Penn Medicine

Harnessing the Immune System to Fight Cancer

May 21st 2021, 18th Focus on Melanoma Conference

Alexander C. Huang, MD

Division of Hematology/Oncology

Cancer Immunotherapy: Science Breakthrough

Cancer Immunotherapy: Science Breakthrough

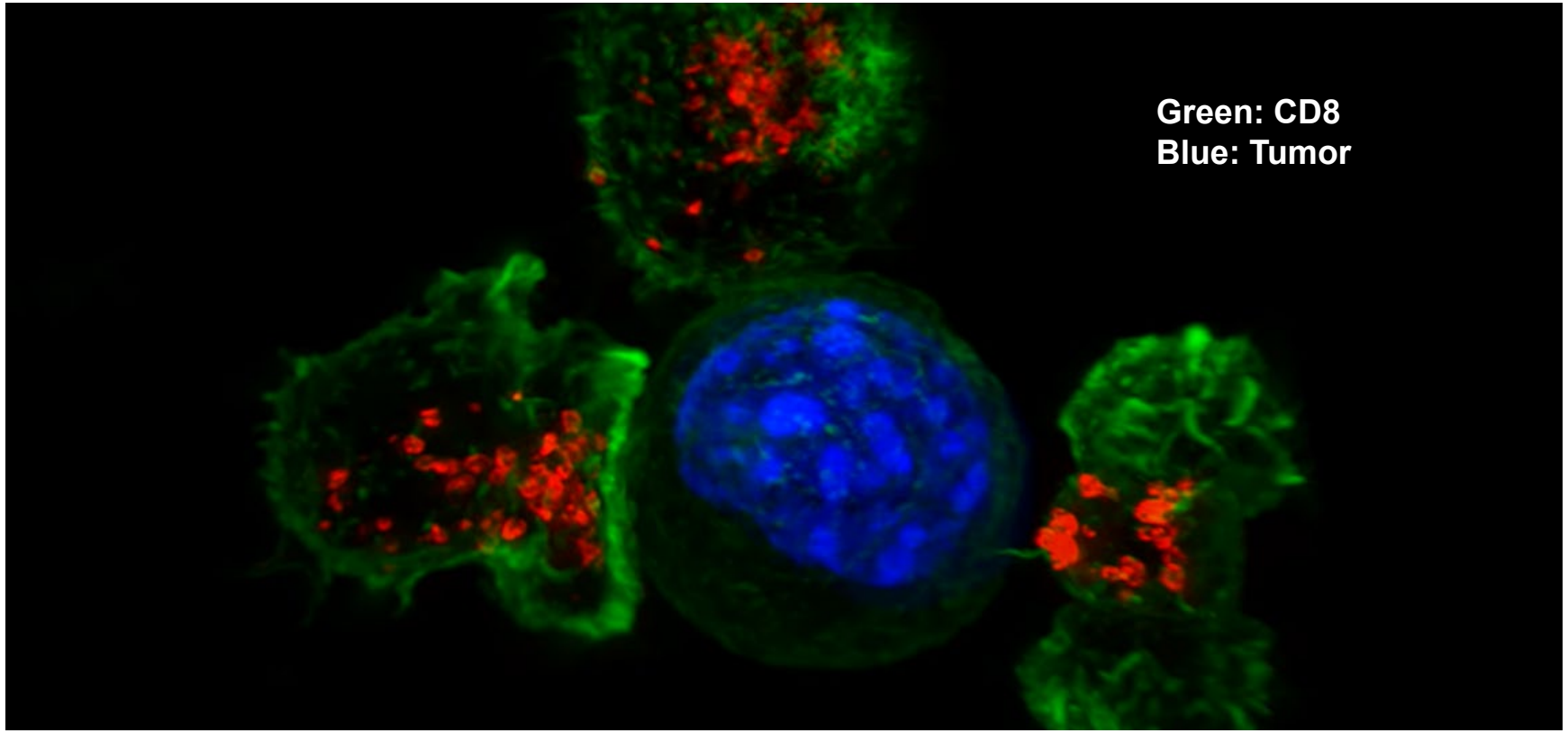
2009

2021

Immunotherapy: “Amphibious assault on cancer”

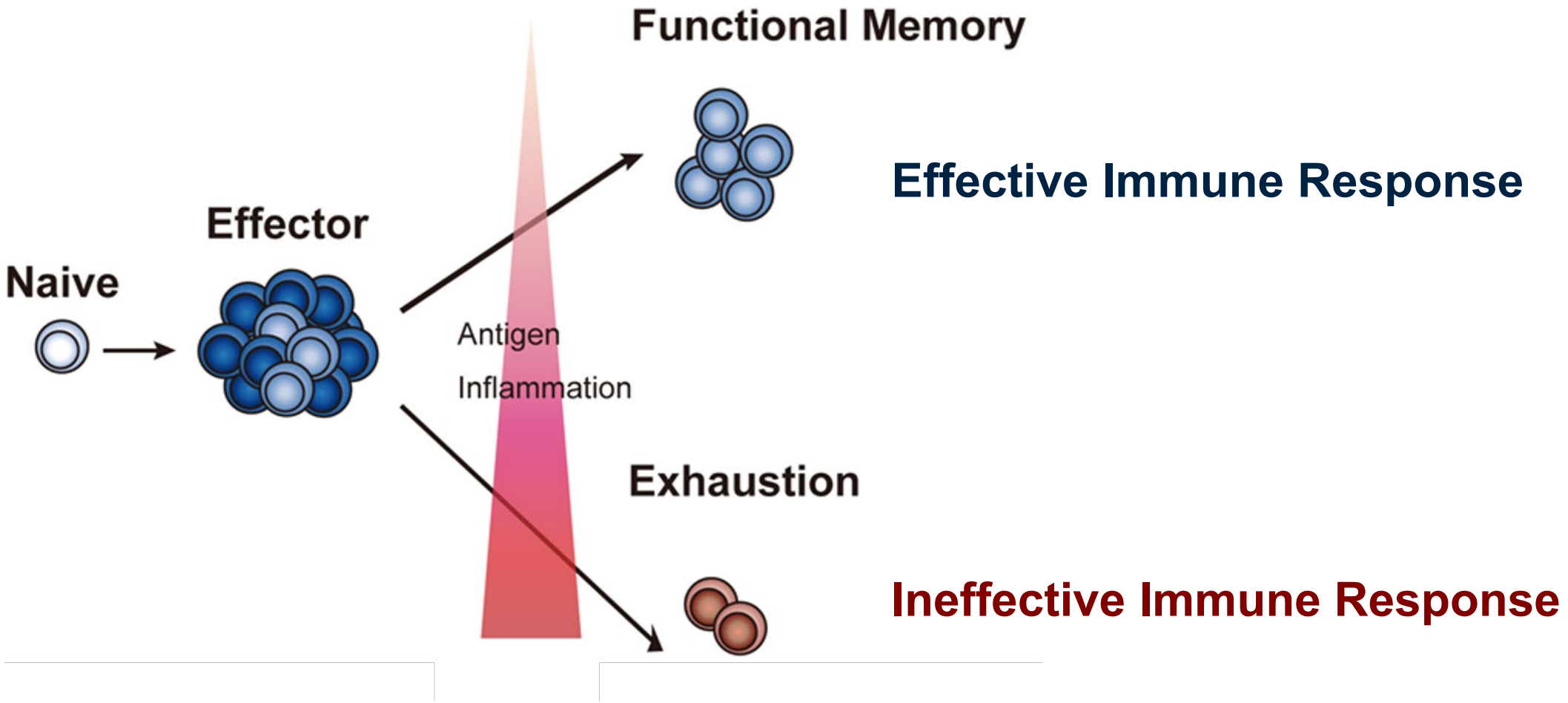
Source: U.S. Department of Defense photo via Wikimedia Commons

CD8 T cells: Foot soldiers of the immune army



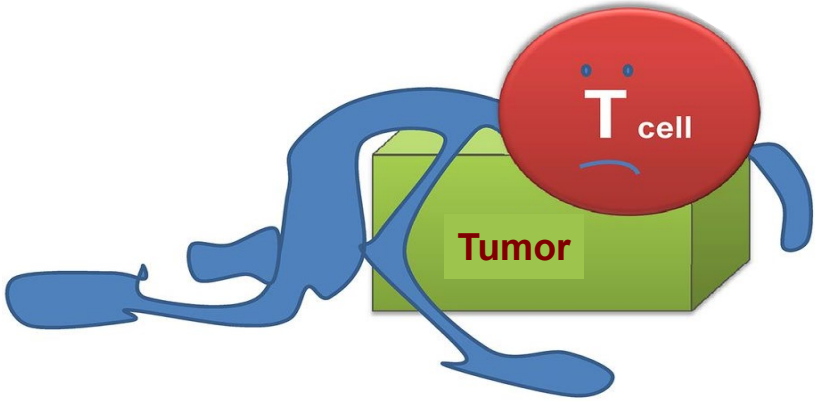
Ritter et al, *Immunity* 2015

CD8 T cell exhaustion



CD8 T cell exhaustion

No Exhaustion | **Partial Exhaustion** | **Mild Exhaustion** | **Moderate Exhaustion** | **Extreme Exhaustion**



Slide courtesy of John Wherry

CD8 T cell exhaustion

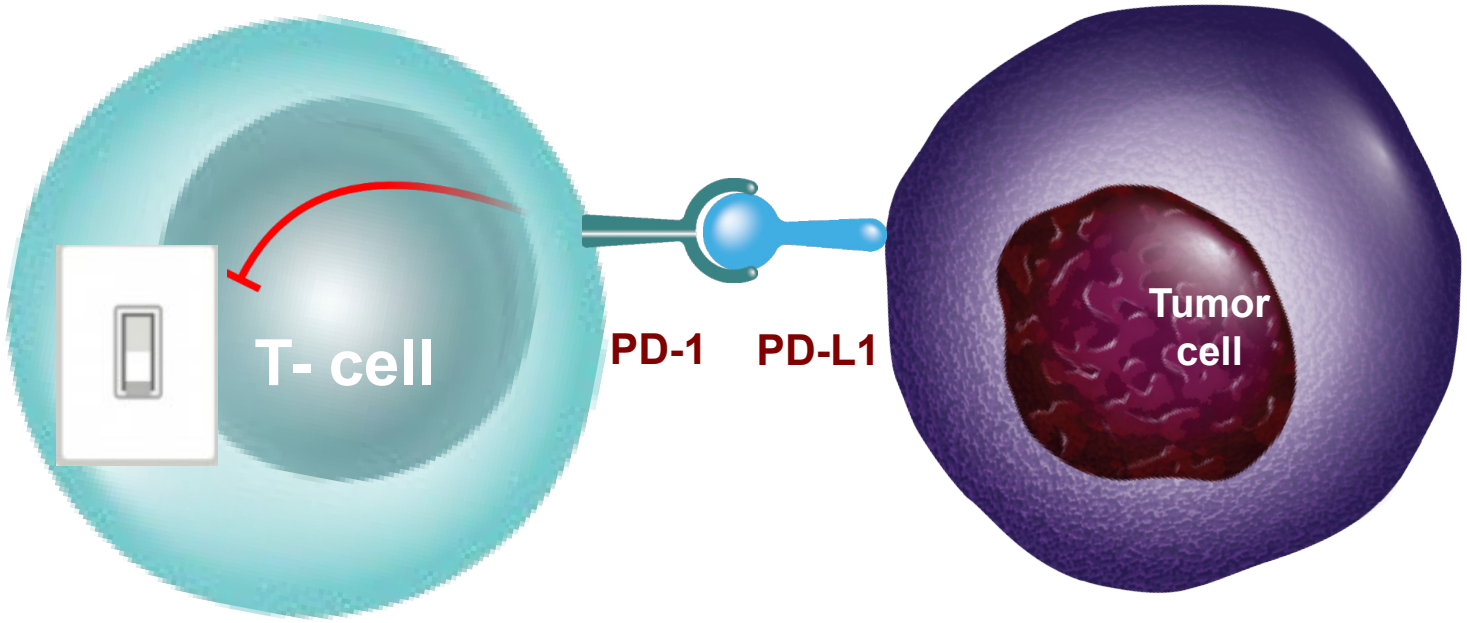
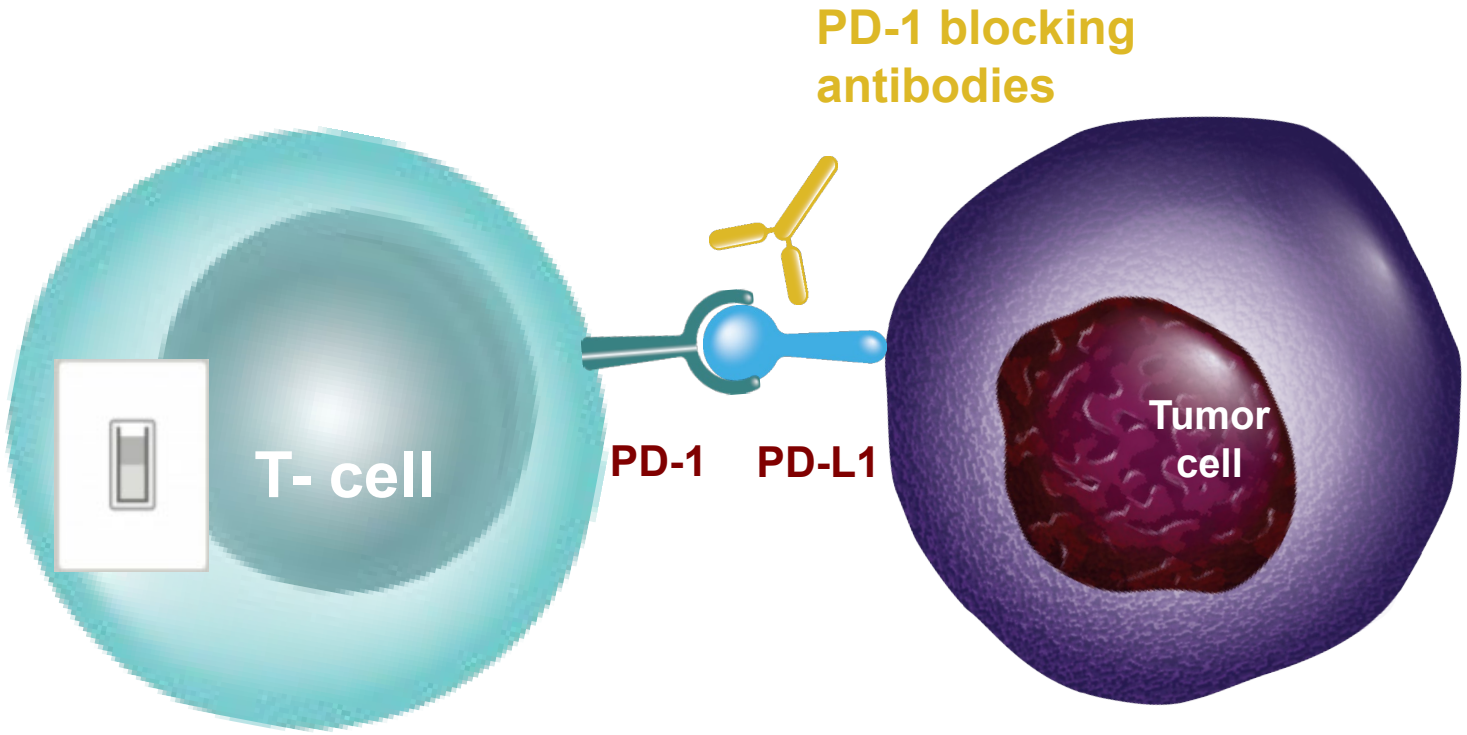


Image credit: Parker Institute and https://pennaelectric.com/electrician-blog

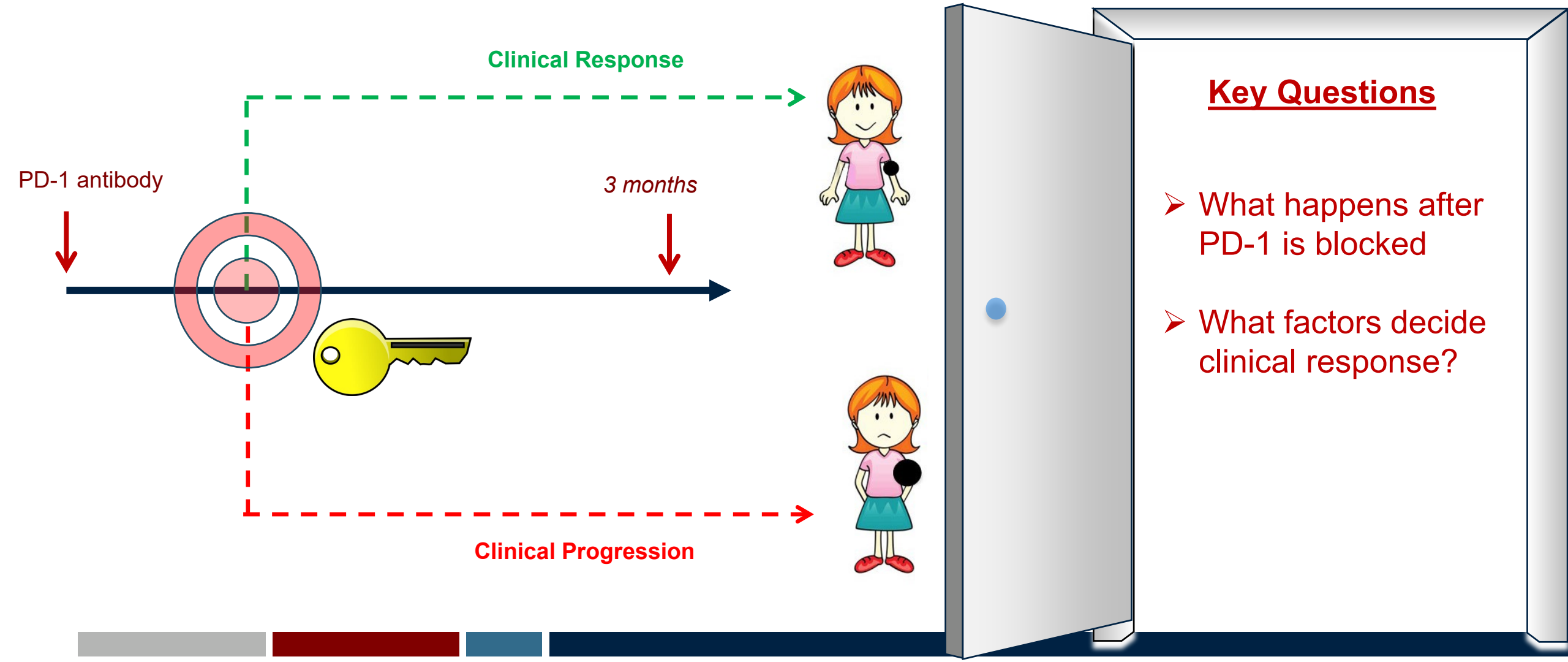
CD8 T cell reinvigoration



Does blocking PD-1 reactivate exhausted T cells?

Image credit: Parker Institute and https://pennaelectric.com/electrician-blog

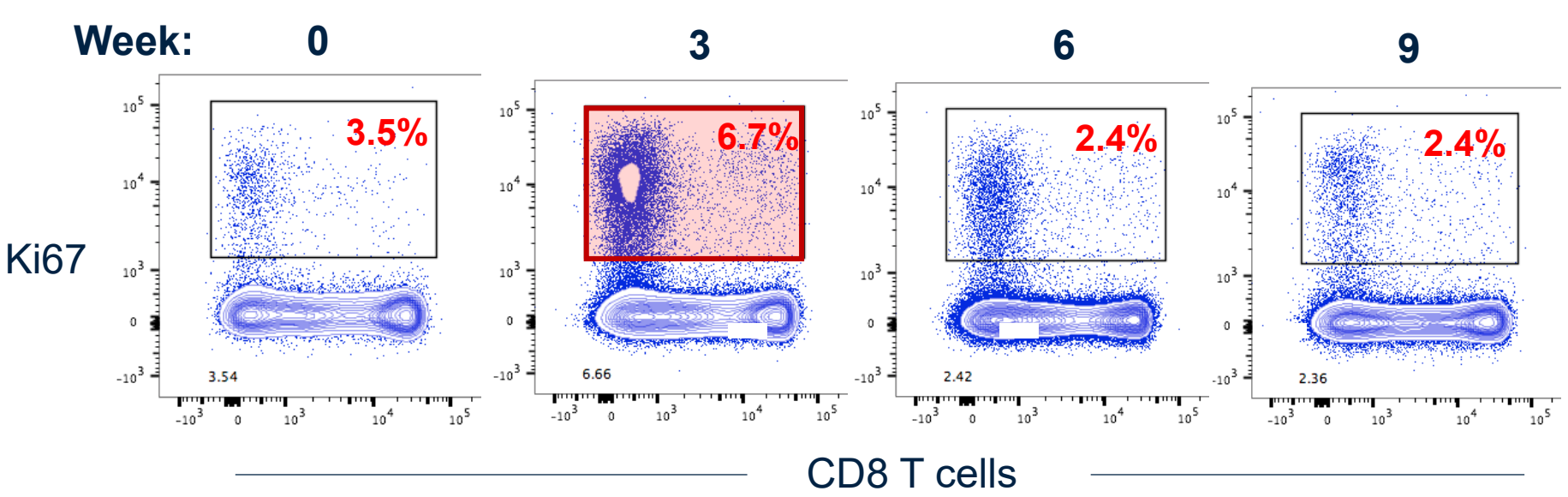
When does the immune response happen after blocking PD-1

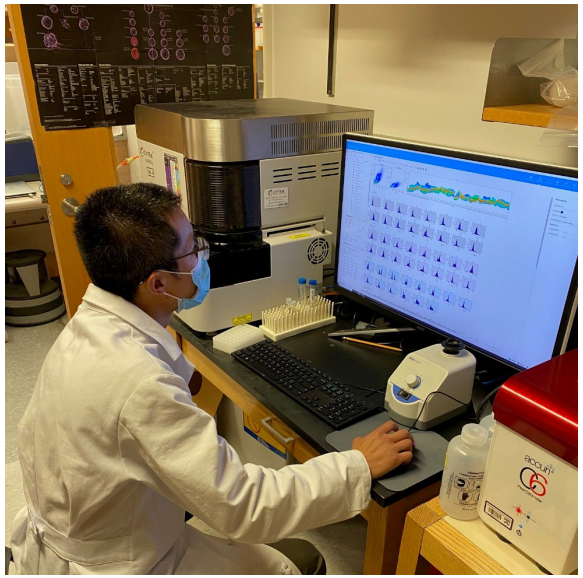


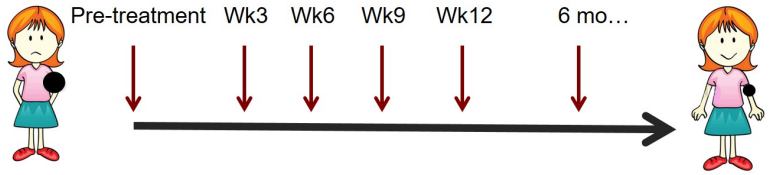
Key Questions

- What happens after PD-1 is blocked
- What factors decide clinical response?

Measuring the immune response to blocking PD-1

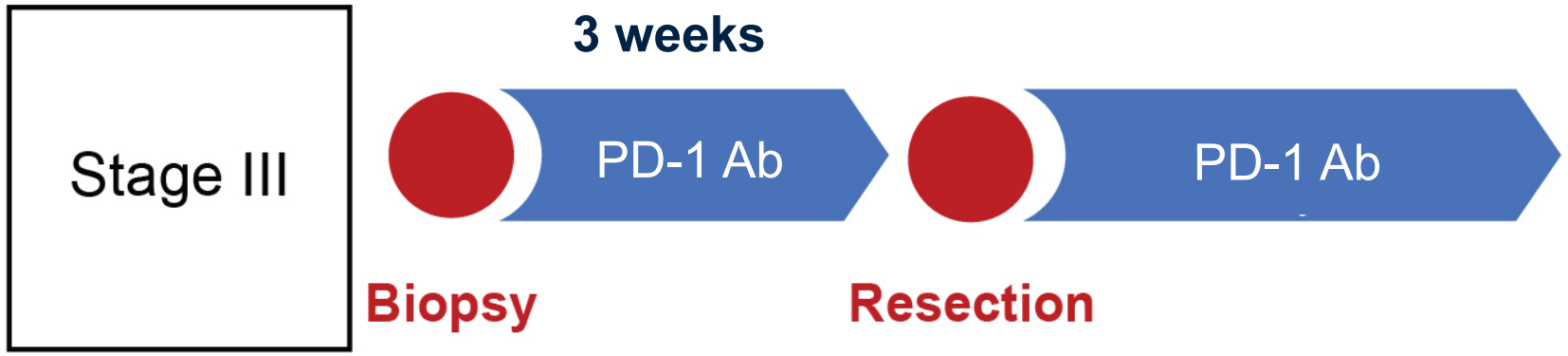




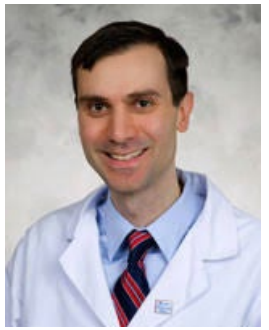


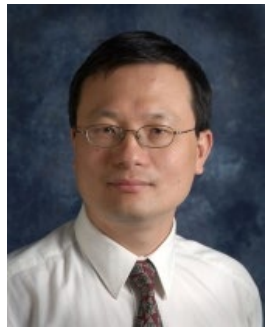
Laboratory science informing clinical trial design

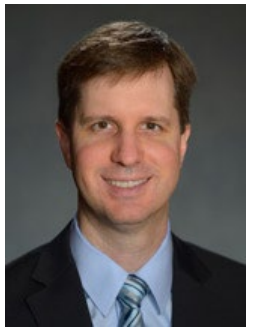
CLINICAL TRIAL OF BLOCKING PD-1 BEFORE SURGERY




T. Mitchell

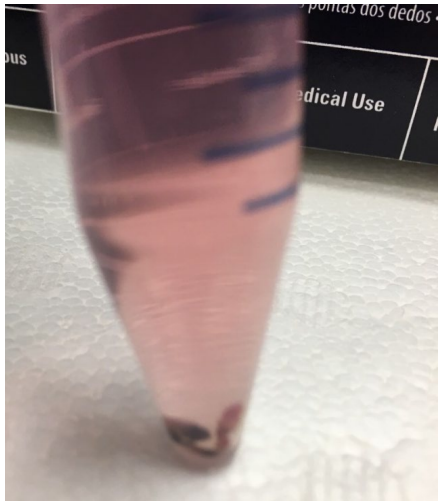

G. Karakousis

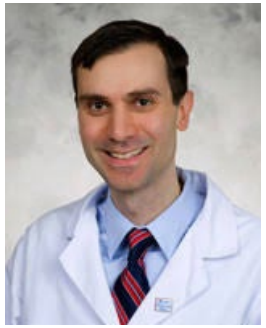

G. Xu


M. Farwell

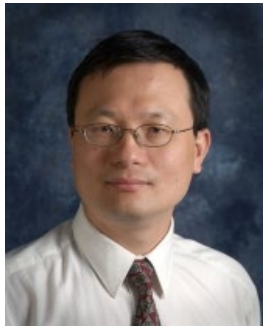
Tissue Processing Pipeline

Biopsy





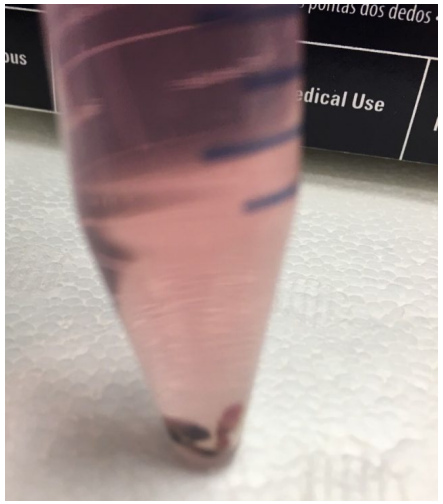
G. Karakousis

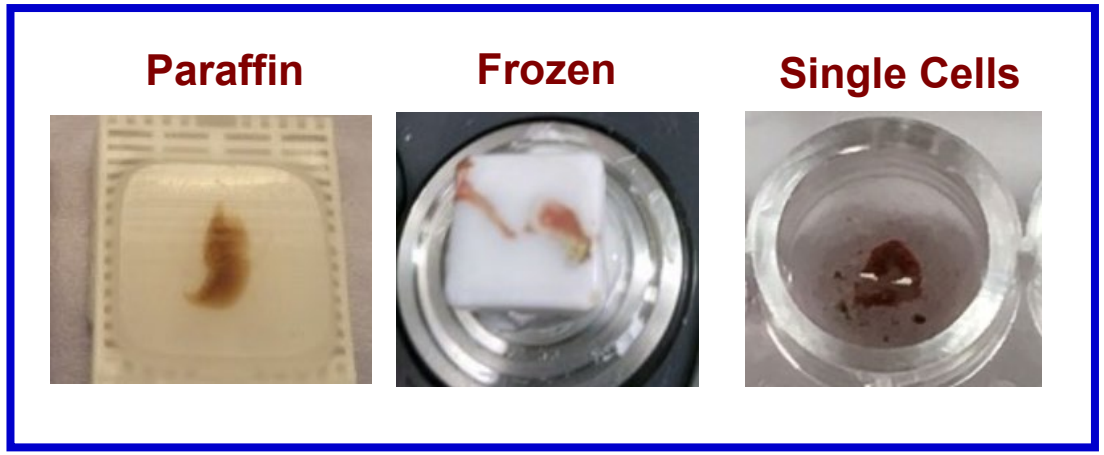


G. Xu

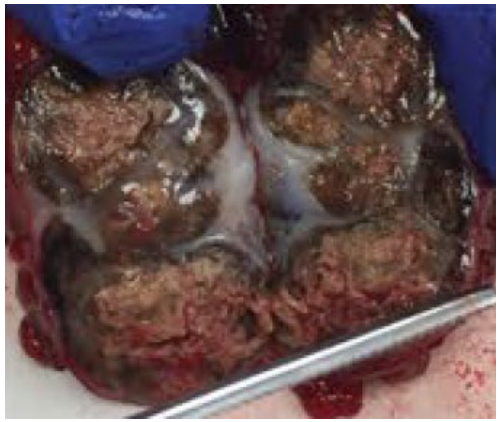
Tissue Processing Pipeline

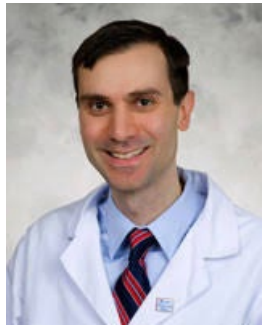
Biopsy



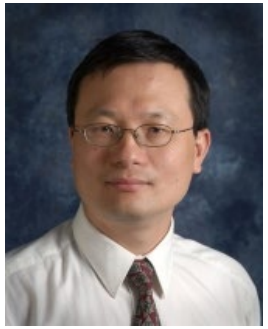


Resection



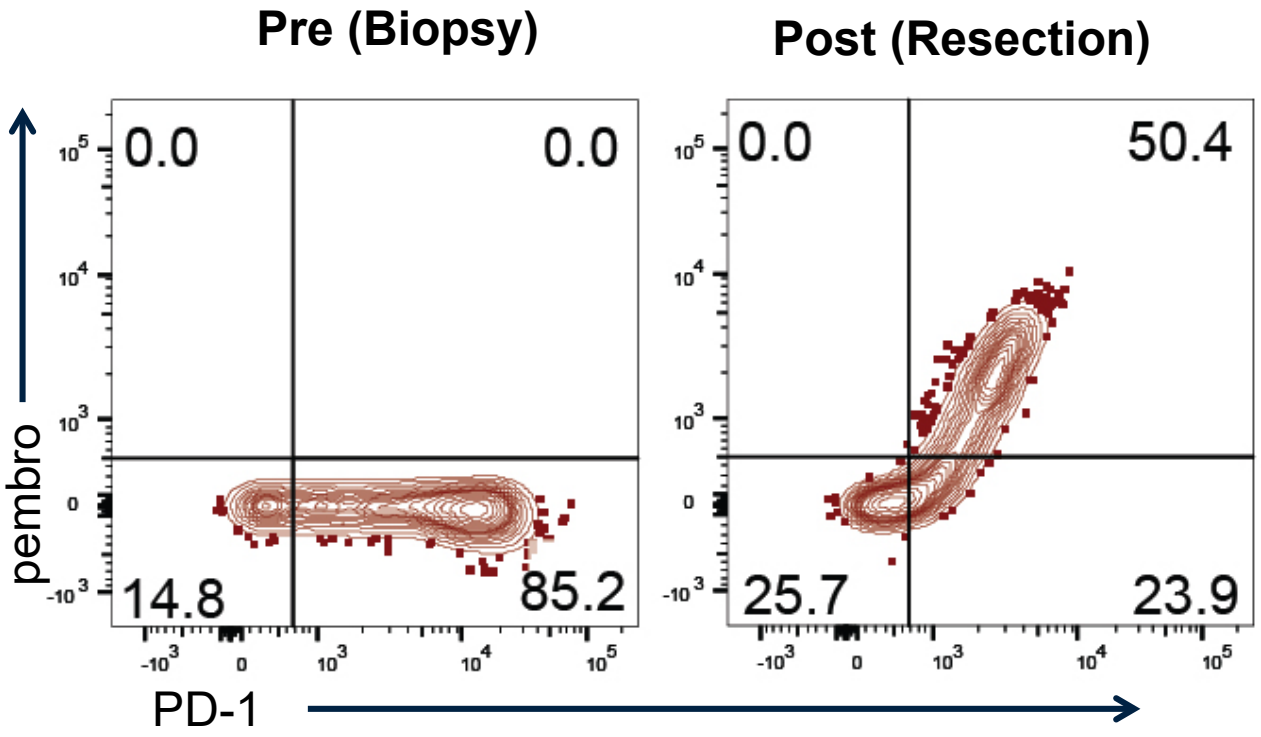


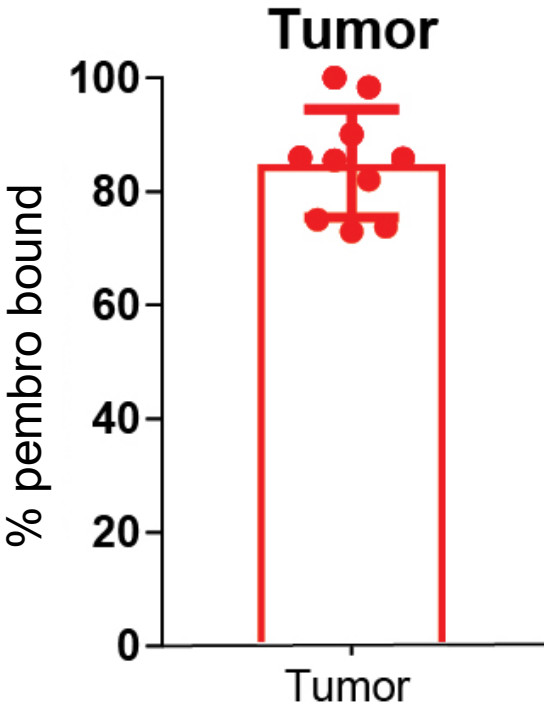
G. Karakousis



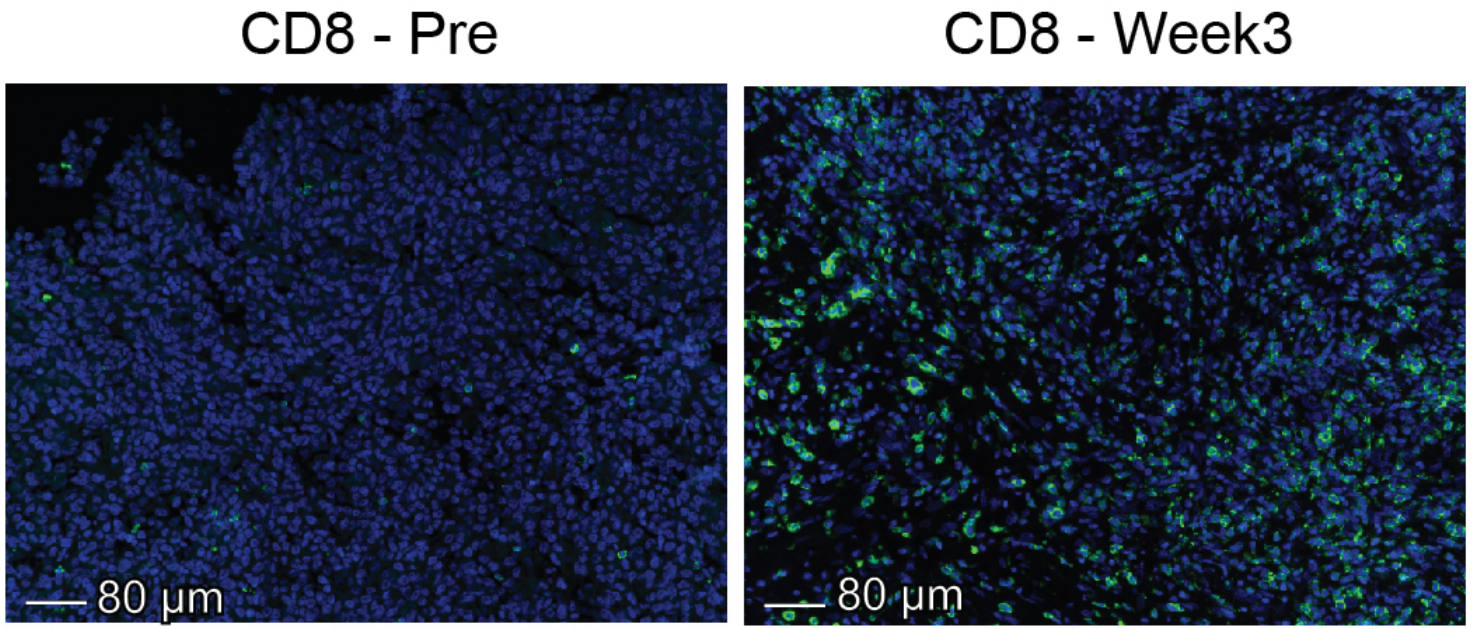
G. Xu

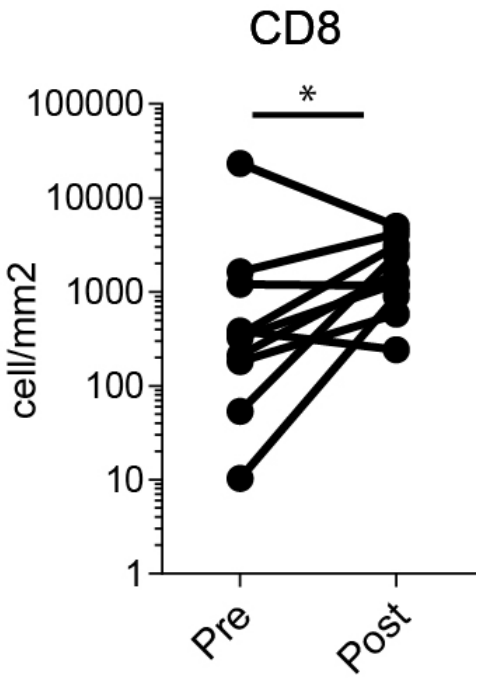
PD-1 antibody reaches the tumor



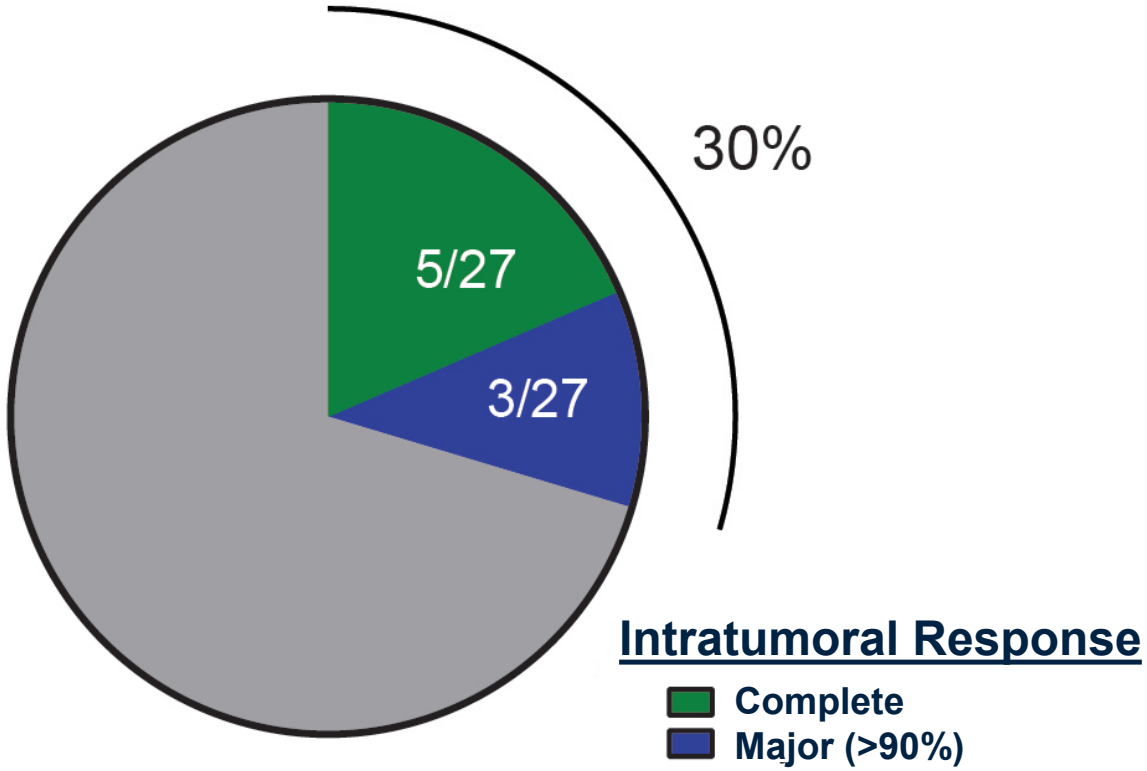


Blocking PD-1 results in increased CD8 T cells in the tumor



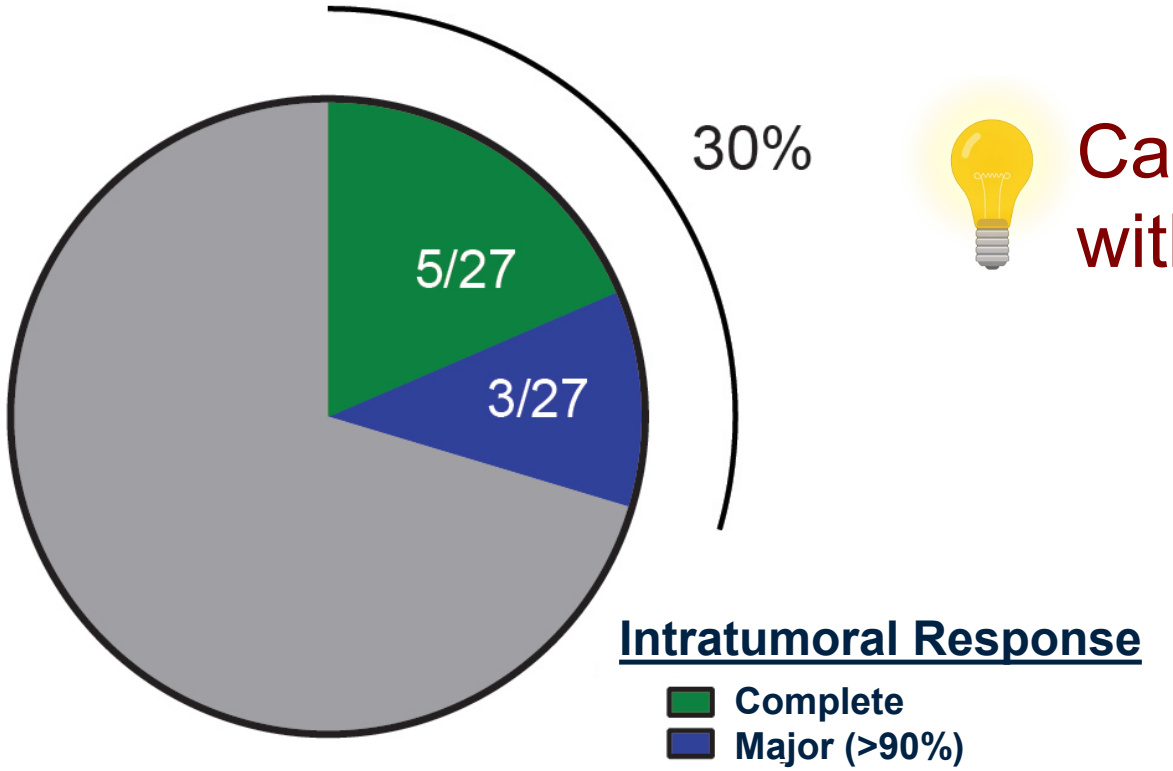


Intratumoral response after a single dose of PD-1 treatment predicts clinical benefit



Huang et al, *Nature Medicine* 2019

Intratumoral response after a single dose of PD-1 antibody predicts clinical benefit



Can we improve outcomes for patients with less than 90% tumor destruction

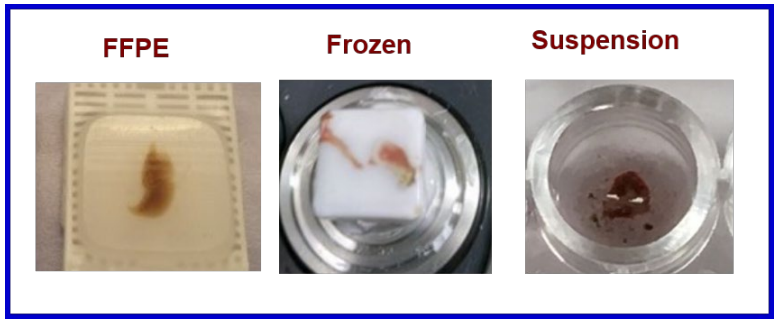
Huang et al, *Nature Medicine* 2019

Question 1: When is the immune response to blocking PD-1

- Immune response occurs after the first dose, within 3 weeks

Question 2: What happens after PD-1 is blocked?

2. What happens after PD-1 is blocked?

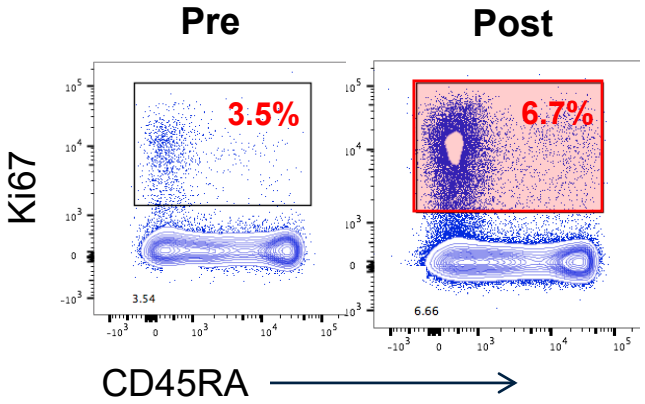


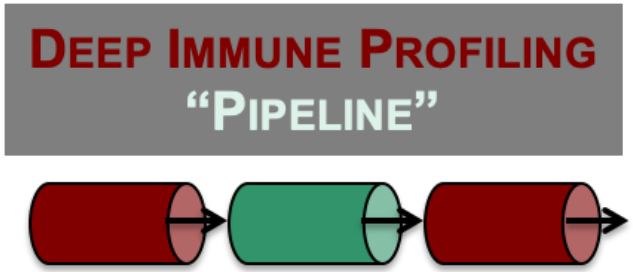
DEEP IMMUNE PROFILNG

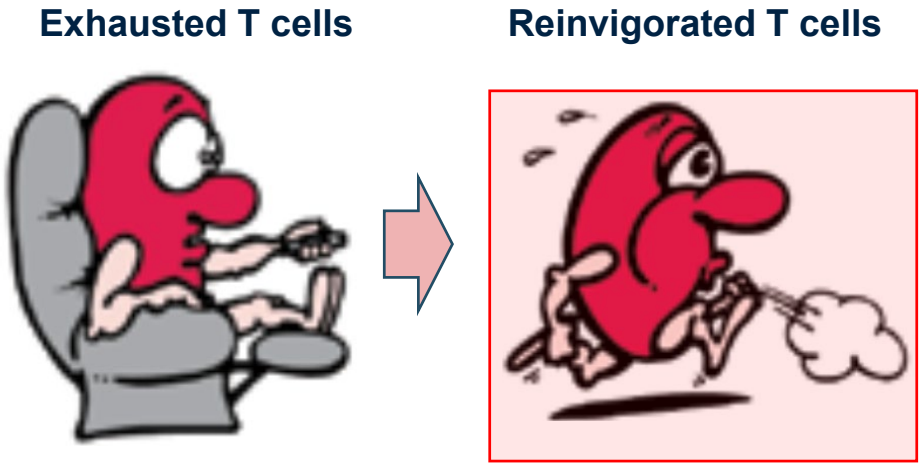
- High dimensional cytometry
- TCR and RNA sequencing
- Tumor Whole Exome Sequencing
- Microscopy

COMPUTATIONAL ANALYSIS

PD-1 treatment is reinvigorating exhausted CD8 T cells

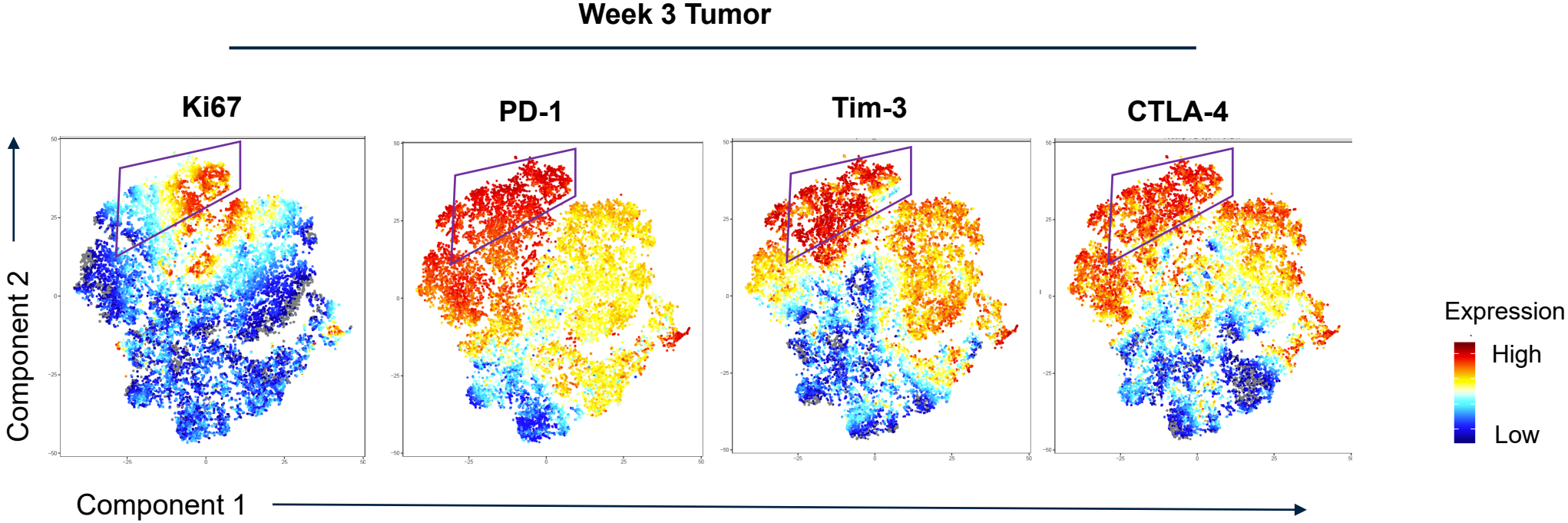




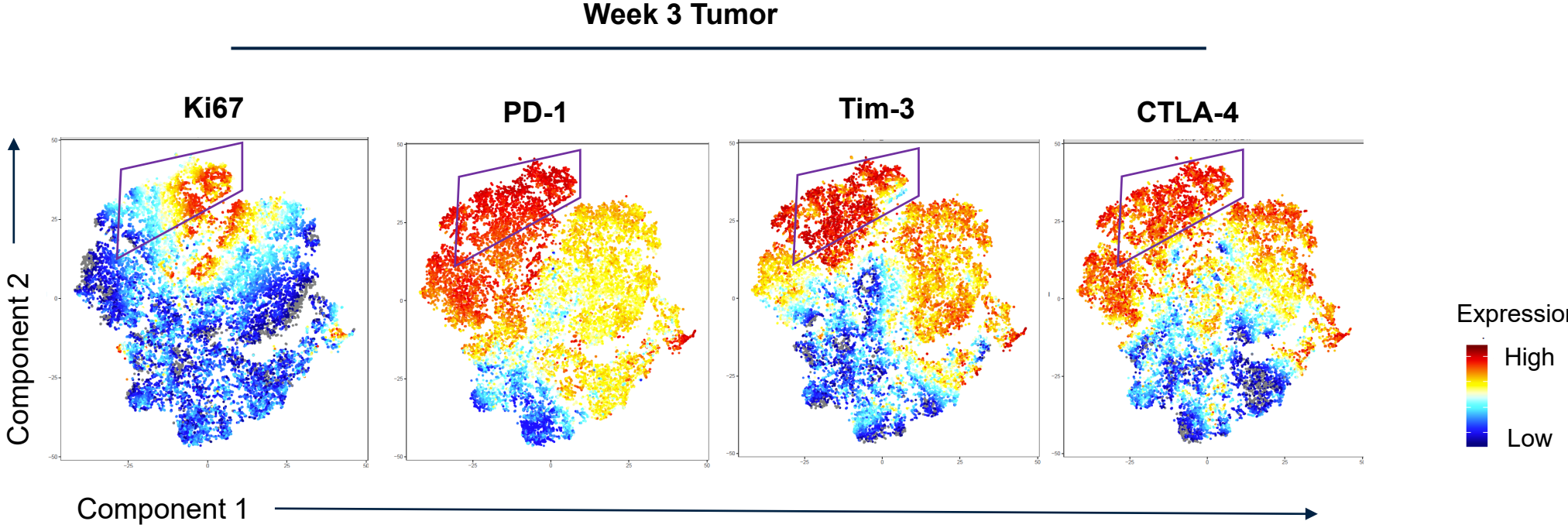


- MULTIPLE INHIBITORY RECEPTORS
- RNA SIGNATURE OF EXHAUSTED T CELLS
- SAME T CELL CLONES FOUND IN TUMOR

Dimensional reduction technique reveal additional therapeutic targets



Dimensional reduction technique reveal additional therapeutic targets



Can we use drugs to block new targets on exhausted CD8 T cells?

Question 1: When is the immune response to blocking PD-1

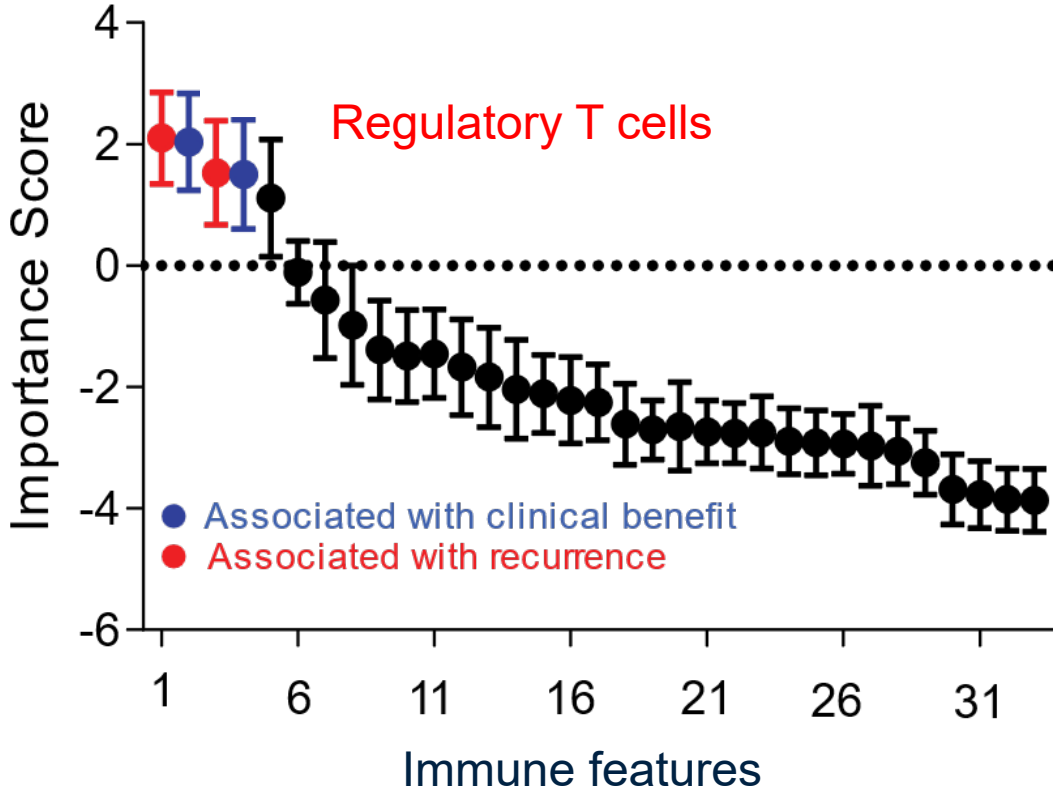
- Immune response to occurs after the first dose, within 3 weeks

Question 2: What happens after PD-1 is blocked?

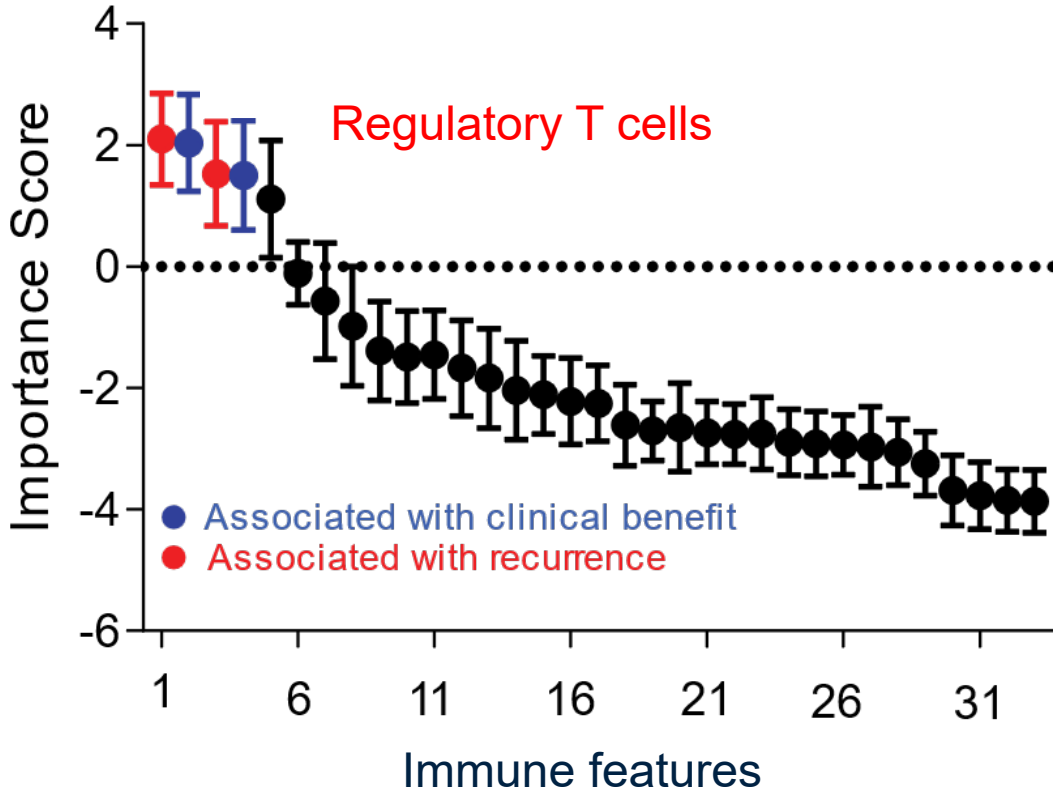
- PD-1 blockade is reinvigorating exhausted CD8 T cells

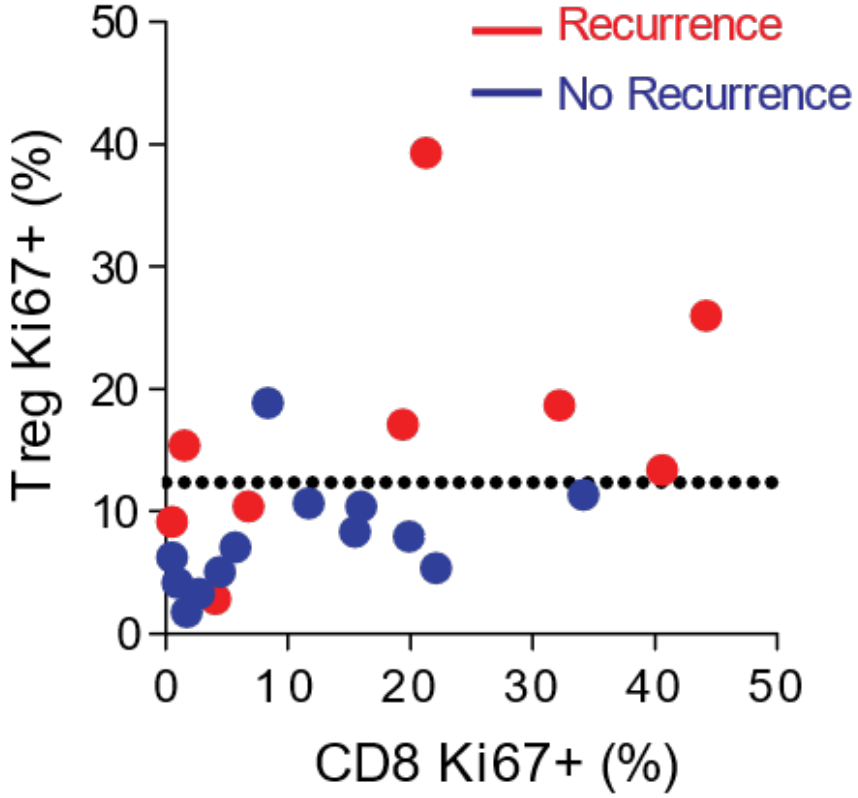
Question 3: What factors decide clinical response?

Machine learning approach reveals that regulatory T cells limit clinical response to PD-1 treatment



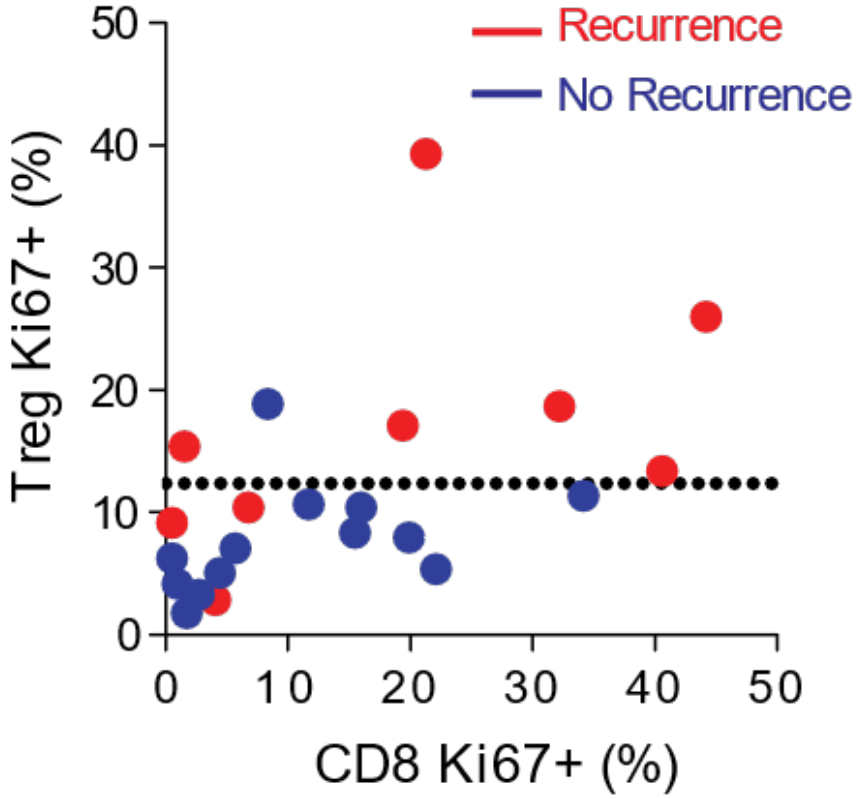
Machine learning approach reveals that regulatory T cells limit clinical response to PD-1 treatment





Machine learning approach reveals that regulatory T cells limit clinical response to PD-1 treatment

- Can we personalize treatment (precision immuno-oncology)
- Can we therapeutically remove regulatory T cells for certain patients?



ARTICLE

doi:10.1038/nature22079

T-cell invigoration to tumour burd… ratio associated with anti-PD-1 res…

Alexander C. Huang[1,2,3,4], Michael A. Postow[5,6]*, Robert J. Orlowski[1,2,3,4]*, Rosemarie Mick[3,4,7], Bertram Ben…
Sasikanth Manne[2,8], Wei Xu[1,3], Shannon Harmon[1,3], Josephine R. Giles[2,4,8], Brandon Wenz[1,3], Matthew Adam…
Deborah Kuk[10], Katherine S. Panageas[10], Cristina Carrera[5,11], Phillip Wong[9,12], Felix Quagliarello[2,8], Bradley V…
Kurt D'Andrea[1,3], Kristen E. Pauken[2,8], Ramin S. Herati[1,2,3], Ryan P. Staupe[2,8], Jason M. Schenkel[13], Suzanne …
Shawn Kothari[1], Sangeeth M. George[2,4,8], Robert H. Vonderheide[1,2,3,4], Ravi K. Amaravadi[1,3], Giorgos C. Kara…
Lynn M. Schuchter[1,3], Xiaowei Xu[3,15], Katherine L. Nathanson[1,3,4], Jedd D. Wolchok[5,12], Tara C. Gangadhar[1,3]§
E. John Wherry[2,3,4,8]§

nature medicine

FOCUS | LETTERS

https://doi.org/10.1038/s41591-019-0357-y

A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma

Alexander C. Huang[1,2,3,4,16]*, Robert J. Orlowski[1,11,16], Xiaowei Xu[4,5], Rosemarie Mick[3,4,6], Sangeeth M. George[7,12], Patrick K. Yan[2,7], Sasikanth Manne[2,7], Adam A. Kraya[1,4], Bradley Wubbenhorst[1,4], Liza Dorfman[1,4], Kurt D'Andrea[1,4], Brandon M. Wenz[1,4], Shujing Liu[4,5], Lakshmi Chilukuri[2,7], Andrew Kozlov[4,8], Mary Carberry[1,4], Lydia Giles[1,4], Melanie W. Kier[1], Felix Quagliarello[2,13], Suzanne McGettigan[1,4], Kristin Kreider[1,4], Lakshmanan Annamalai[9], Qing Zhao[9], Robin Mogg[9,14], Wei Xu[1,4], Wendy M. Blumenschein[9], Jennifer H. Yearley[9], Gerald P. Linette[1,2,3,4], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Ramin S. Herati[1,2], Bertram Bengsch[2,15], Katherine L. Nathanson[1,3,4], Michael D. Farwell[4,8,17], Giorgos C. Karakousis[4,10,17], E. John Wherry[2,3,4,7,17]* and Tara C. Mitchell[1,4,17]*

Huang, Amaravadi, Xu, Schuchter, Karakousis, Mitchell, Wherry et al, Nature 2017
Huang, Orlowski, Amaravadi, Schuchter, Xu, Farwell, Karakousis, Wherry, Mitchell, Nature 2019

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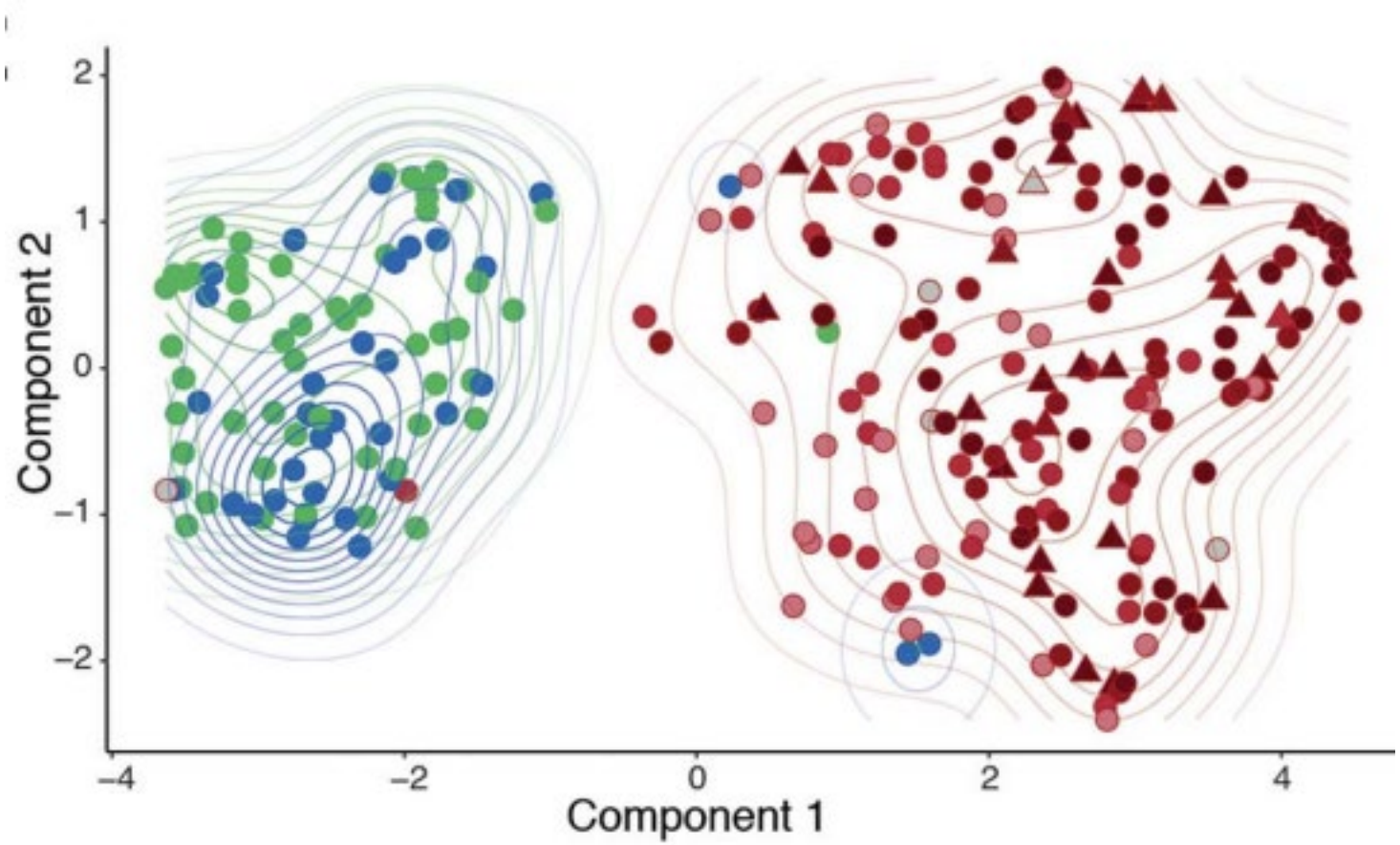
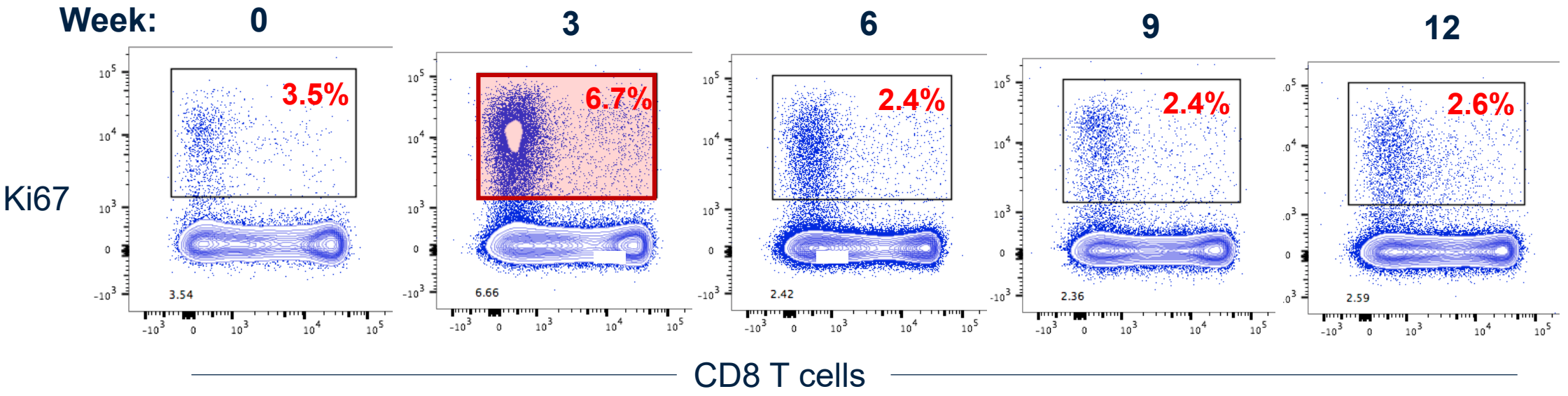
Immune fingerprint in peripheral blood



- Severe COVID-19
- Recovered COVID-19
- Not infected

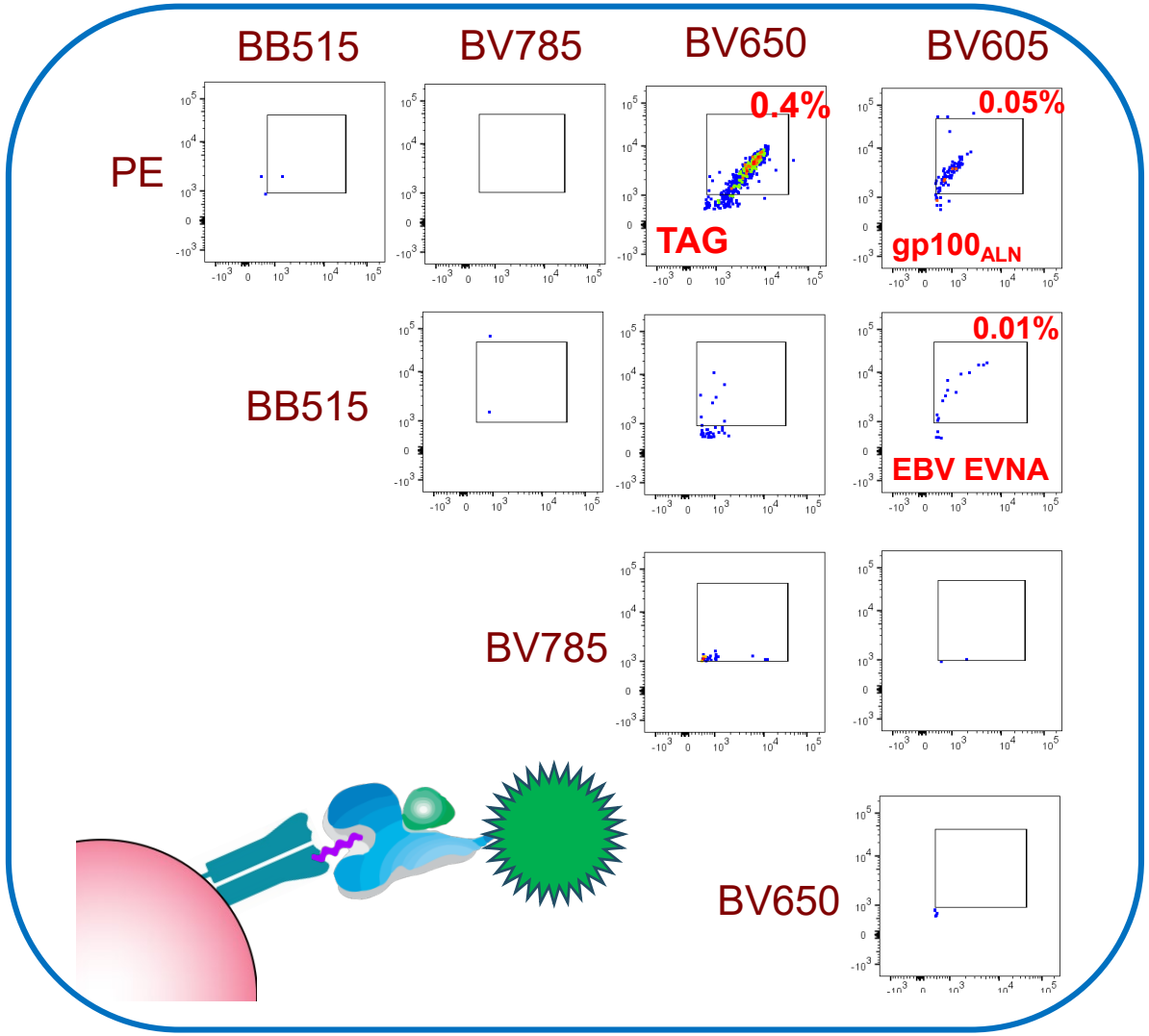
Mathew, Giles, Baxter, Oldridge, Greenplate, Wu, Alanio et al, *Science* 2020

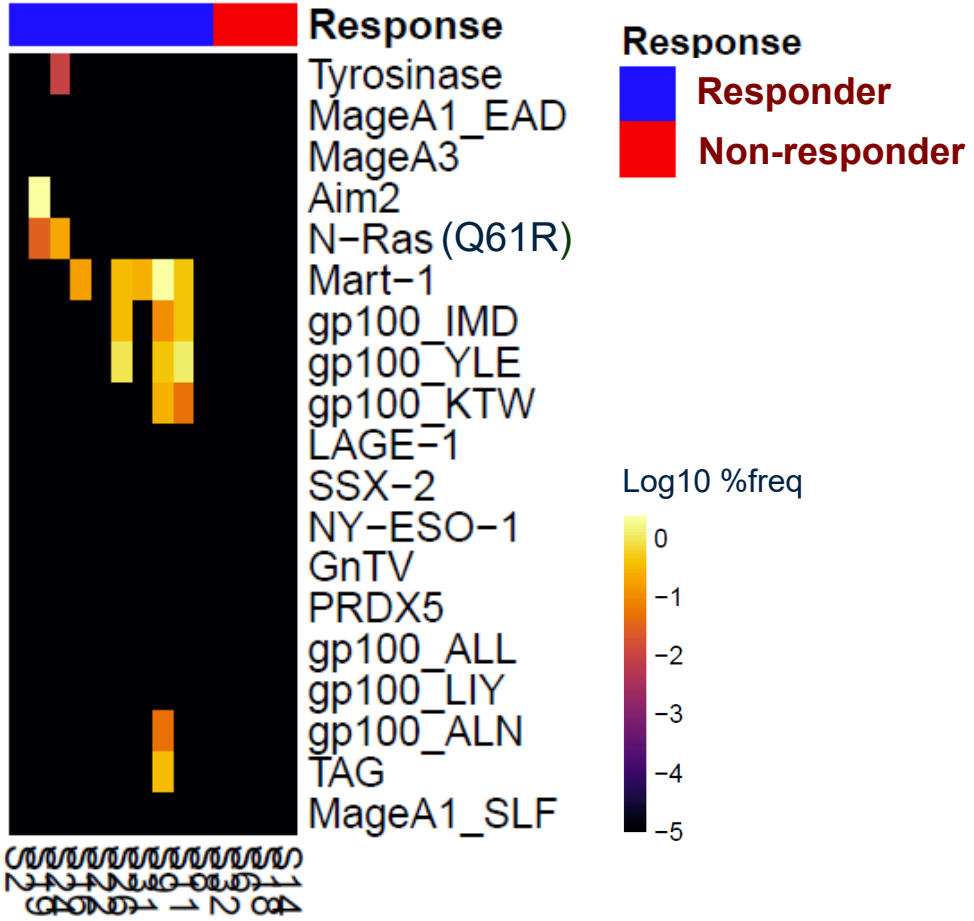
Precision Immuno-Oncology



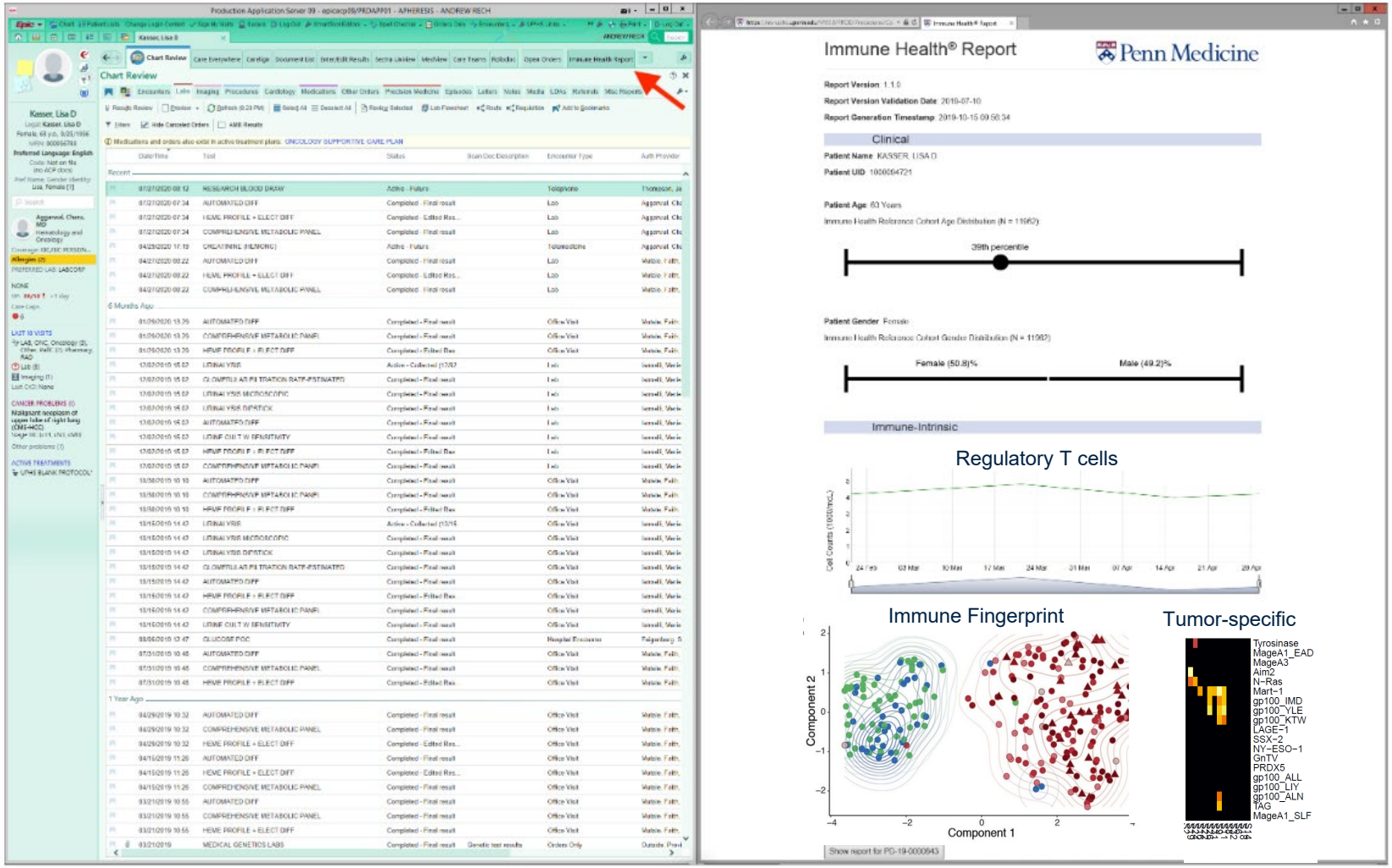
Can we be more precise in measuring the immune response to checkpoint blockade?

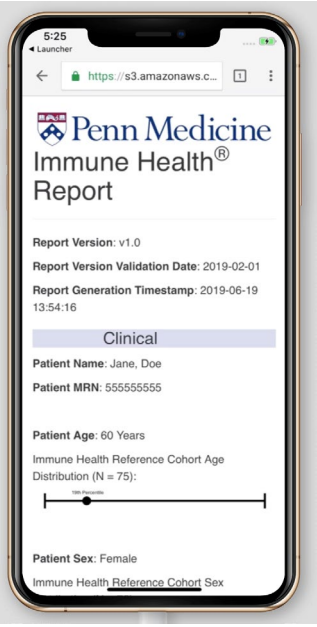
Tumor-Specific T cells





IMMUNE HEALTH REPORT





Adapted from John Wherry

Acknowledgements

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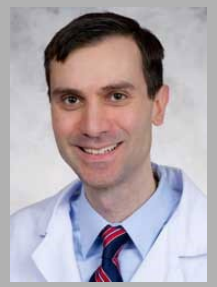

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Lydia Giles
Mary Carberry

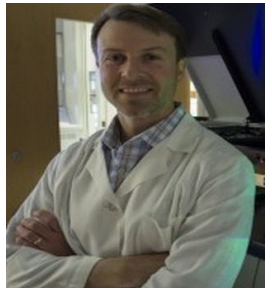
Huang Lab

Nick Han

Justin Kim

Sangeeth George
Patrick Yan
Stella Park
Daniel Yoon
Nick Frazette
Joanna Lee

Wherry Lab



Robert Orlowski
Ramin Herati
Cecile Alanio
Zeyu Chen
Shin Ngiow
Kristen Pauken
Sasi Manne
Josephine Giles

Penn
University of Pennsylvania
Parker Institute for Cancer Immunotherapy

Tara Miller melanoma foundation
#makethebestofit