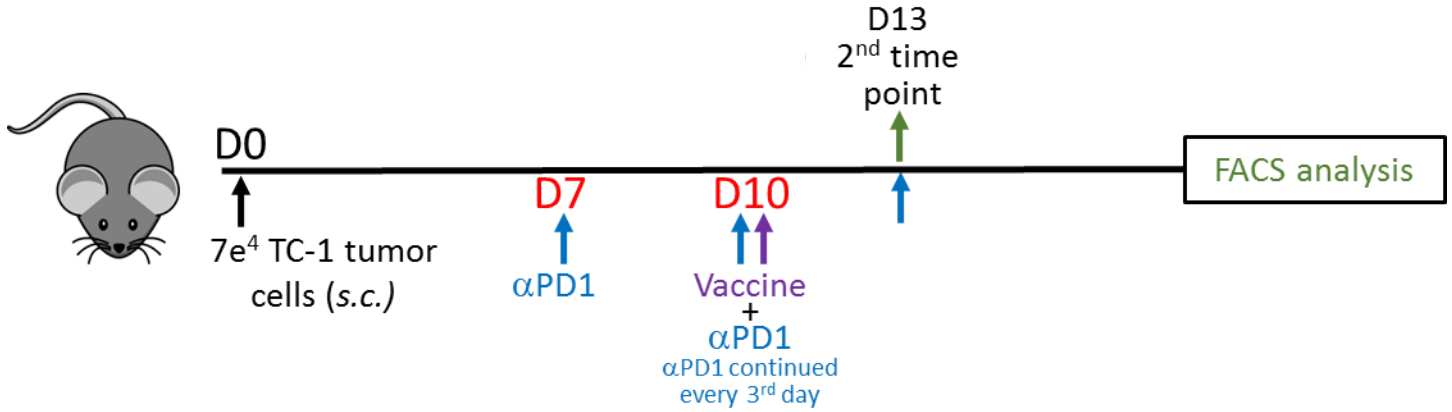


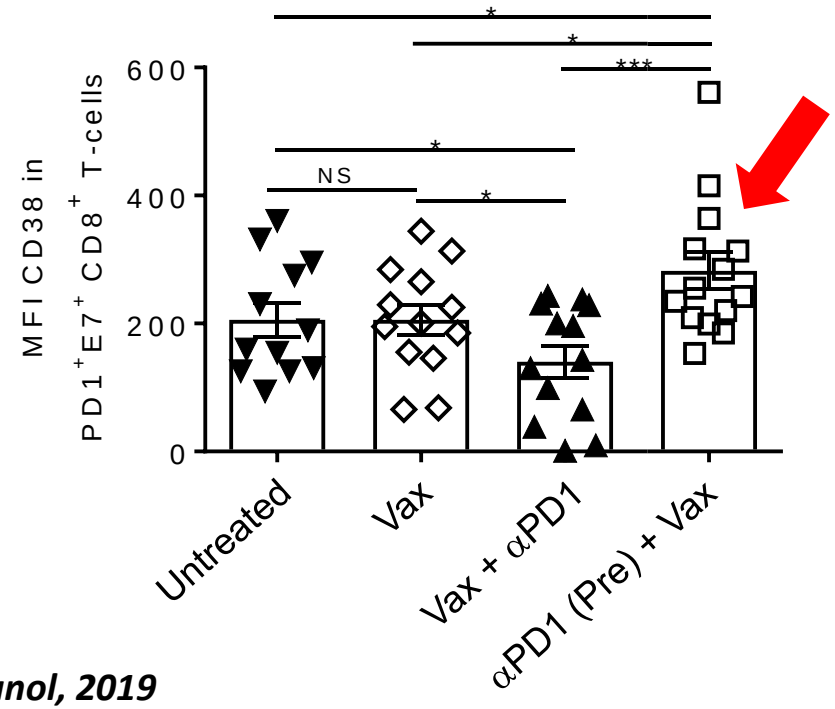


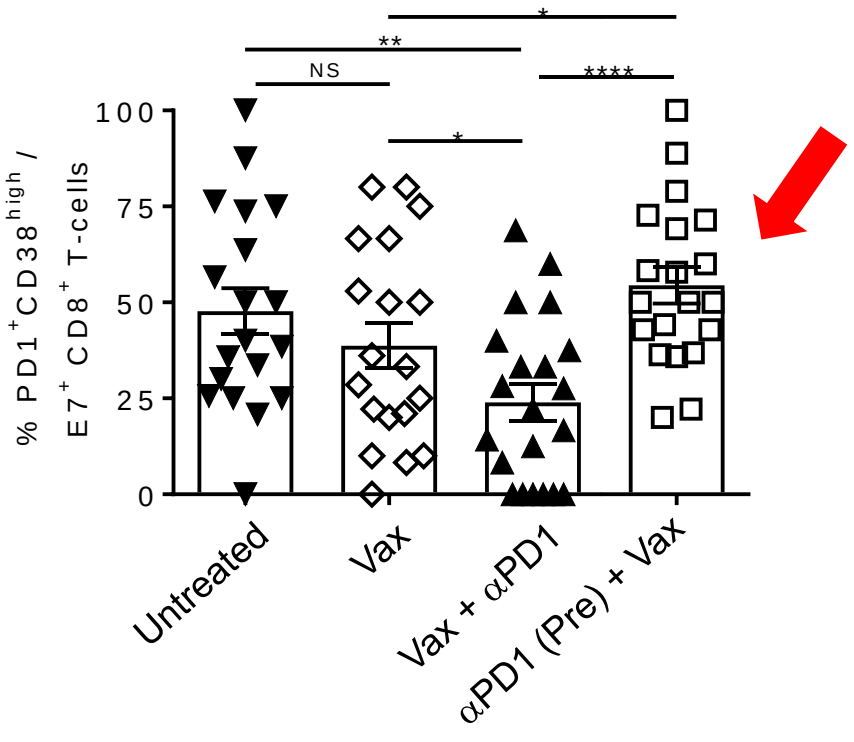
X > A = B

PD-1 blockade prior to antigenic stimulation generates dysfunctional CD8⁺ T-cells



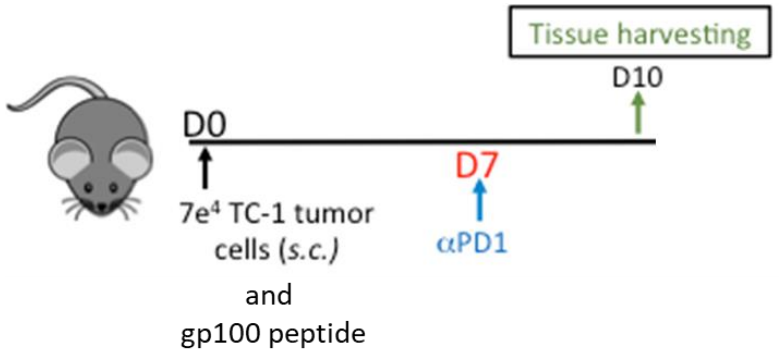


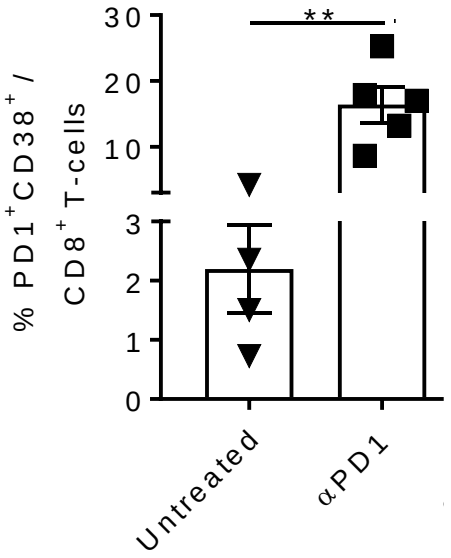




Verma, et al, *Nature Immunol, 2019*

Optimal priming of CD8+ T-cells is essential for enhancement of anti-PD-1-mediated functionality of cells

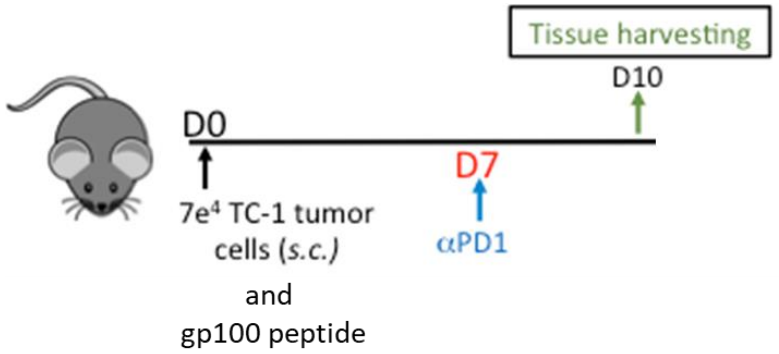


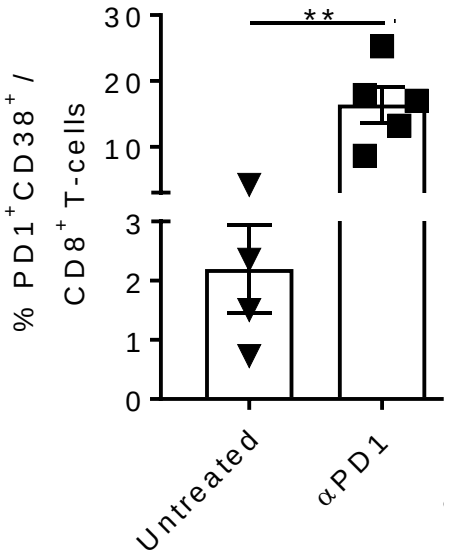


Verma, et al, *Nature Immunol*

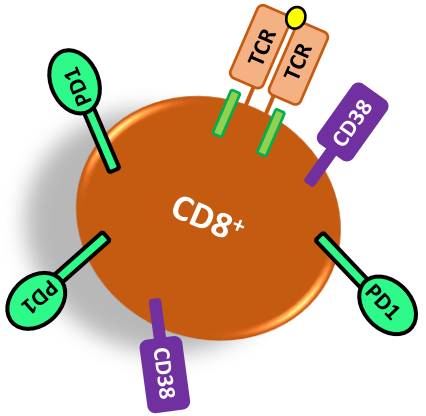
What are these cells?

Optimal priming of CD8$^+$ T-cells is essential for enhancement of anti-PD-1-mediated functionality of cells



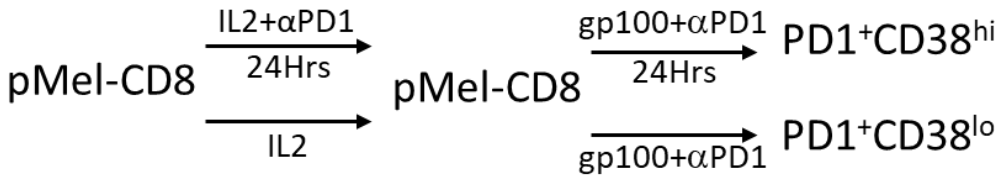


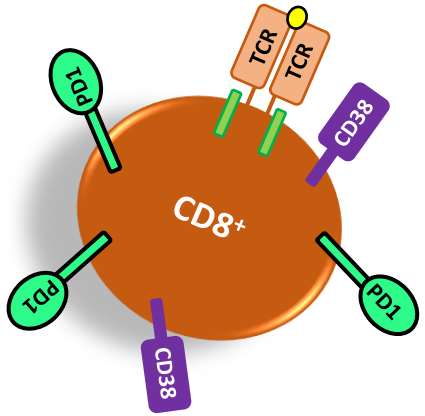
What are these cells?

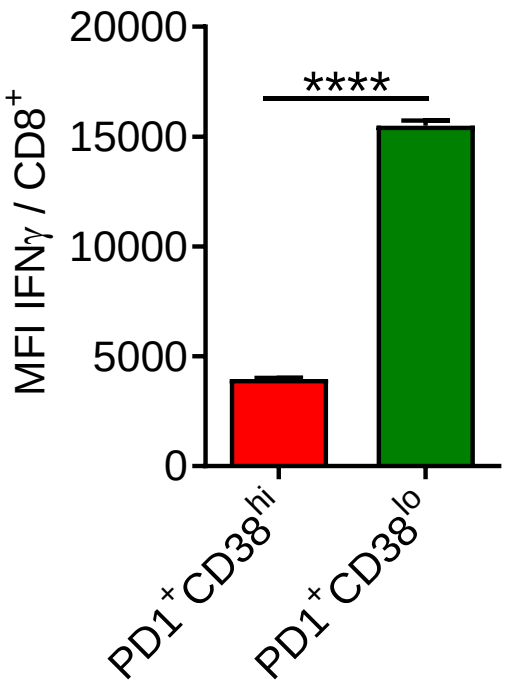


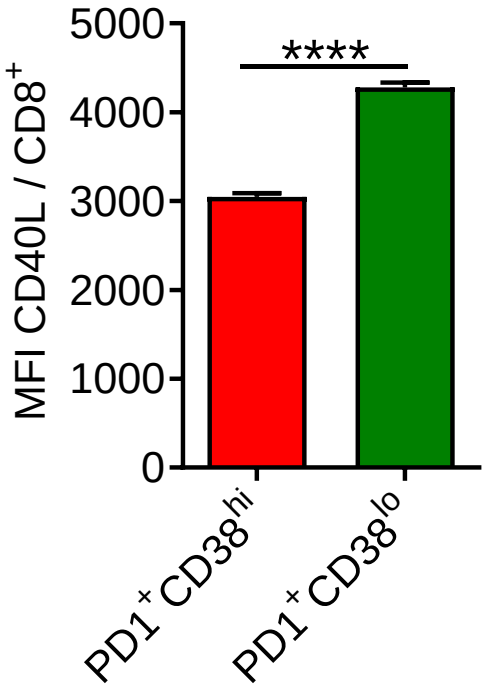
Verma, et al, *Nature Immunol*

PD1^{+}CD38^{hi} CD8^{+} T cells show less effector functions and activation, which is critically dependent on CD38 expression



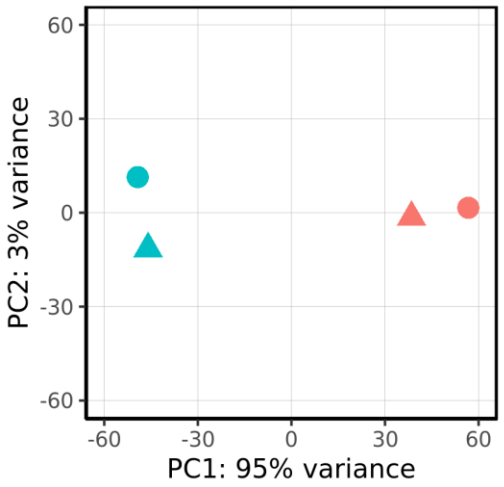






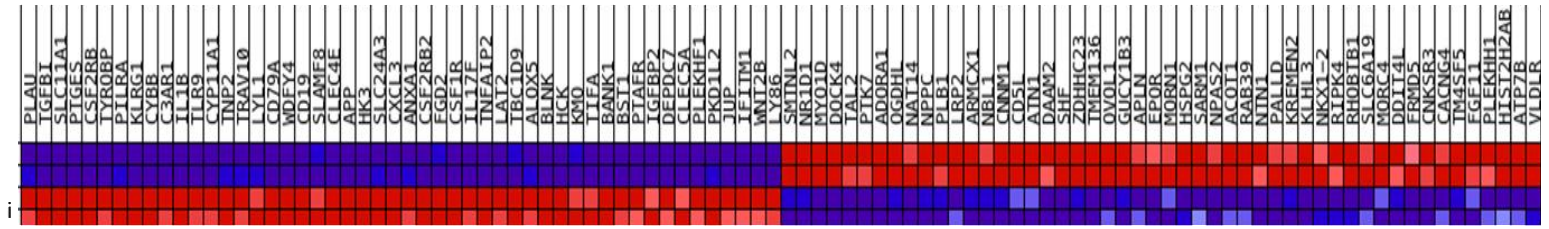
Verma, et al, *unpublished*

PD-1^{+}CD38^{hi} CD8^{+} T cells are unique cells with distinct characteristics



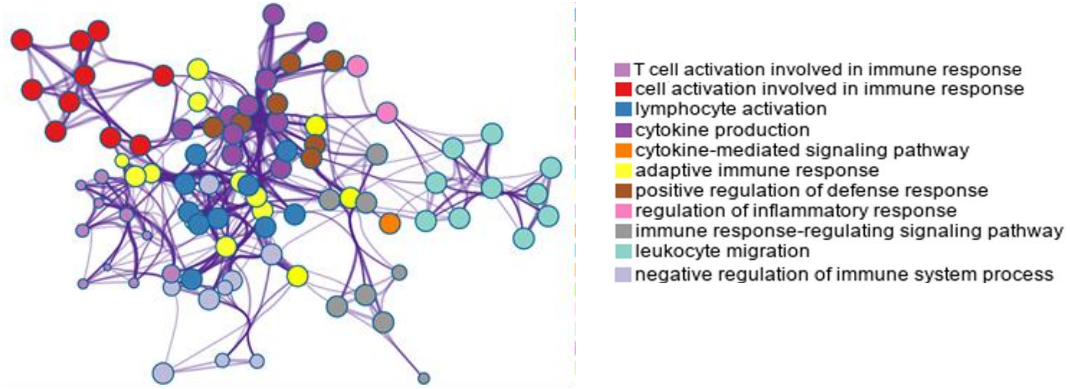
Replicate
rep1
rep2

Group
PD-1^{+}CD38^{lo}
PD-1^{+}CD38^{hi}



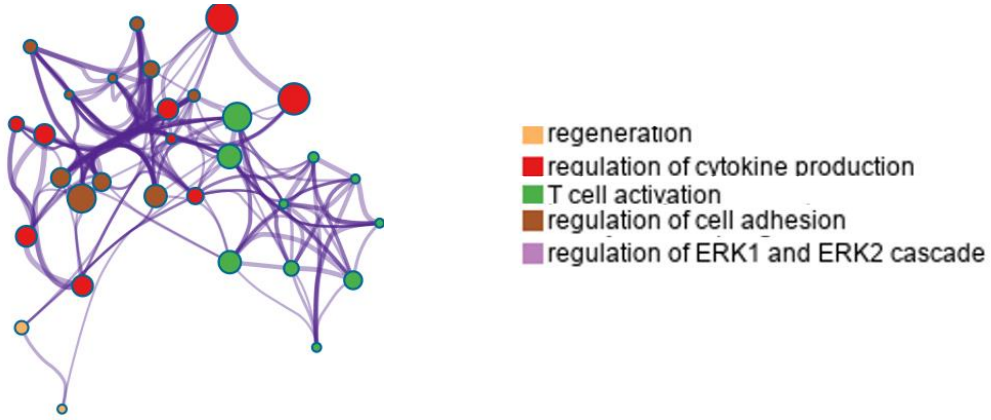
Top genes with significant changes

Upregulated pathways in PD-1^{+}CD38^{hi} cells

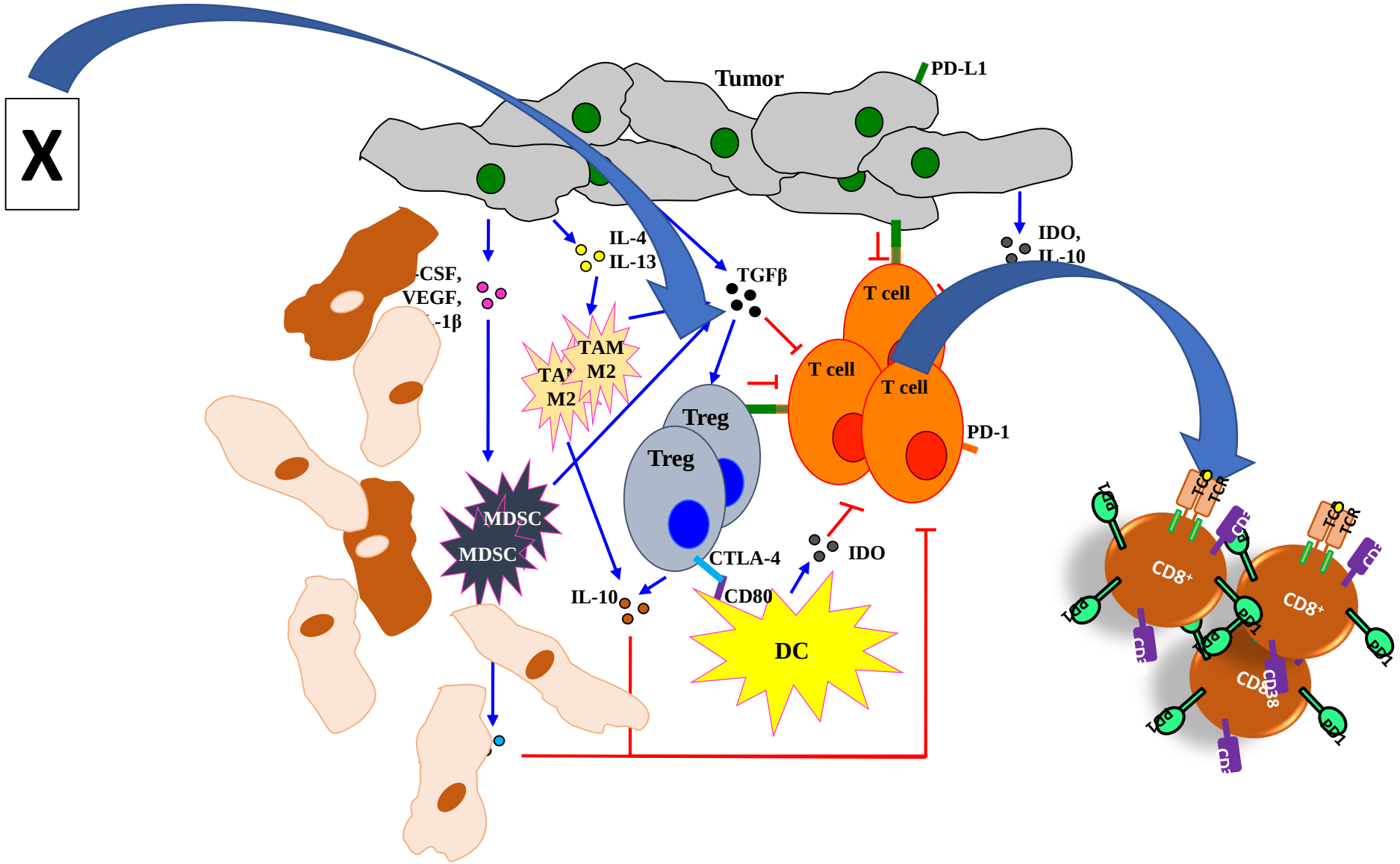


Verma, et al, *unpublished*

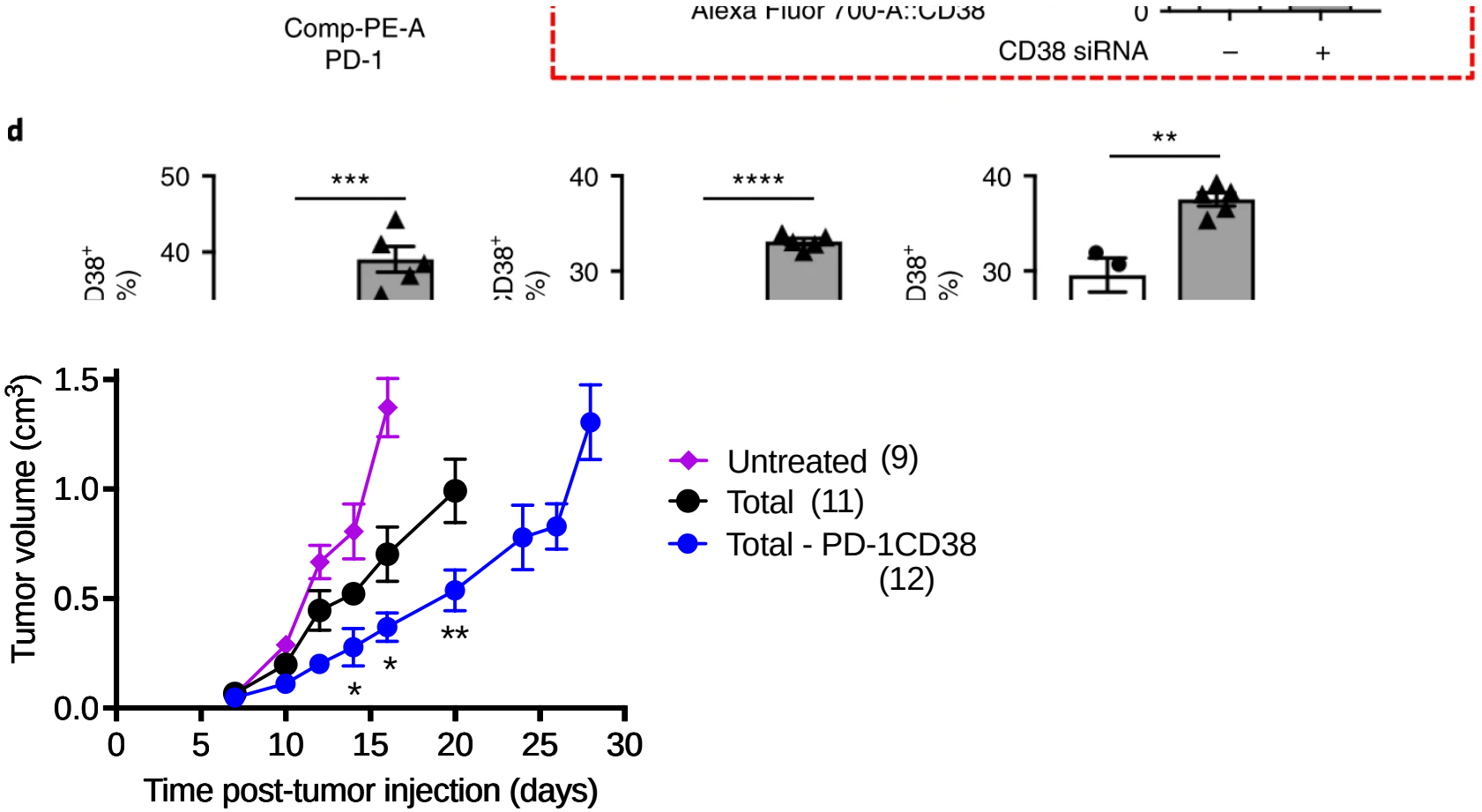
Downregulated pathways in PD-1^{+}CD38^{hi} cells



Tumor-Immune Interaction



PD1^{+}CD38^{hi} CD8^{+} T cells are a major factor in diminished anti-tumor activity of activated CD8^{+} T cells



Verma et al, 2019; Nat Immunol

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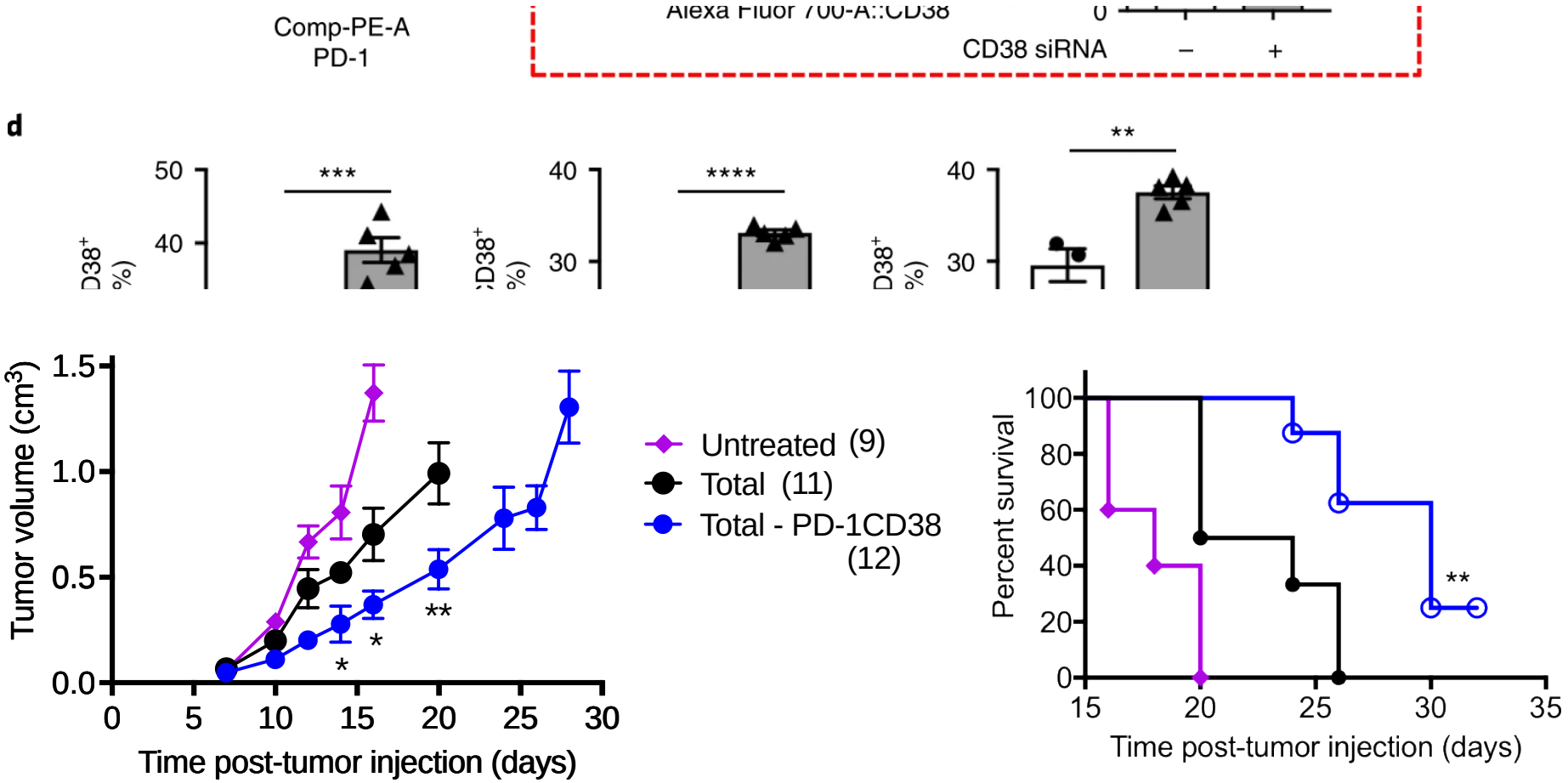


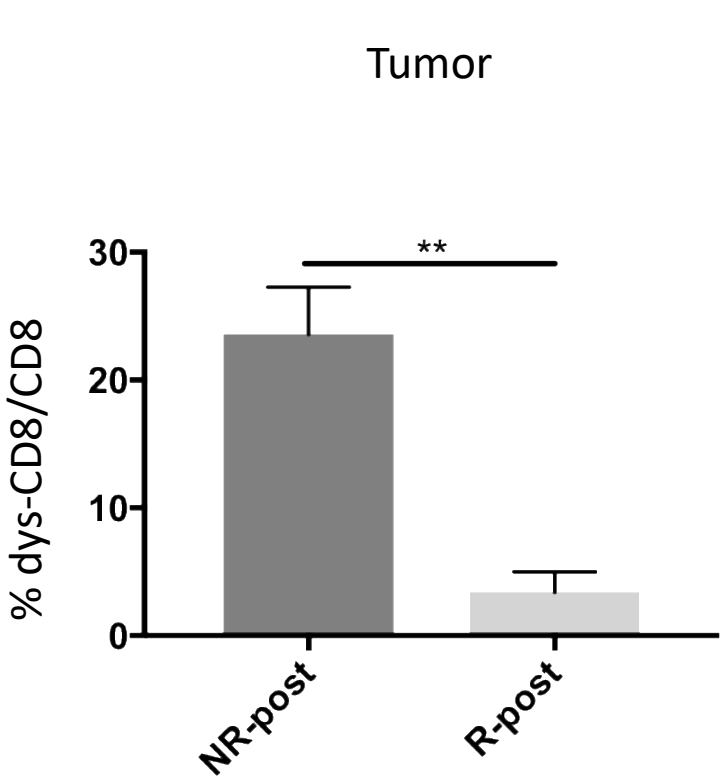
Verma et al, 2019; Nat Immunol

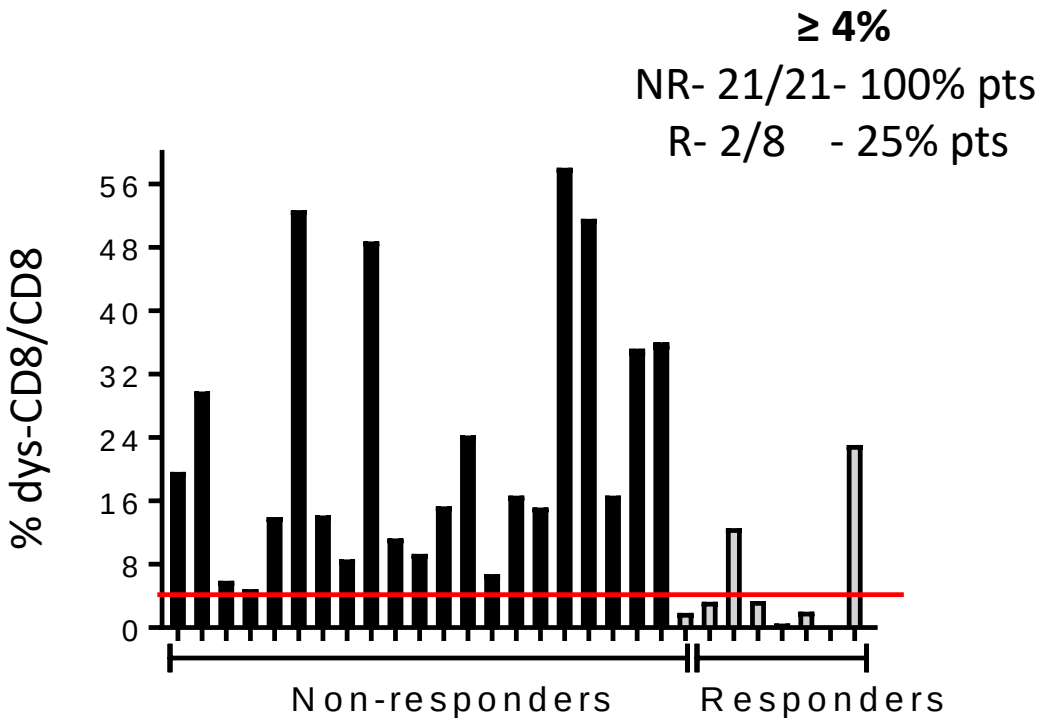
Immuno-therapy Resistance

- Immunotherapy biologic incompatibility
- Immuno-Combination incompatibility
- Adaptive resistance

Human

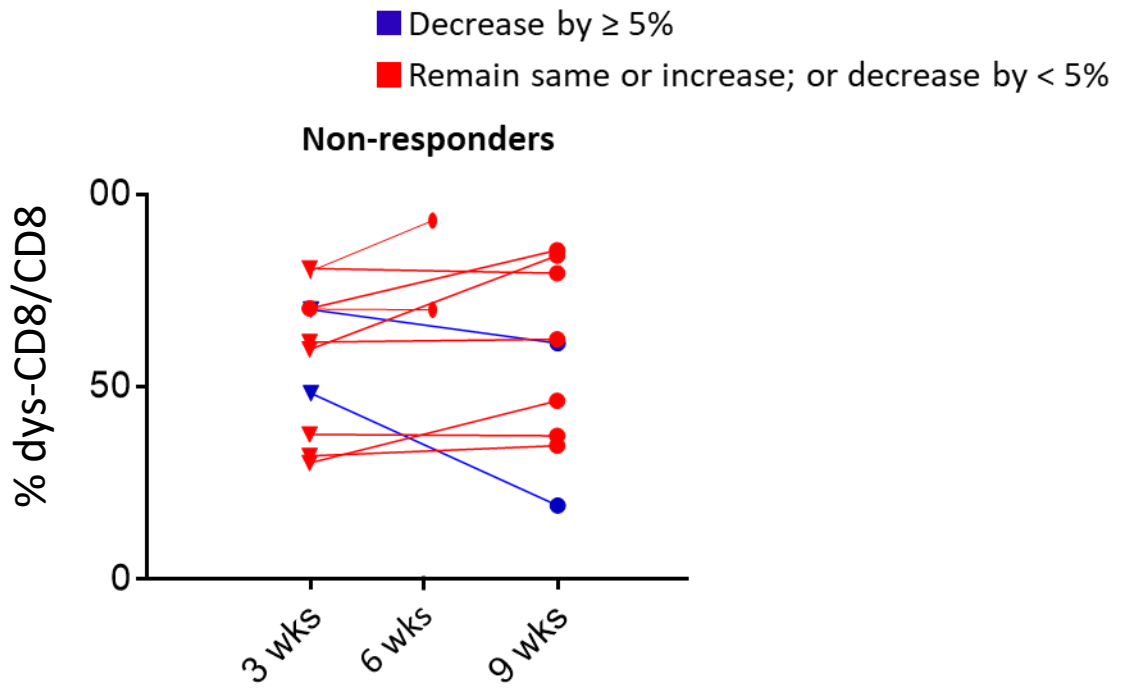
Number of dys-CD8^{+} T-cells in the tumors and PBMCs correlate with the anti-PD-1 therapeutic response in patients





Verma, et al, *Nature Immunol, 2019*

High numbers of dys-CD8^{+} T-cells in the tumors and PBMCs serve as a predictor of failure of anti-PD-1 therapy



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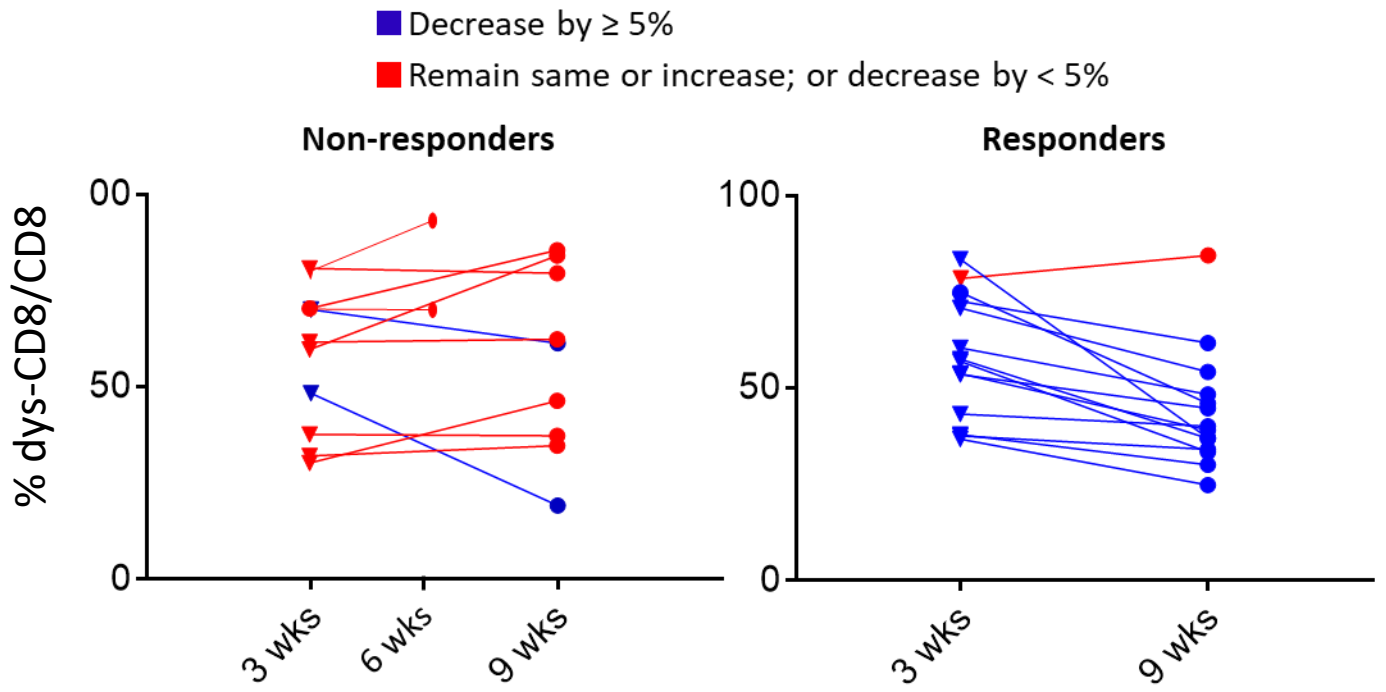
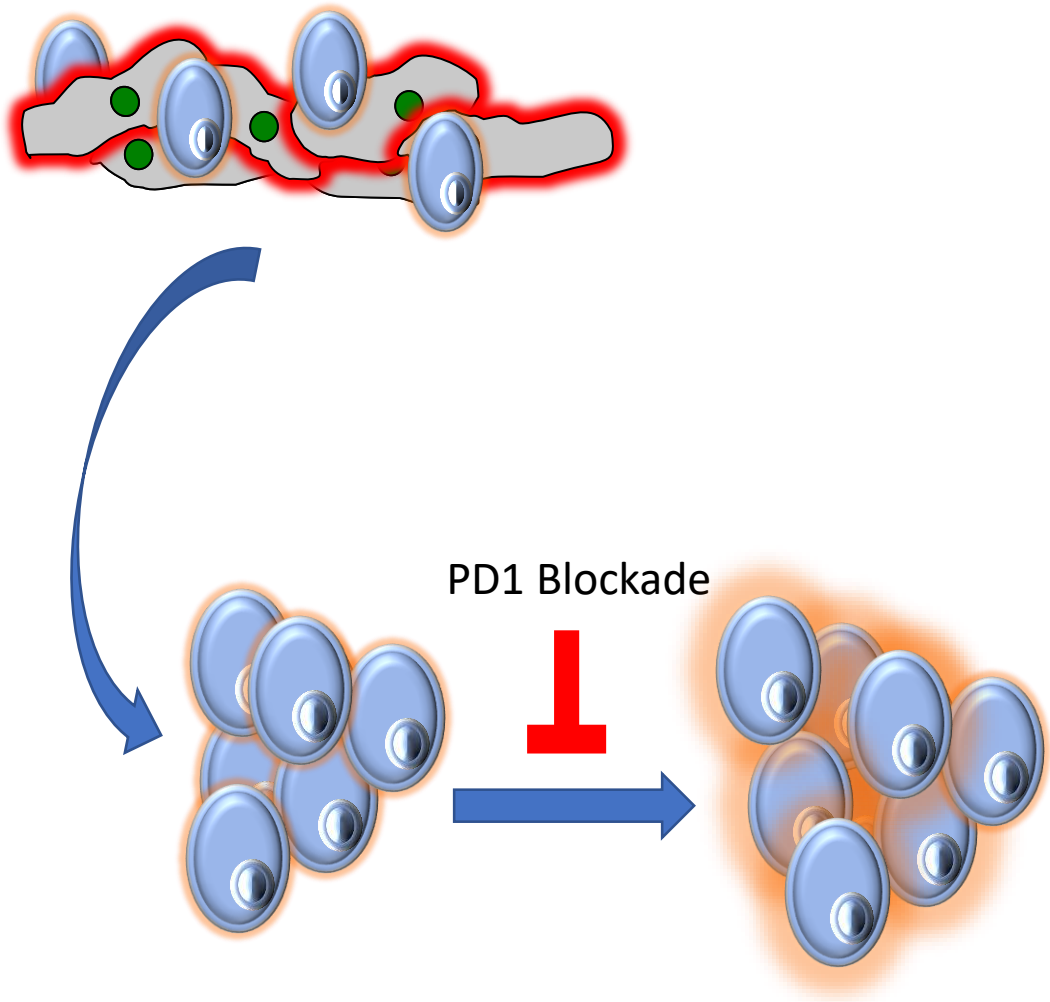


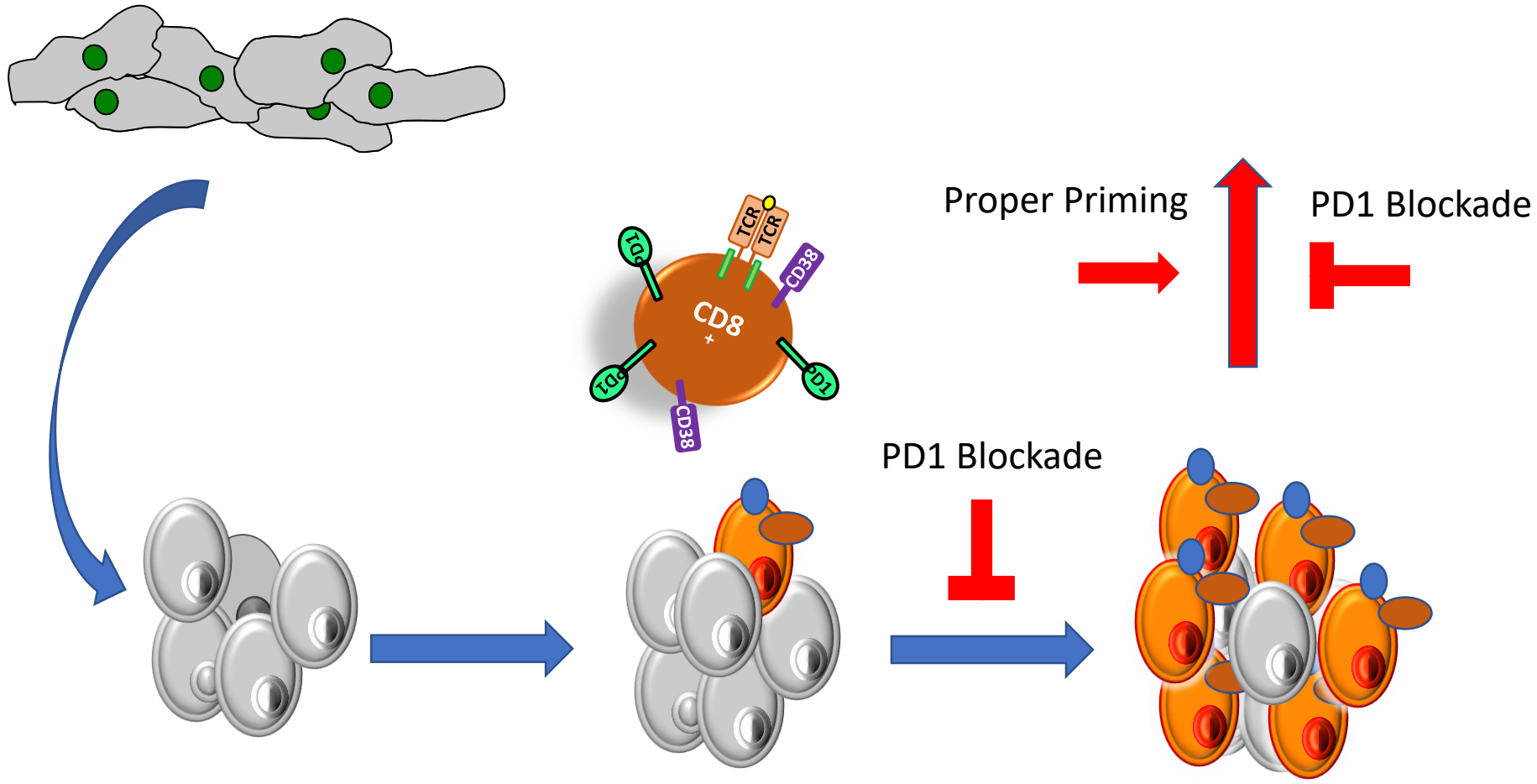
Verma, et al, *Nature Immunol, 2019*

Are CD38+/PD1+ bad cells?

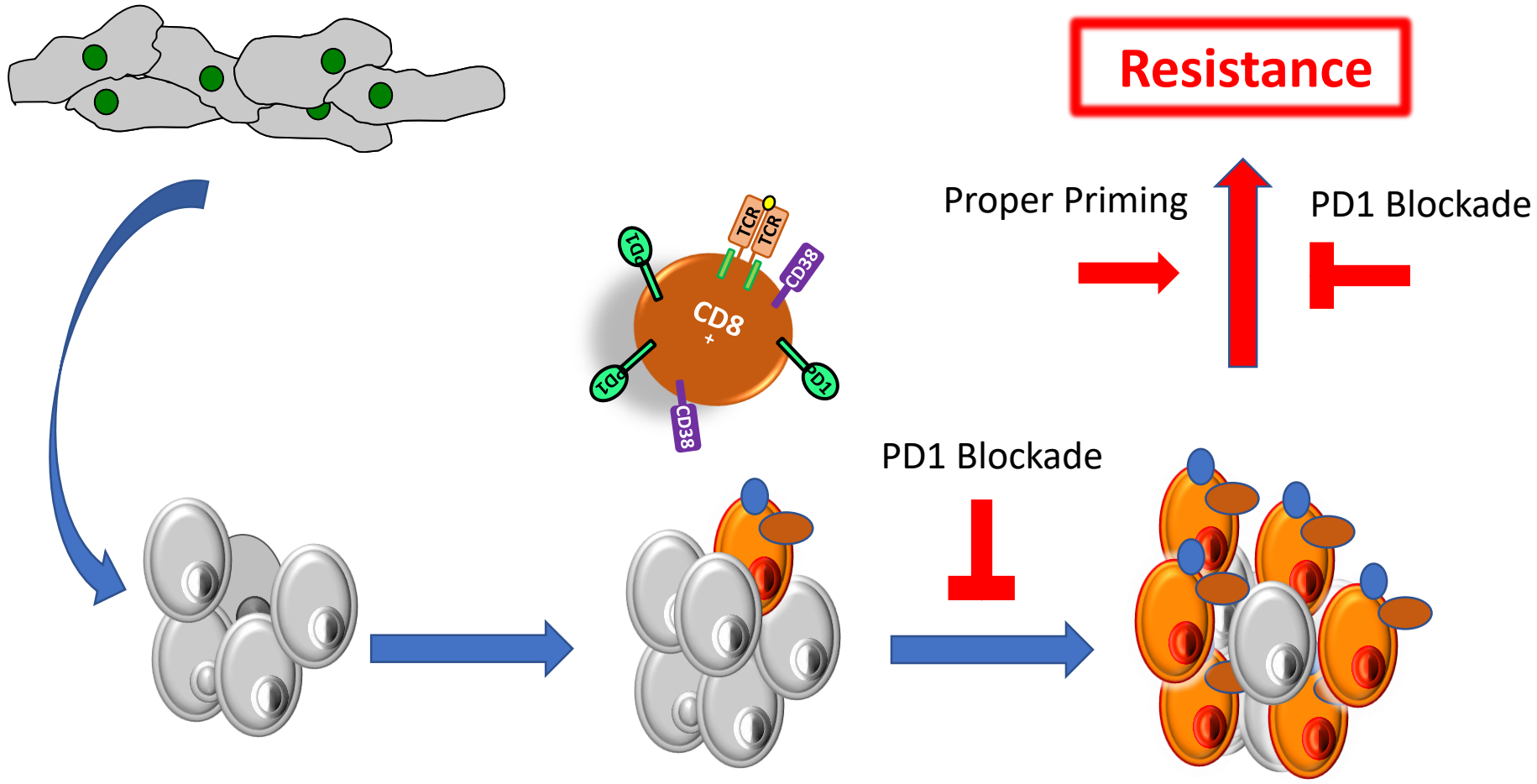
Anti-PD1 plus Anti-OX40 Agonist Resistance



Anti-PD1 Resistance



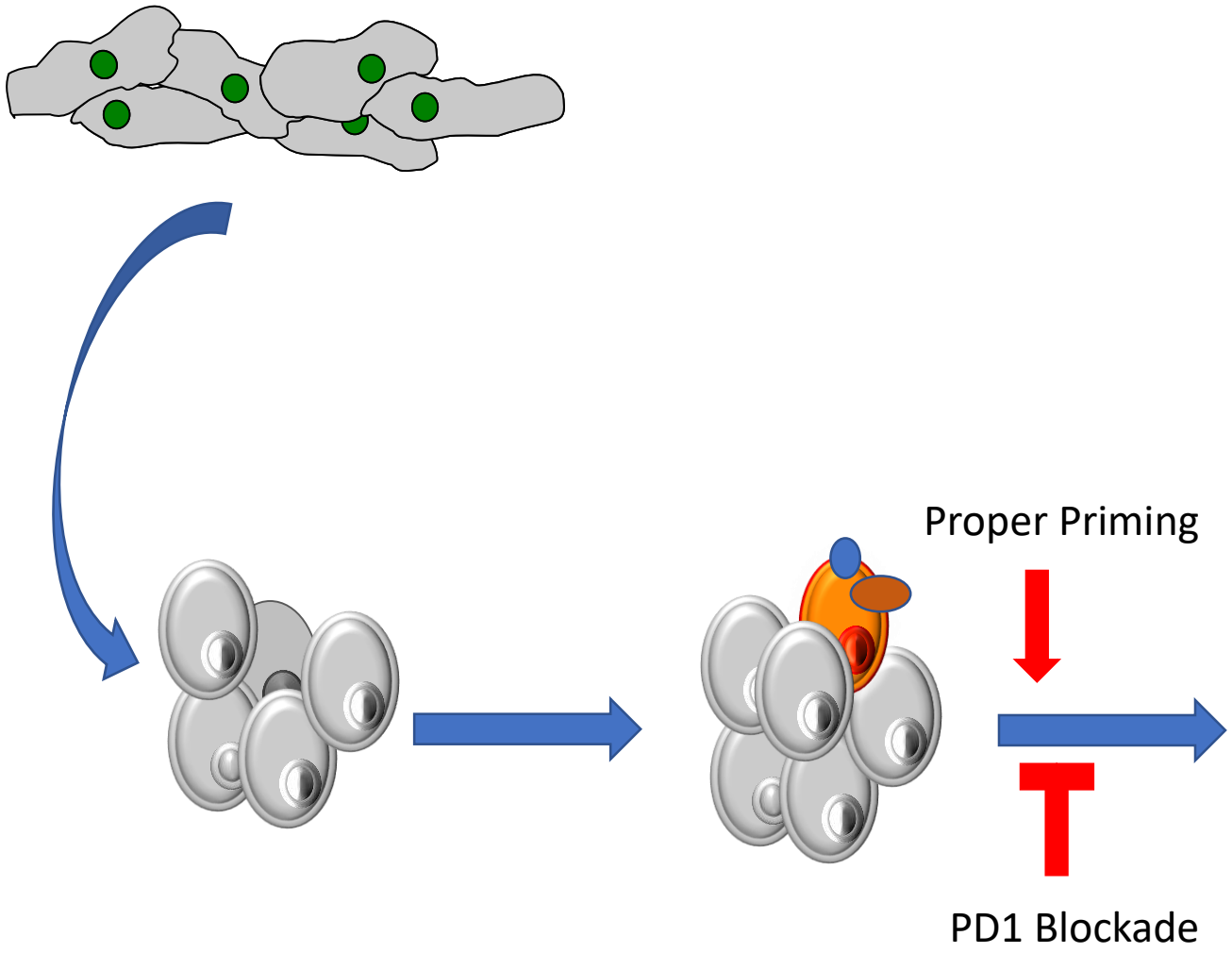
Anti-PD1 Resistance



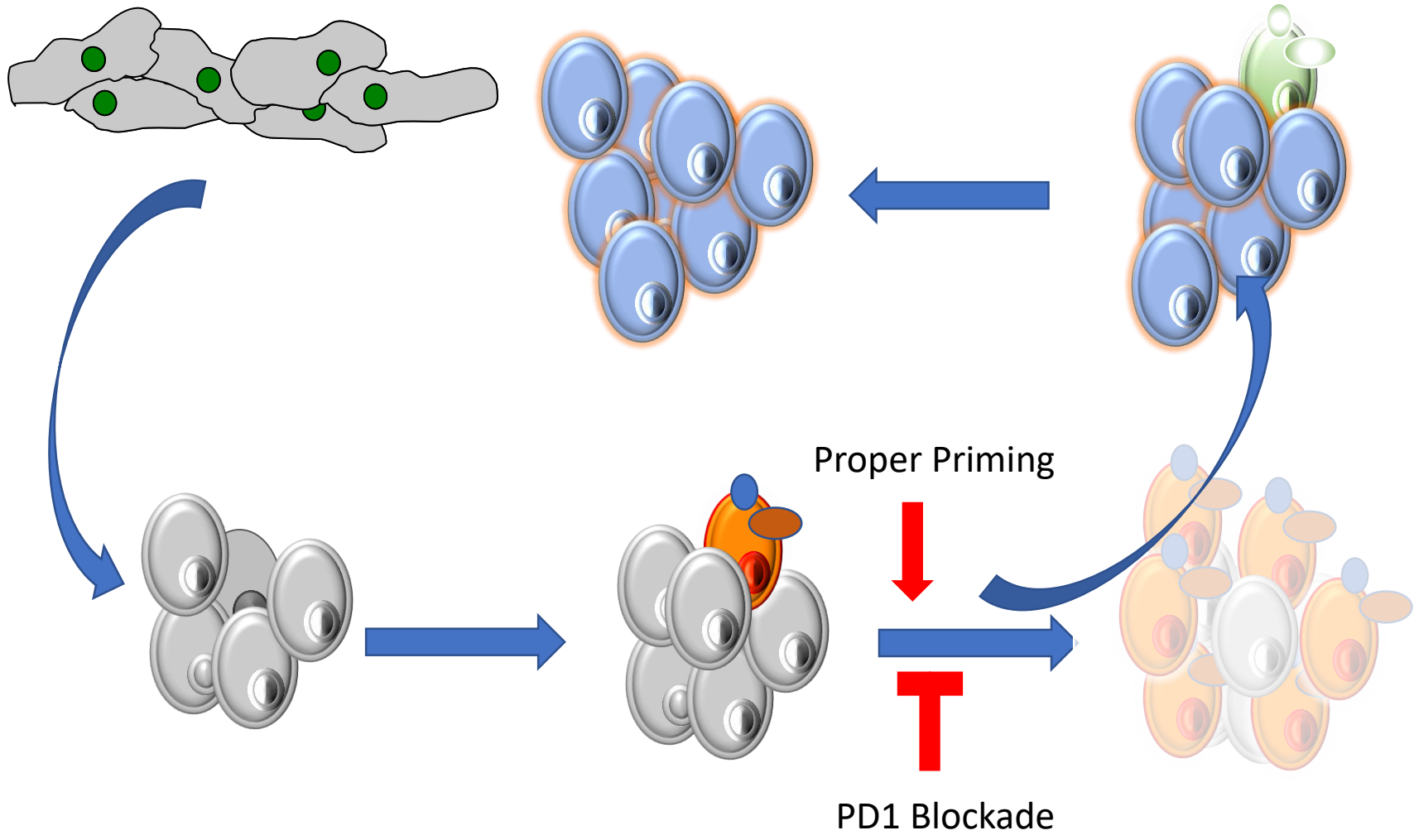
Immuno-therapy Resistance

- Immunotherapy biologic incompatibility
- Immuno-Combination incompatibility
- Adaptive resistance

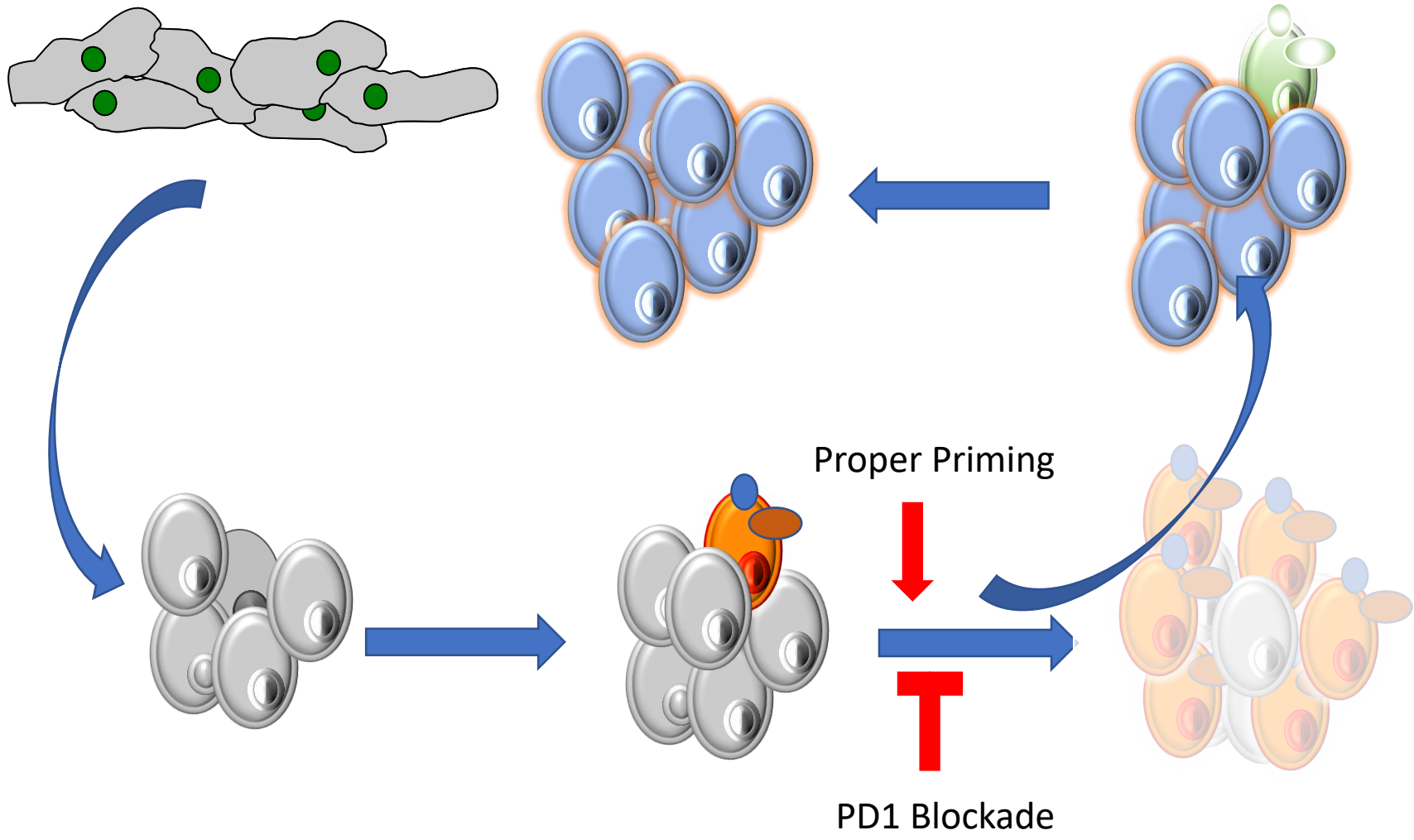
Reversing Anti-PD1 Resistance



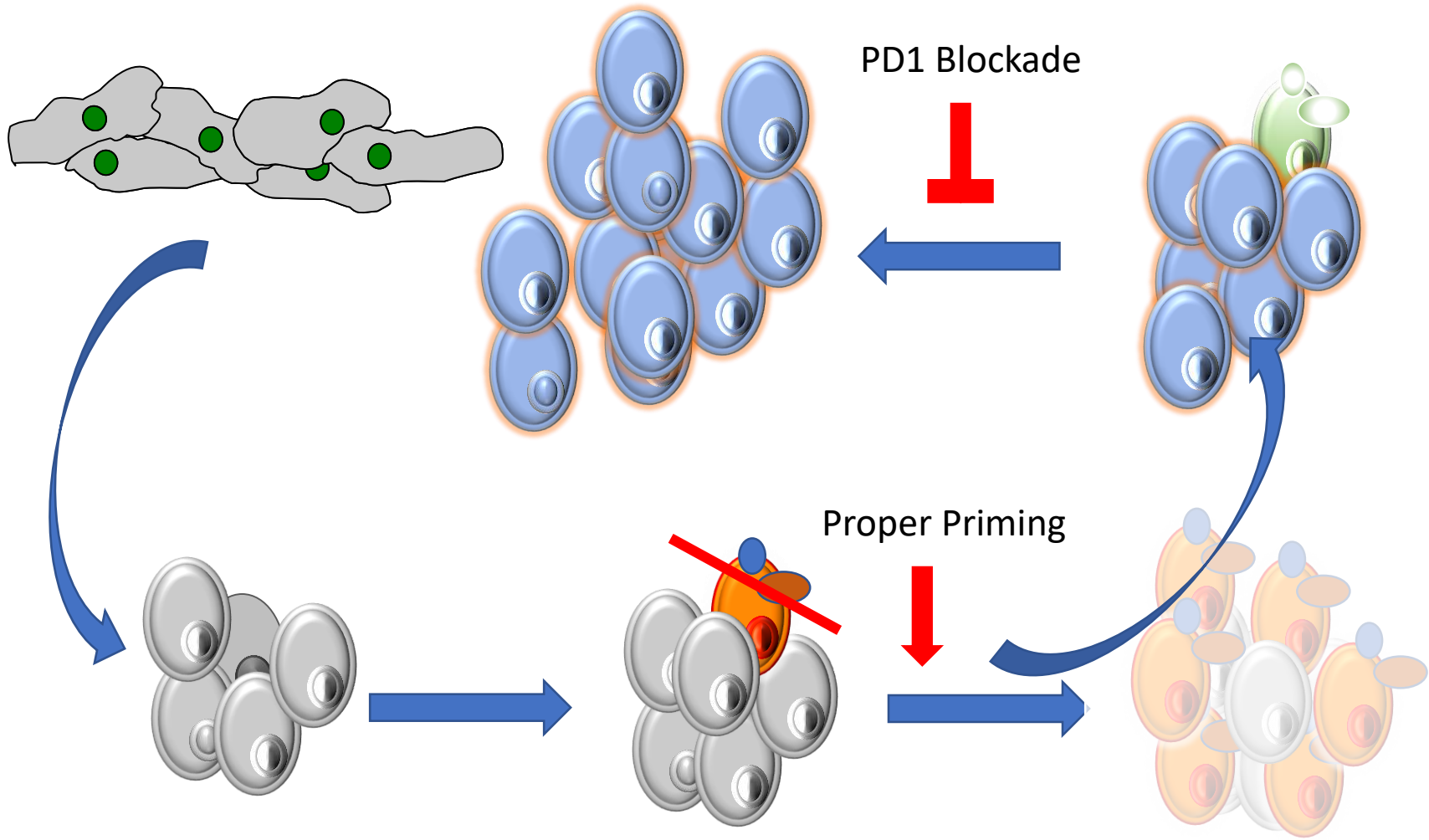
Reversing Anti-PD1 Resistance



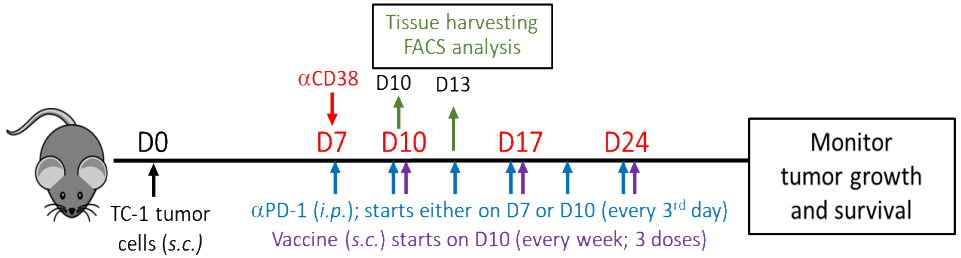
Reversing Anti-PD1 Resistance

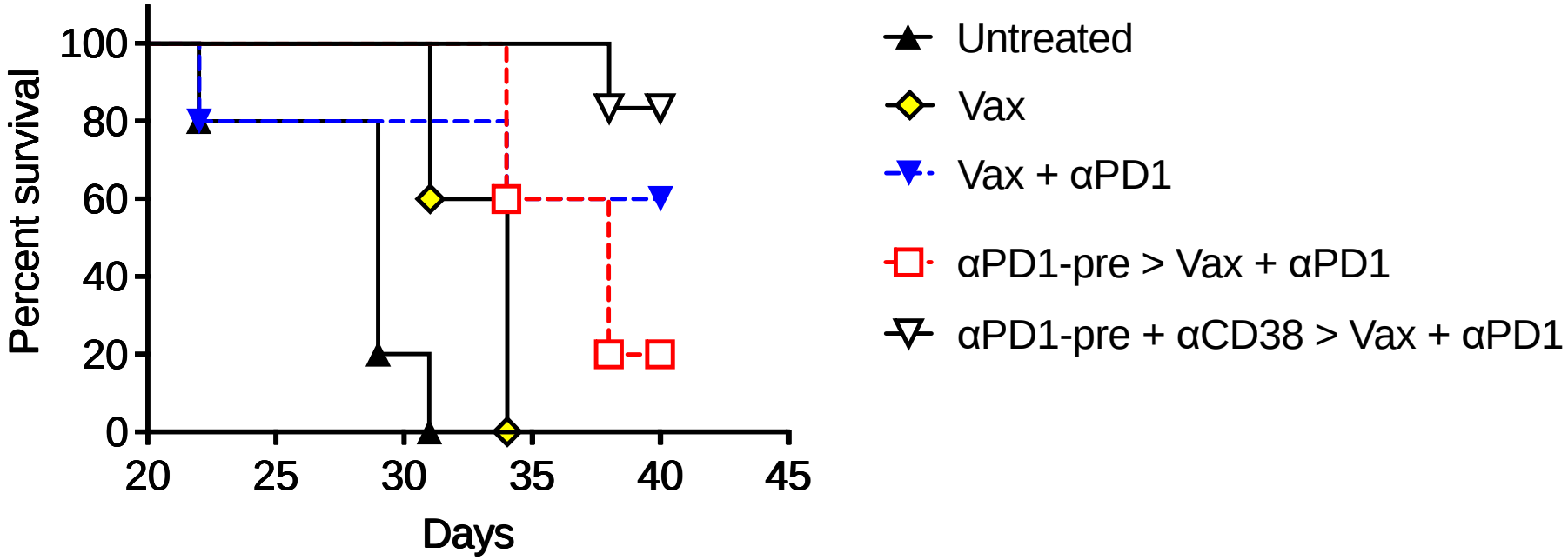


Reversing Anti-PD1 Resistance



Treatment with anti-CD38 along with anti-PD-1 results in reversal of anti-PD-1 therapy resistance





Verma et al, Unpublished

Identified a way to reverse the resistance

Clinical Trial

A Phase 2 Study Exploring the Safety, Tolerability, and Efficacy of Anti-CD38 antibody in Combination with KRAS vaccine and Anti-PD-1 Antibody in Subjects with Pancreatic Ductal Adenocarcinoma and Refractory Non-Small Cell Lung Cancer–

Janssen supported collaboration- Argovax

Immuno-therapy Resistance

- Immunotherapy biologic incompatibility
- Immuno-Combination incompatibility
- Adaptive resistance

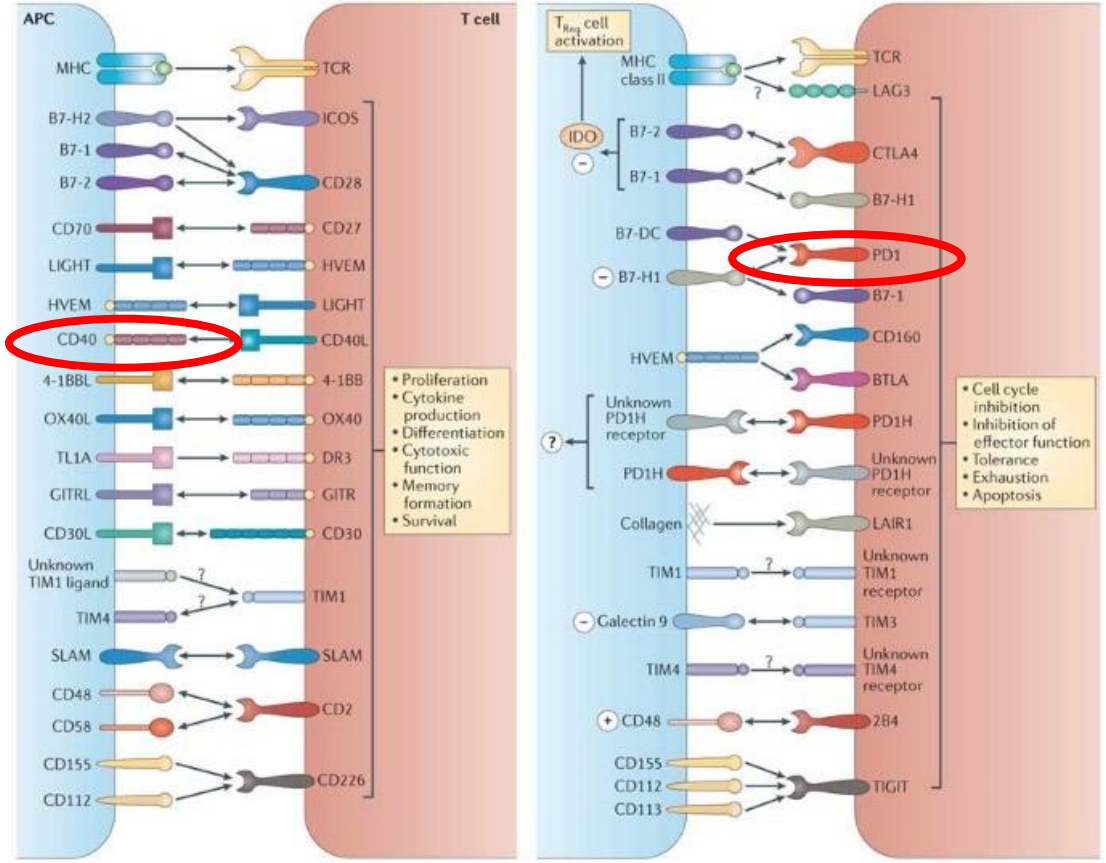
Combination of PD1 blockade with Co-stim Agonist

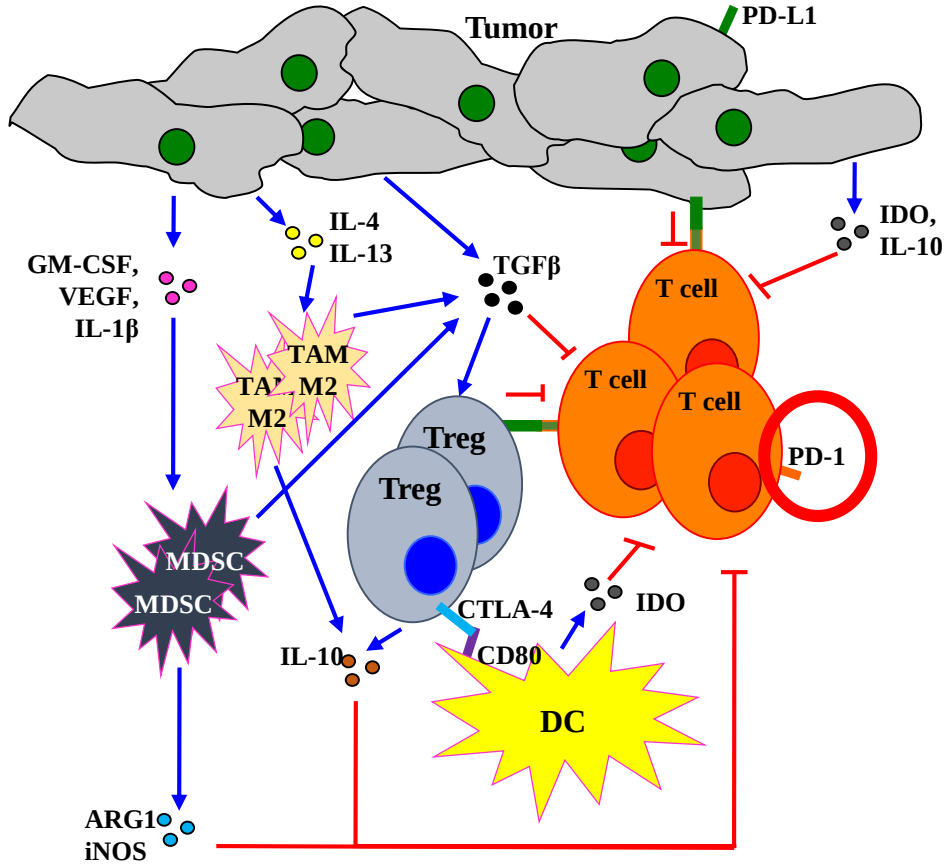
- 3 large clinical trials of anti-PD1 in combination with OX40 agonist

- Clinical trials of anti-PD1 in combination with GITR agonist

Combinational Immunotherapy

- Vaccines
- Immune Modulators





Research Article

Cancer Immunology Research

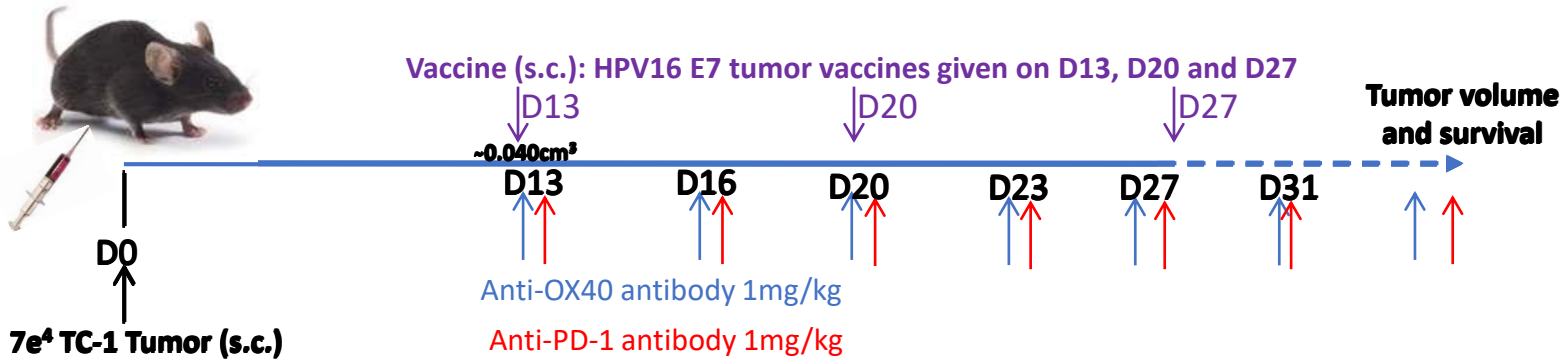
Concurrent PD-1 Blockade Negates the Effects of OX40 Agonist Antibody in Combination Immunotherapy through Inducing T-cell Apoptosis

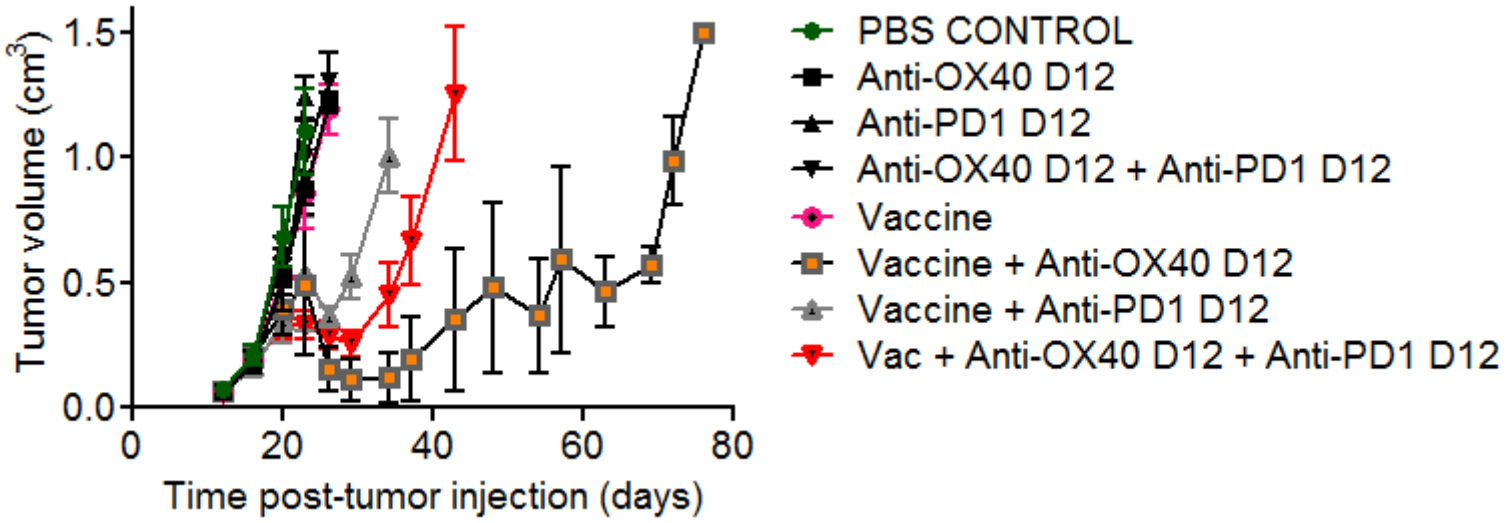
Rajeev K. Shrimali[1], Shamim Ahmad[1], Vivek Verma[1], Peng Zeng[1], Sudha Ananth[1], Pankaj Gaur[1], Rachel M. Gittelman[2], Erik Yusko[2], Catherine Sanders[2], Harlan Robins[2,3], Scott A. Hammond[4], John E. Janik[1], Mikayel Mkrtichyan[1], Seema Gupta[1], and Samir N. Khleif[1]

Rajeev Shrimali

Shamim Ahmed

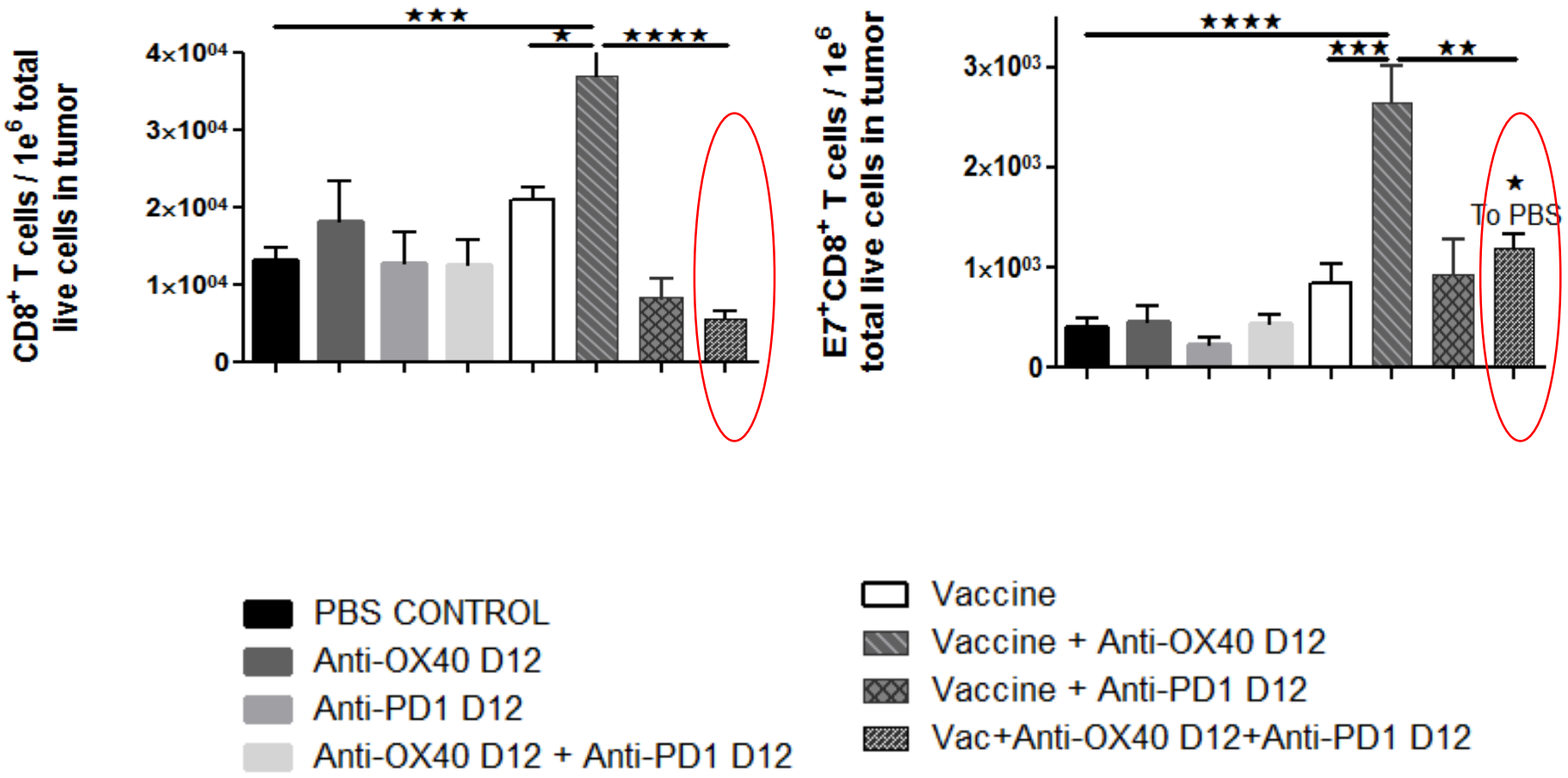
Combination of α-PD1 to α-OX40





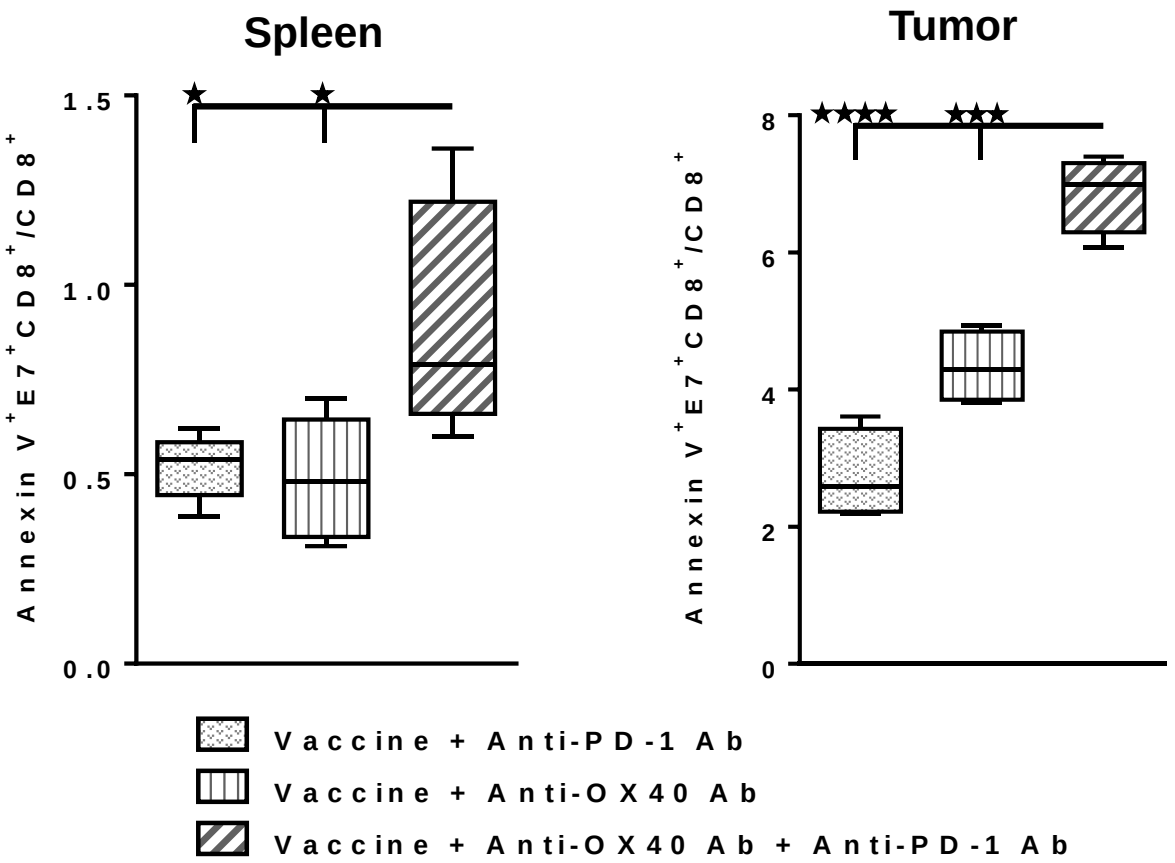
Shrimali, et al, *CRI*

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



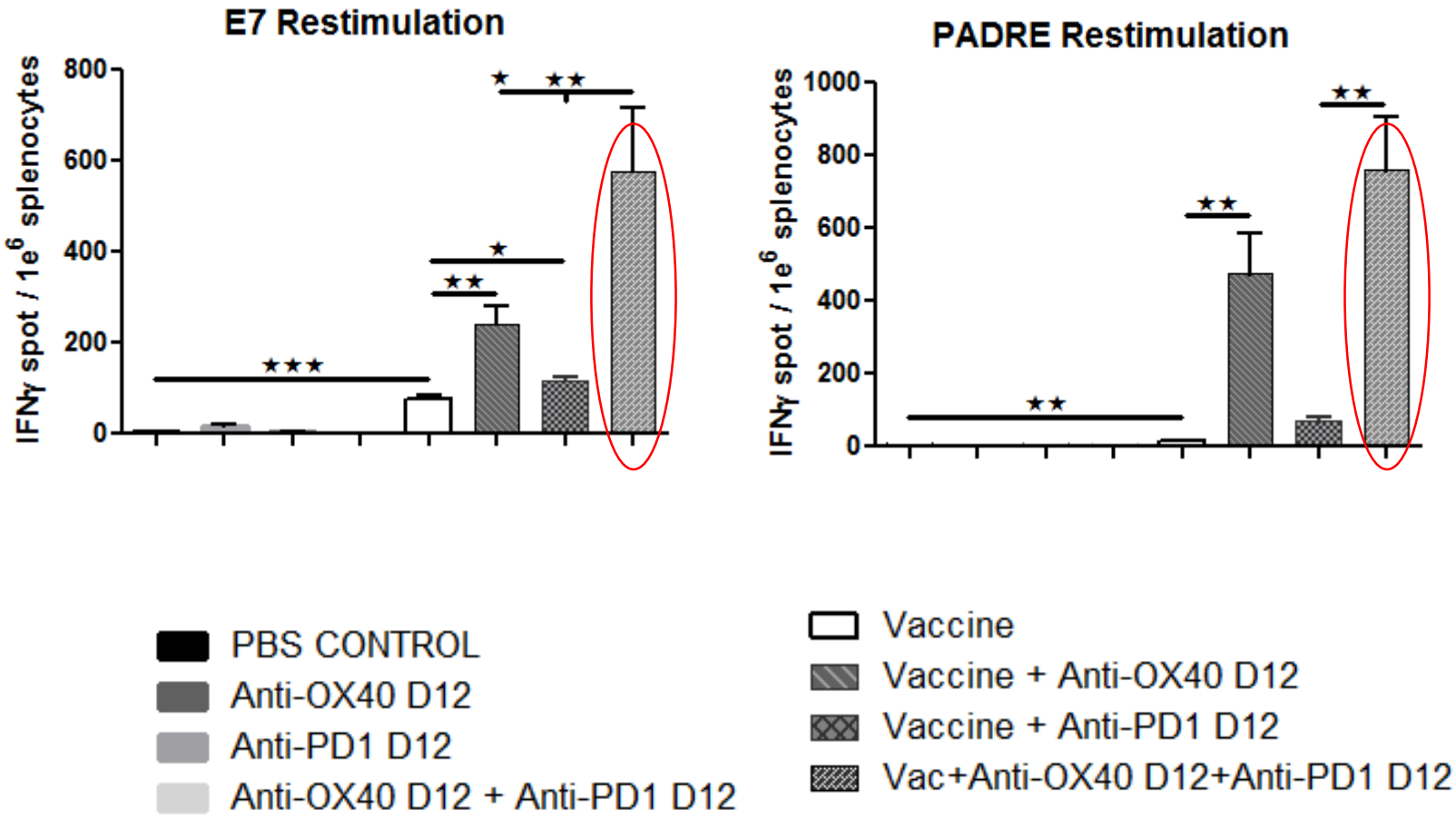
Shrimali, et al, *CRI*

Combination of α-PD1 and α-OX40 induces apoptosis of antigen specific T cells *in vivo*



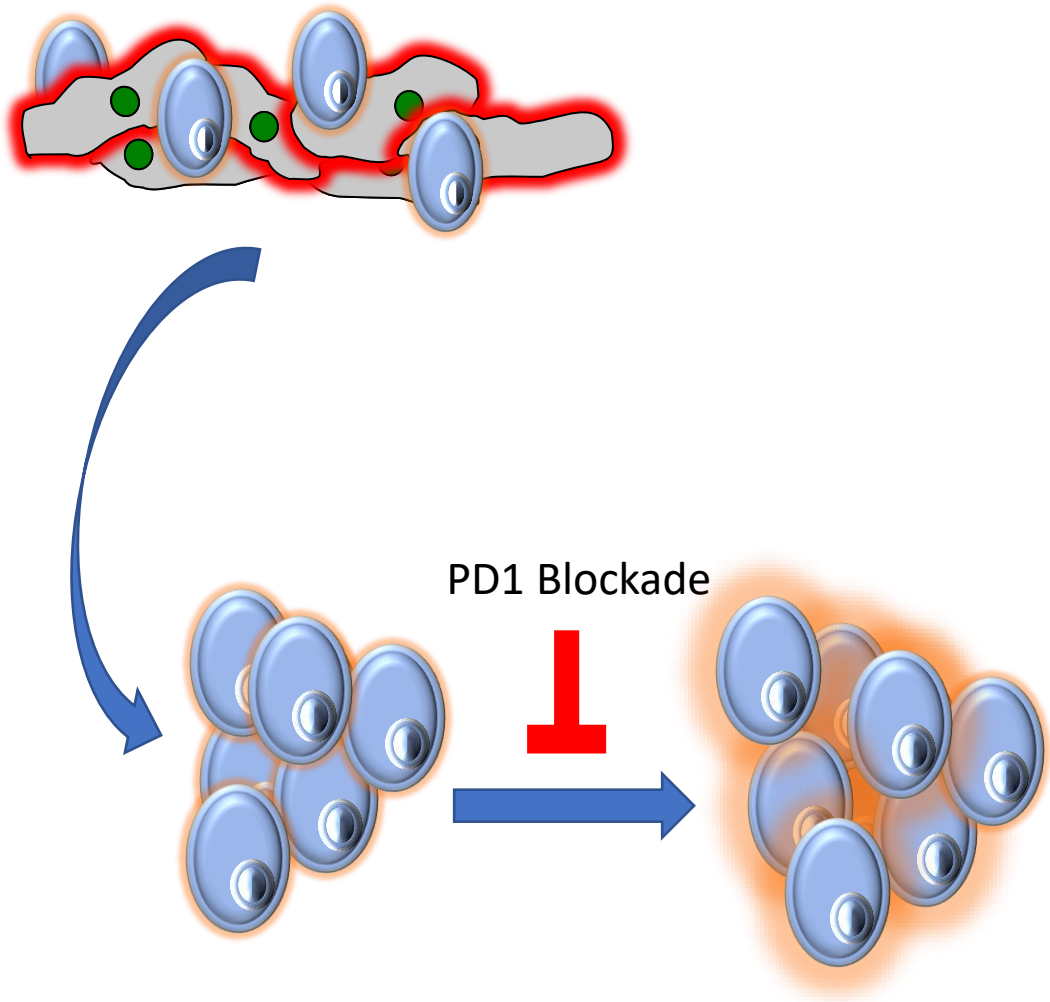
Shrimali, et al, *CRI*

IFNγ responses- ELISPOT



Shrimali, et al, *CRI*

Anti-PD1 plus Anti-OX40 Agonist Resistance



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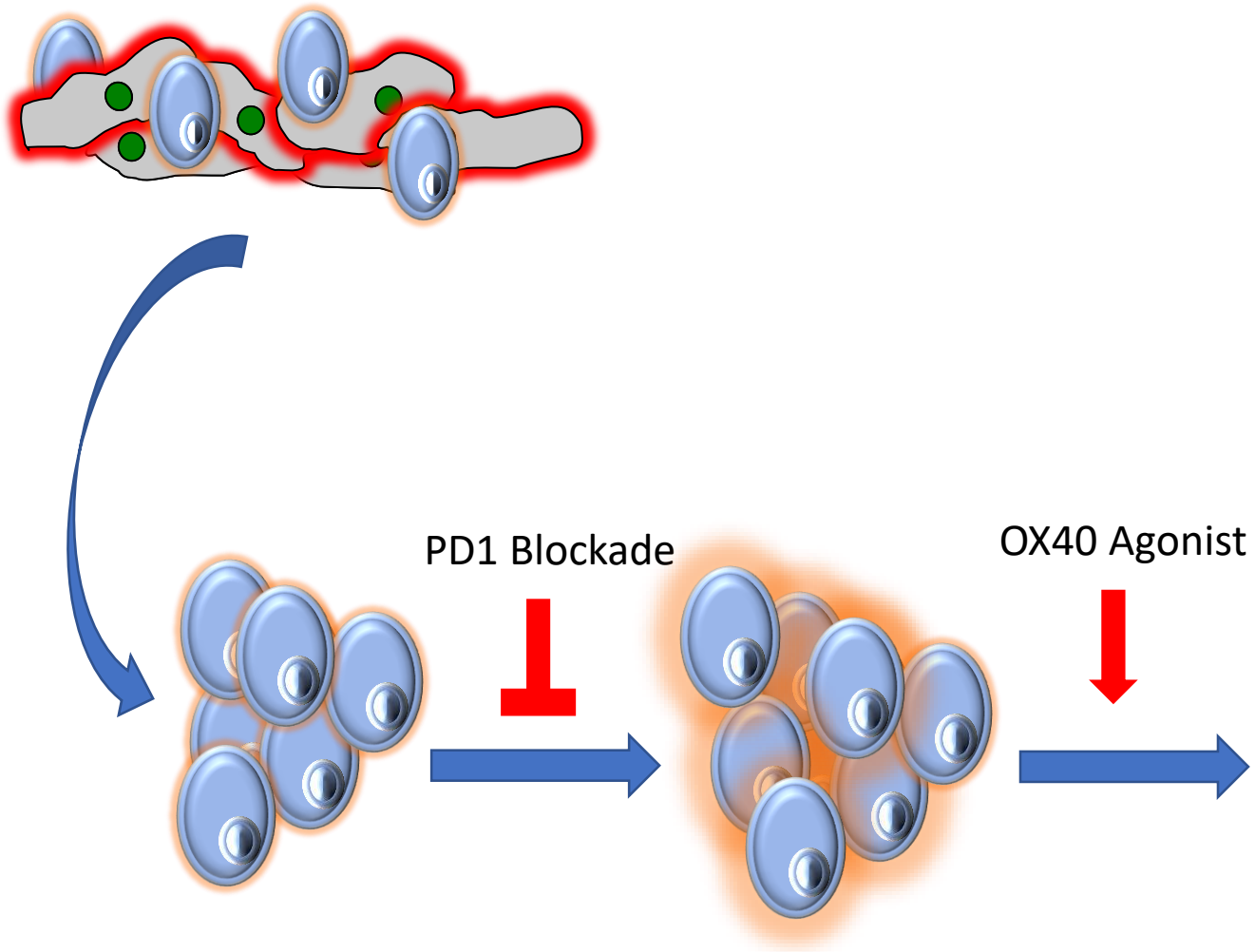
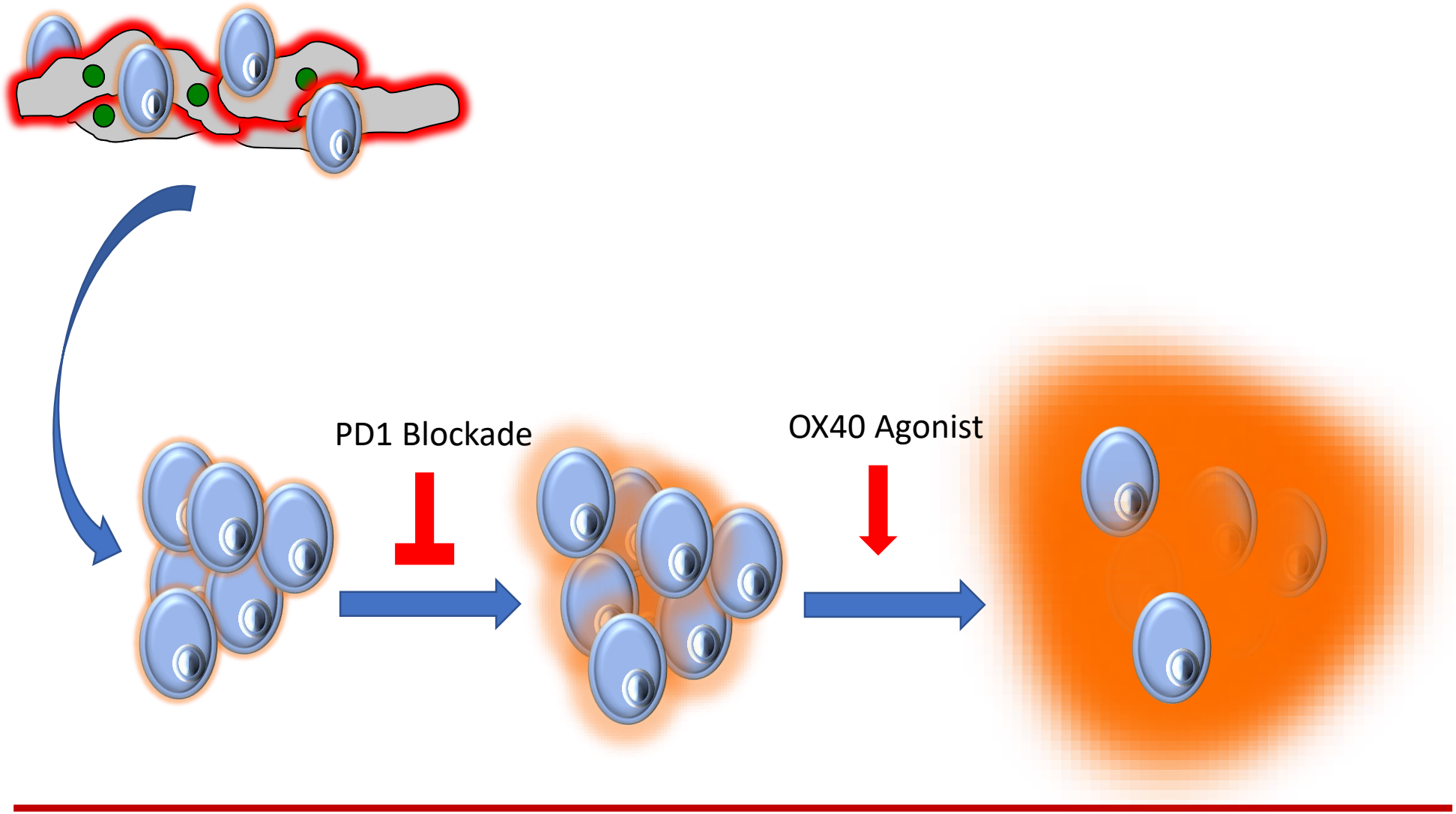


Anti-PD1 plus Anti-OX40 Agonist Resistance



Immuno-therapy Resistance

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- Immuno-Combination incompatibility
- Adaptive resistance

Preclinical Models in Immunotherapy

- Immune biology is transferable:
  - TME re-organization
  - Mechanism of Response
  - Mechanism of Resistance
  - Sequencing
- Immune biologic models are crucial in answering questions
- Organ-specific models are less relevant

Acknowledgments

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- Taha Magroubi, MSKC
- P Wong, MSKCI