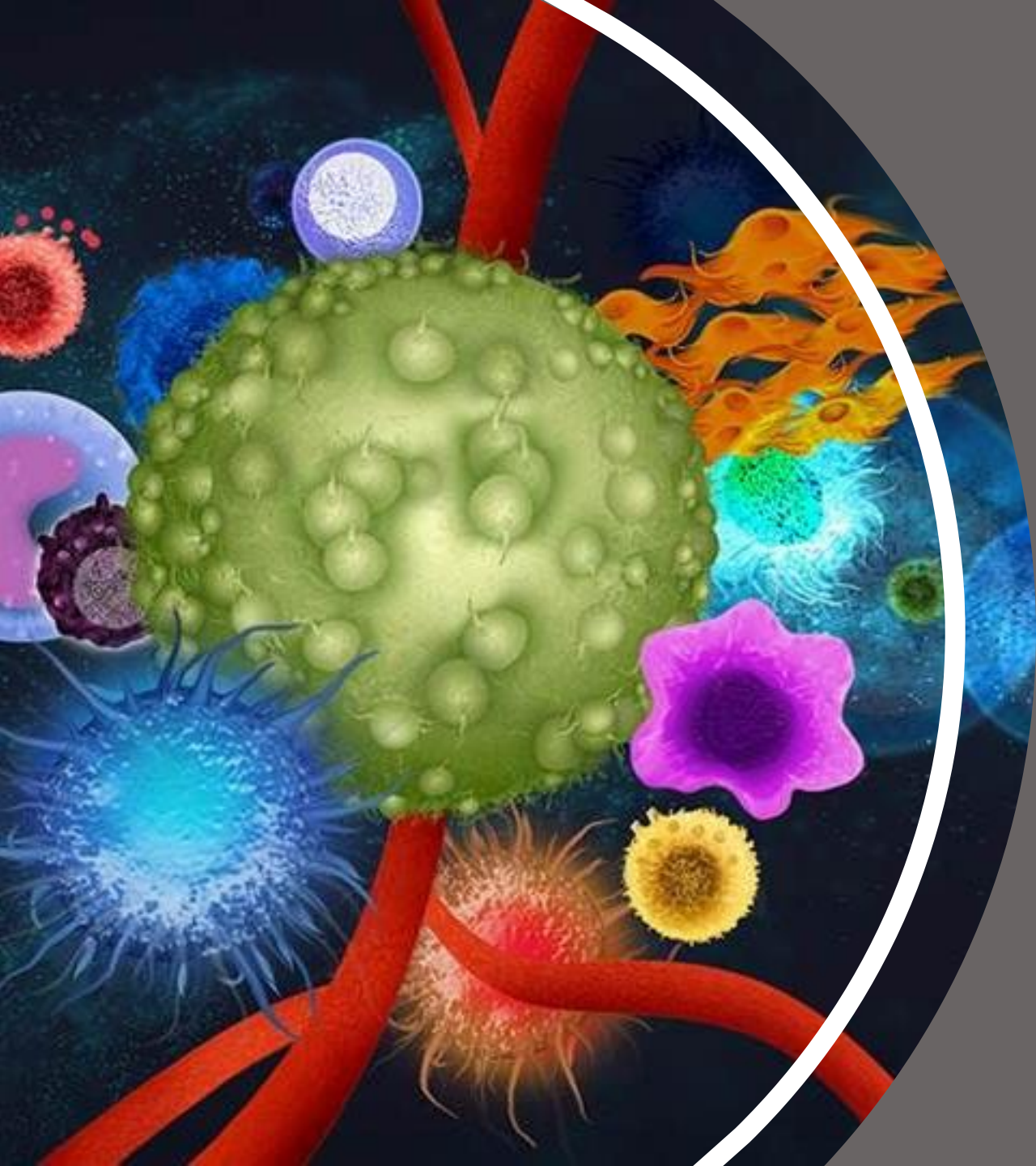




IMMUNOTHERAPY IN THE CURATIVE SETTING RAD ONC

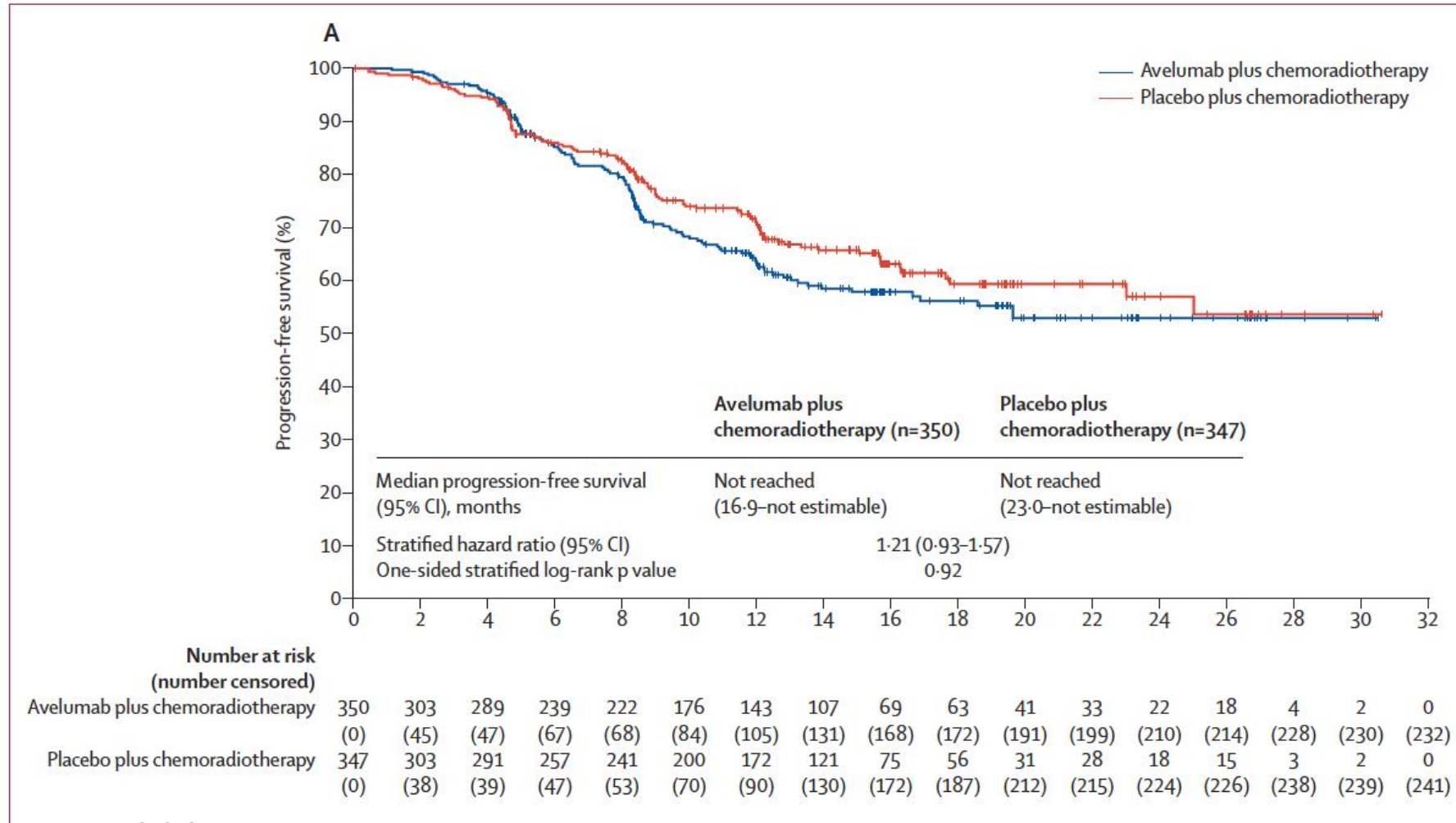
Sana Karam, MD, PhD
Associate Professor & Vice Chair
of Translational Research
University of Colorado, Dept. of
Radiation Oncology



Clinical Trial
Funding:
AstraZeneca,
Genentech, Ionis

Preclinical
Funding: Roche

JAVELIN PHASE III: AVELUMAB+CRT → Φ BENEFIT



GORTEC REACH PHASE III: AVELUMAB+CETUXRT → Φ BENEFIT

430 patients randomized

The number of PFS events was not reached, at the time of analysis

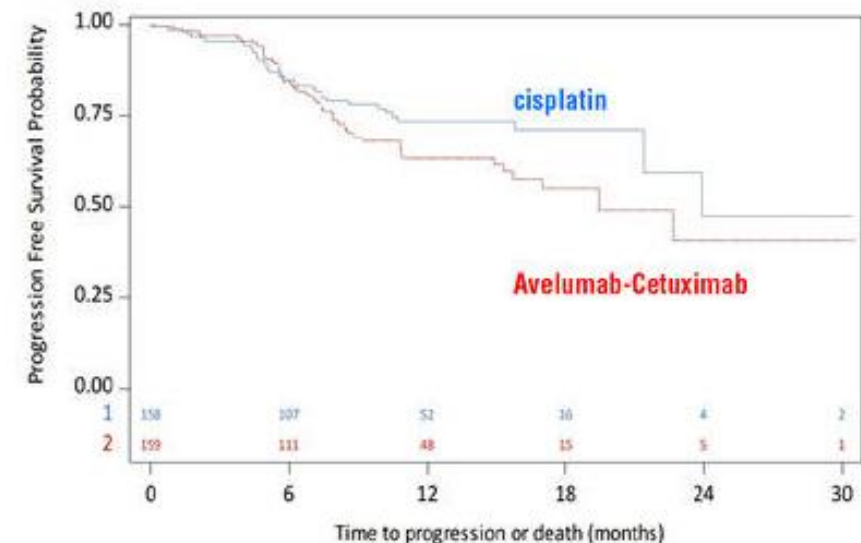
The planned interim analysis for futility based on 89 events in 317 patients showed a 1-year PFS rate of :

73% (95%CI 65%-81%) in SOC-cisplatin-RT

VS

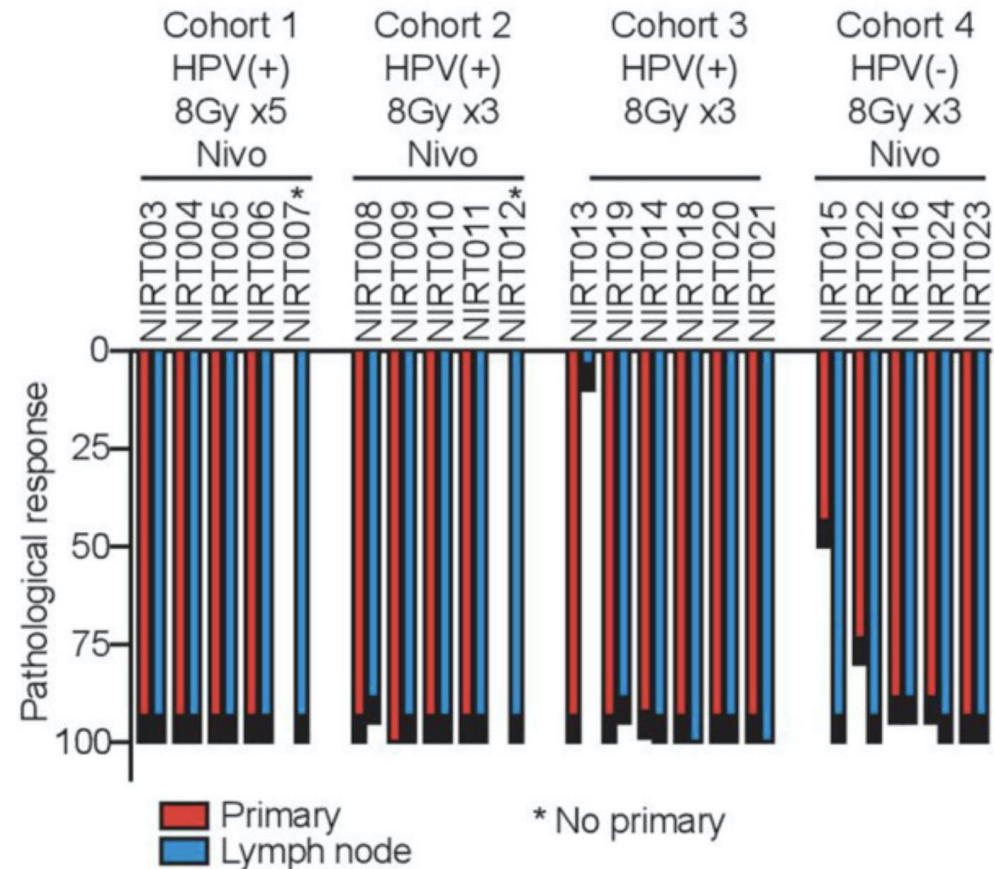
64% (95%CI 54%-72%) in Avelumab-Cetuximab-RT

-----> HR 1.27 (95%CI 0.83-1.93),
crossing the futility boundary



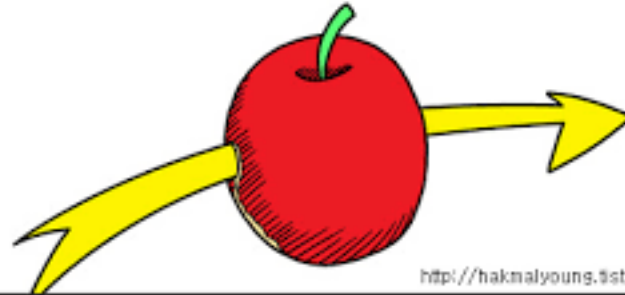
THERE IS HOPE: PHASE I NEOADJUVANT SBRT + NIVOLUMAB

**mPR and pCR rate
was 86% and 67%,**

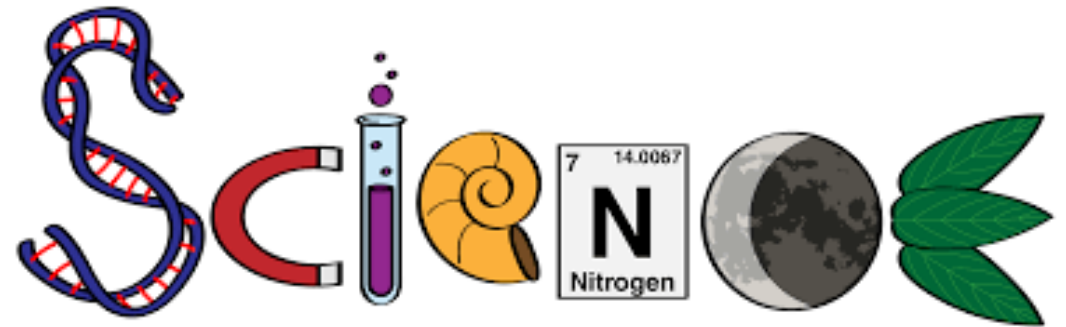


ADVANCE the CURE

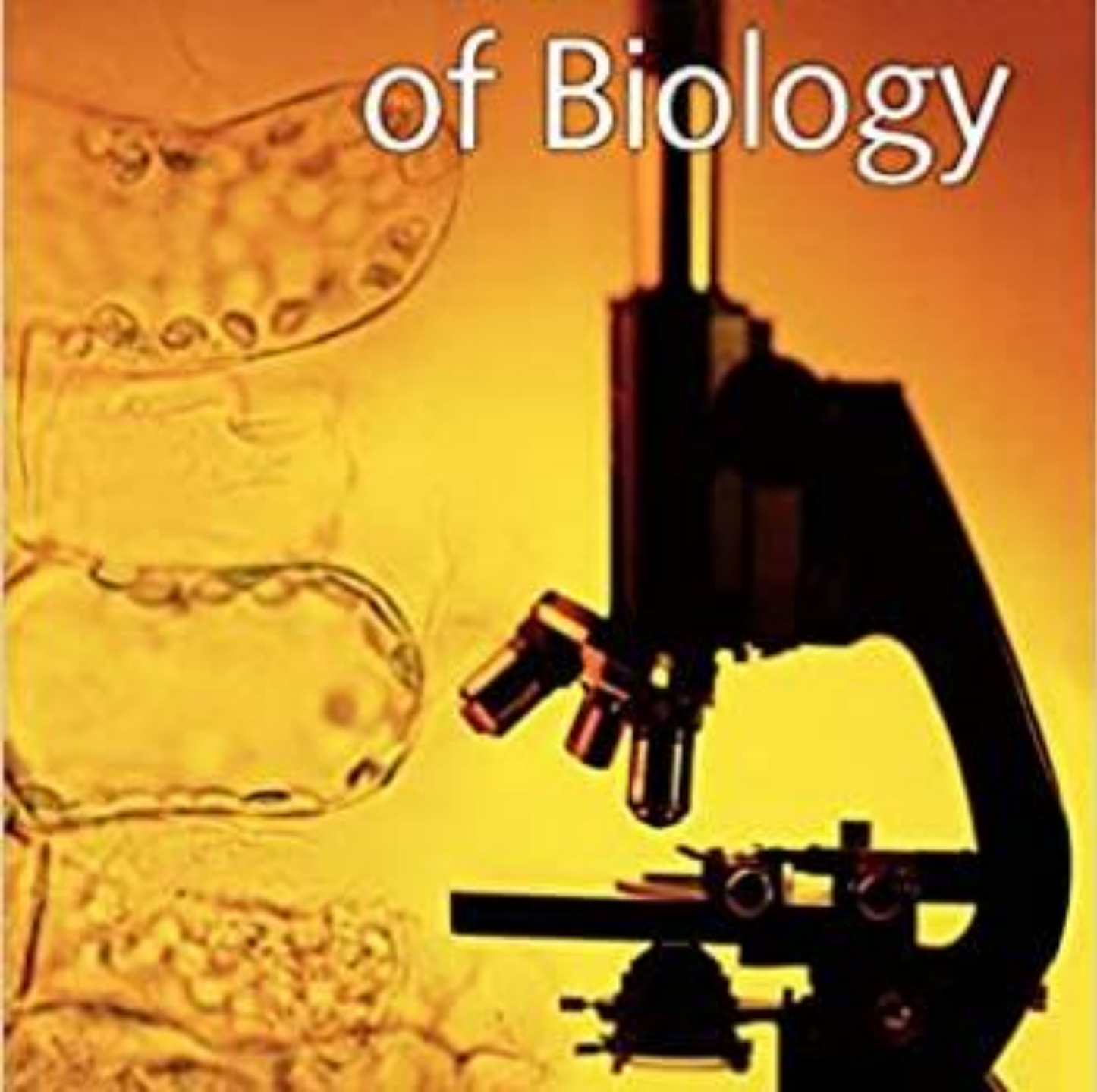
through



<http://haknalyoung.9story.com>



of Biology

A composite image featuring a black and red compound microscope in the foreground, set against a warm, yellow-orange background. In the background, several petri dishes containing various biological specimens, including what appear to be bacterial cultures and plant tissue, are visible. The overall aesthetic is scientific and educational.

BIOLOGY: MECHANISMS OF RESPONSE & RESISTANCE





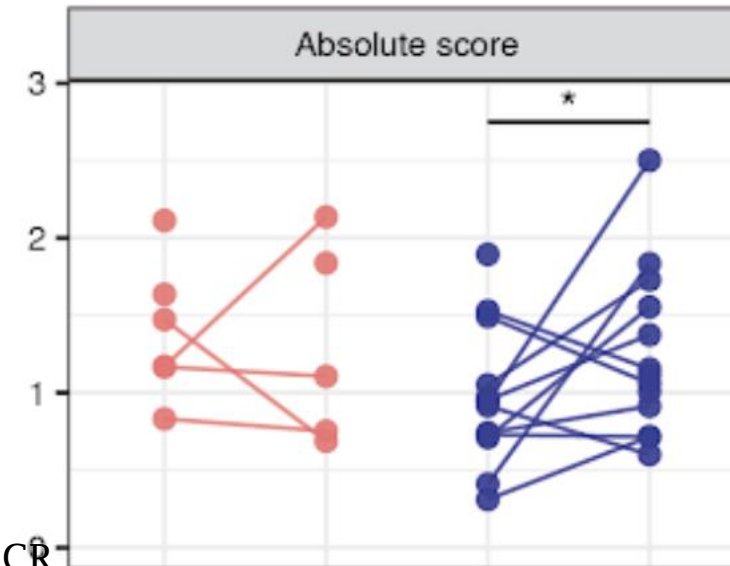
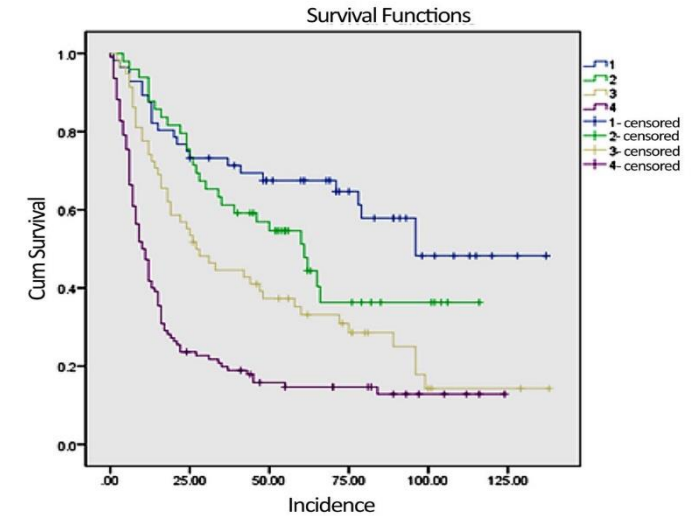
BUT
FIRST A
BRIEF
INTRO



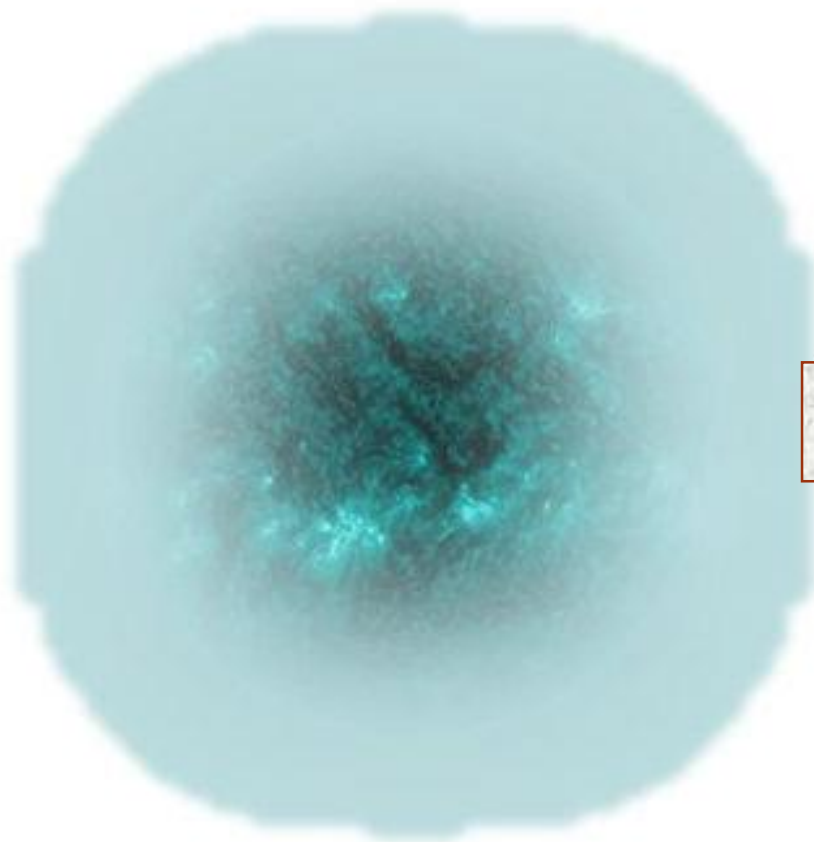
ORAL CANCER: BAD ACTORS COLD



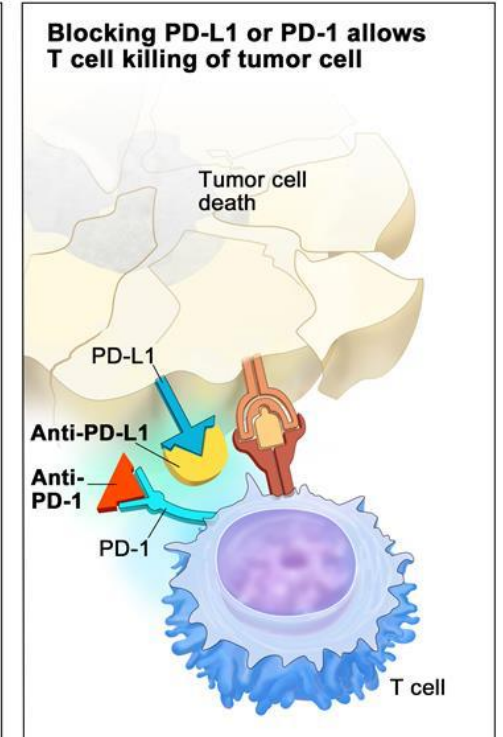
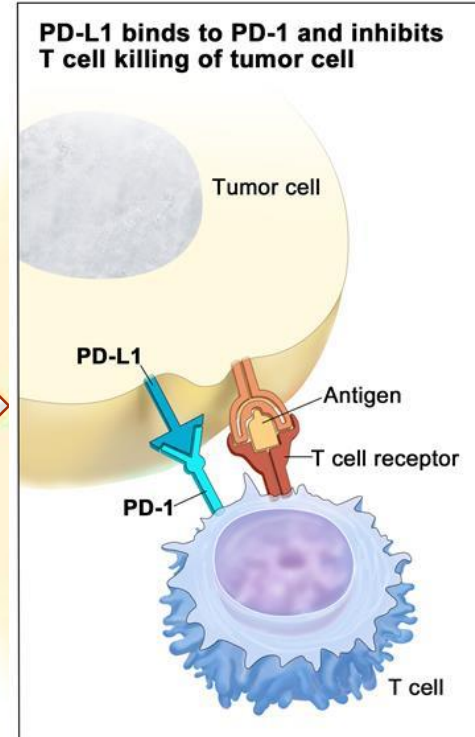
- Subset of HNSCC, poor outcomes, mortality rates 25%-50%
- Treatment associated with substantial morbidity & toxicity
- Cold tumors with poor response to immunotherapy



CAN RT TURN HNC INTO “HOT TUMORS”?



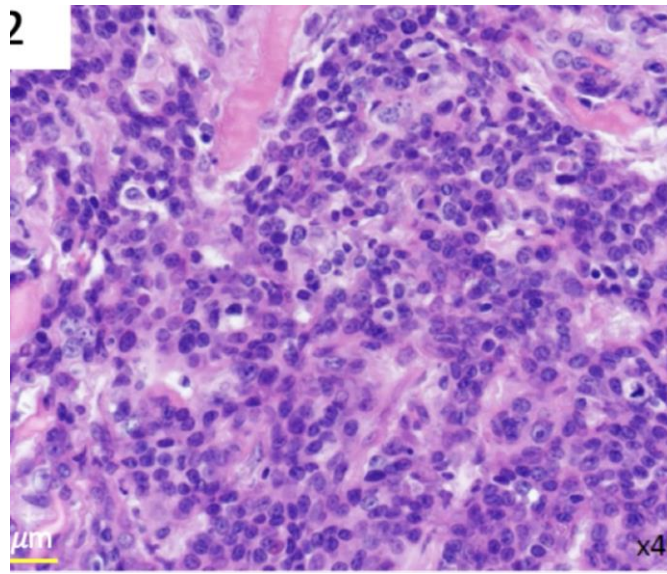
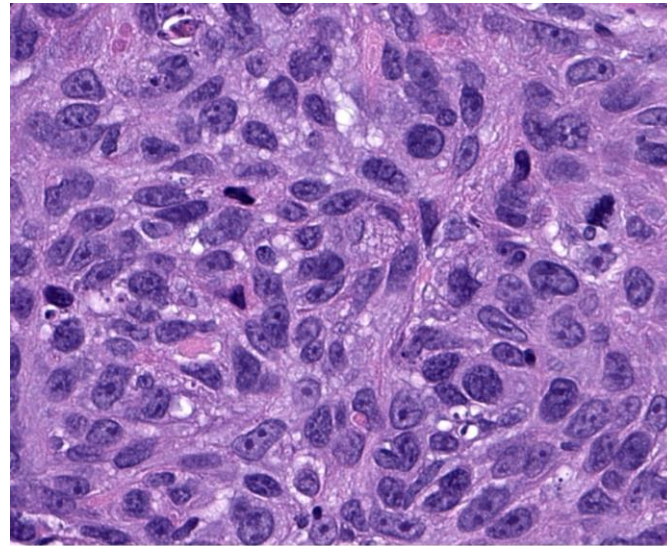
Radiation



© 2015 Terese Winslow LLC
U.S. Govt. has certain rights

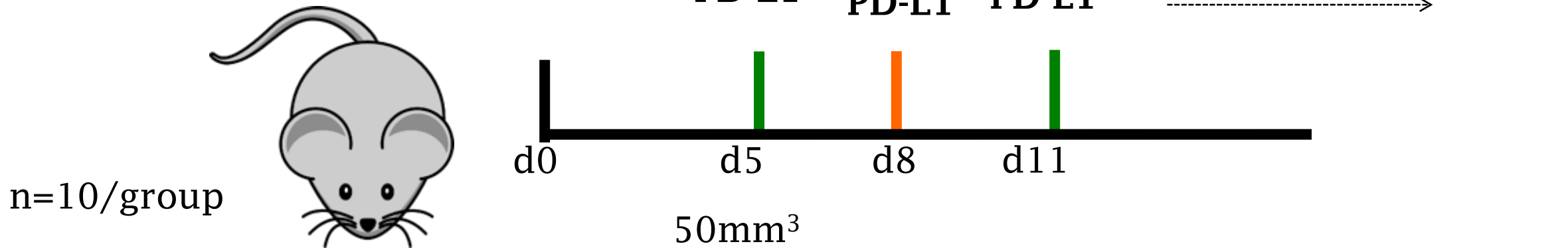


ORTHOTOPIC HNSCC MODEL: FAITHFUL TO TME

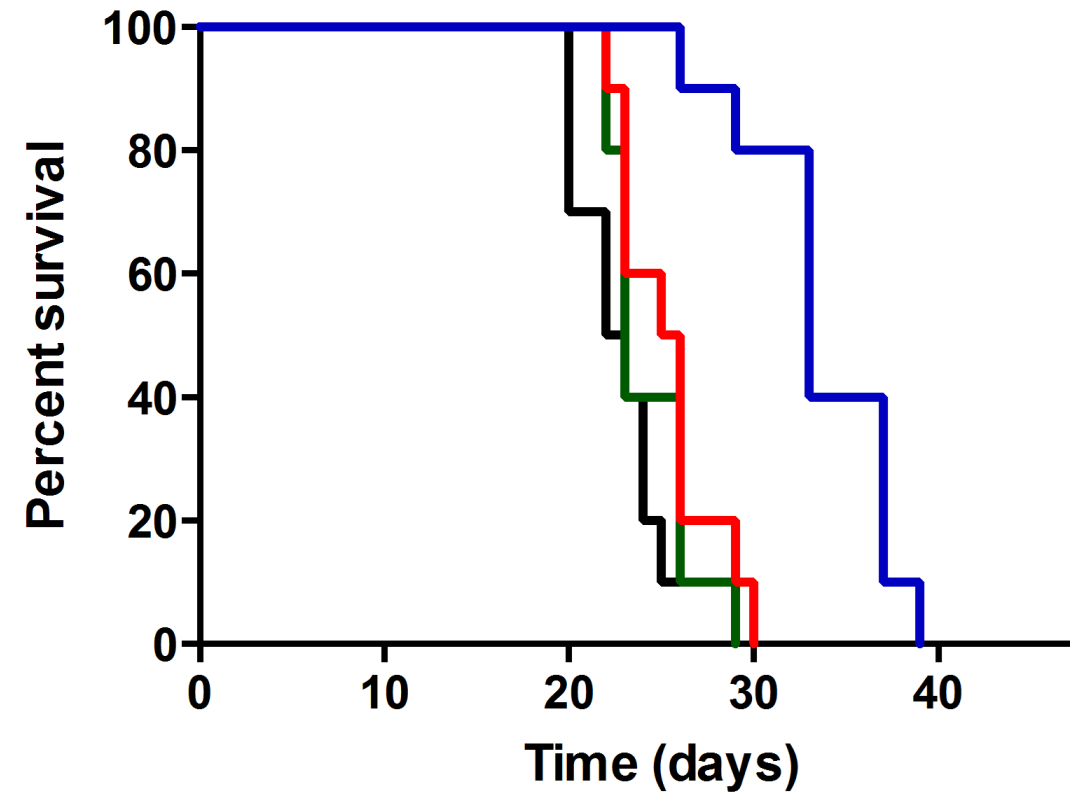
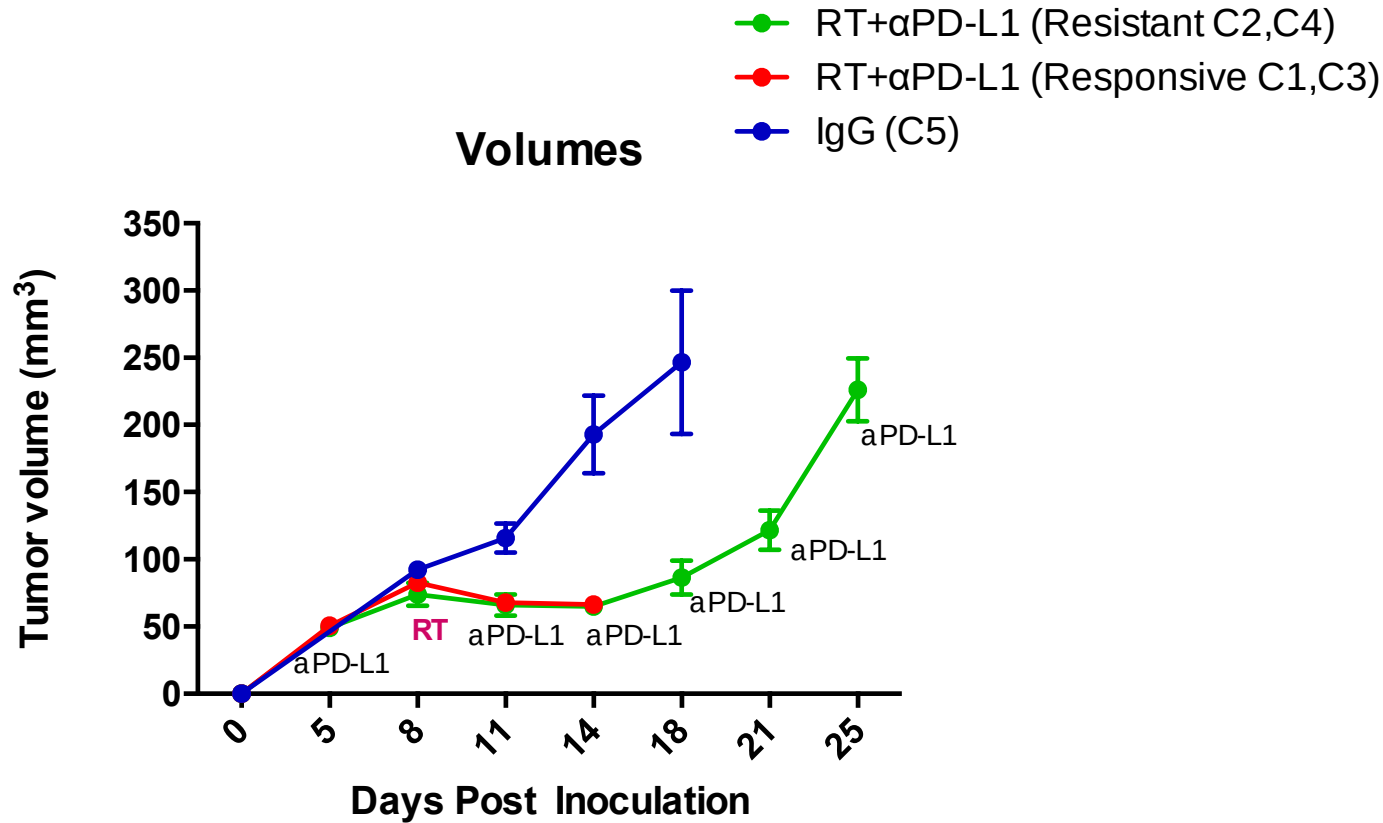


RT-IO TREATMENTS

Survival
Tumor growth experiments

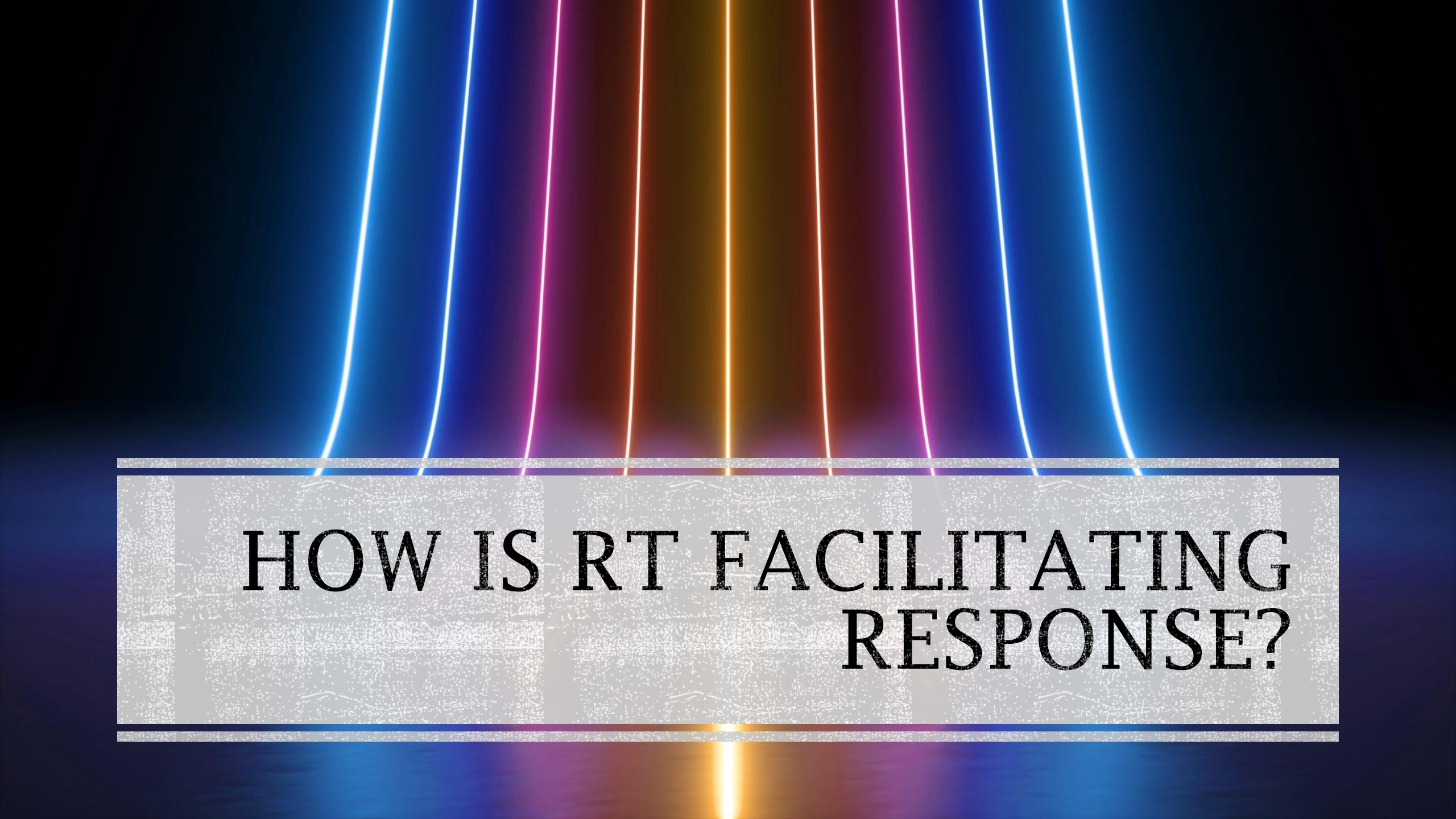


RT-ANTI-PDL1 → TUMOR GROWTH DELAY

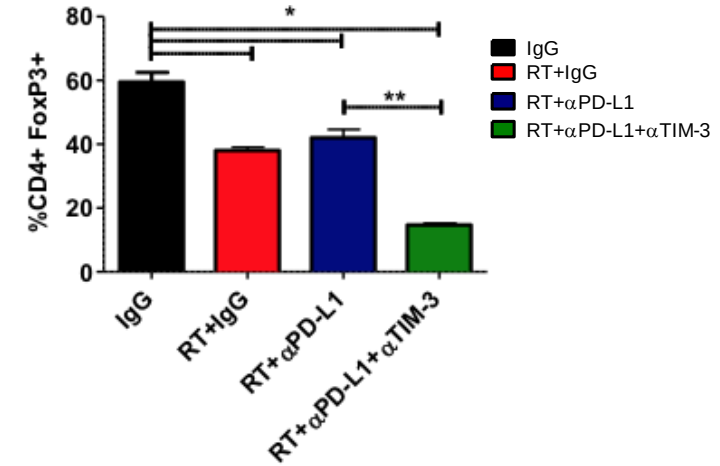
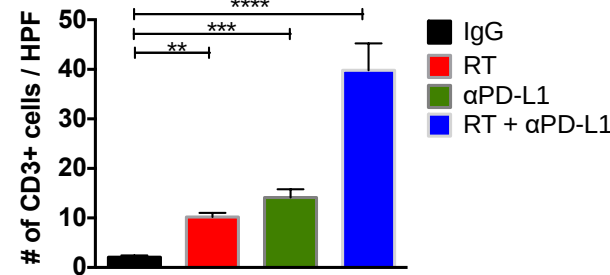
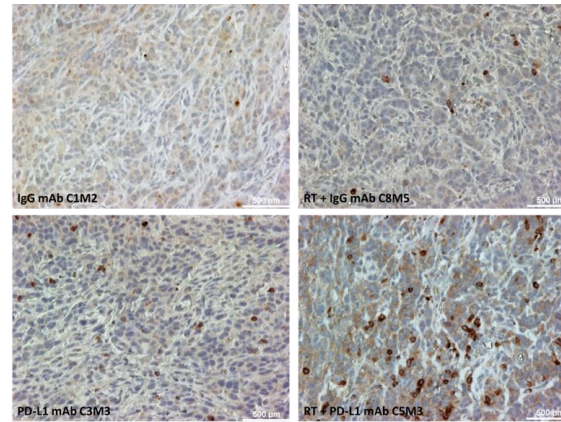
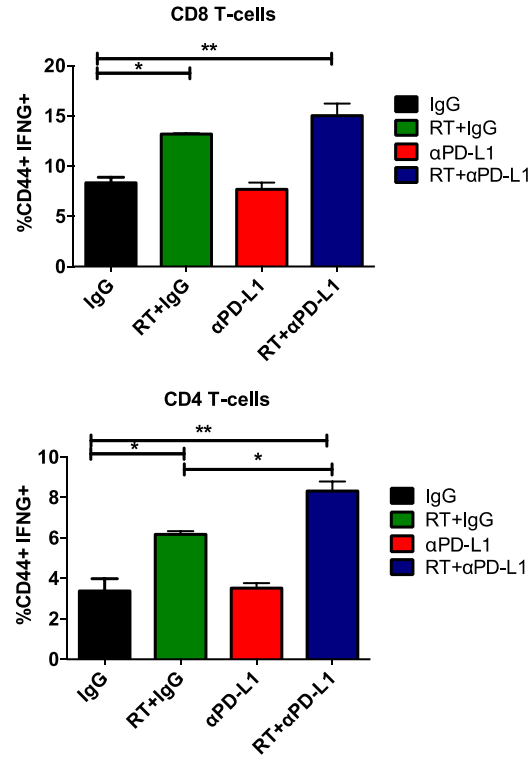
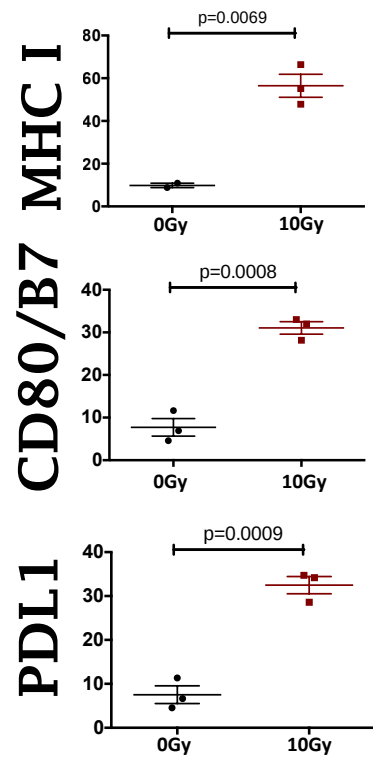


THE
DEVIL IS IN
THE **DETAILS**





HOW IS RT FACILITATING
RESPONSE?



Oweida A, et al. 2017; OncoImmunology

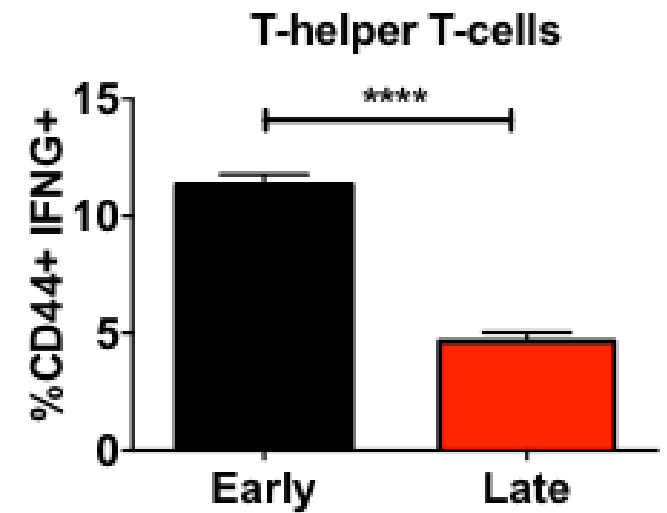
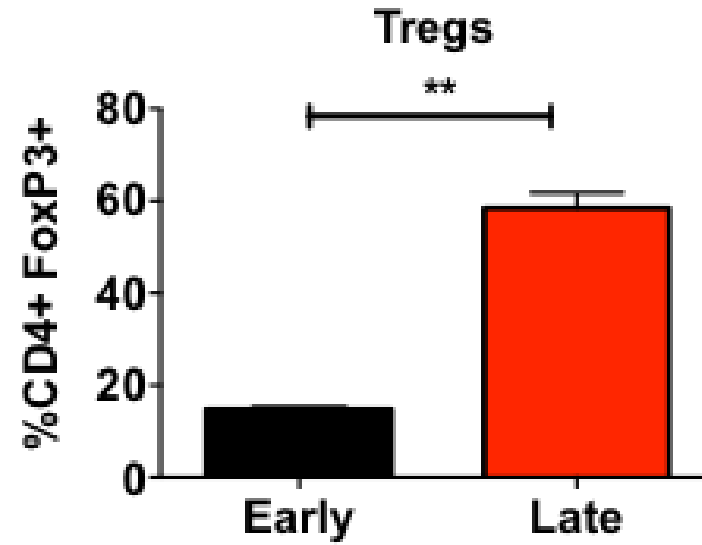
Oweida et al. 2018. CCR

RESPONSIVE PHASE: ↑ T-CELL INFILTRATION, ACTIVATION, IMMUNOGENICITY, & ↓ TREGS





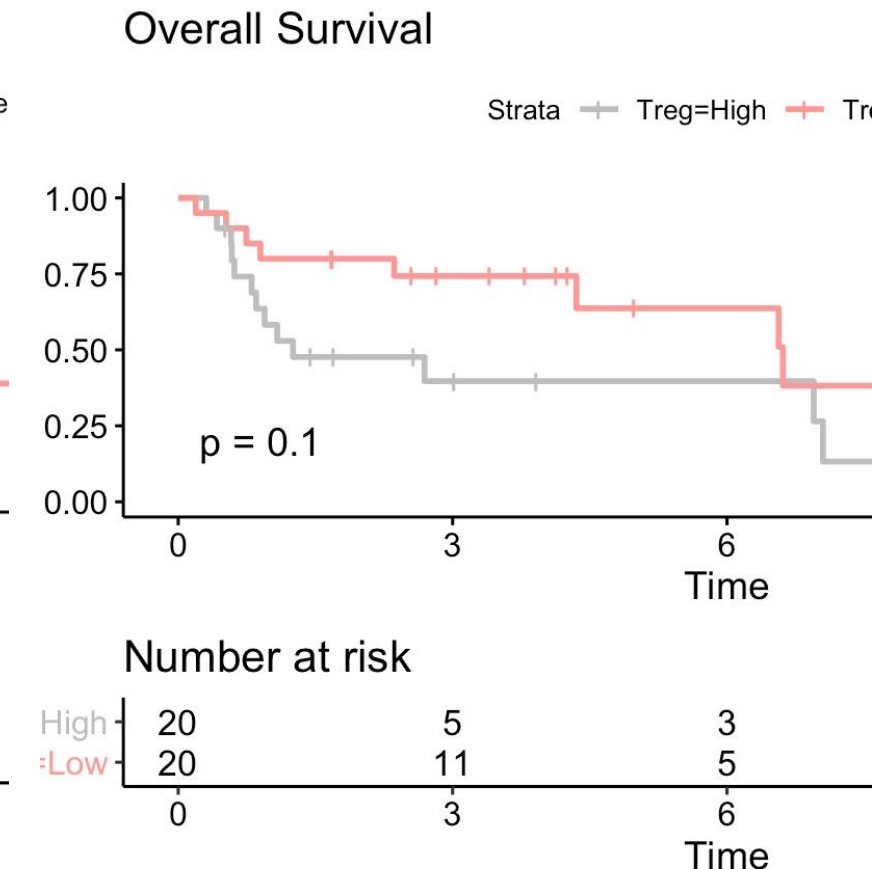
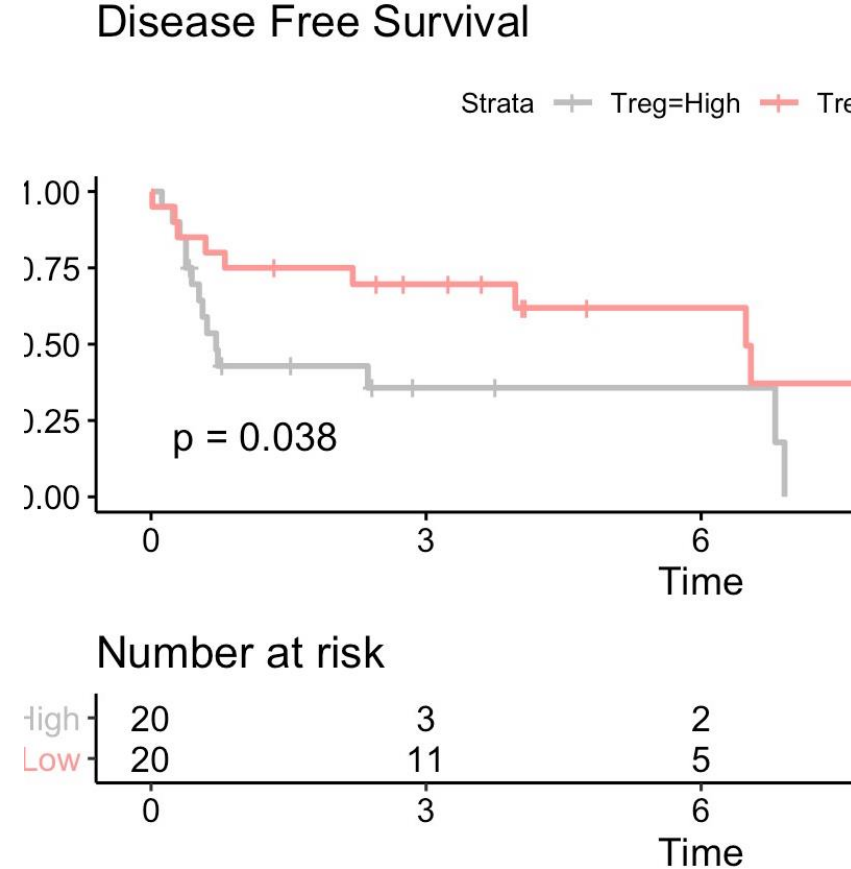
RESISTANCE PHASE: RESURGENCE OF TREGS



RELEVANCE: TREGS MEDIATING RESISTANCE

Genomic Characterization of Squamous Cell Carcinoma: Frequent Somatic

Linxin Zhang², Suk Young Yoo², Linnea Bengtsson¹, David M. Neskey¹, Mei Zhao¹, Marcus V. Orntoft¹, Drummond⁷, Elsa Cortez¹, Tong-xin Xie¹, David A. Gibson^{7,8}, Patrick A. Zweidler-McKracken¹, Naggar⁵, John N. Weinstein^{2,6}, Jing Wang², David A. Wheeler⁷, Mitchell J. Frederick¹



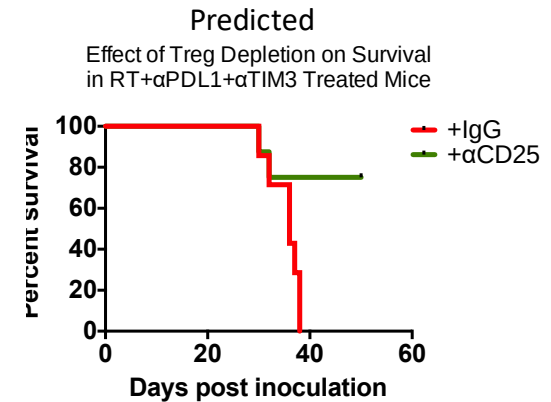
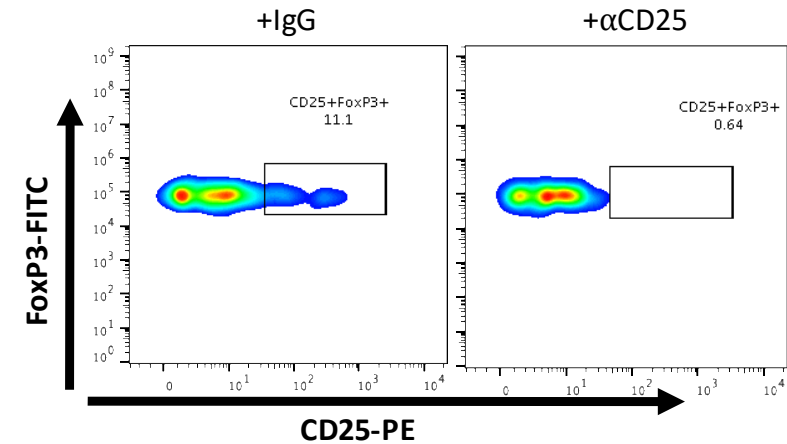
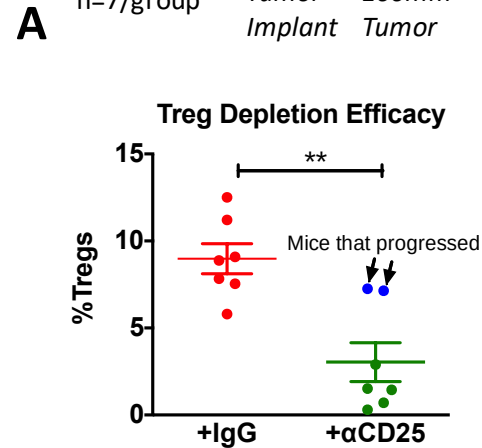
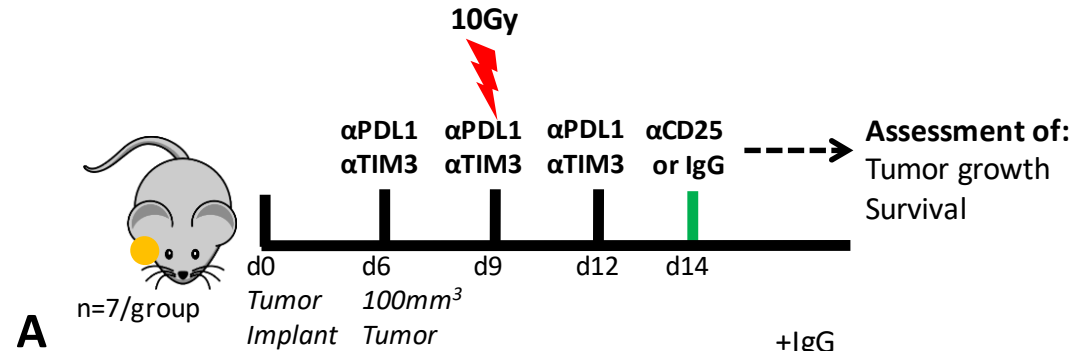
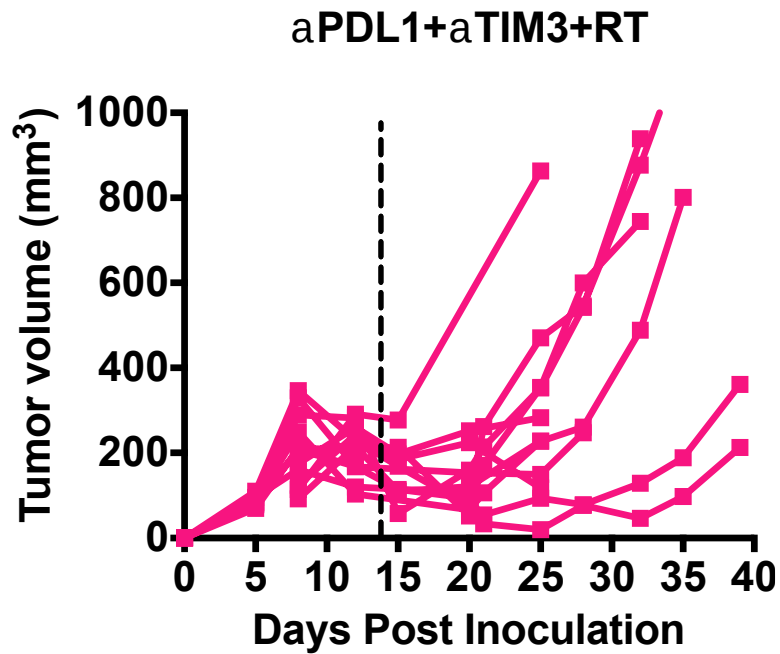
Knitz et al. 2020. JTO

TREGS ARE PROGNOSTIC IN ORAL CAVITY TUMORS



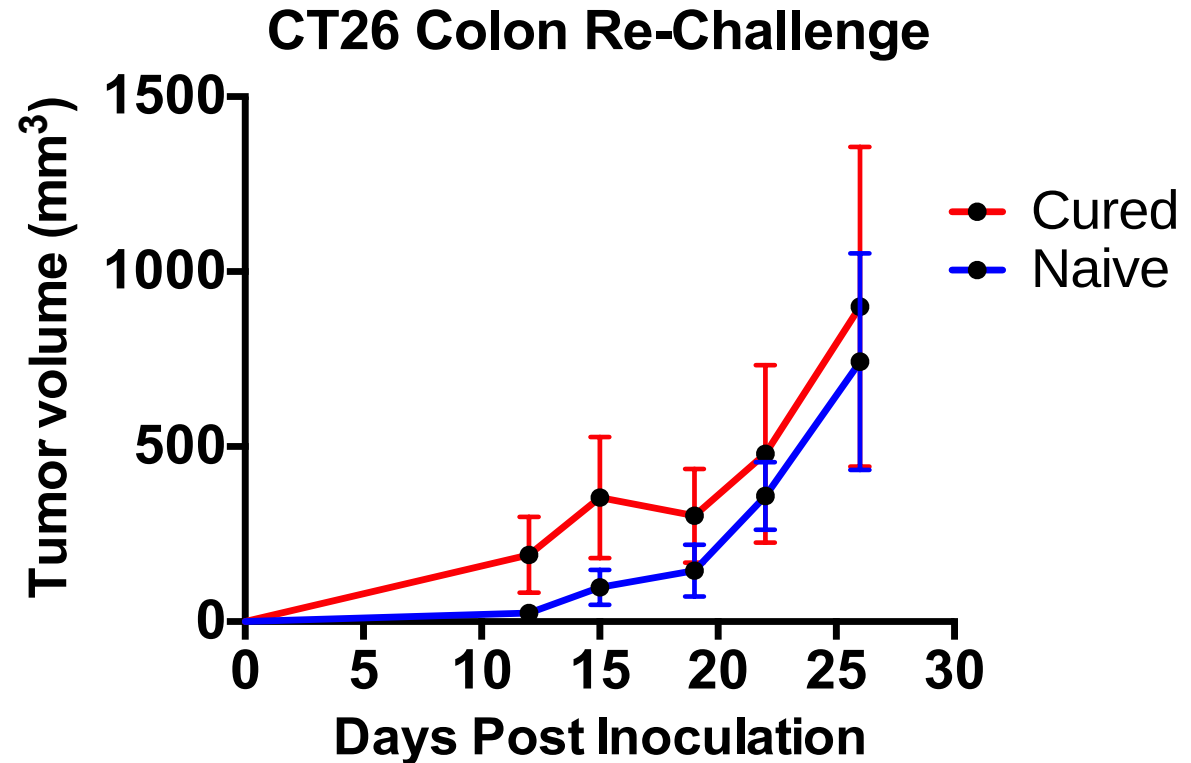
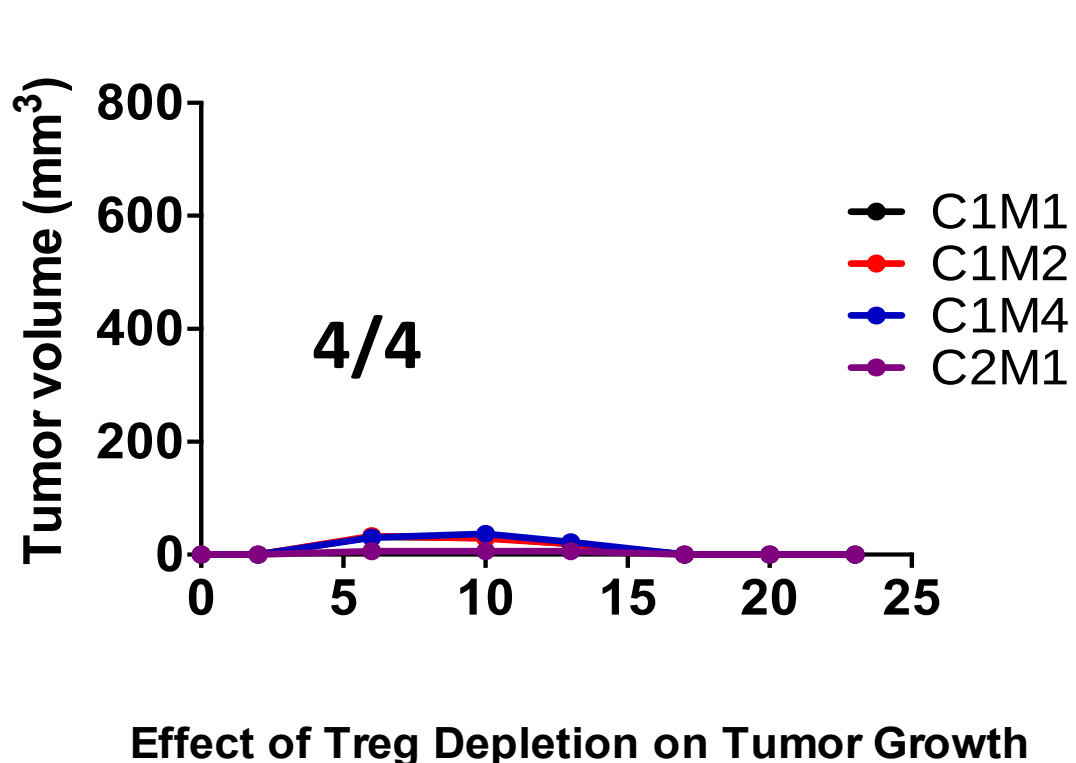


Treg Depletion Restores Anti-tumor Immunity

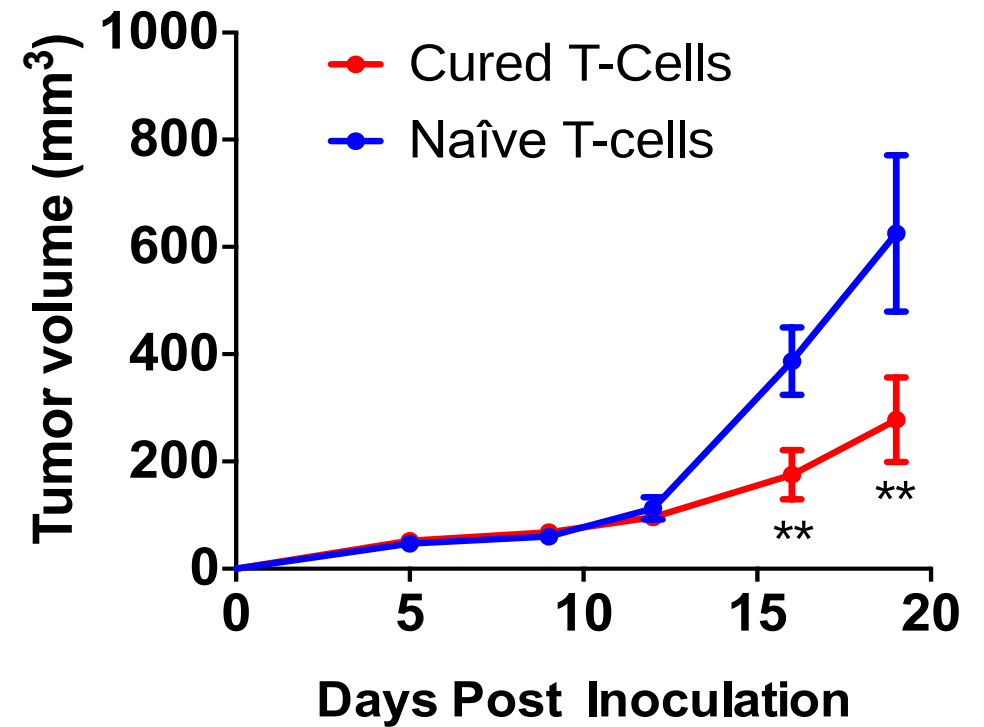
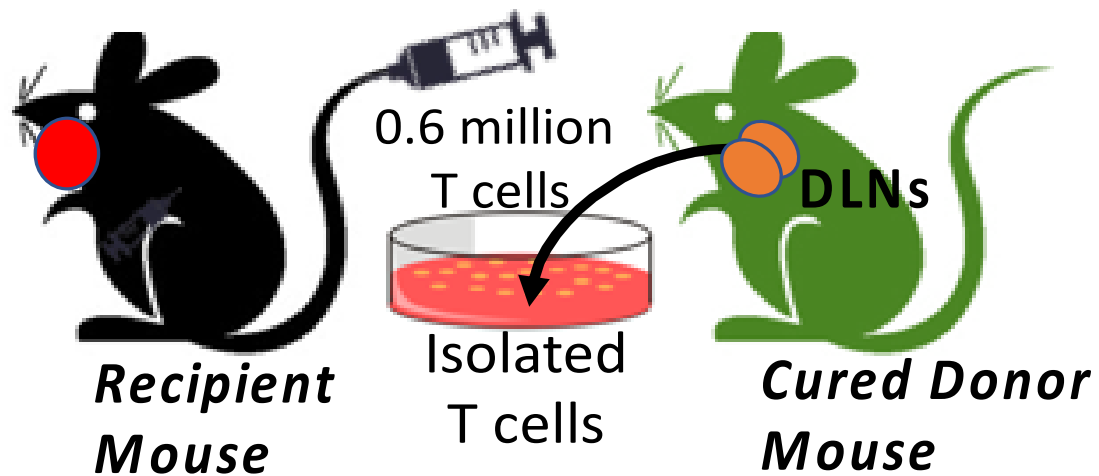


Oweida et al.
2018. CCR

NO REGROWTH POST RE-CHALLENGE... FOR HSNCC CELL LINES

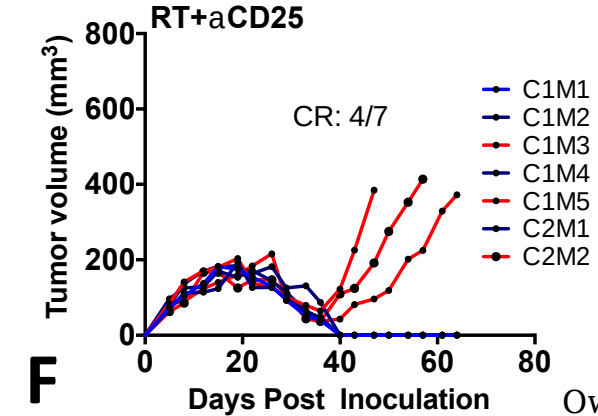
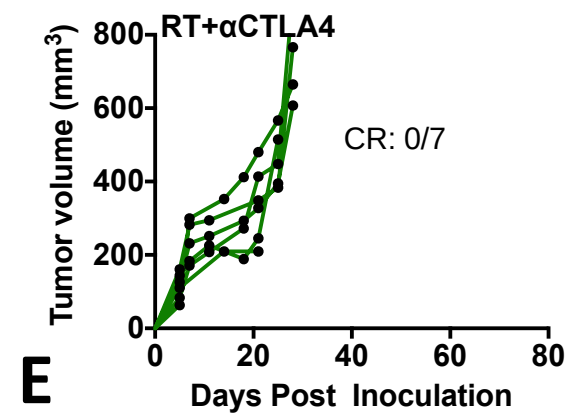
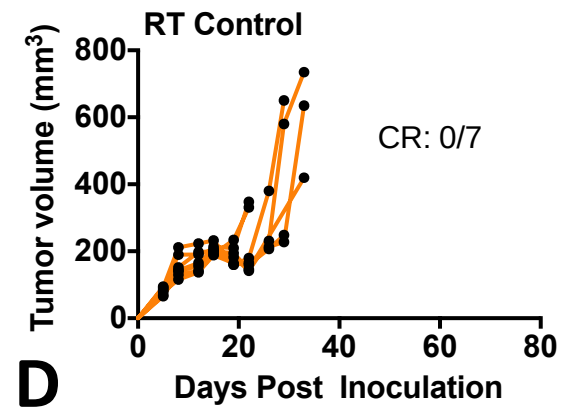
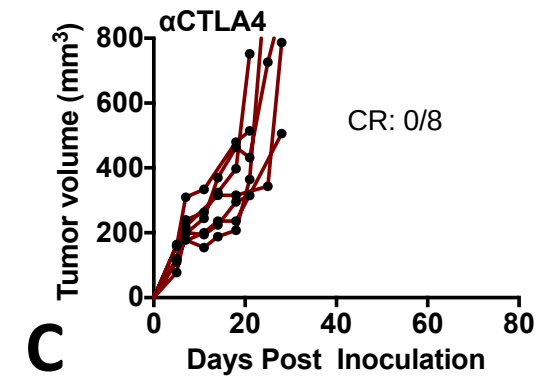
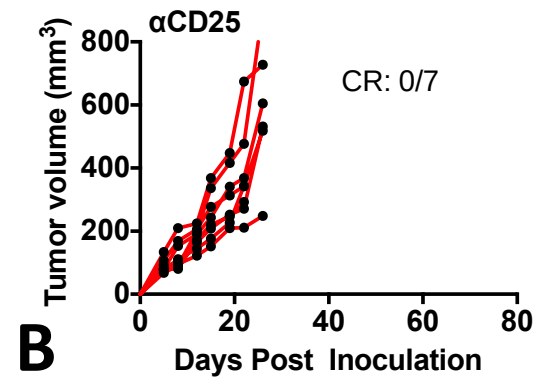
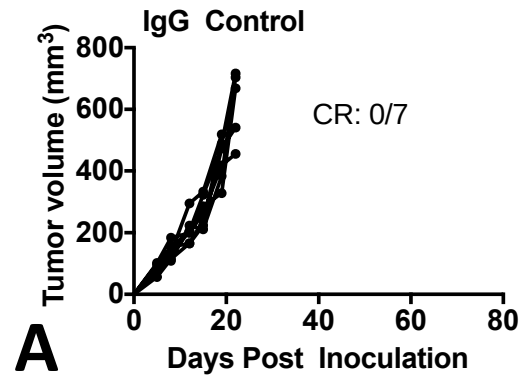


NO REGROWTH POST RE-CHALLENGE



Oweida et al. 2019. JNCI.



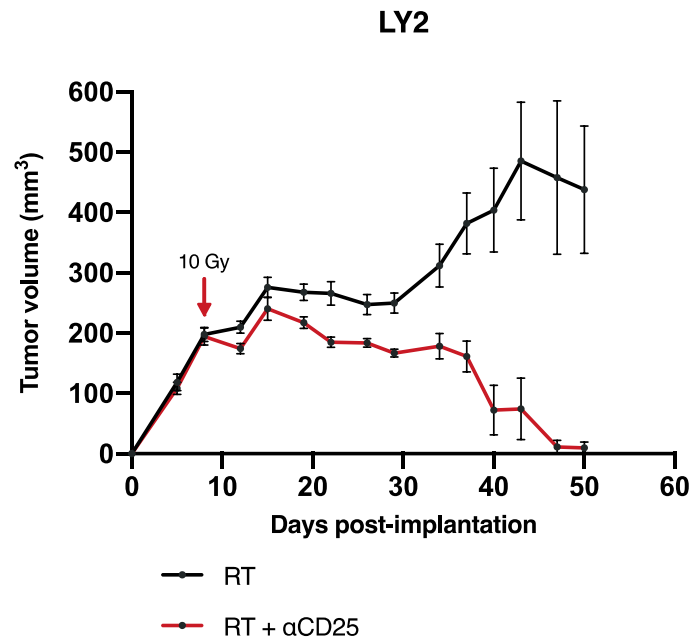
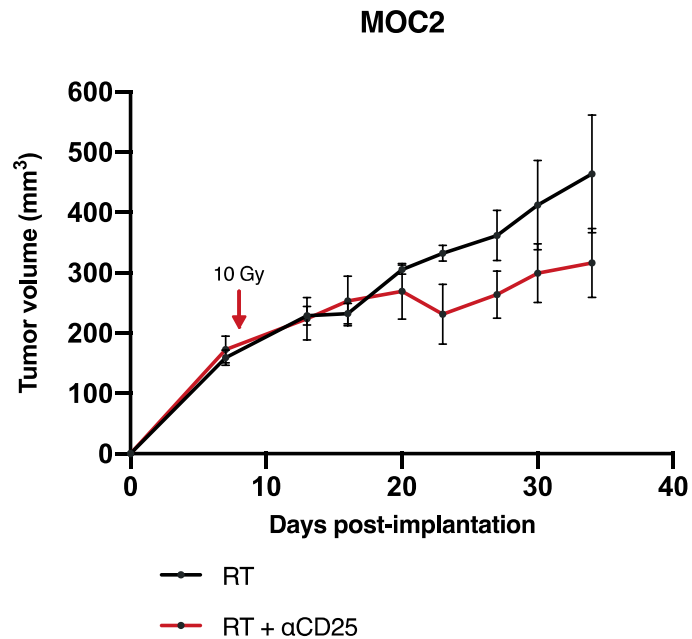


Oweida et al. 2019. JNCI.

**BOTH RT AND A-CD25
ARE NEEDED**



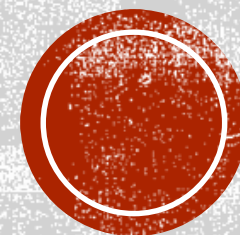
DON'T



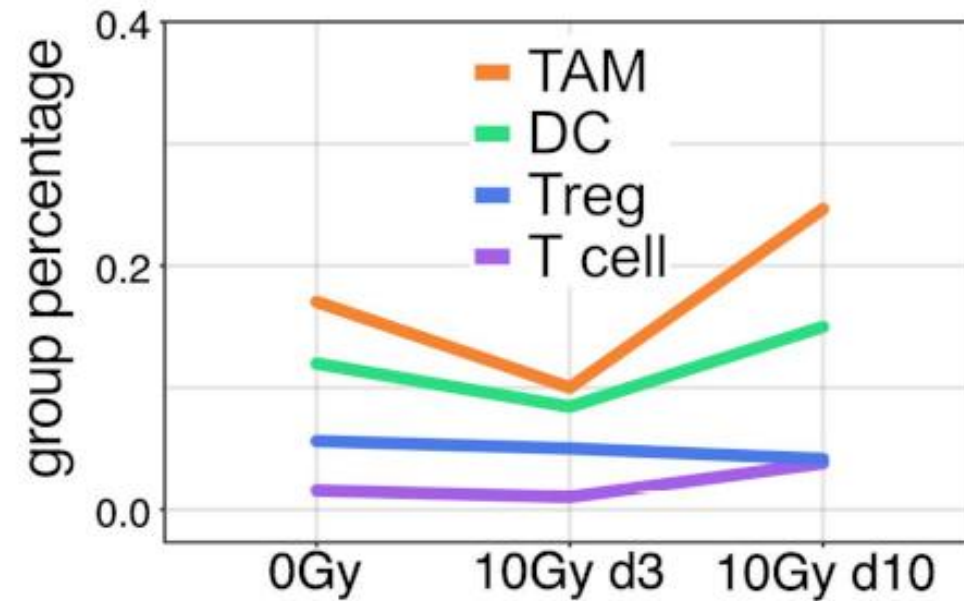
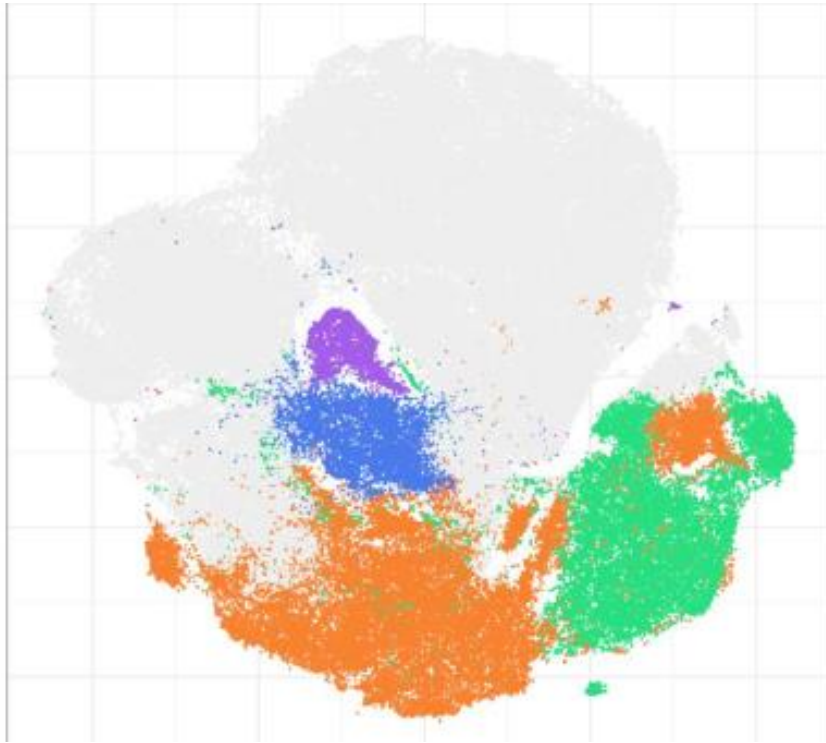
**ONE SIZE
DOES NOT
FIT ALL**

Knitz et al. 2020. JITC.

**RESPONSE TO RT + ANTI-
CD25 VARIES BY TUMOR
MODEL**

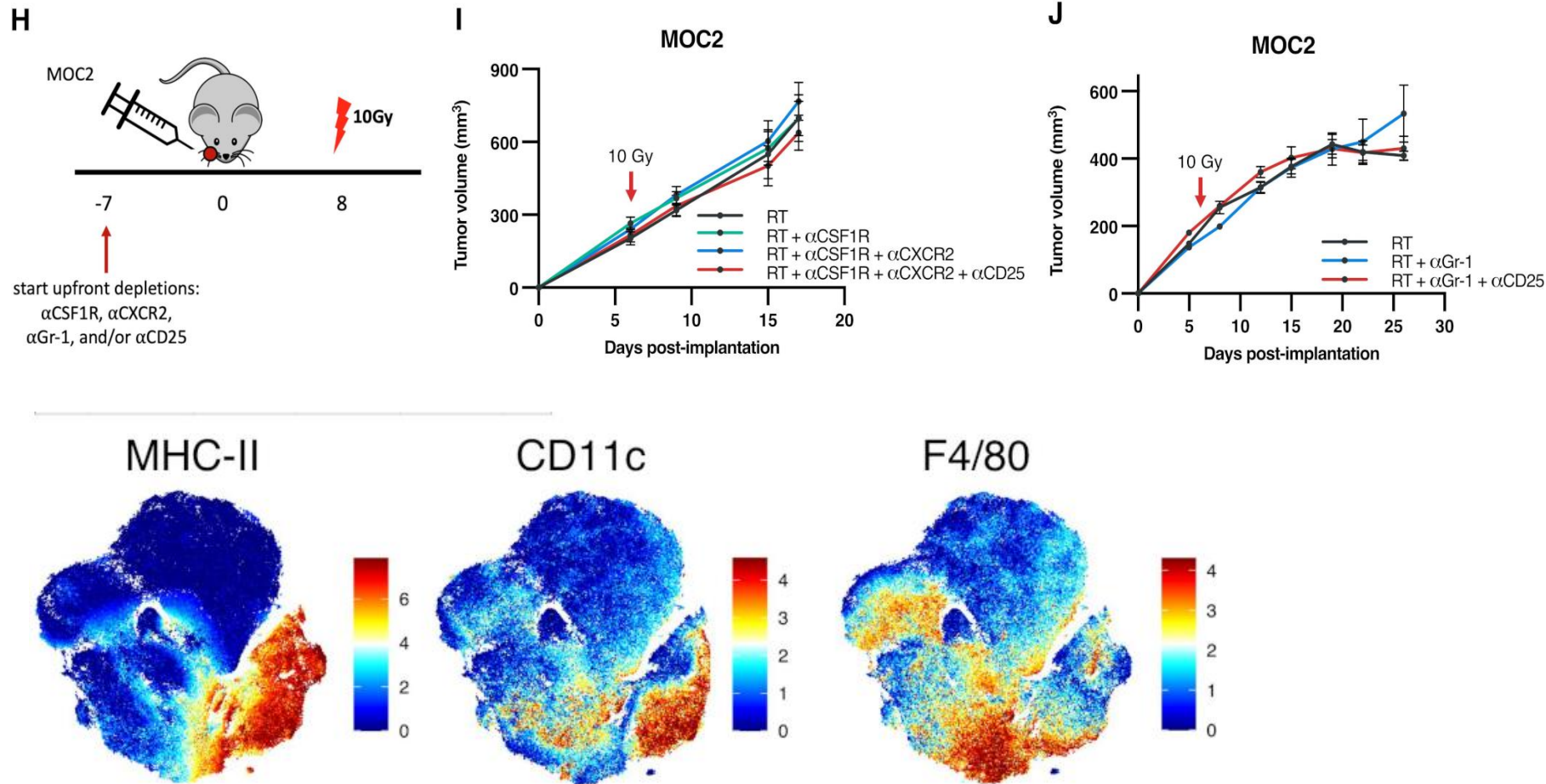


ROOT CAUSE ANALYSIS: MYELOIDS & TREGS

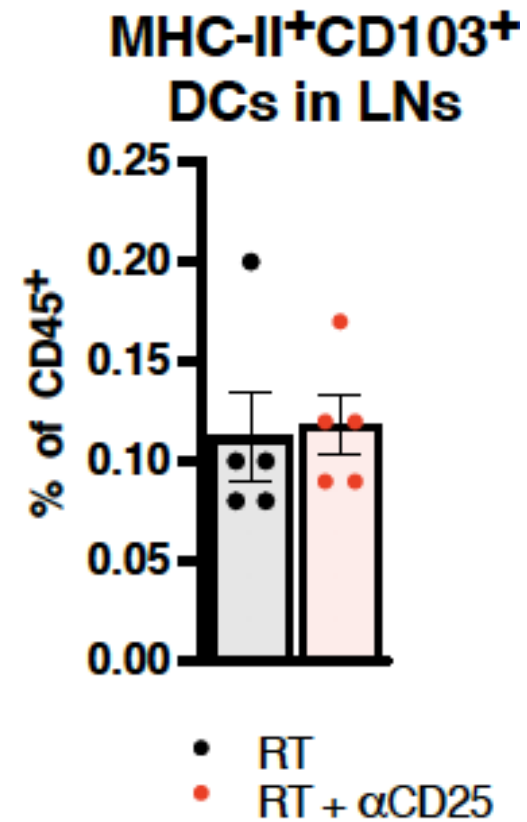
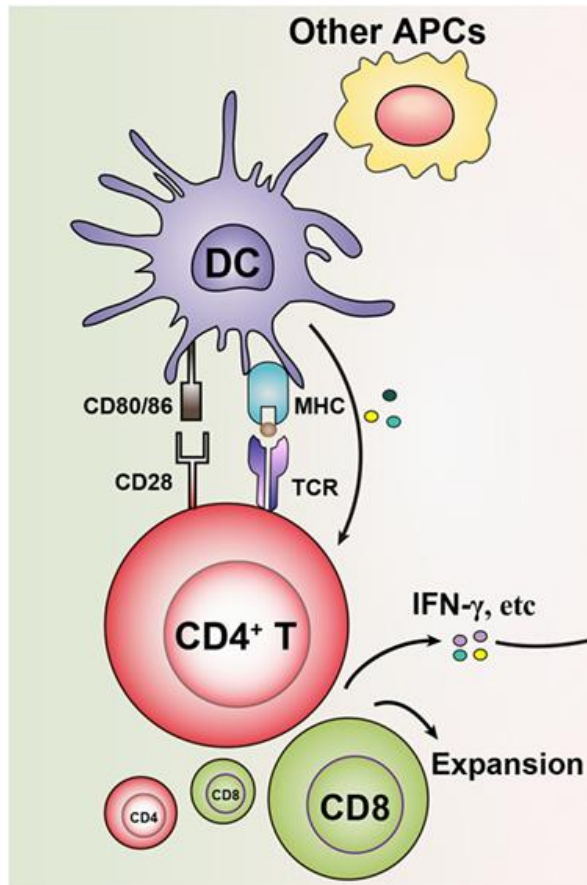


TARGETING MYELOIDS

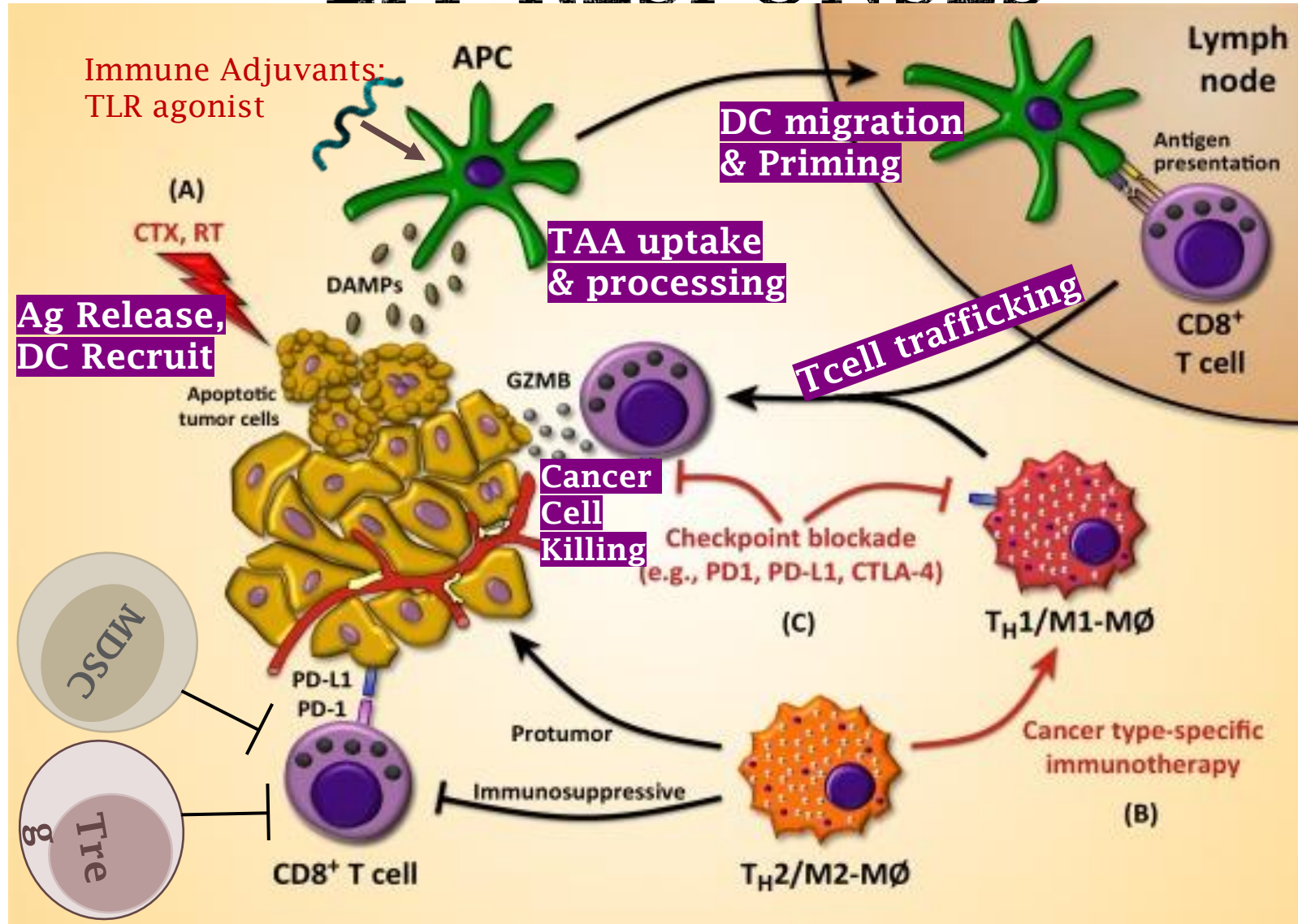
TARGETING MYELOIDS +/- TREGS: CXCR2, CSFR1, GR1



DYSFUNCTIONAL ANTIGEN PRESENTING CELLS? NO CHANGE IN MHCII DCS



REQUIREMENTS FOR GENERATION OF T-EFF RESPONSES

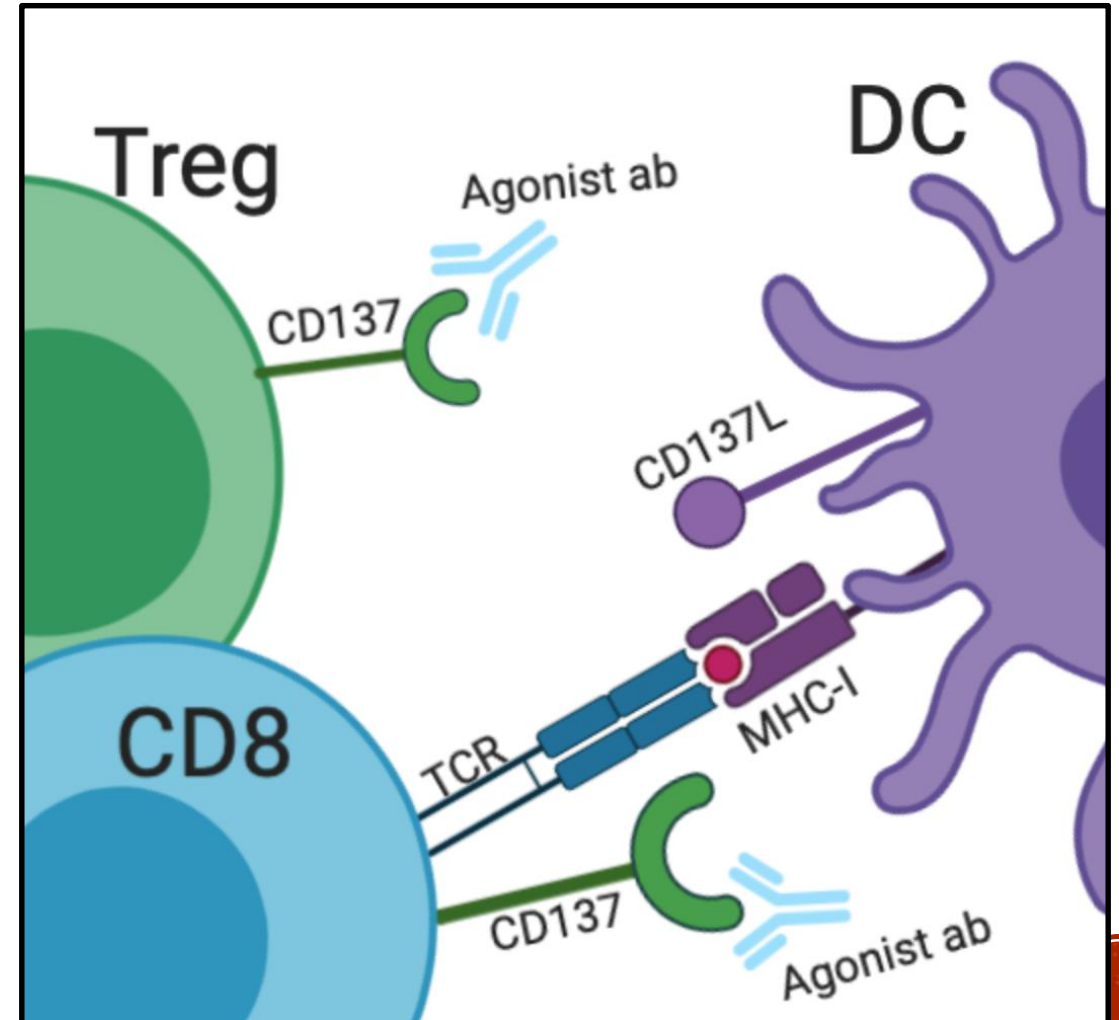
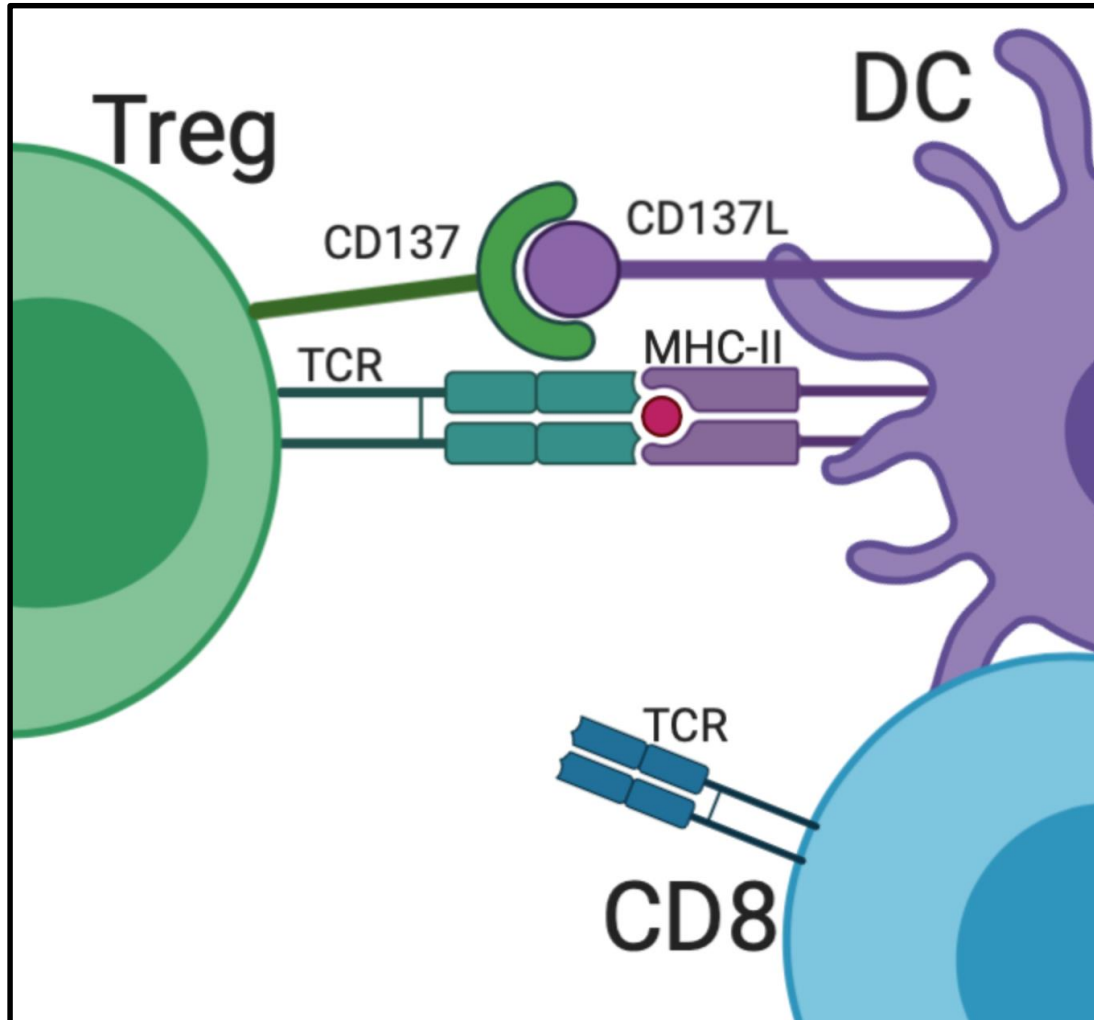


ENHANCING APC FUNCTION: DATA MINING FOR TARGETS

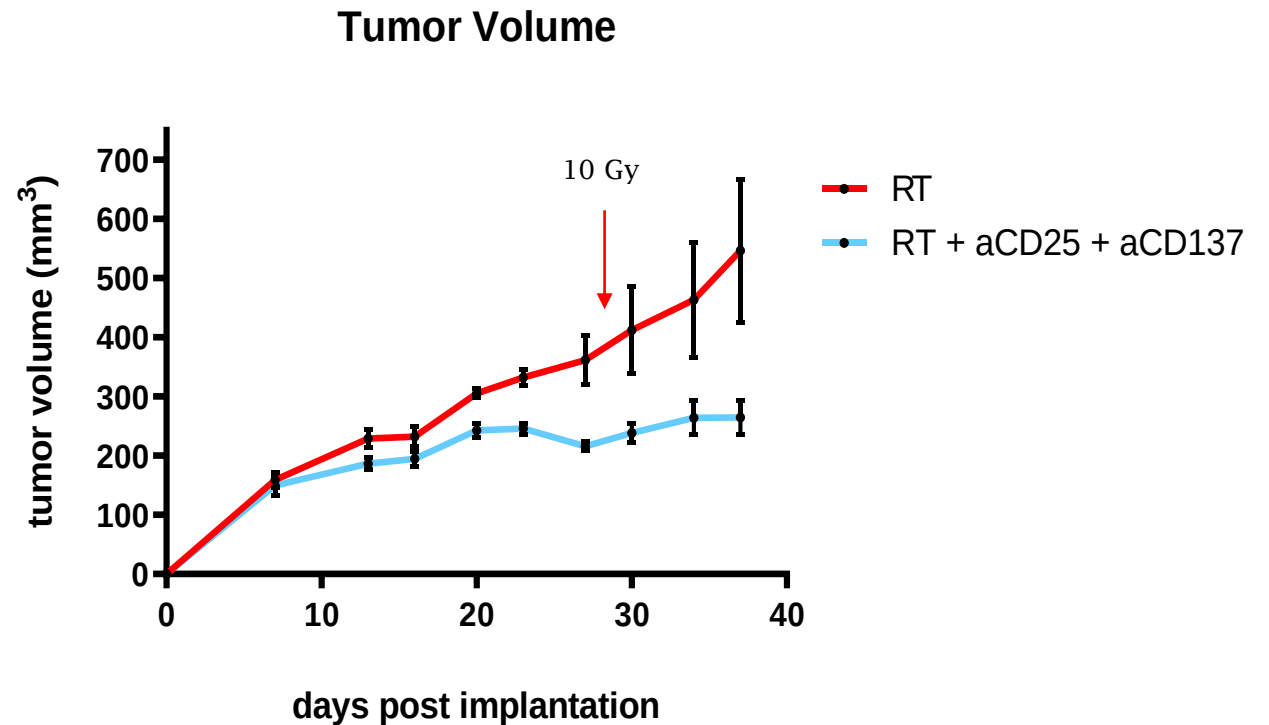
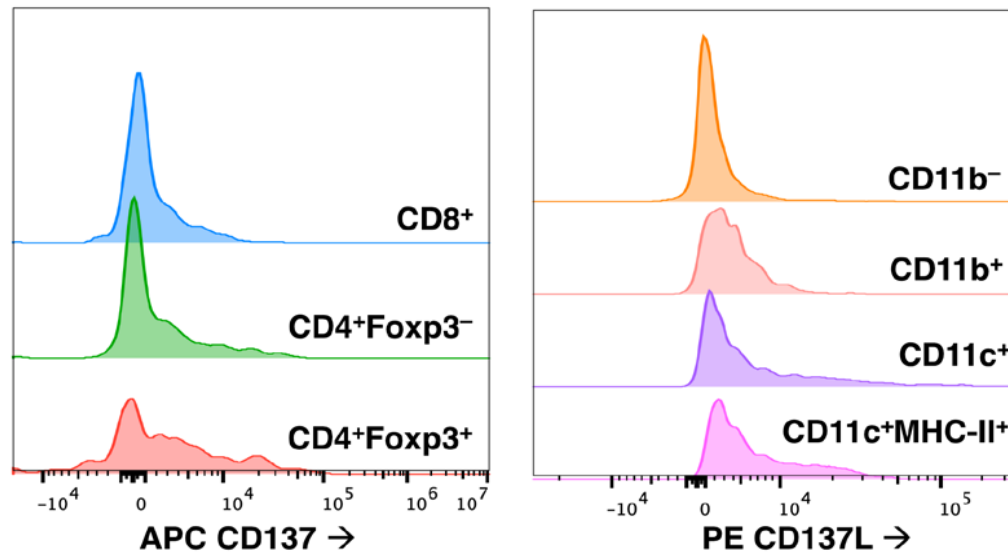
- 41BB (a-CD137)
- FLT3



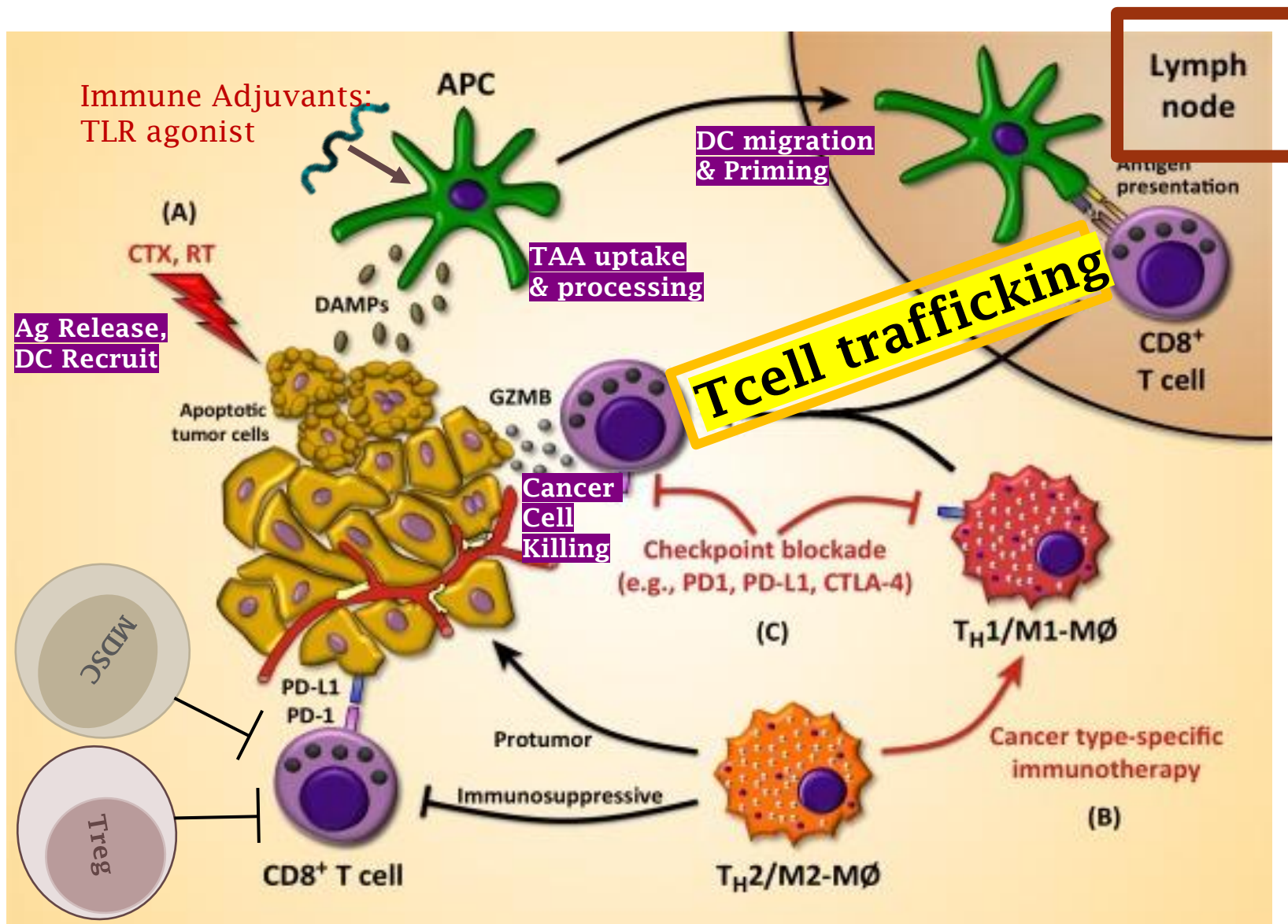
A-CD137 (41BB) TO ENHANCE DC/APC FUNCTION

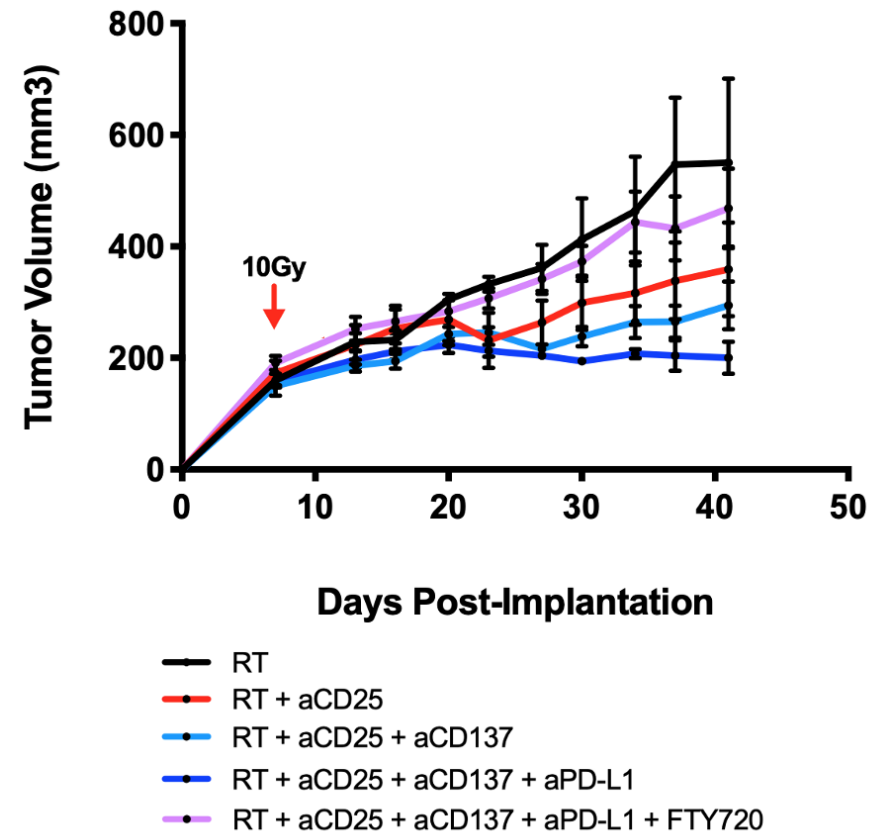
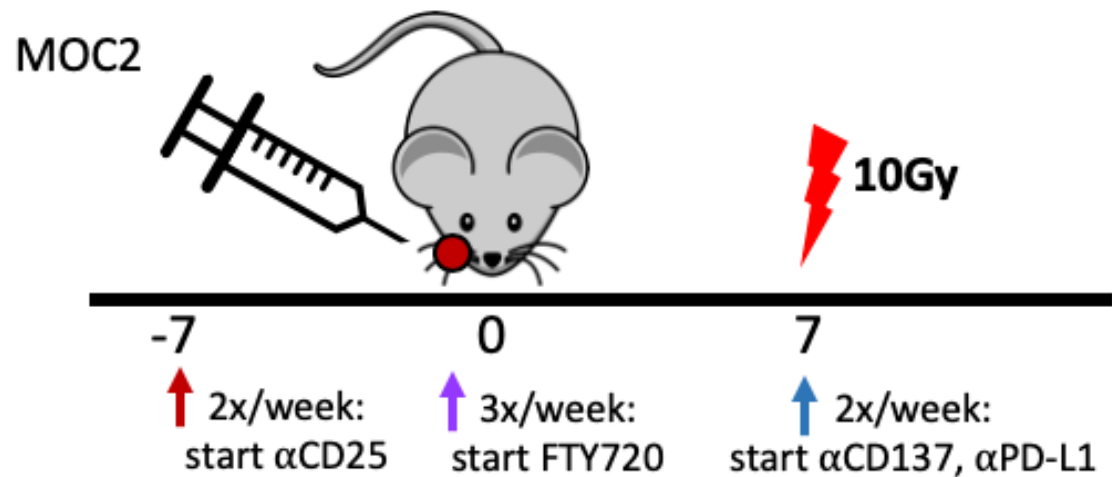


TRIPLE COMBO THERAPY: RT + DC AGONIST ANTI-CD137 (4-1BB) + ACD25



LYMPH NODES AND TRAFFICKING

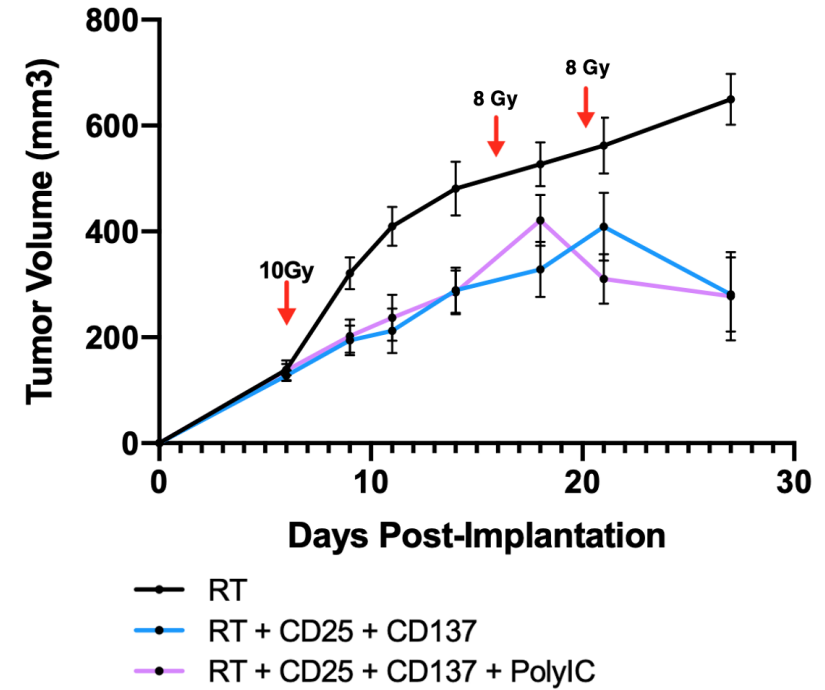
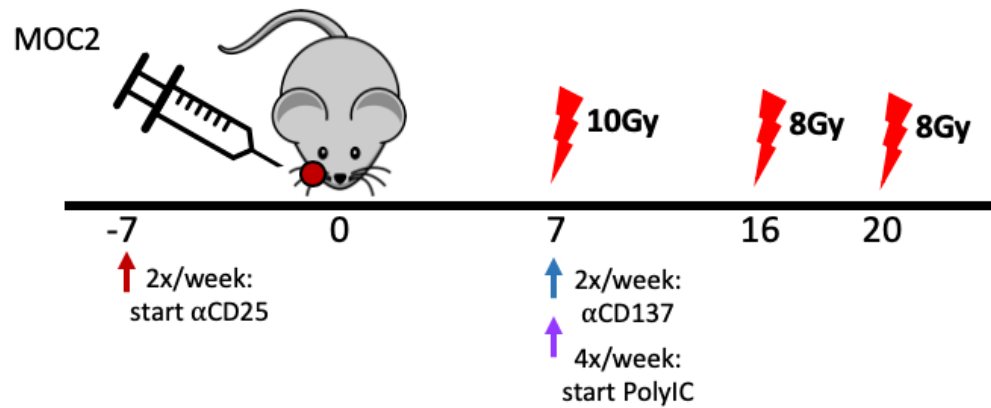




Knitz et al. JITC. 2020

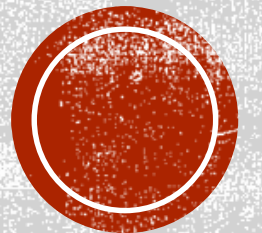
TRIPLE COMBO DEPENDS ON PRIMING IN LYMPH NODES





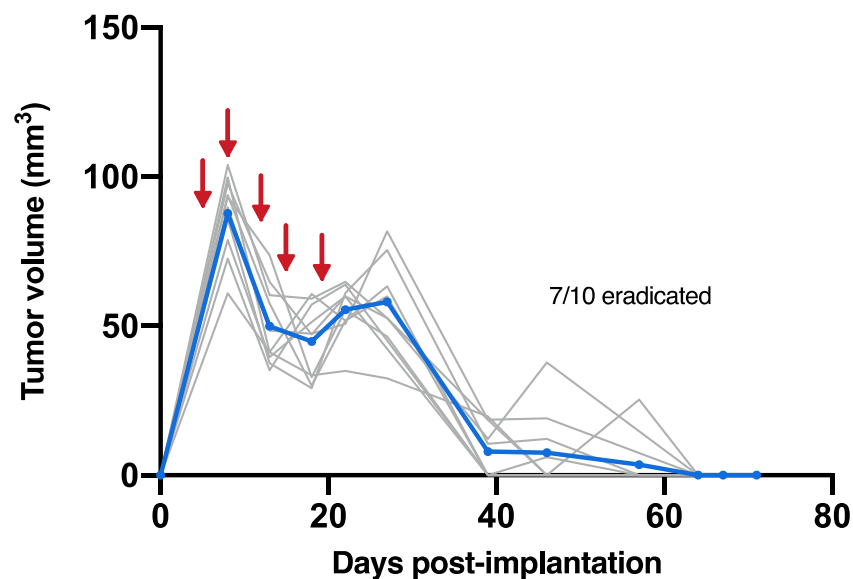
Knitz et al. JTC. 2020

TRIPLE COMBO IS NOT ENHANCED BY POLY-IC



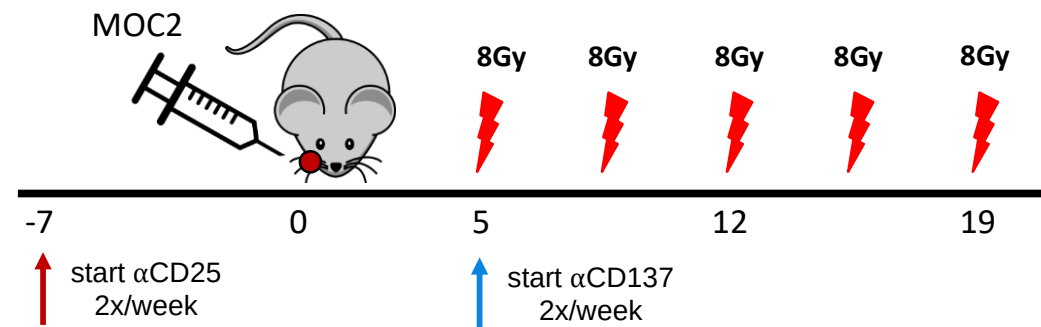


eradication



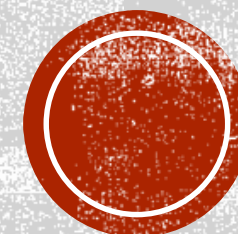
RT + αCD25 + αCD137

↓ = 8Gy



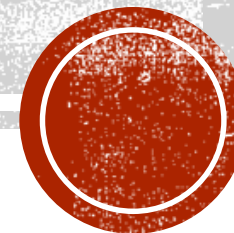
Knitz et al. JITC. 2020

HYPOFRACTIONATED SBRT + ANTI-CD25 + ANTI- CD137 → ERADICATION

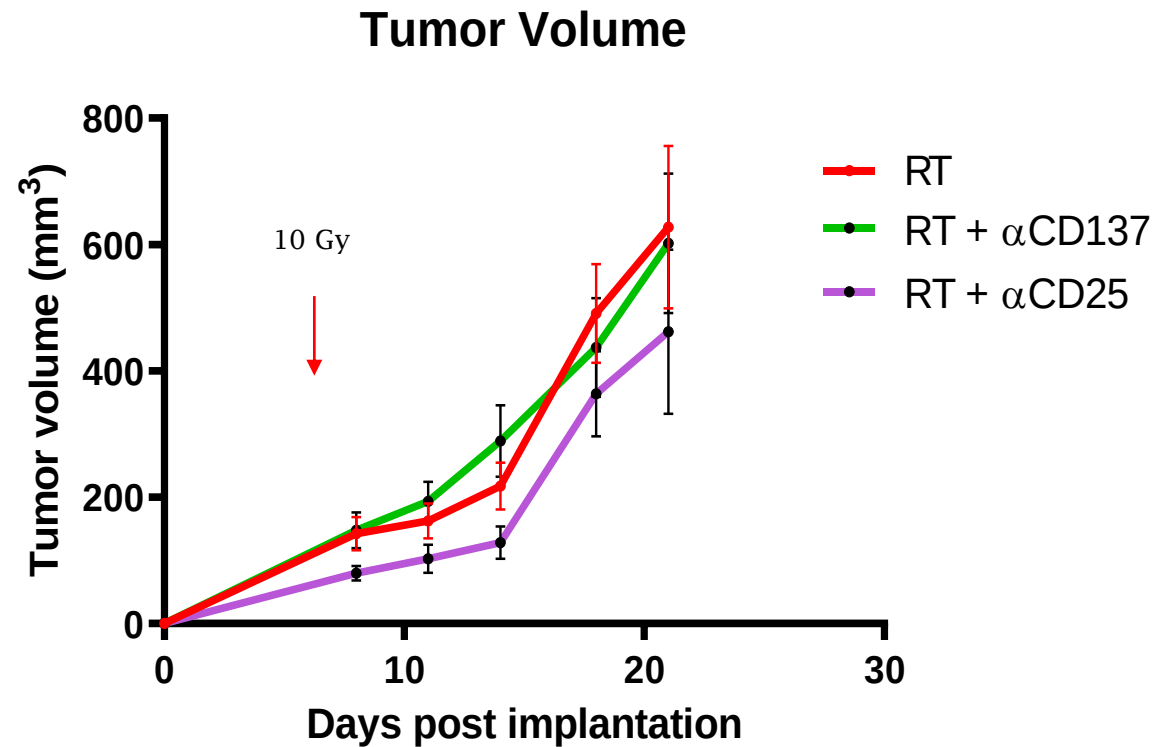




THINKING TRIALS?



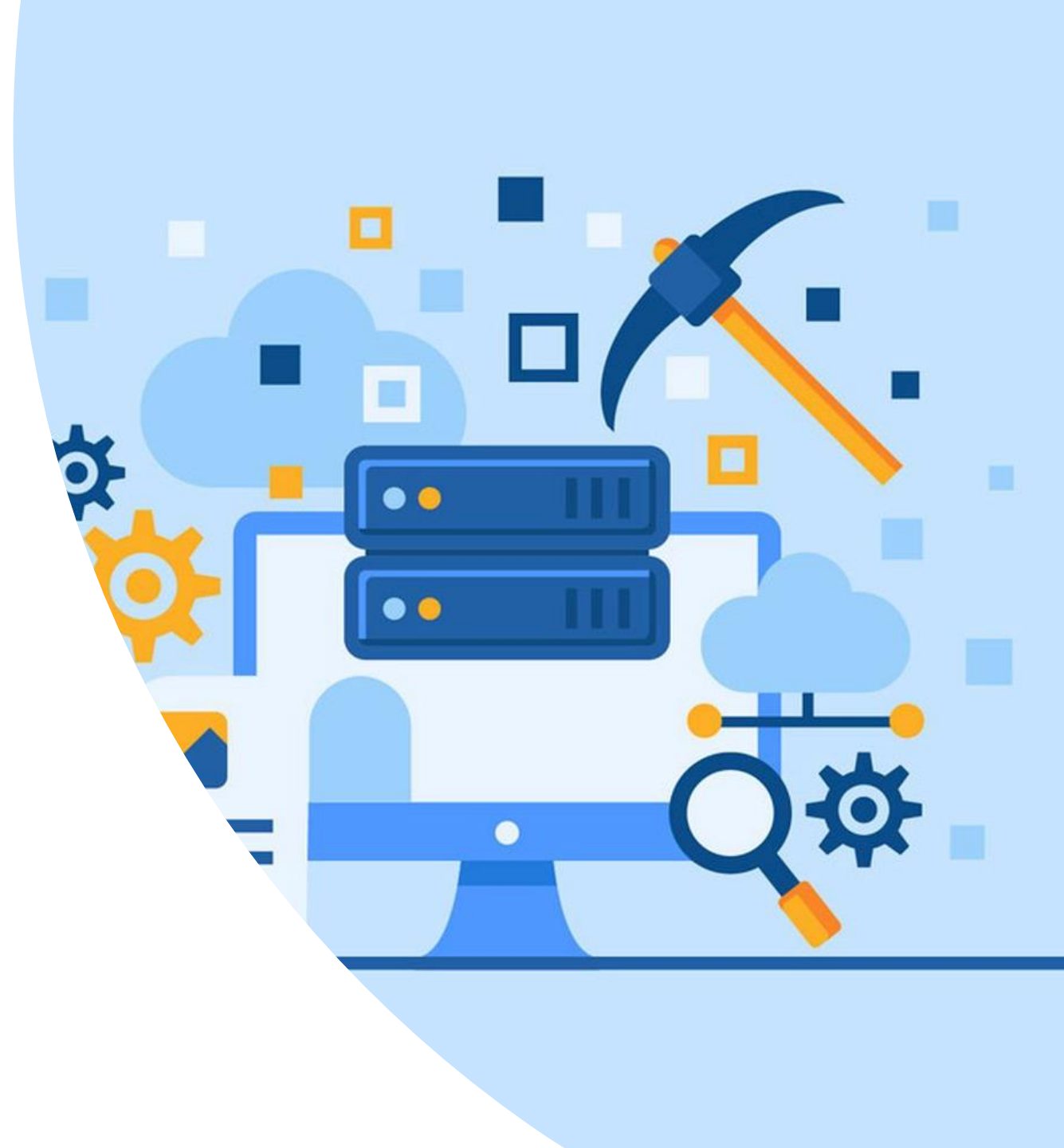
FOLLOW THE DATA: DOUBLET THERAPY DOES NOT WORK



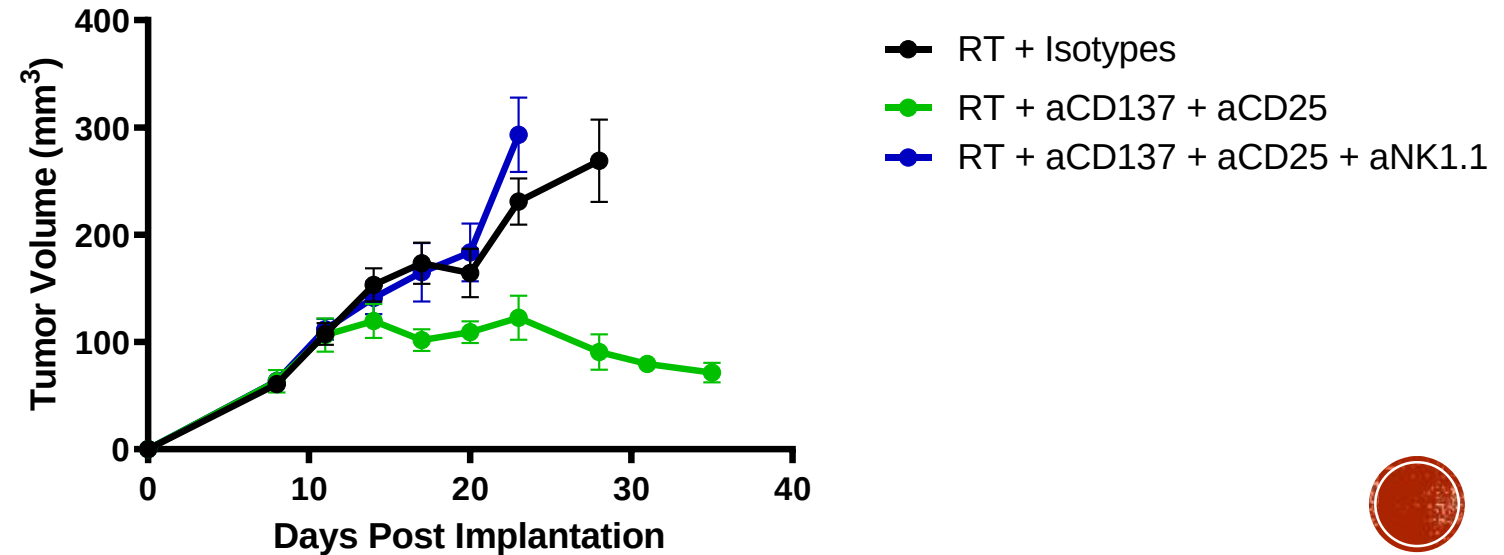
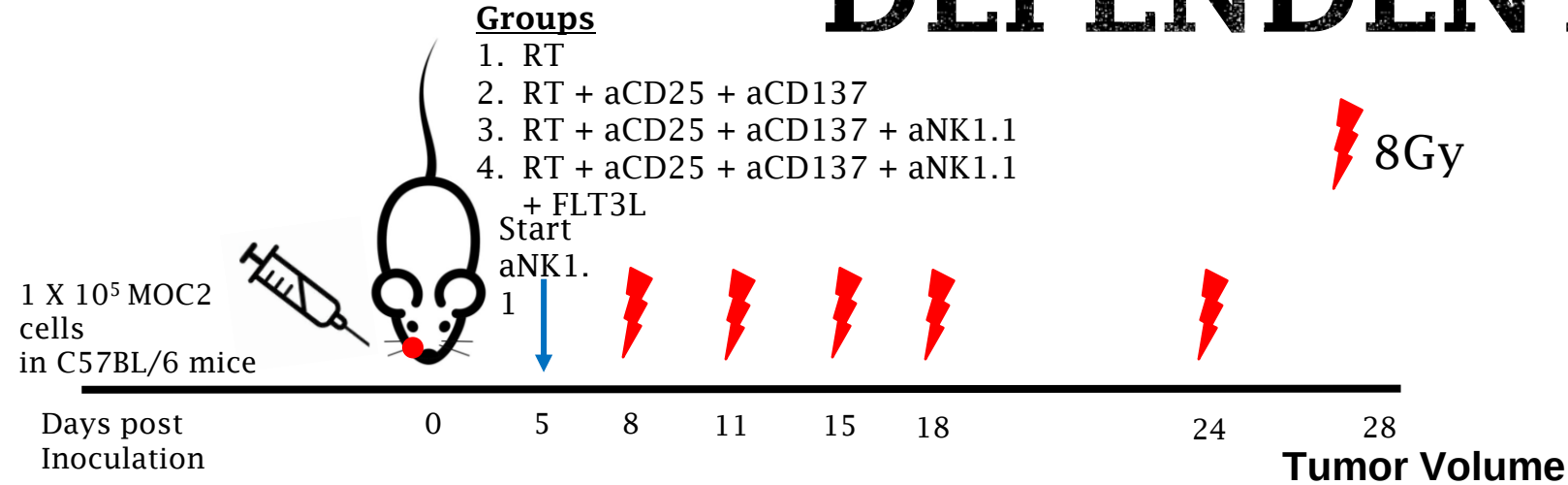
ENHANCING APC FUNCTION: DATA MINING FOR TARGETS

- 41BB (a-CD137)

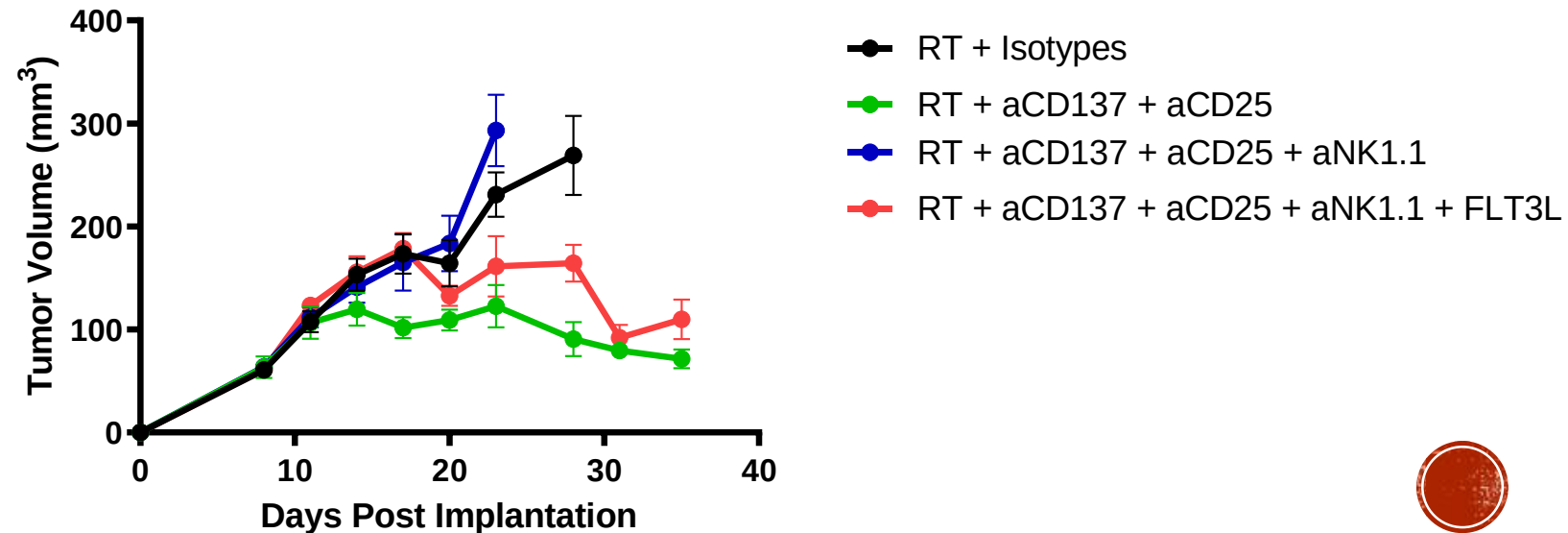
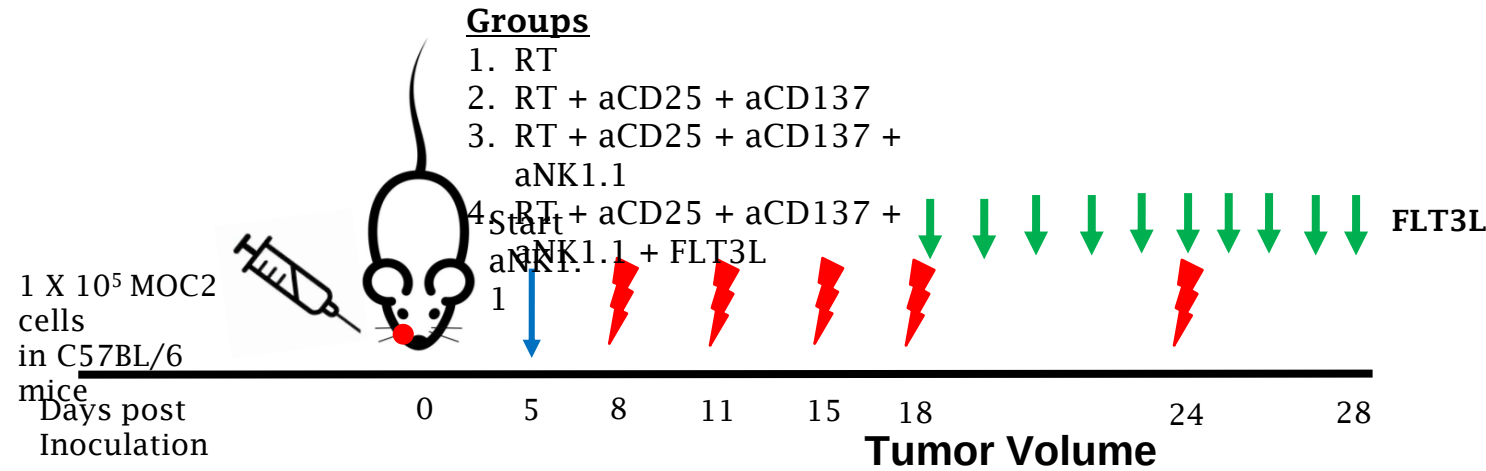
- **FLT3**

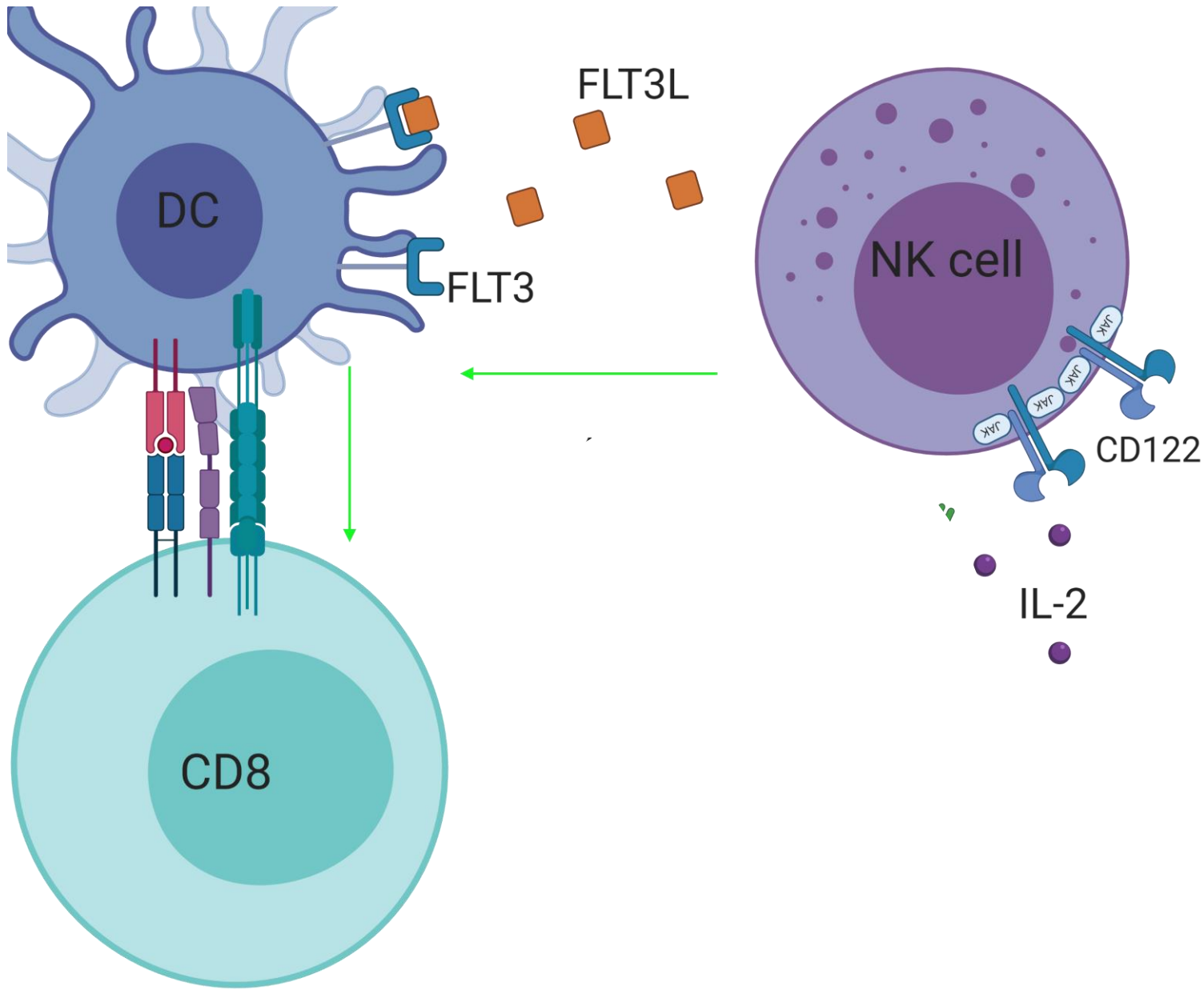


DISCOVERY: TRIPLE COMBO THERAPY IS NK CELL DEPENDENT



THERAPY RESCUES NK CELL FUNCTION

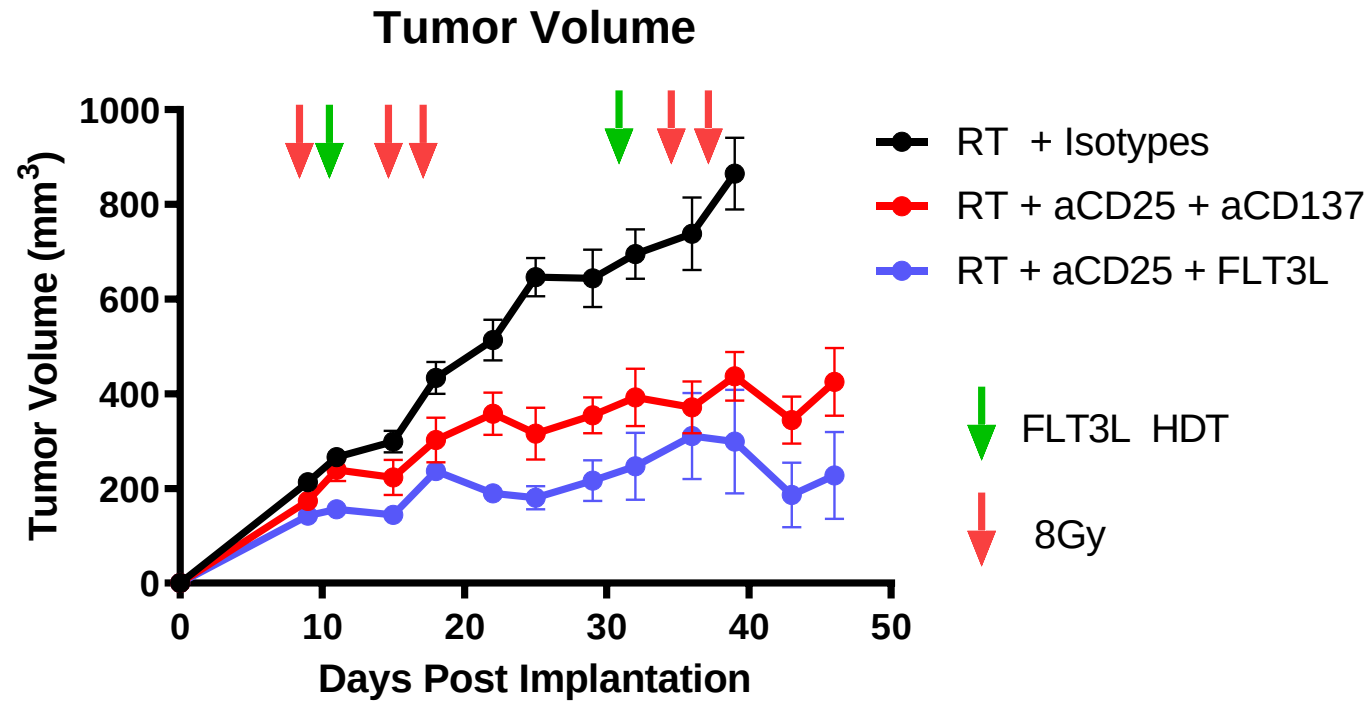




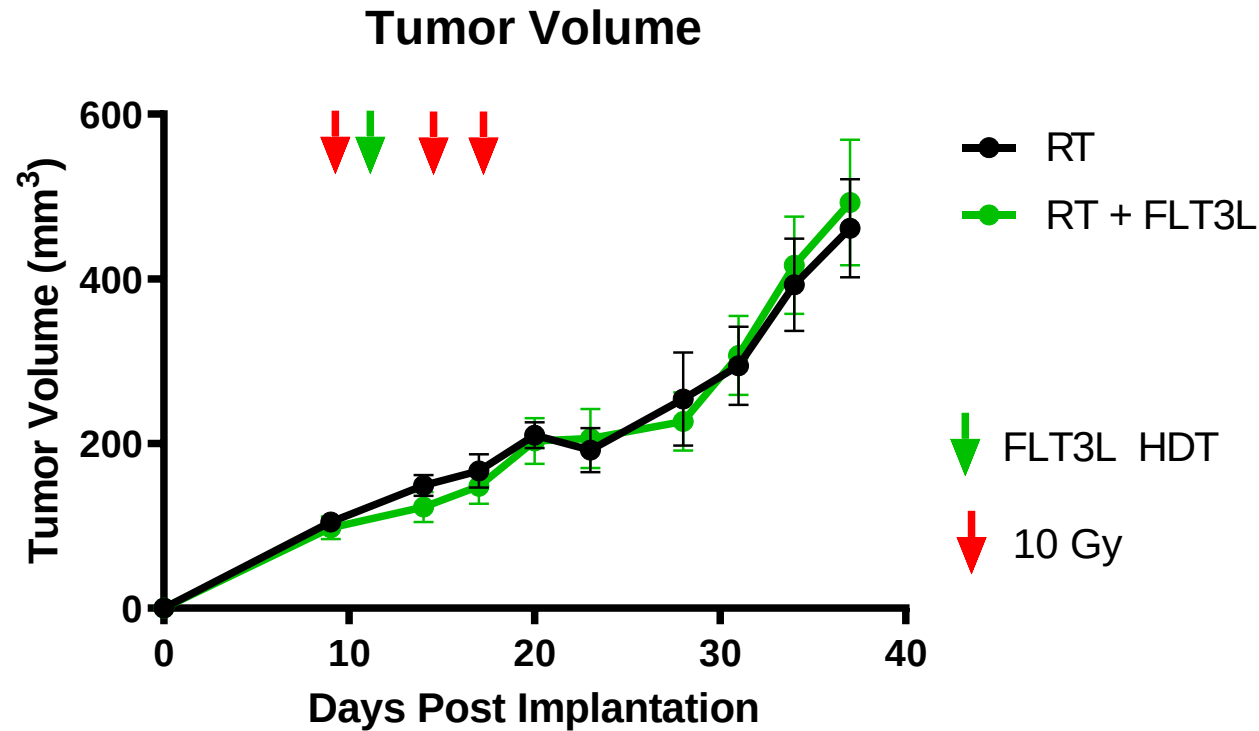
TARGETING
APCS:
FLT3



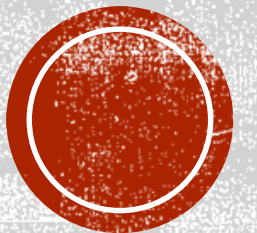
FLT3+SBRT+A-CD25 WORKS



HINT FOR TRANSLATION: DOUBLET FLT3+RT DOESN'T WORK

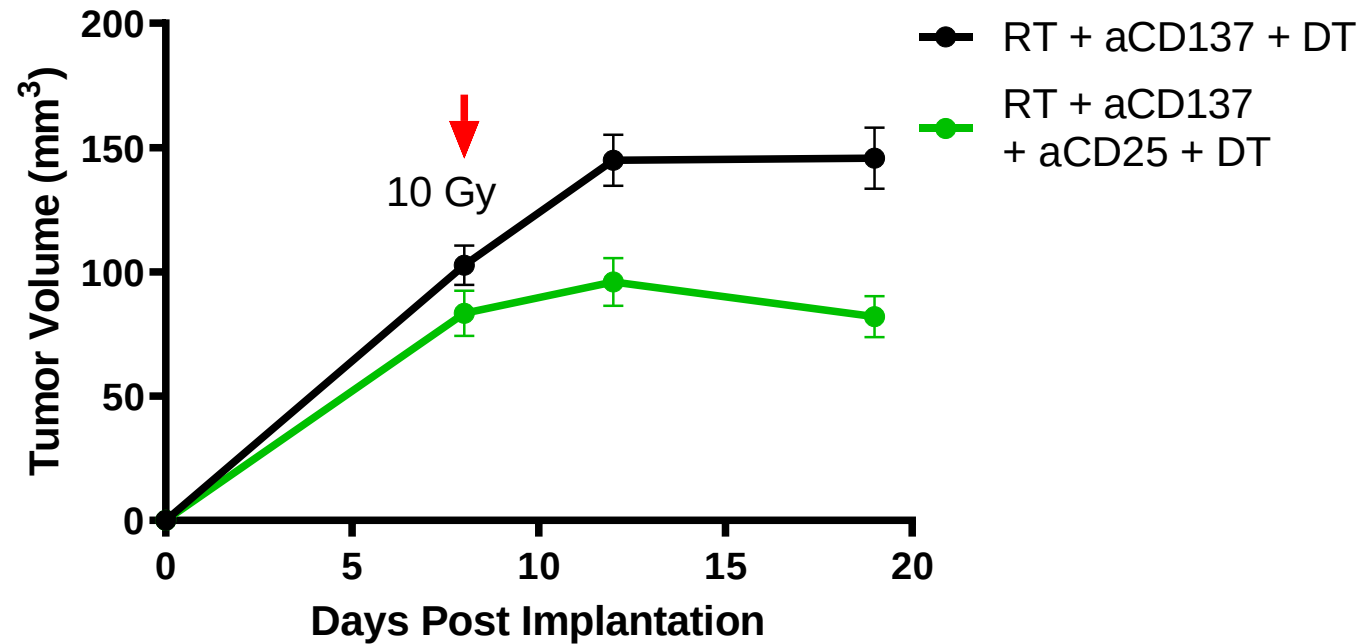


SO WHY DO WE
NEED ACD25?

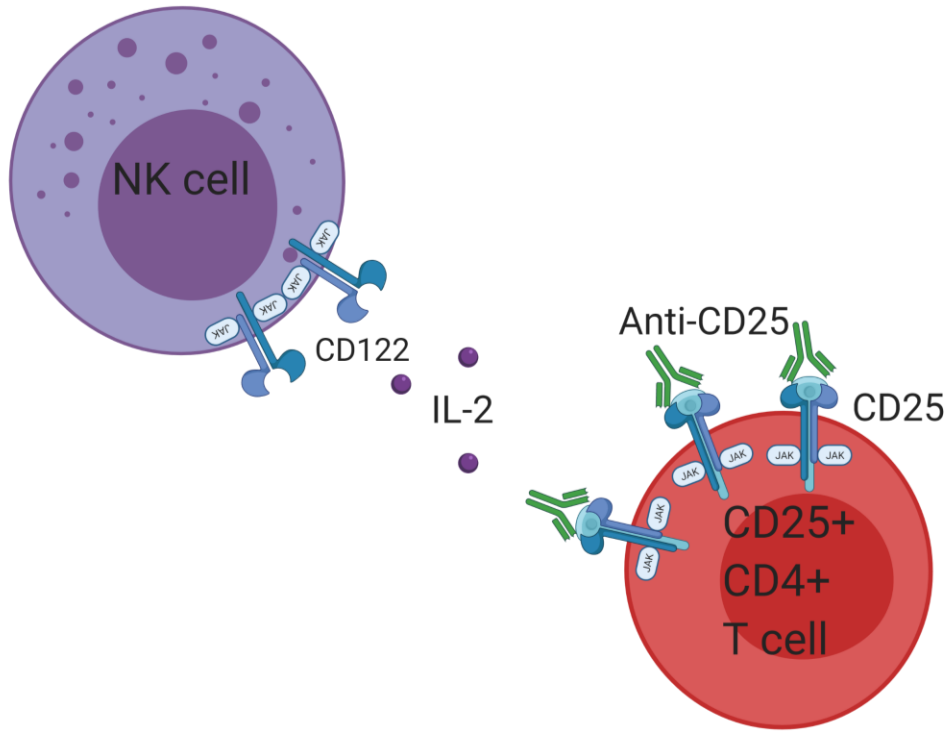


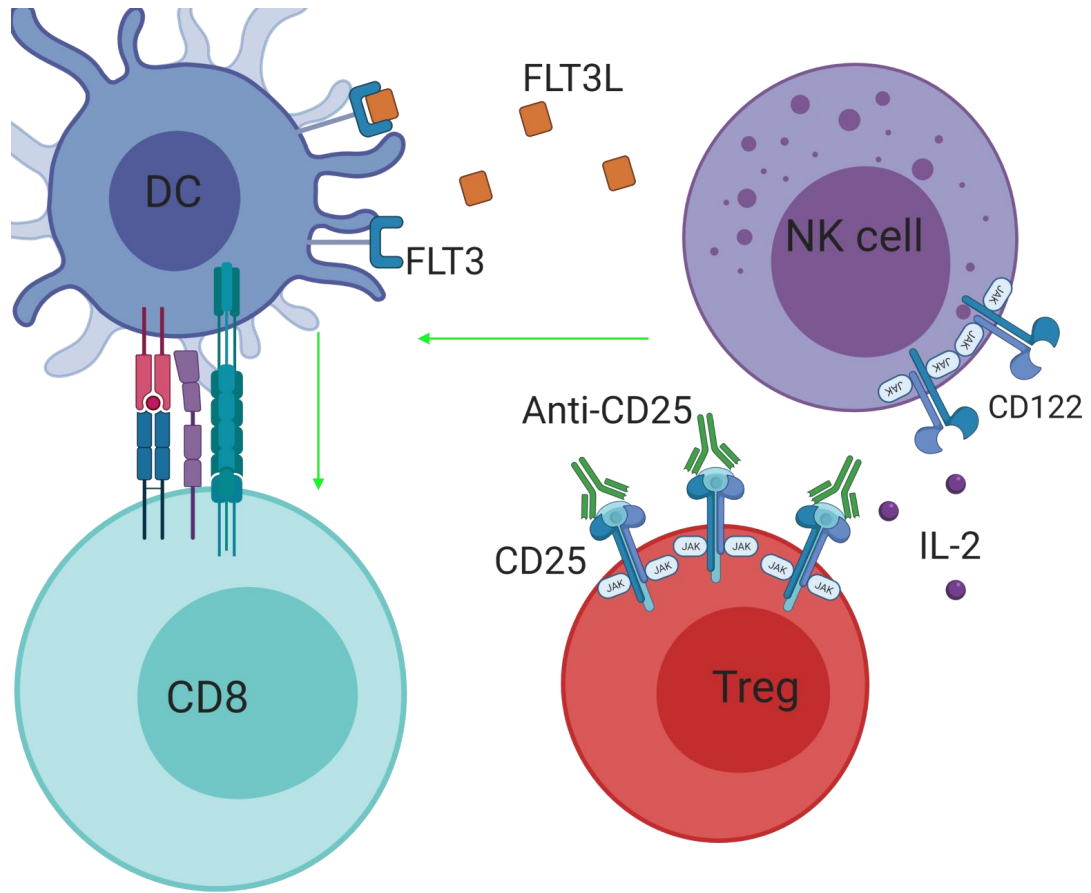
ANTI-CD25 SHOWS ADDITIONAL BENEFIT IN A TREG KNOCKOUT MODEL

Tumor Volumes in DEREg mice



**A-CD25
DEPLETES
CD25+ CD4+ T
CELLS
ALLOWING
FOR EXCESS IL-
2 TO
STIMULATE NK
CELLS VIA
CD122**





CONCLUSIONS



Karam Lab

Miles Piper, BS
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Laurel Darragh, MSTP
Shilpa Bhatia, PhD
Jake Gadwa, MS
Tiffany Pham, MD
Mike Knitz, MS
Thomas Bickett, PhD
Sophia Corbo, BS
Ben Van Court, BS
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Sarah Douglas
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past and present

Funding

Wings of Hope
R01 DE028529-01
R01 DE028282-01
P50 CA261605-01
CLC

Eric Clambey, PhD
Curtis Pickering, PhD
Ross Kedl, PhD
Kevin Barry, PhD
Laurel Lenz, PhD
Jim Hu, PhD
Kirk Hansen, PhD
Laurel Lenz, PhD

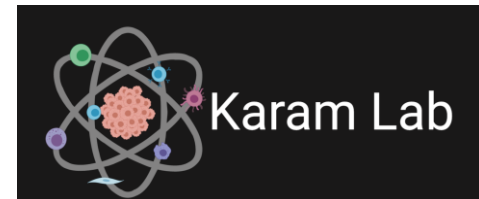
Thank you!!



Xiao Jing Wang, MD, PhD and lab
Antonio Jimeno, MD, PhD and lab
Raphael Nemenoff, PhD and lab
Lynn Heasley, PhD and lab
Philip Owens, PhD and lab

BDC and Cancer Flow
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Animal Irradiation Core

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Thank
you

