Hot is *Not* Enough:
using *in situ* vaccine to
make cold tumors hot *and* cross-priming

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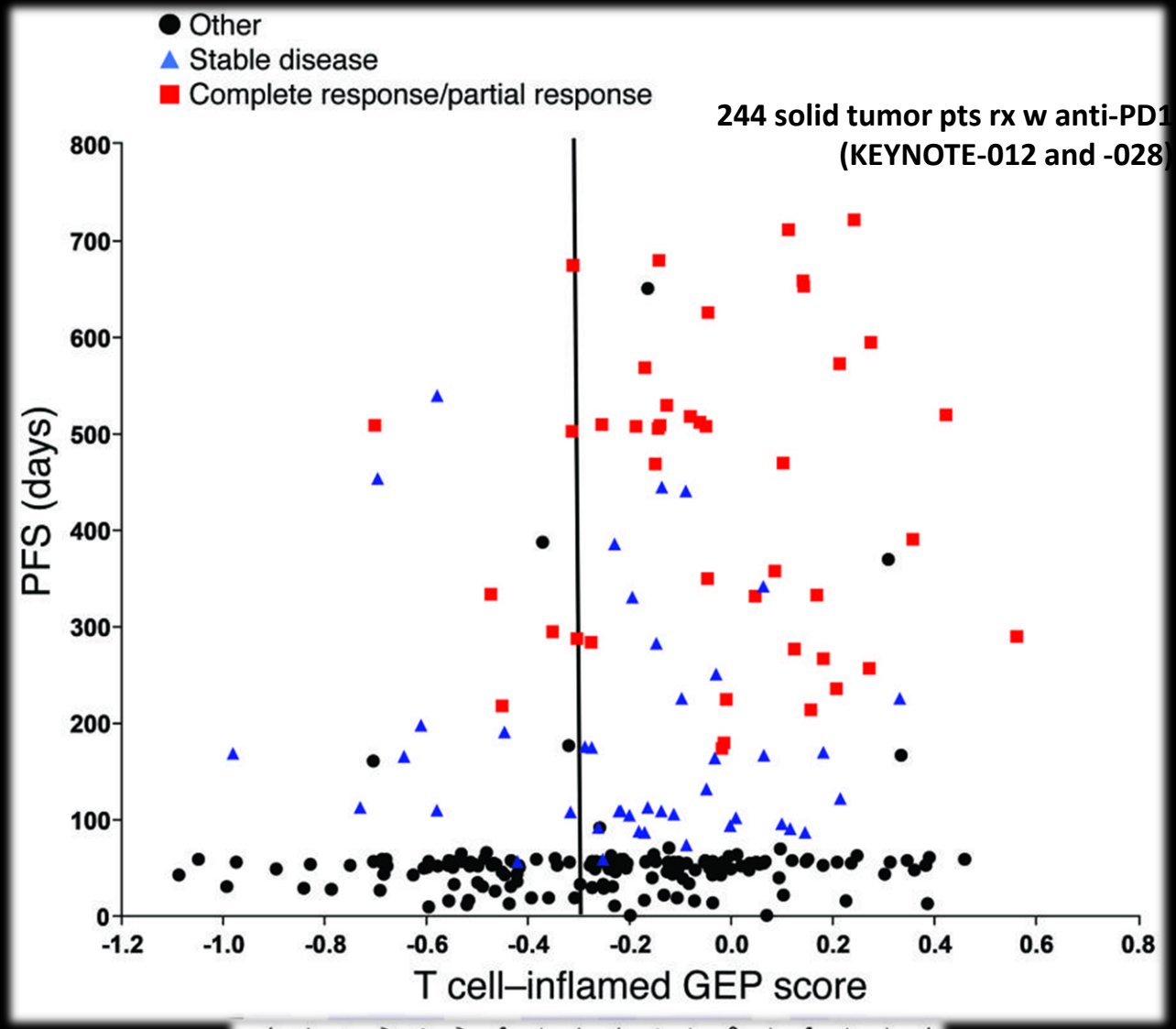
Director, Lymphoma Immunotherapy
Mount Sinai School of Medicine

SITC 2019
NOVEMBER 6 -10
NATIONAL HARBOR, MARYLAND
Gaylord National Hotel & Convention Center

“Hot” tumors ***correlate*** with response checkpoint blockade



Ayers M et al., J Clin Invest.
2017 Aug 1;127(8):2930-2940.

IF you want anti-tumor CD8 T cells
THEN cross-presentation is crucial.

Cancer Cell

Article

Density of immunogenic antigens does not explain the

Cancer Immunotherapy with Immunomodulatory Anti-CD137 and

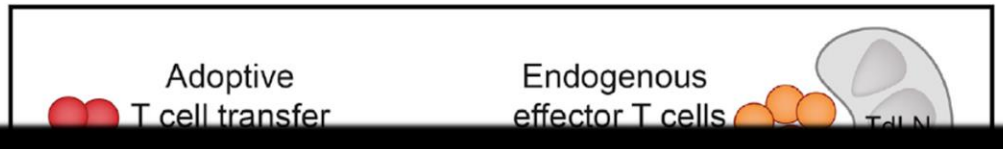
Immunity

Expansion and Activation of CD103+ Dendritic Cell

Cancer Cell

Tumor-Residing Batf3 Dendritic Cells Are Required for Effector T Cell Trafficking and Adoptive T Cell Therapy

Graphical Abstract



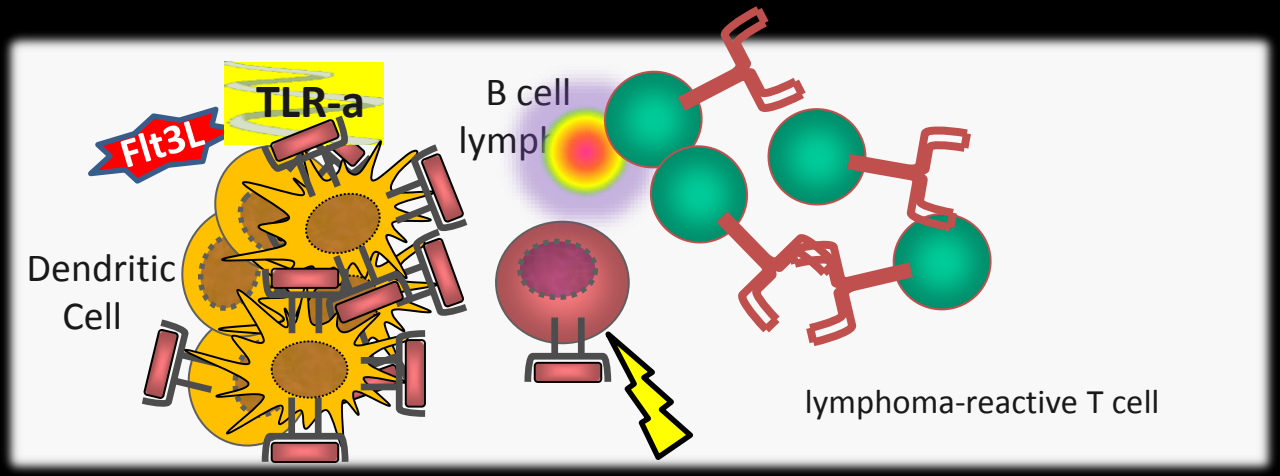
Authors

Stefani Spranger, Daisy Dai,
Brendan Horton, Thomas F. Gajewski

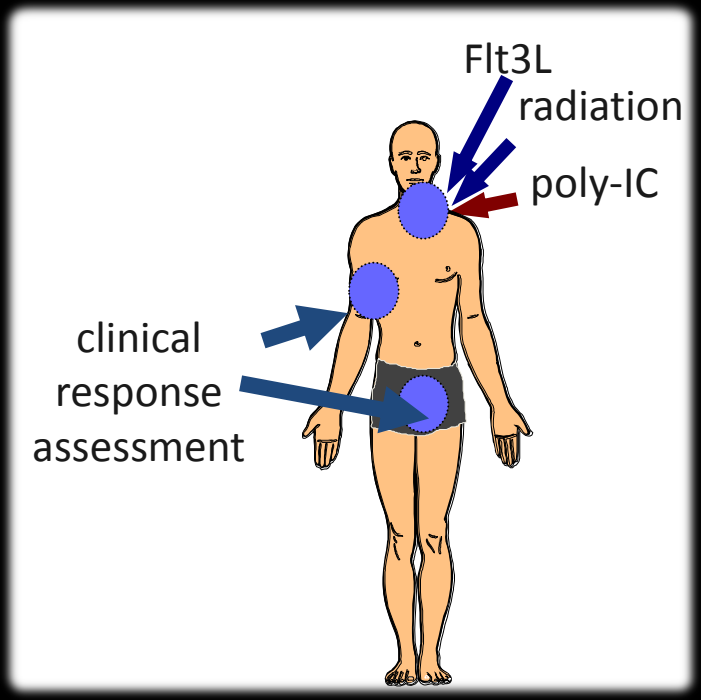
IF you want anti-tumor CD8 T cells THEN cross-presentation is crucial.

What intratumoral therapy requires to cross-prime T cells and be effective *in situ* vaccines:

1) Recruit DC
2) Load DC (with tumor antigen)
3) Activate DC



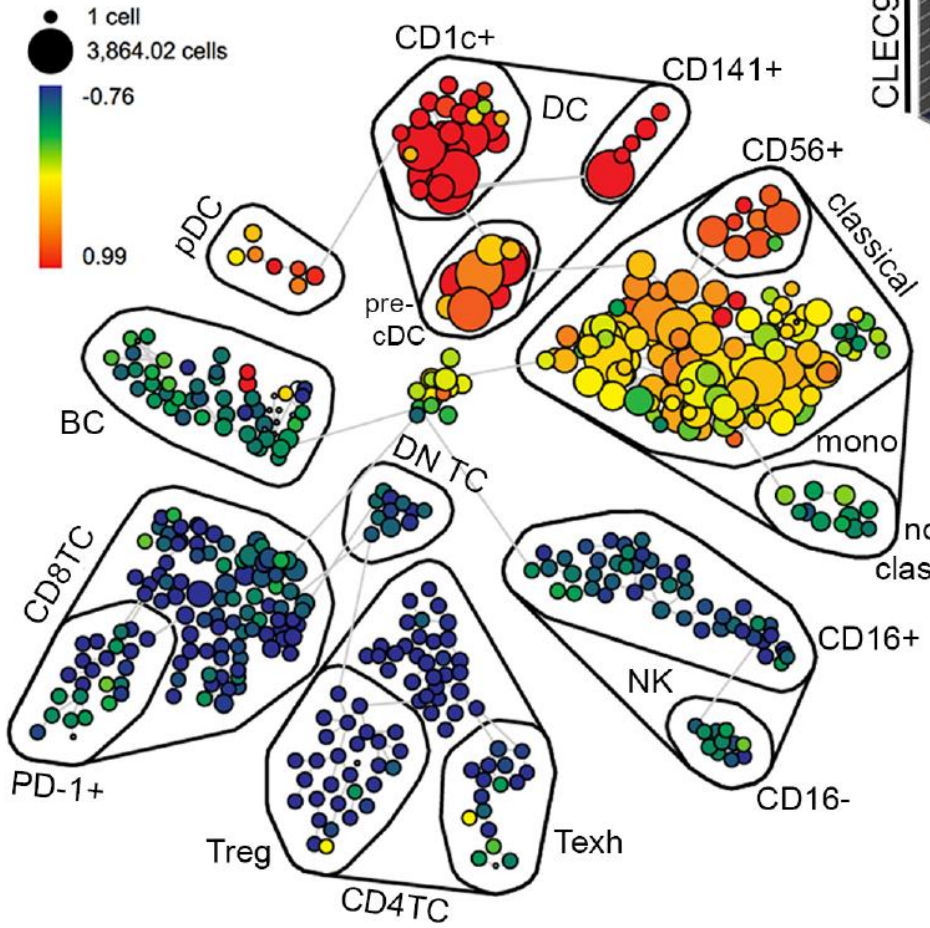
Flt3L-primed *in situ* vaccine: NCT01976585

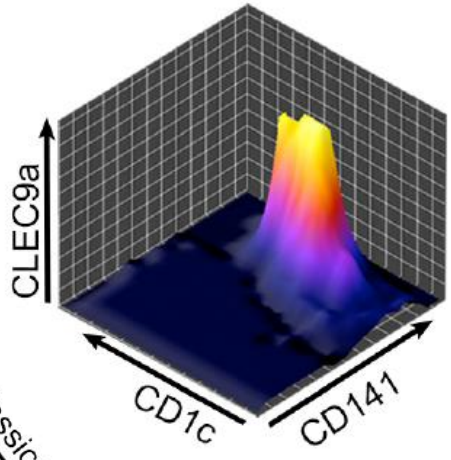


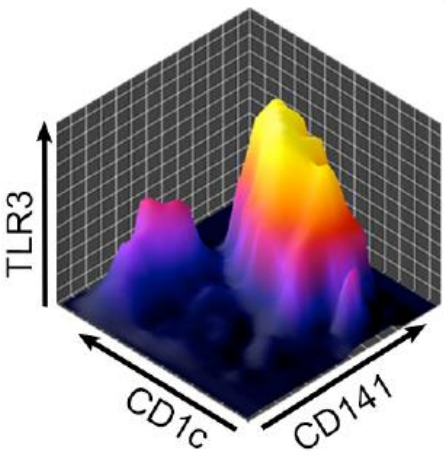
Damon Runyon
Cancer Research
Foundation

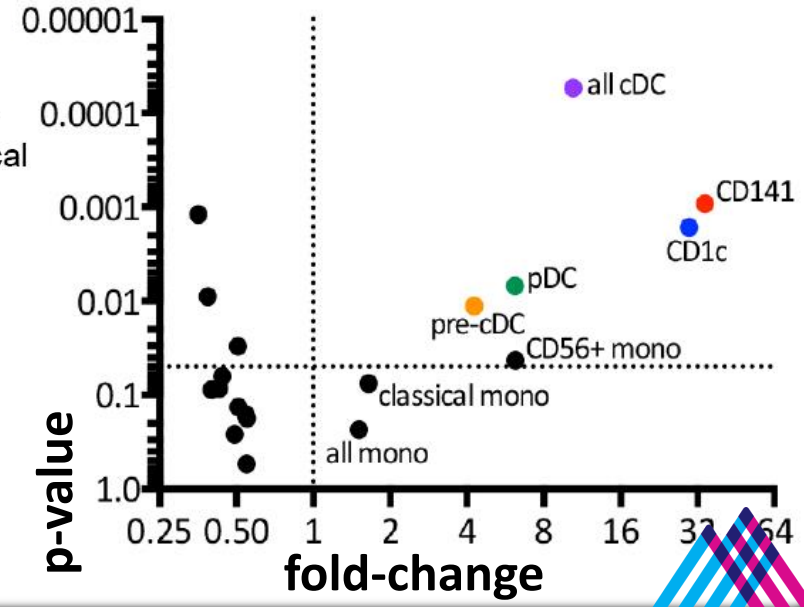
Tom Marron MD,PhD

Flt3L mobilizes cross-presenting DC subsets

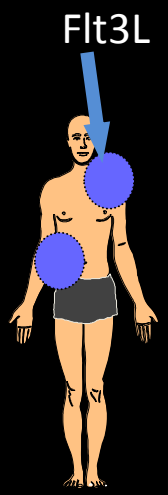








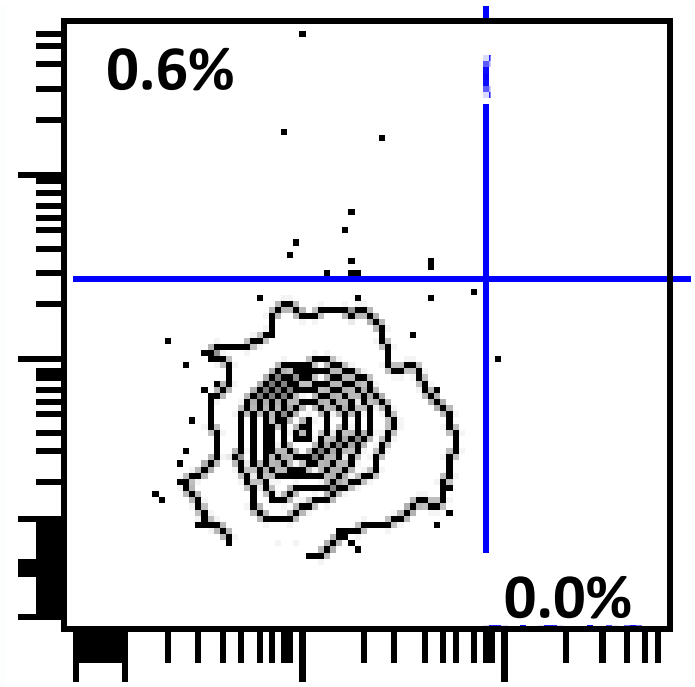
Hammerich,L, et al., *Nat Med.* 2019

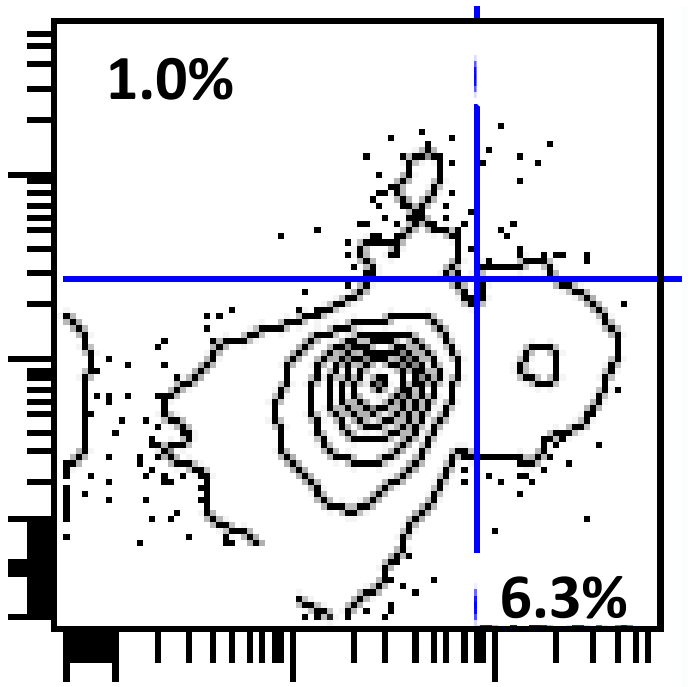


Flt3L recruits DC to the tumor

pre-rx

post-Flt3L

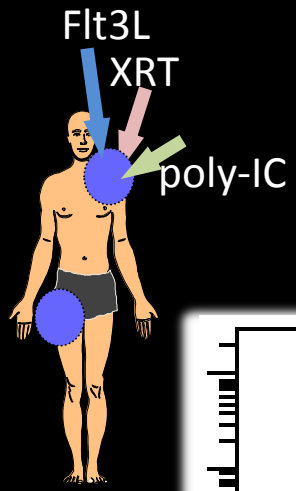




CD141

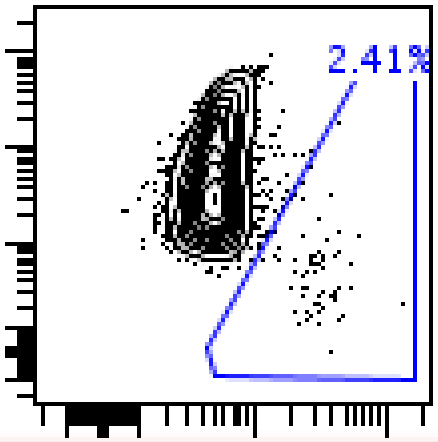
CD1c

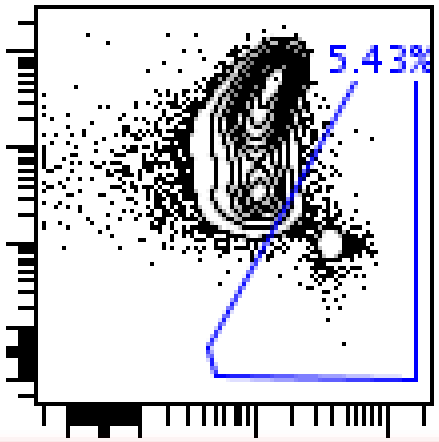
Tom Marron MD,PhD

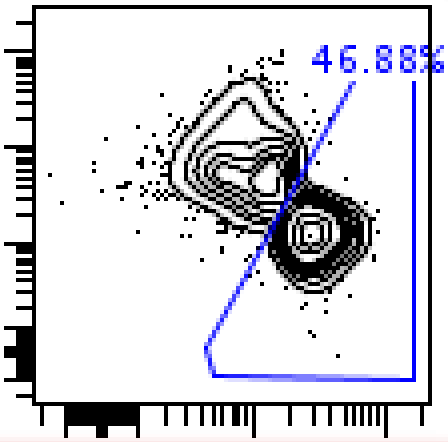


Flt3L→Poly-ICLC activates myeloid TME

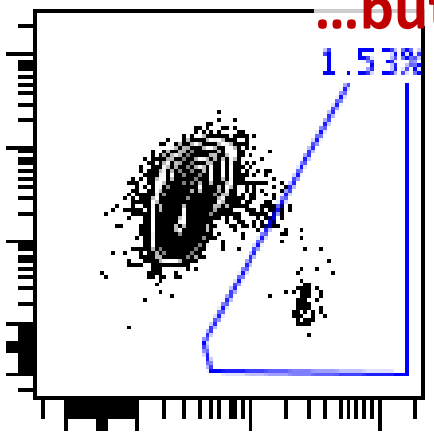
pre-rx | post-Flt3L | post-poly-ICLC

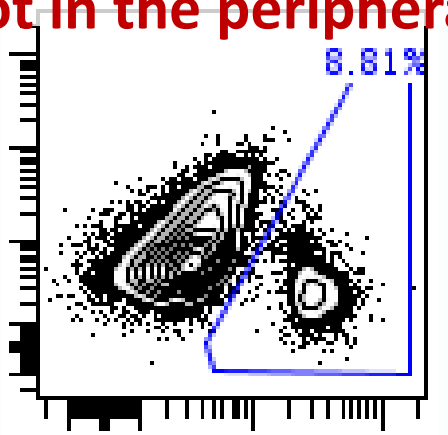


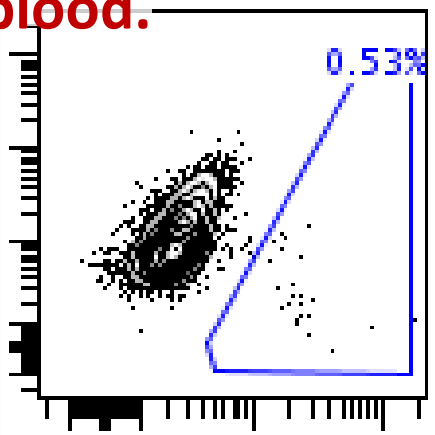




…but not in the peripheral blood.





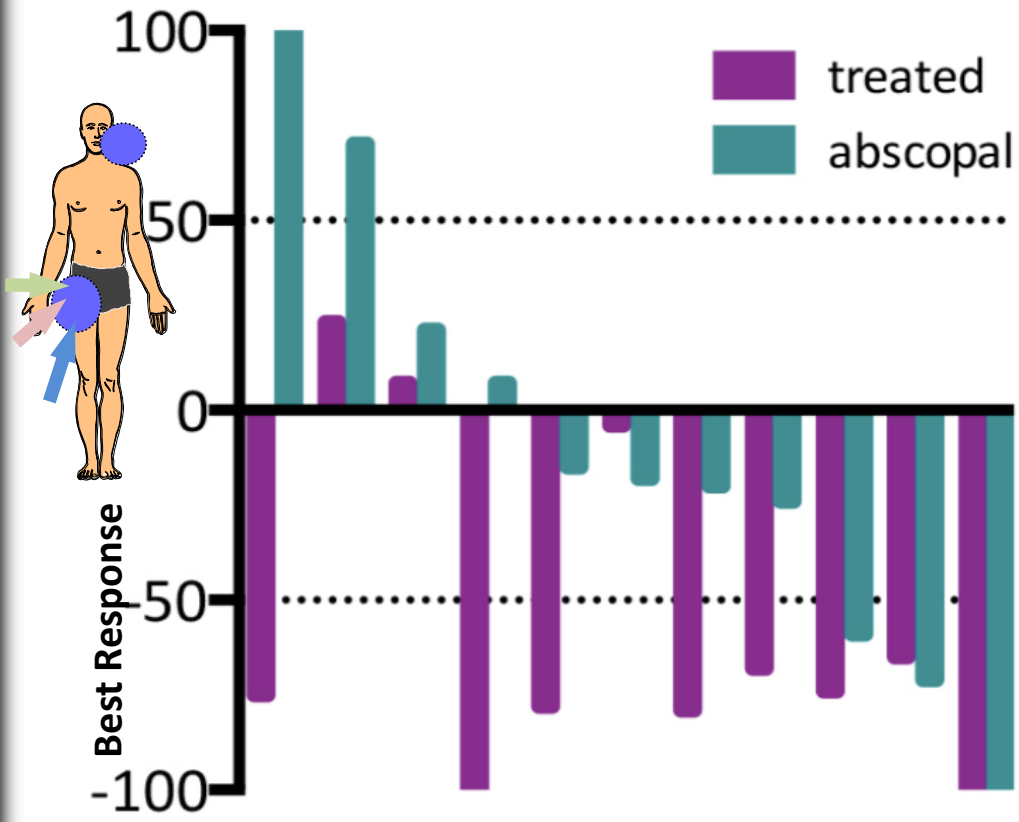


PD-L1

CD80

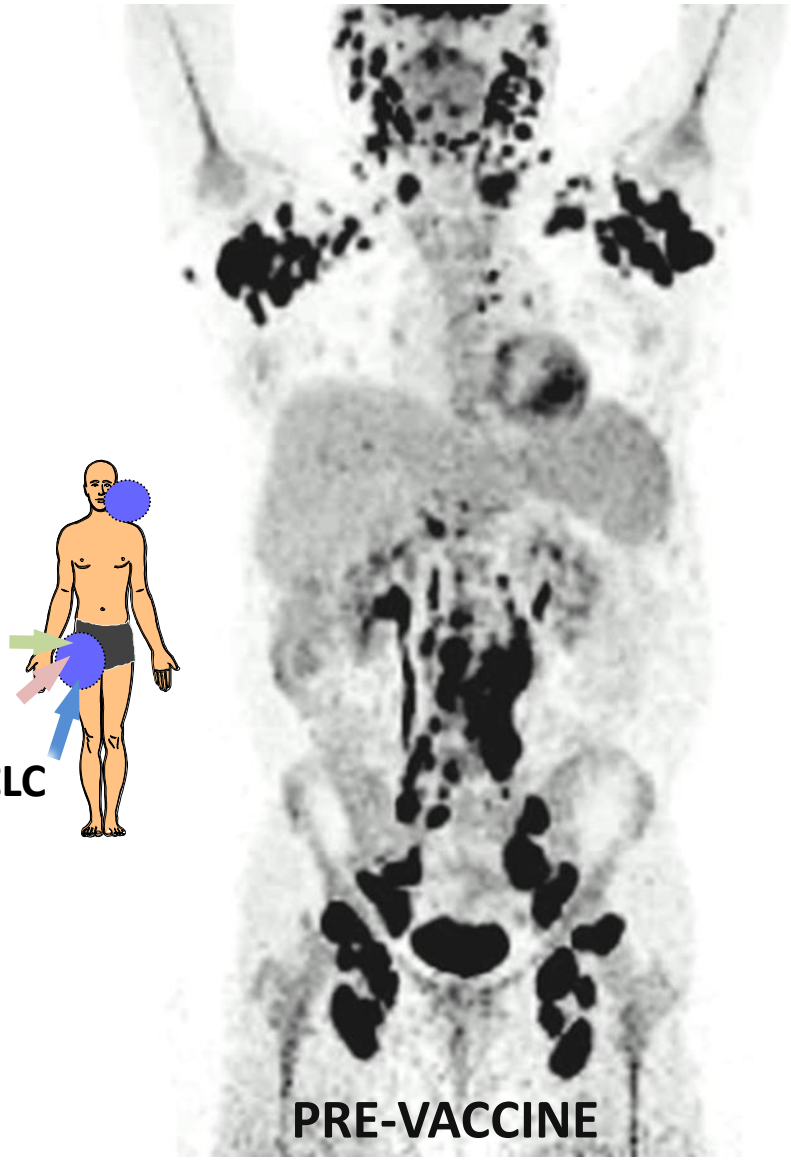
Tom Marron MD,PhD

Flt3L-primed *in situ* vaccine
Reproducible abscopal tumor regressions

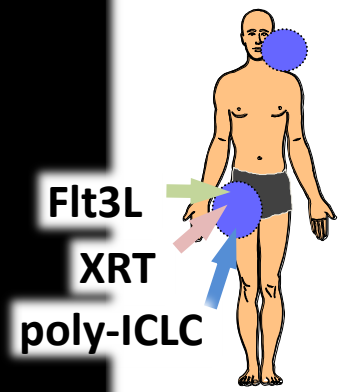


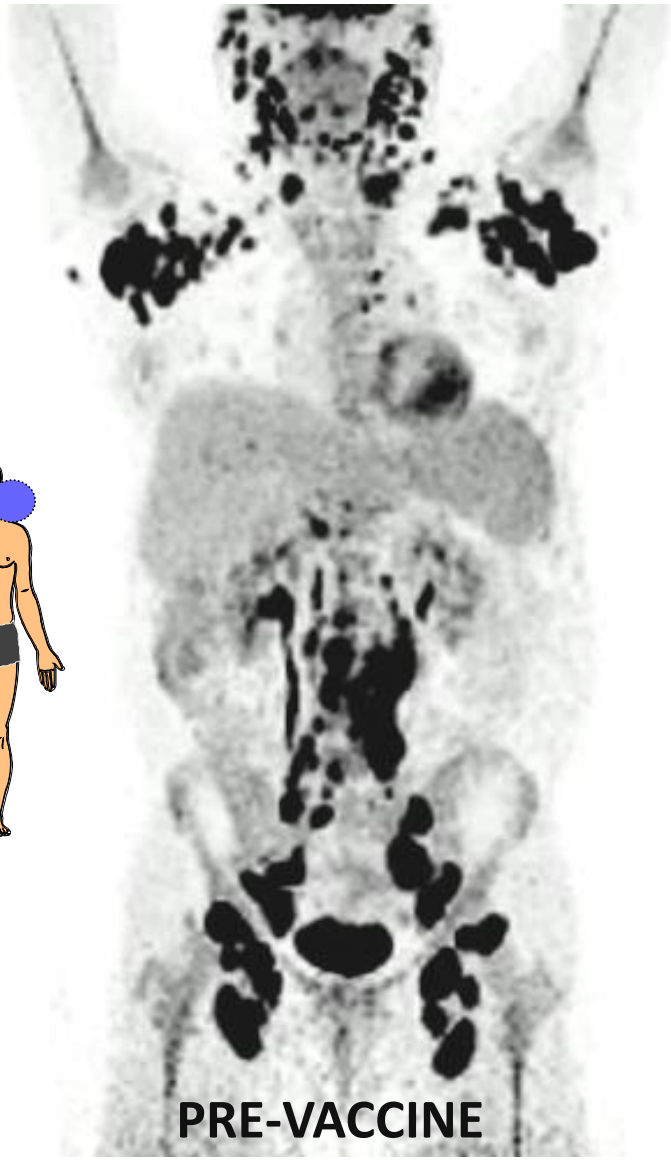
Hammerich,L, et al., *Nat Med.* 2019

Flt3L-primed *in situ* vaccine
Regression of Bulky Tumors



Flt3L-primed *in situ* vaccine
Regression of Bulky Tumors



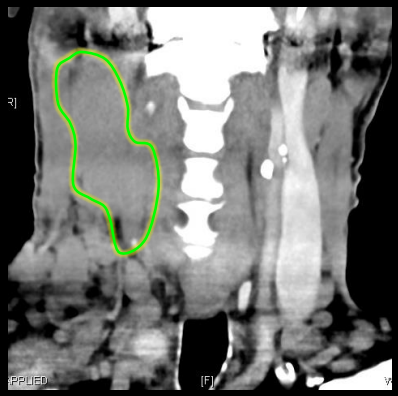


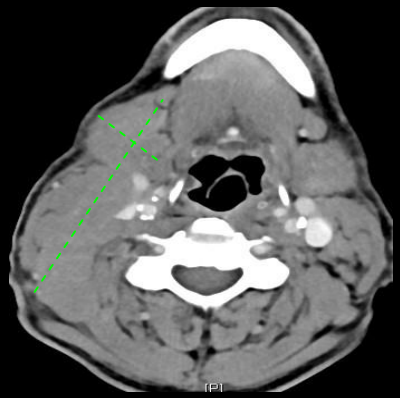
PRE-VACCINE

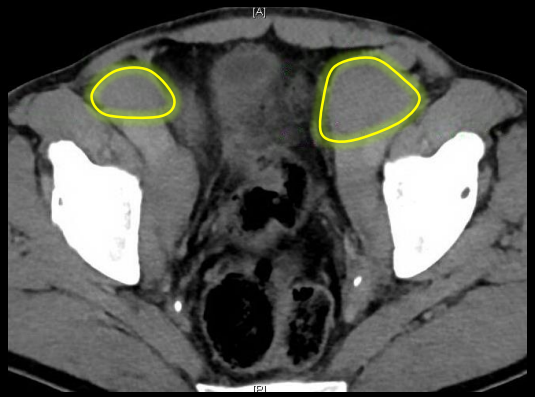
9 MONTHS
POST-VACCINE

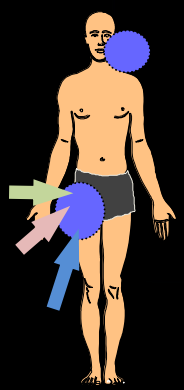
Flt3L-primed *in situ* vaccine
Regression of Bulky Tumors

pre-vaccine





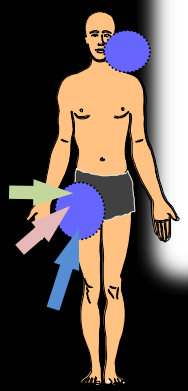


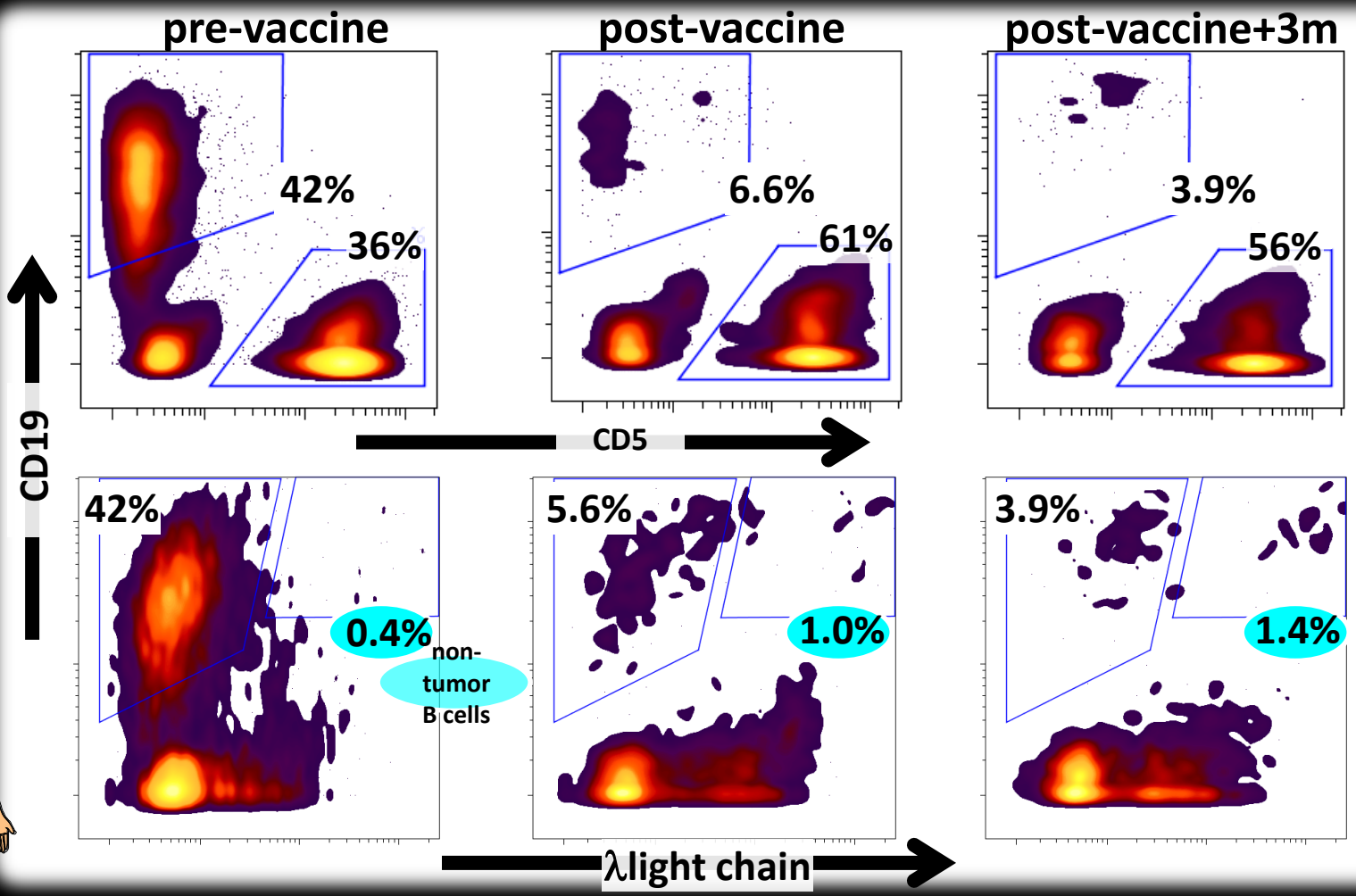


Hammerich,L, et al., *Nat Med.* 2019

Flt3L-primed *in situ* vaccine

Regression of Leukemic-phase Lymphoma

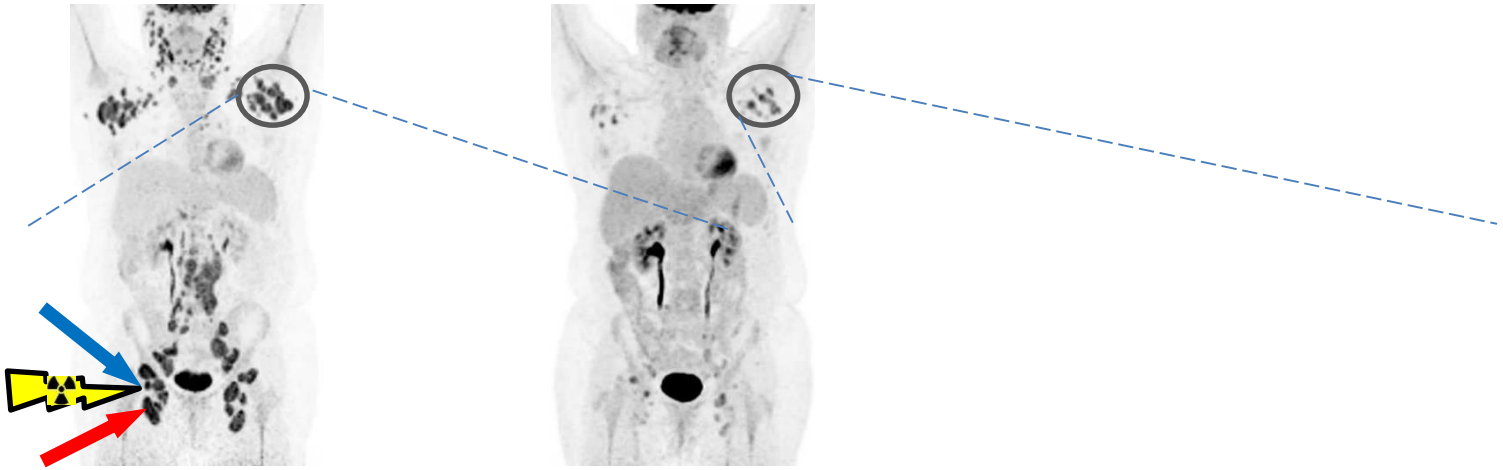


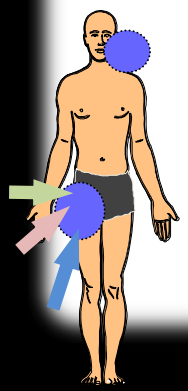


Hammerich,L, et al., *Nat Med.* 2019

Flt3L-primed *in situ* vaccine

T cell recruitment to abscopal sites





Hammerich,L, et al., *Nat Med.* 2019

Flt3L-primed *in situ* vaccine

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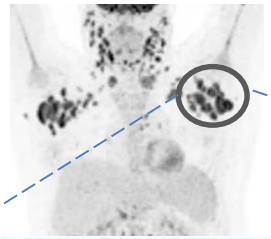
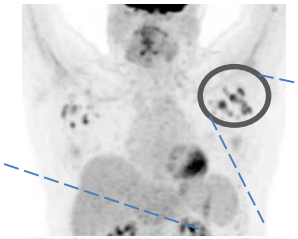
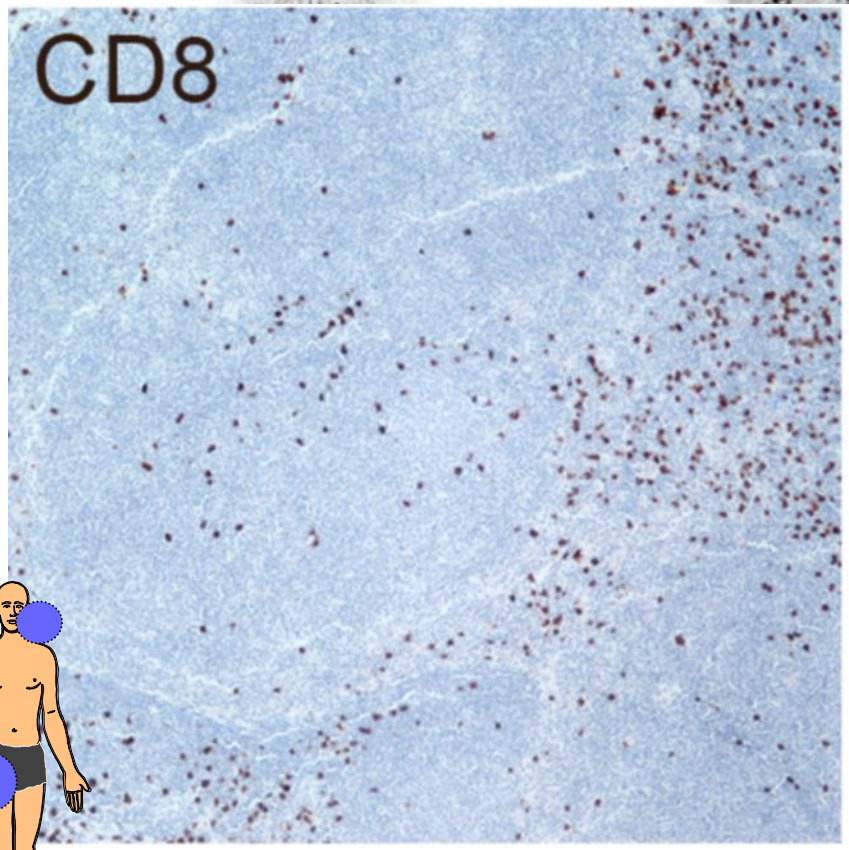
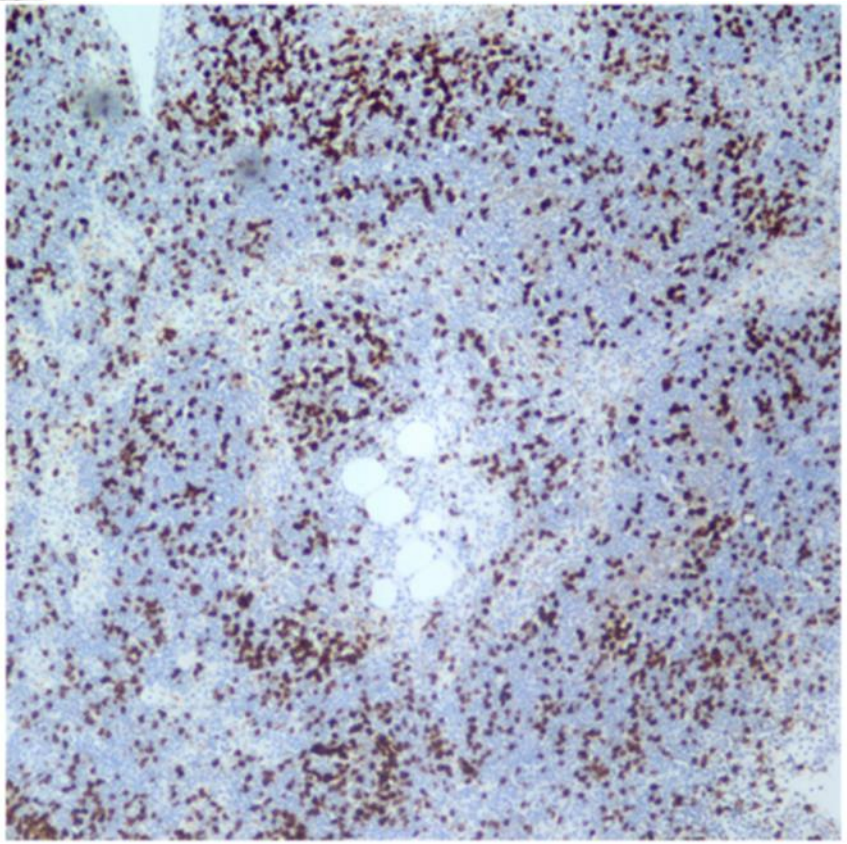
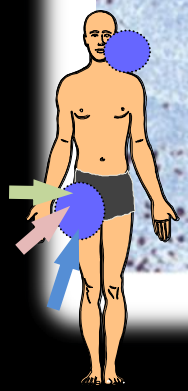






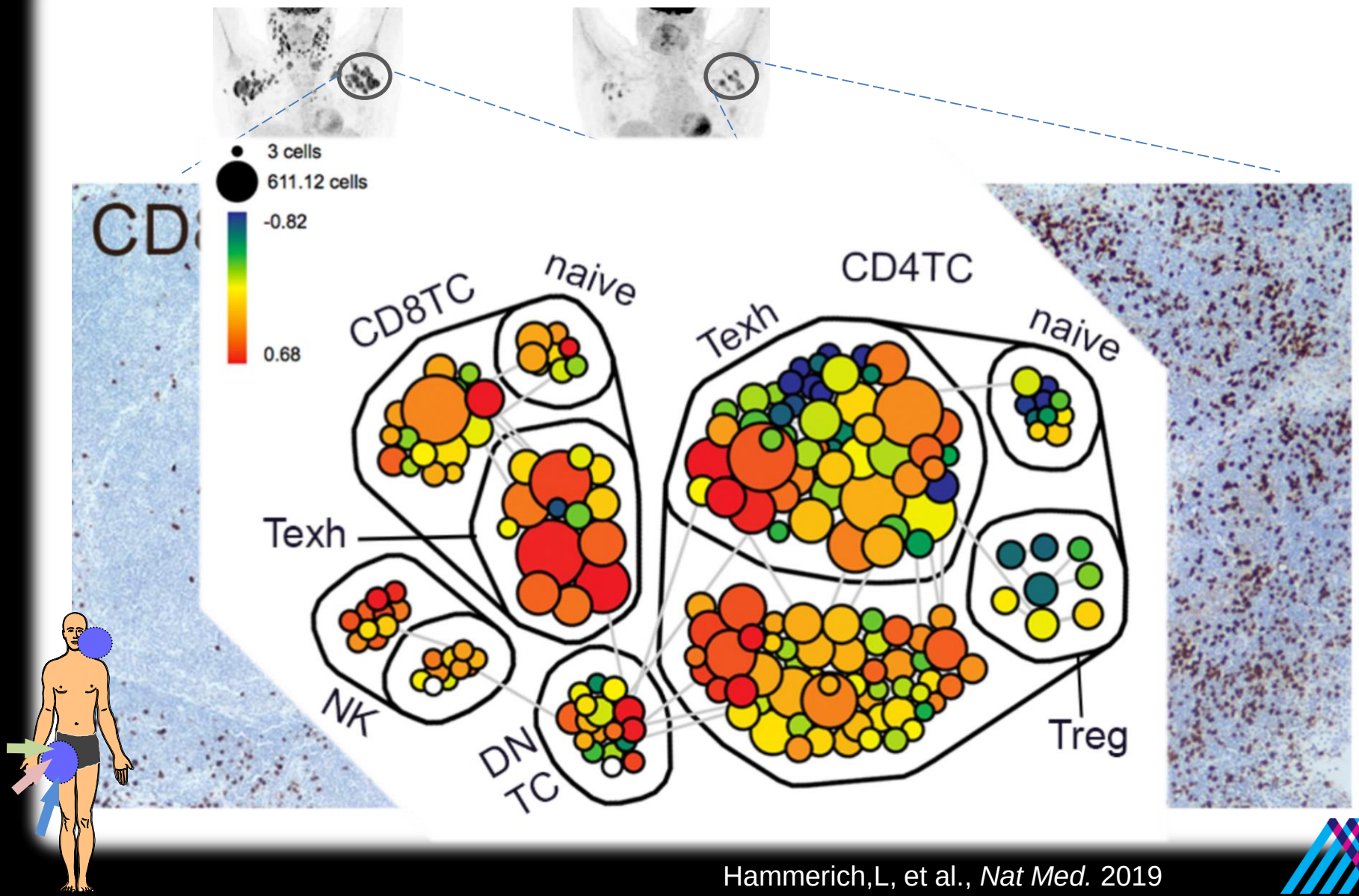




Hammerich,L, et al., *Nat Med.* 2019

Flt3L-primed *in situ* vaccine

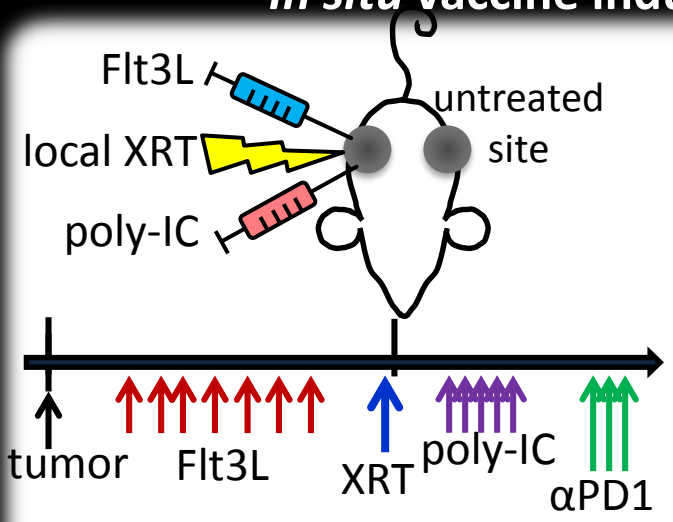
T cell recruitment to abscopal sites

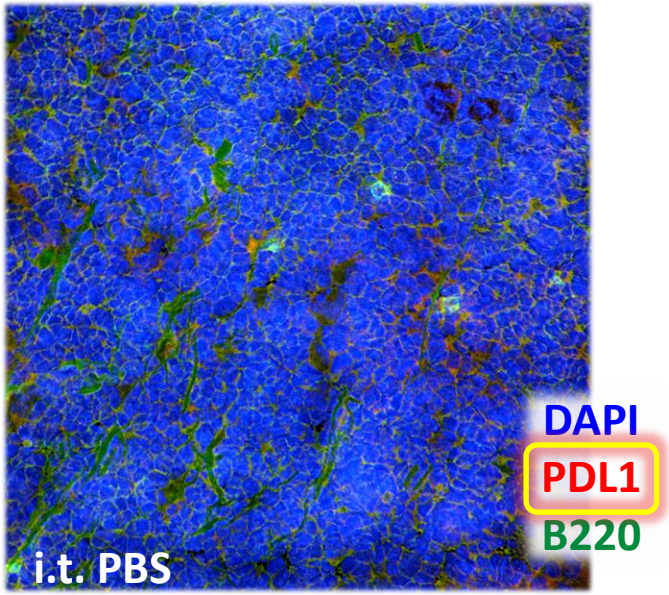


Hammerich,L, et al., *Nat Med.* 2019

Improving Flt3L *in situ* vaccine:

In situ vaccine induces PD-L1 and synergizes with anti-PD1





Hammerich,L, et al., Nat Med. 2019

Bringing Flt3L *in situ* vaccine + PD1/PDL1 blockade to patients

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In Situ Vaccine for Low-Grade Lymphoma: Combination of Intratumoral Flt3L and Poly-ICLC With Low-Dose Radiotherapy

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Vaccination With Flt3L, Radiation, and Poly-ICLC

ClinicalTrials.gov Identifier: NCT03789097

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

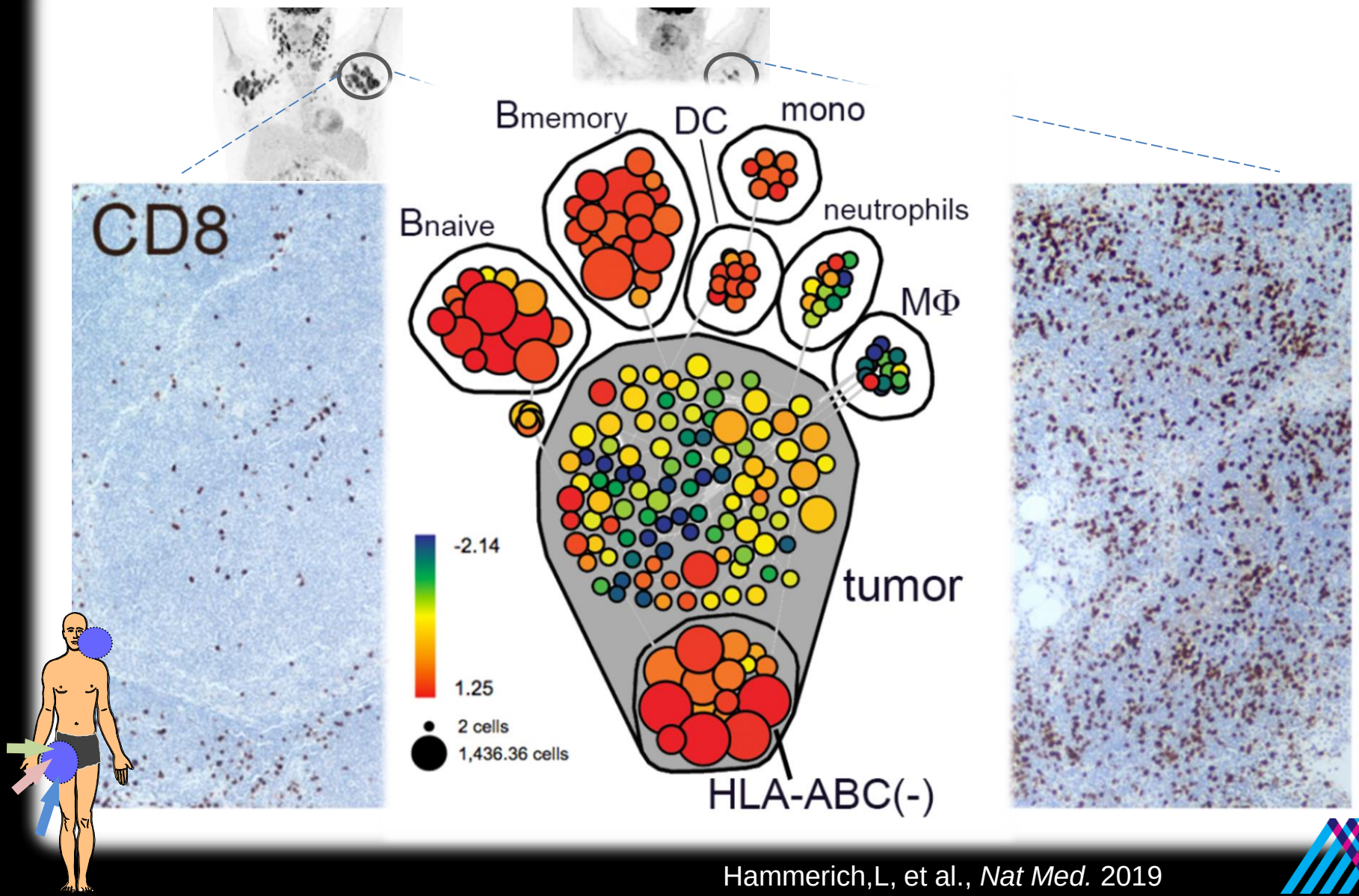
Study Description

Go to

Condition or disease	Intervention/treatment	Phase
Non-Hodgkin's Lymphoma	Drug: Pembrolizumab	Phase 1
Metastatic Breast Cancer	Drug: Flt3L	Phase 2
Head and Neck Squamous Cell Carcinoma	Radiation: Radiation	
	Drug: Poly ICLC	

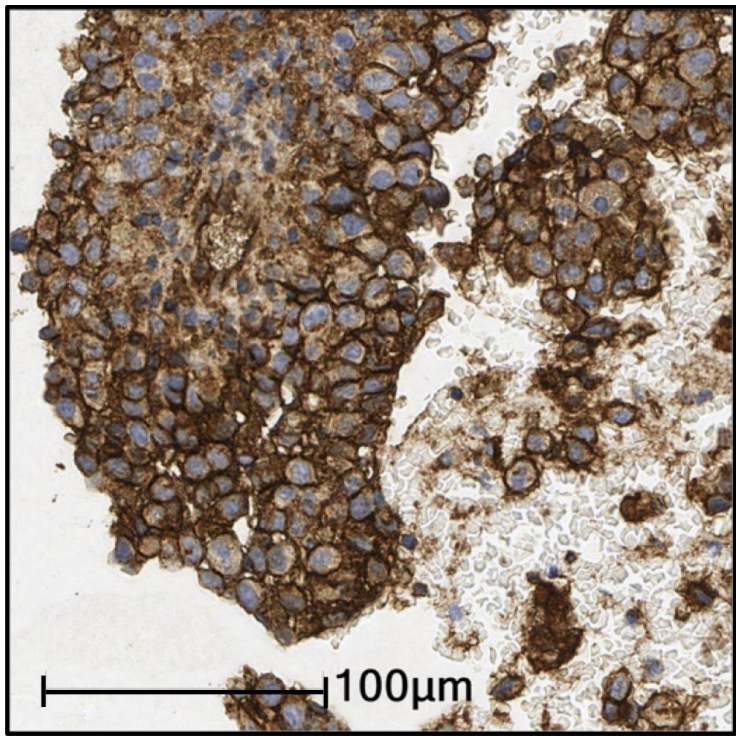
Flt3L-primed *in situ* vaccine

MHC loss tumor seems to resist elimination!

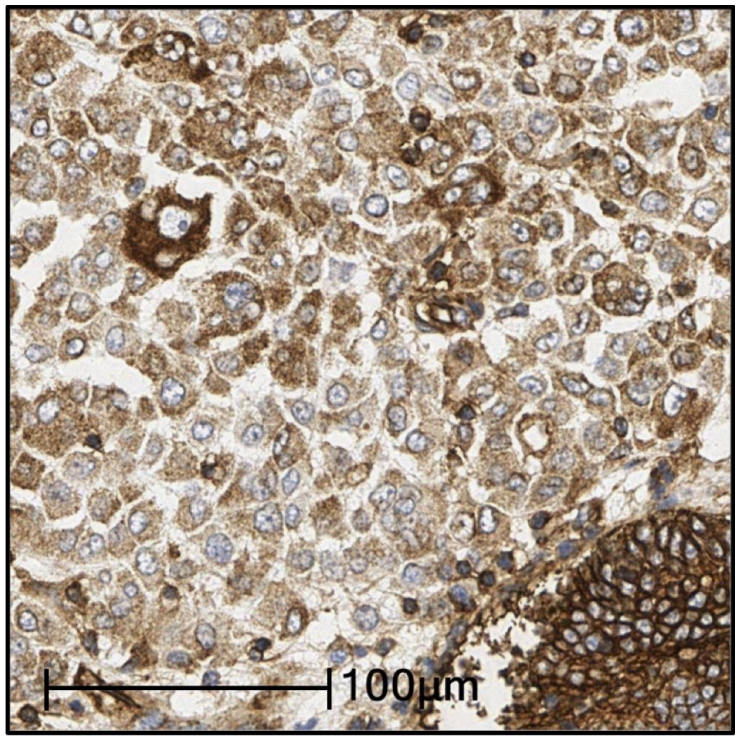


Hammerich,L, et al., *Nat Med.* 2019

Even *if* we generate anti-tumor T cells, antigen-loss is a problem



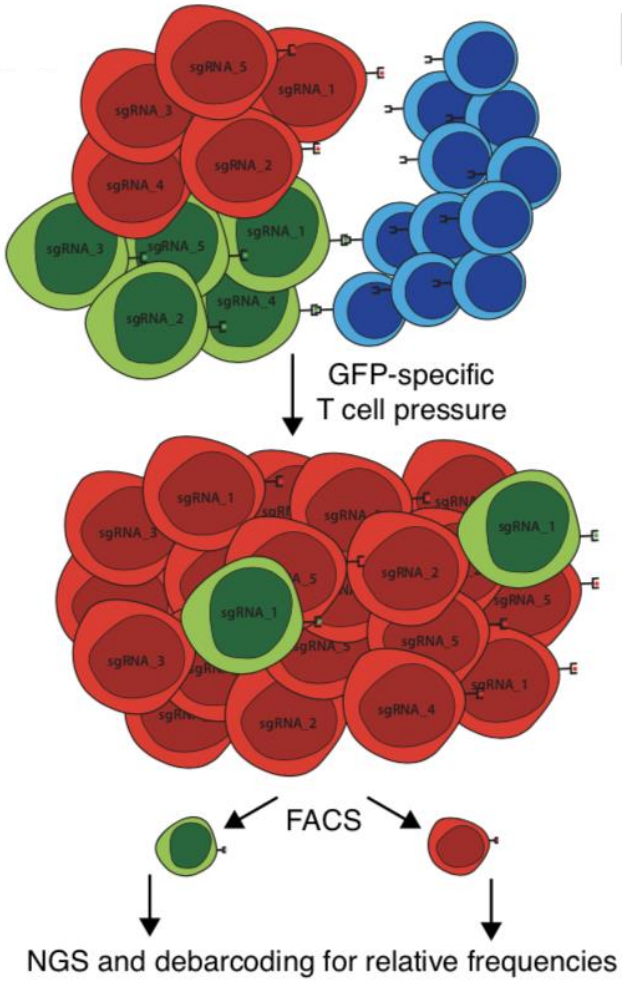
MHC I (Pre-Tx)

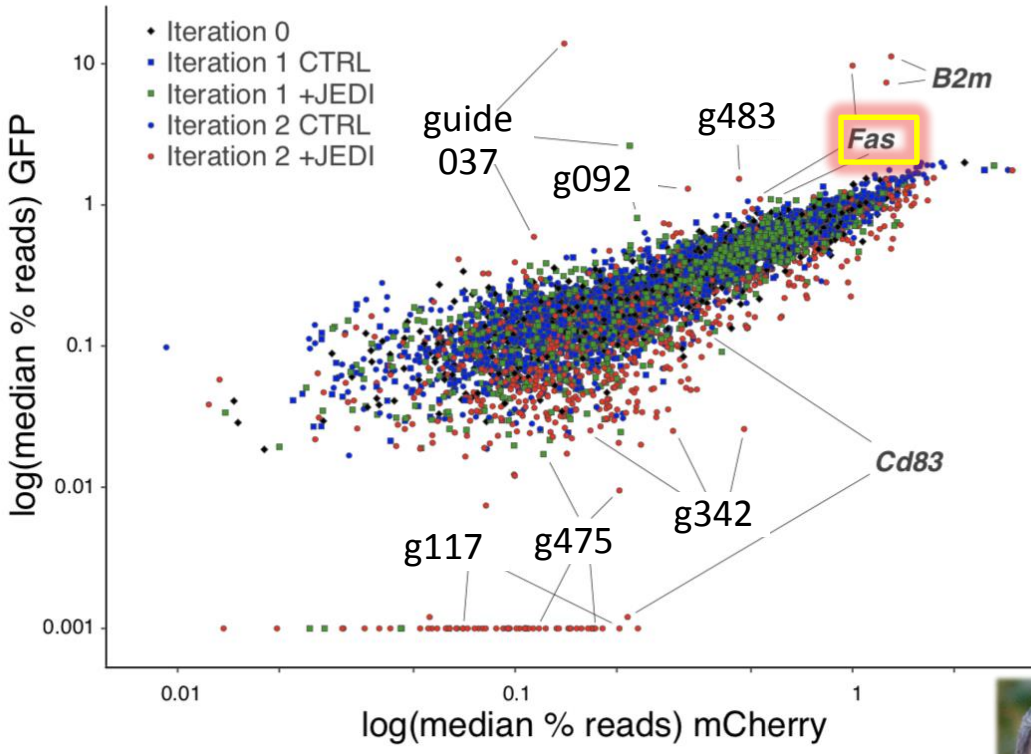


MHC I (Relapse)

Zaretsky et al, NEJM 2016

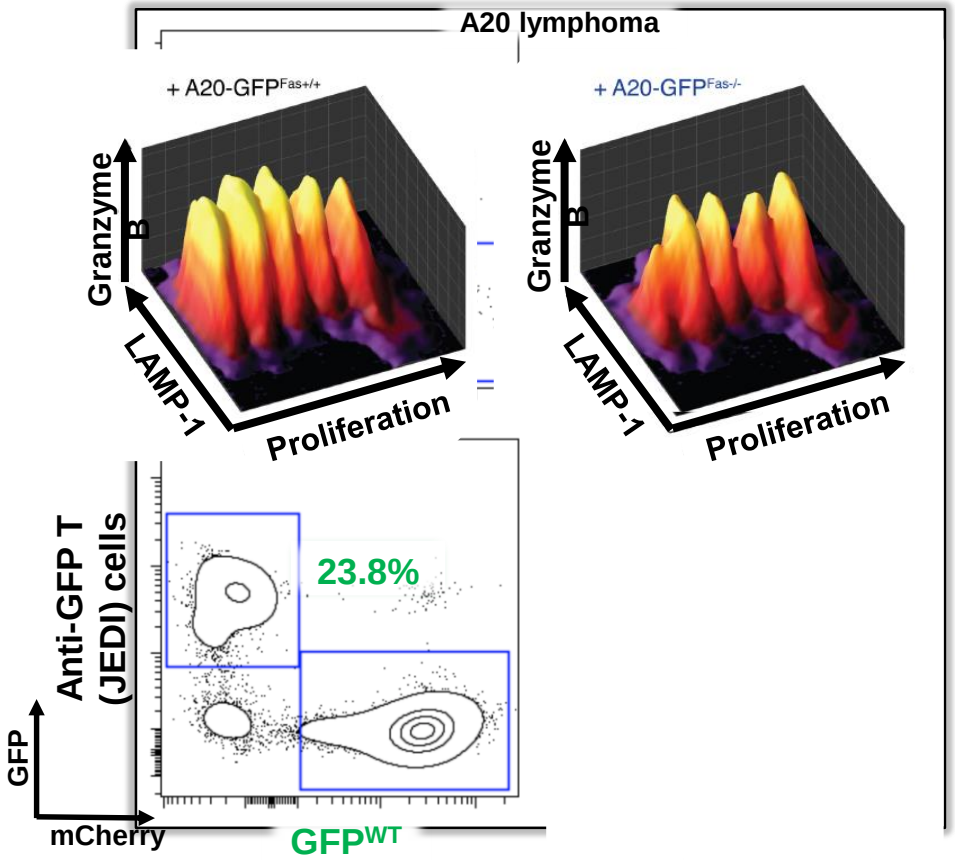
Murine T cells: CRISPR library screen discovers that lymphoma killing is critically fas-dependent





Ranjan Upadhyay

Fas mediates T cell killing of NHL & breast cancer cells



Ranjan Upadhyay

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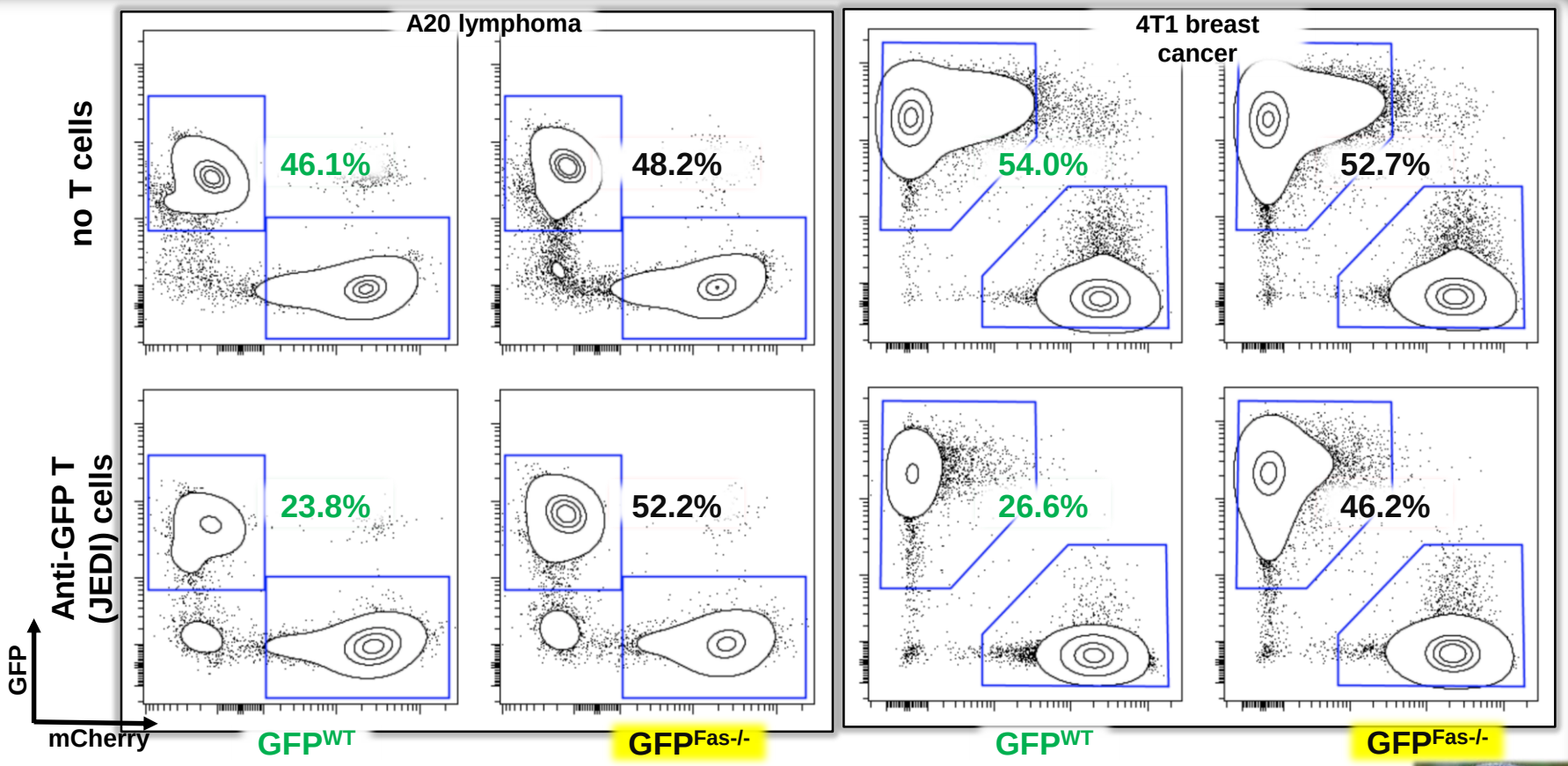
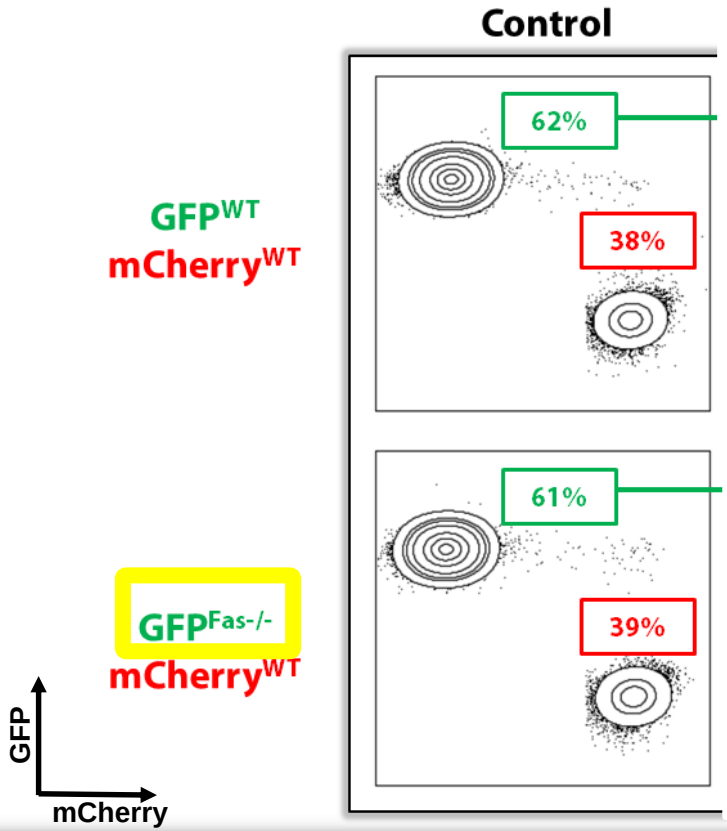
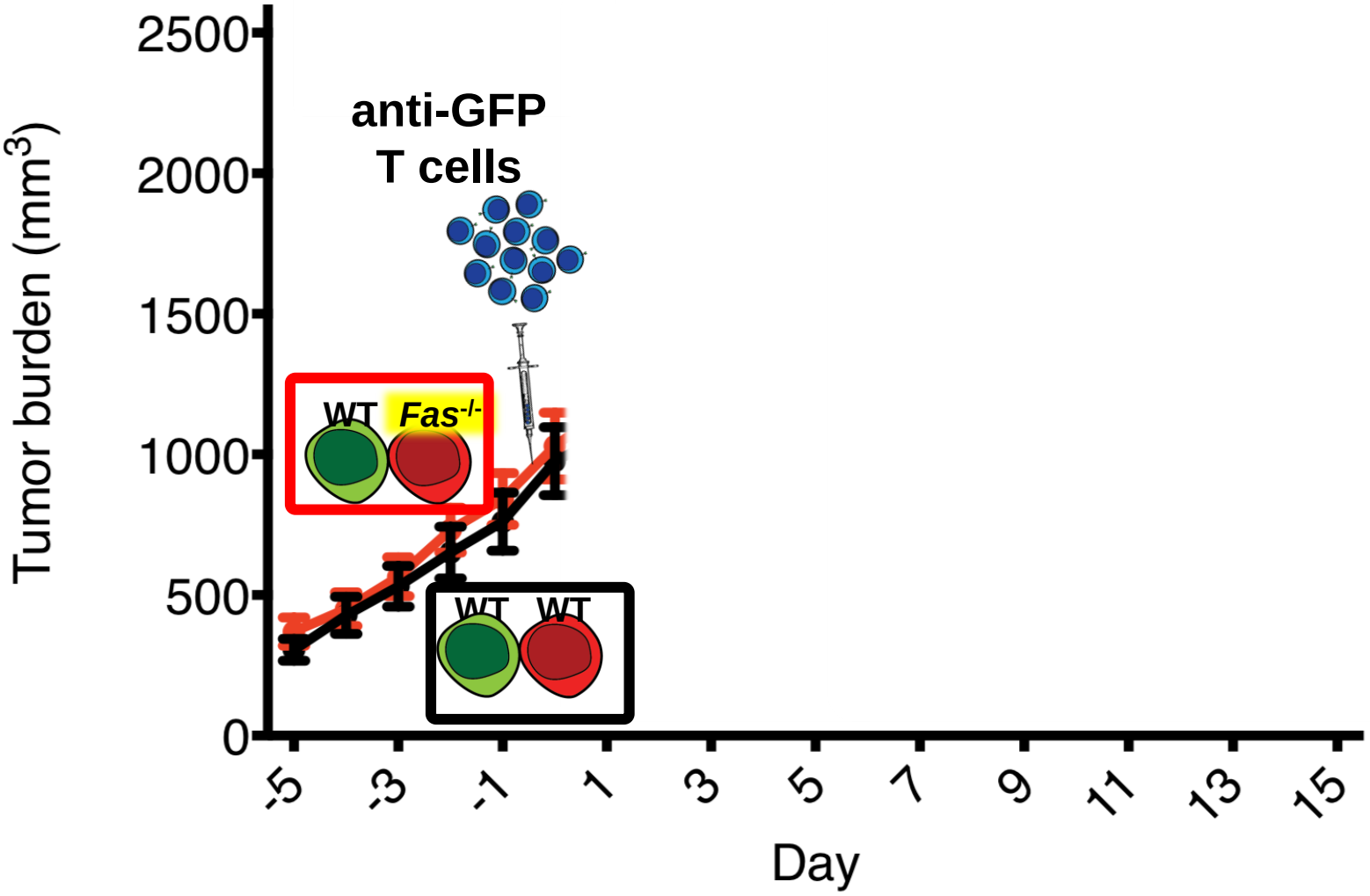


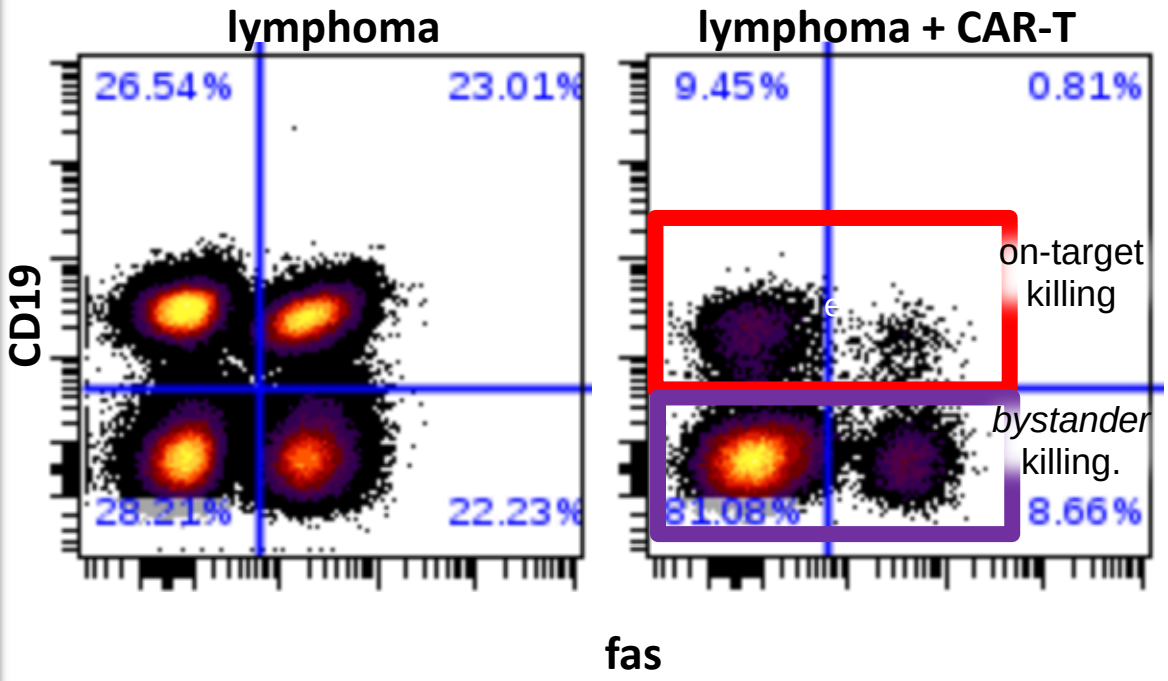
Fas-deletion reveals unexpected bystander tumor killing



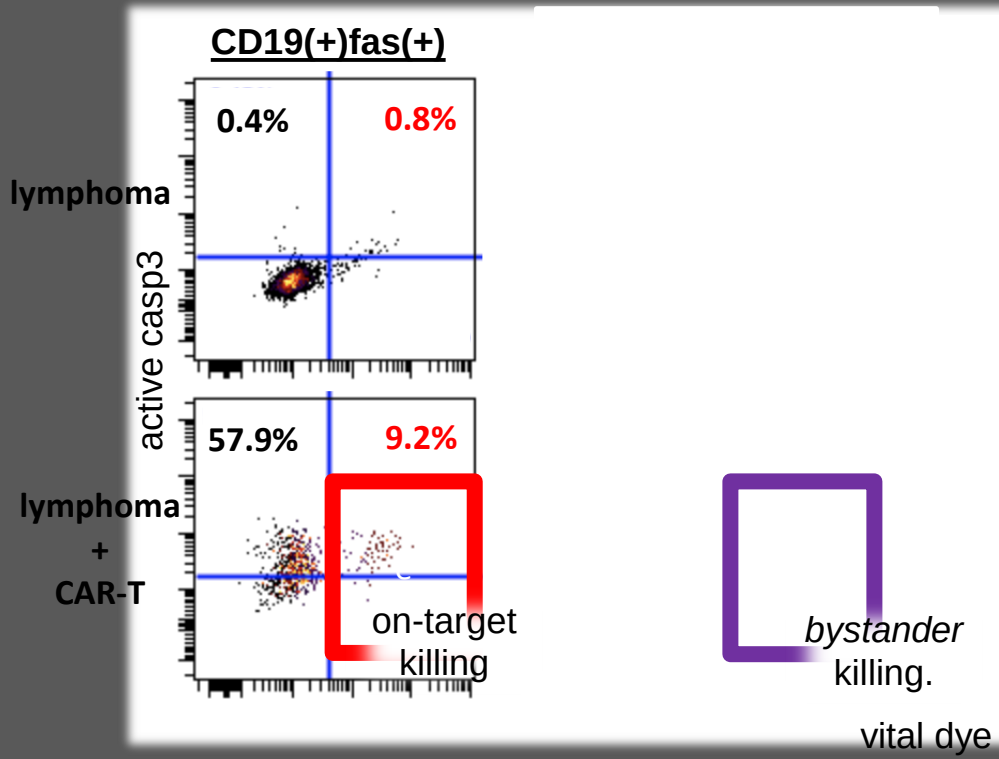
Fas mediates bystander killing *in vivo.*



Fas is important for on-target killing, but *critical* for '*bystander*' killing. (Murine CAR-T)



Fas is important for on-target killing, but *critical* for '*bystander*' killing. (Human CAR-T)



Fas expression predicts outcomes in CAR-T patients.

The NEW ENGLAND JOURNAL of MEDICINE

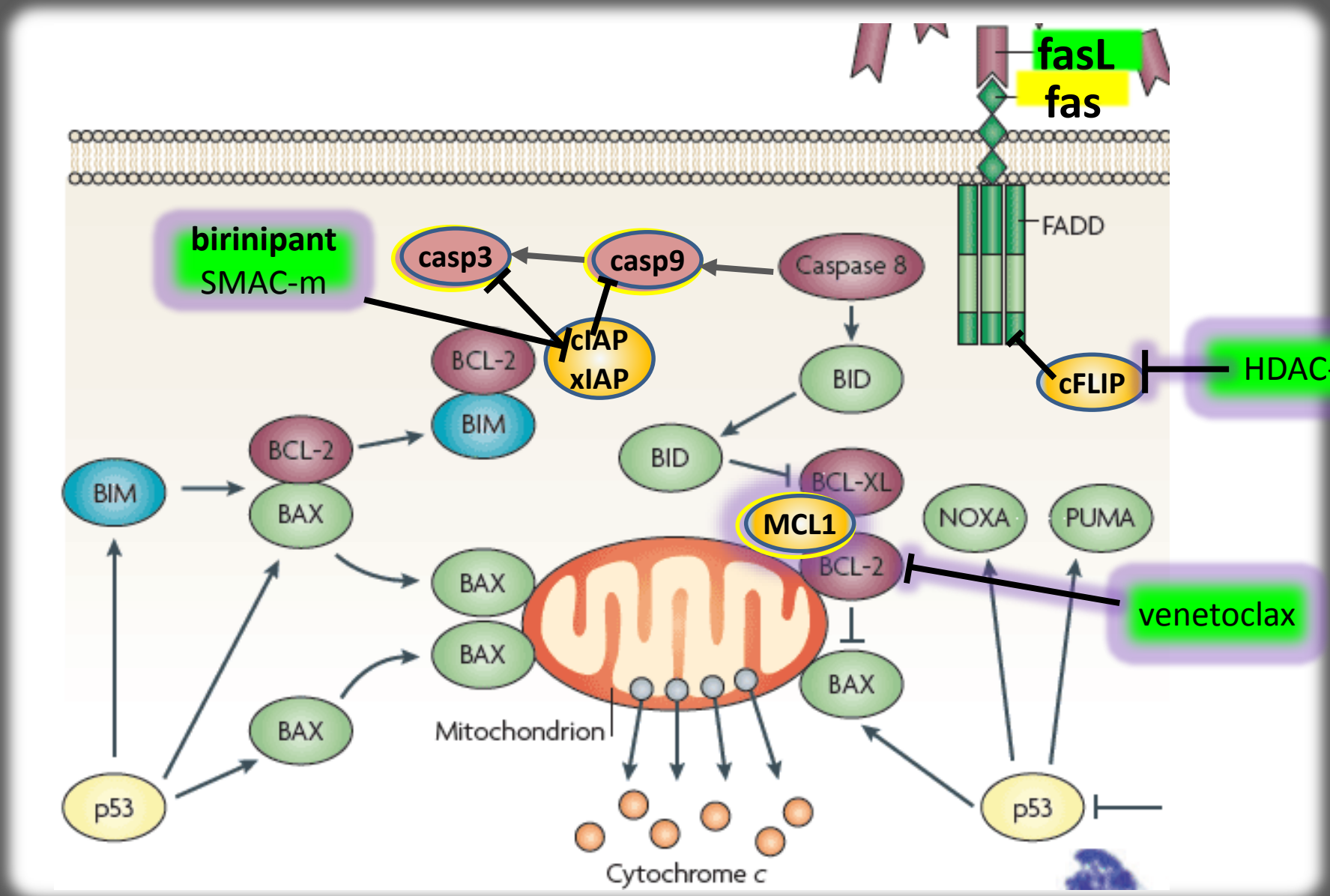
Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.
I. Braunschweig, O.O. Oluwole, T. Sidd
J.W. Friedberg, I.W. Flinn, A. Goy, B.T.
P. McSweeney, J. Munoz, I. Avivi, J.E. Cast
K.V. Komanduri, R. Levy, E.D. Jacobsen,
L. Navale, Y. Jiang, J. Aycock, M. Elias,

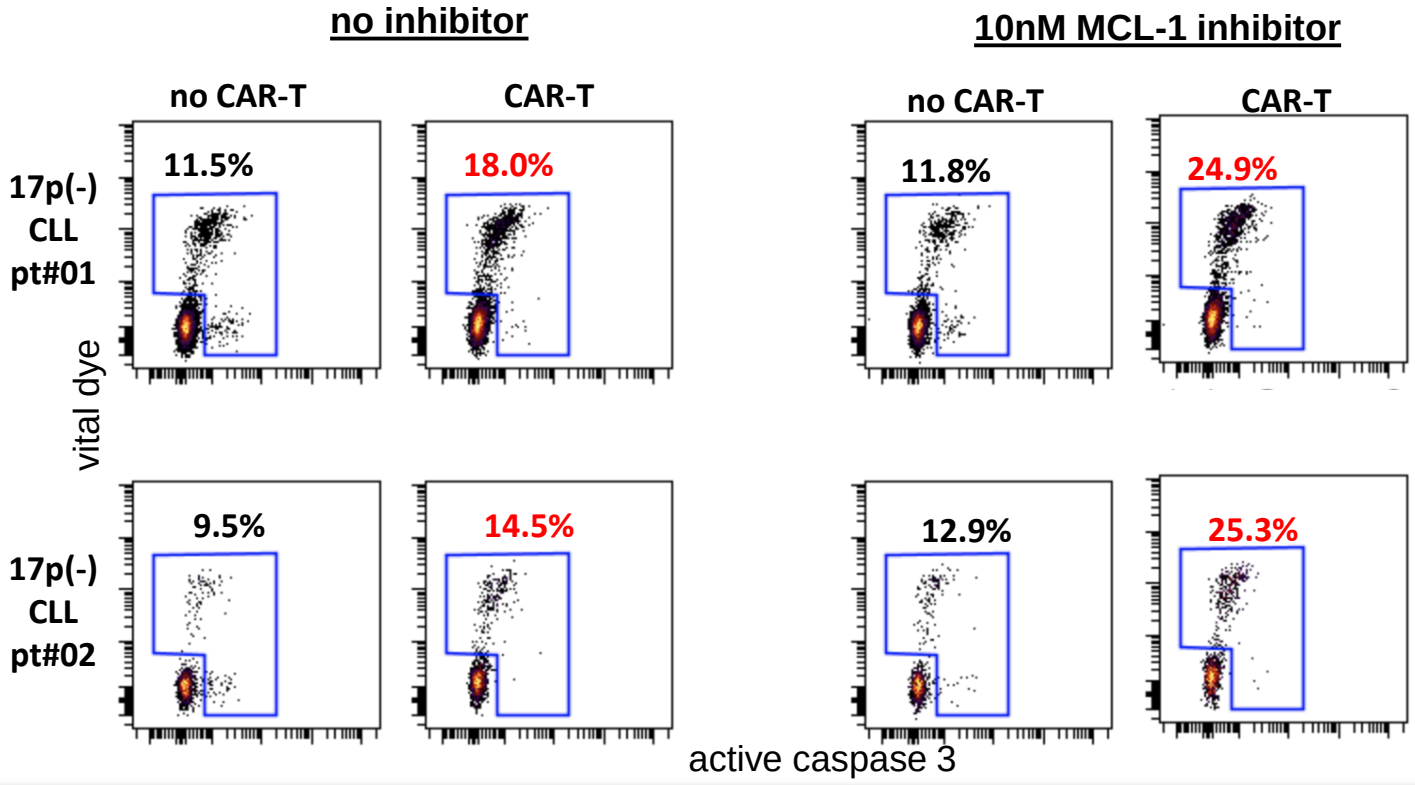
disease (response rate, 88%) a
who had a history of autologou
plantation (response rate, 76
rates did not appear to be influ
covariates, such as the prevale
of CD19 expression, or by pr
tics, such as the ratio of CD4

Neelapu. NEJM. 2017;377:2531

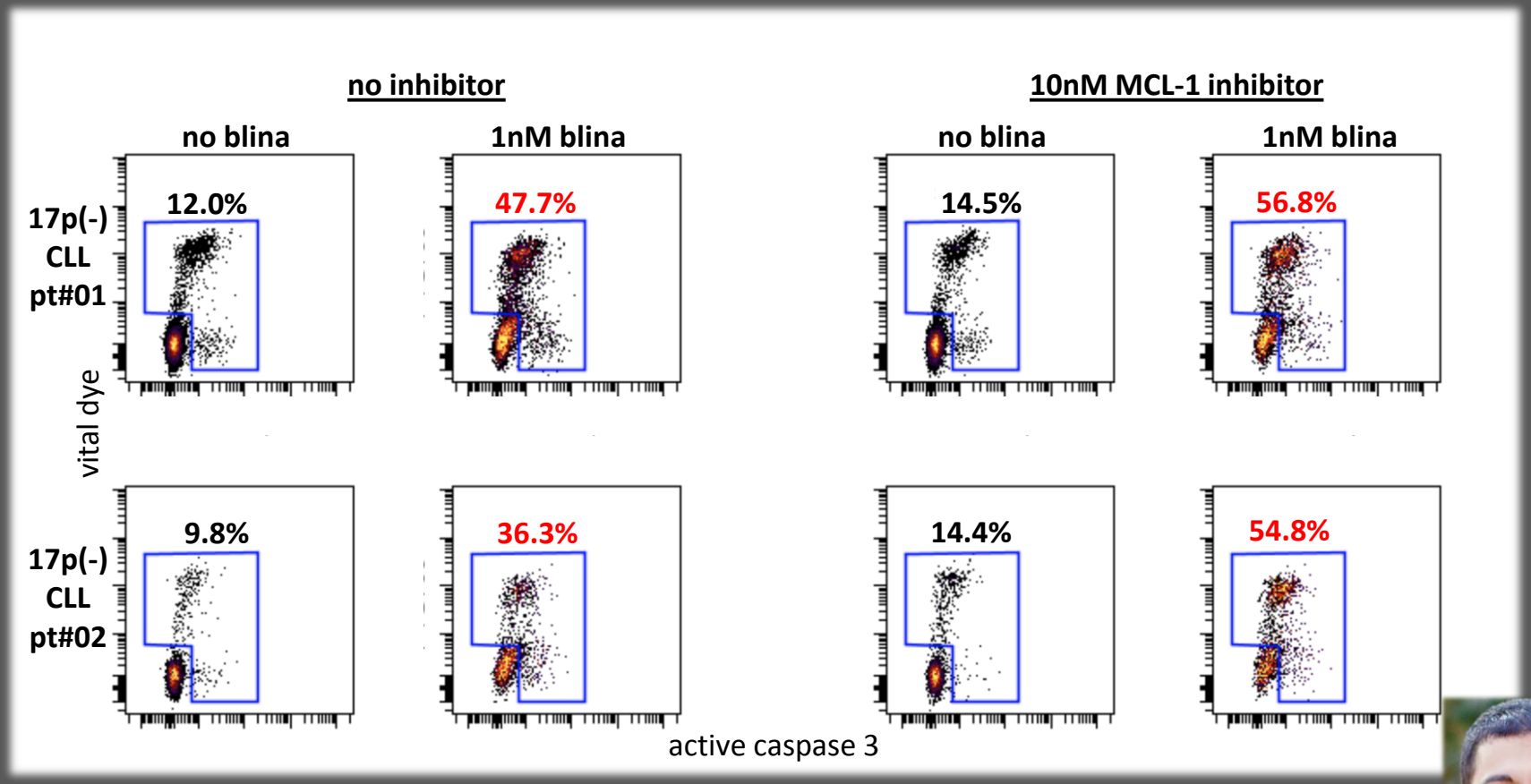
On-target & bystander fas-killing is improve-able?



Improving fas-killing
Human CAR-T killing 17p(-) CLL



Improving fas-killing
Bi-specific mAb killing 17p(-) CLL



Thanks to:

Lab Members
Linda Hammerich
Netonia Marhsall
Ranjan Upadhyay
Mark Aleynick
Tom Marron
Judit Arvelund
Jon Boiarsky

Collaborators
Miriam Merad
Nina Bhardwaj
Brian Brown
Alessia Baccarini

Immune Core
Adeeb Rahman

Study Patients on:
NCT00185965
NCT01976585
NCT00880581

Funding
Damon Runyon Cancer Foundation
Tisch Cancer Institute
NIH/NCI Howard Temin R00
Kite Pharma
Genentech
Celldex Therapeutics
Merck & Co Inc

icahn.mssm.edu/research/tisch/research/immunology