INTEGRATION OF IMMUNOTHERAPY INTO TREATMENT FOR HEMATOLOGICAL MALIGNANCIES

Friday, November 30, 2018

MEDICAL EDUCATION FOR BETTER OUTCOMES

Postgraduate Institute for Medicine

Jointly provided by The Leukemia & Lymphoma Society, RMEI Medical Education, LLC, and Postgraduate Institute for Medicine.

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IMMUNOTHERAPY INTRODUCTION

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Disclosures

Helen E. Heslop, MD, DSc (Hon), has affiliations with Cytosen, Gilead, Novartis *(Consulting Fees)*; Cell Medica, Tessa Therapeutics *(Contracted Research)*; Marker Therapeutics, Viracyte *(Ownership Interest).*

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Immunotherapy for Hematologic Malignancies

- Manipulation of the immune system to treat or prevent disease
  - Innate immunity
    - Immediate defense
    - Alerts and guides adaptive immunity
  - Adaptive immunity
    - Specific
    - Expands
    - Memory

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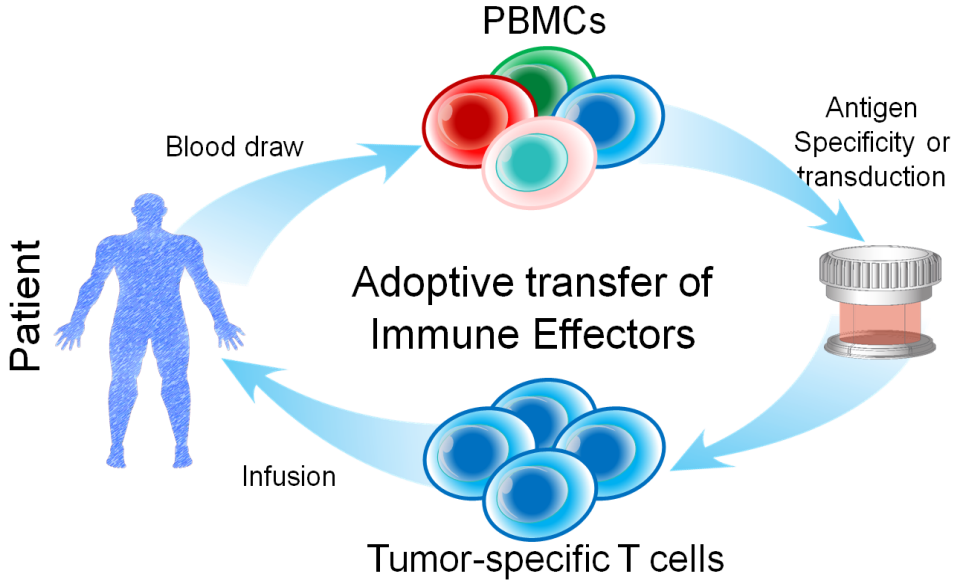
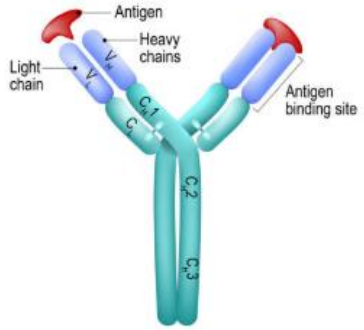
Immunotherapy for Hematologic Malignancies

- Enhance natural anti-tumor immunity
  - Cytokines
  - Antibodies
  - Vaccination
  - NK cells
  - T cells
- Enhance immunogenicity of tumors
  - Epigenetics
  - Tumor vaccines





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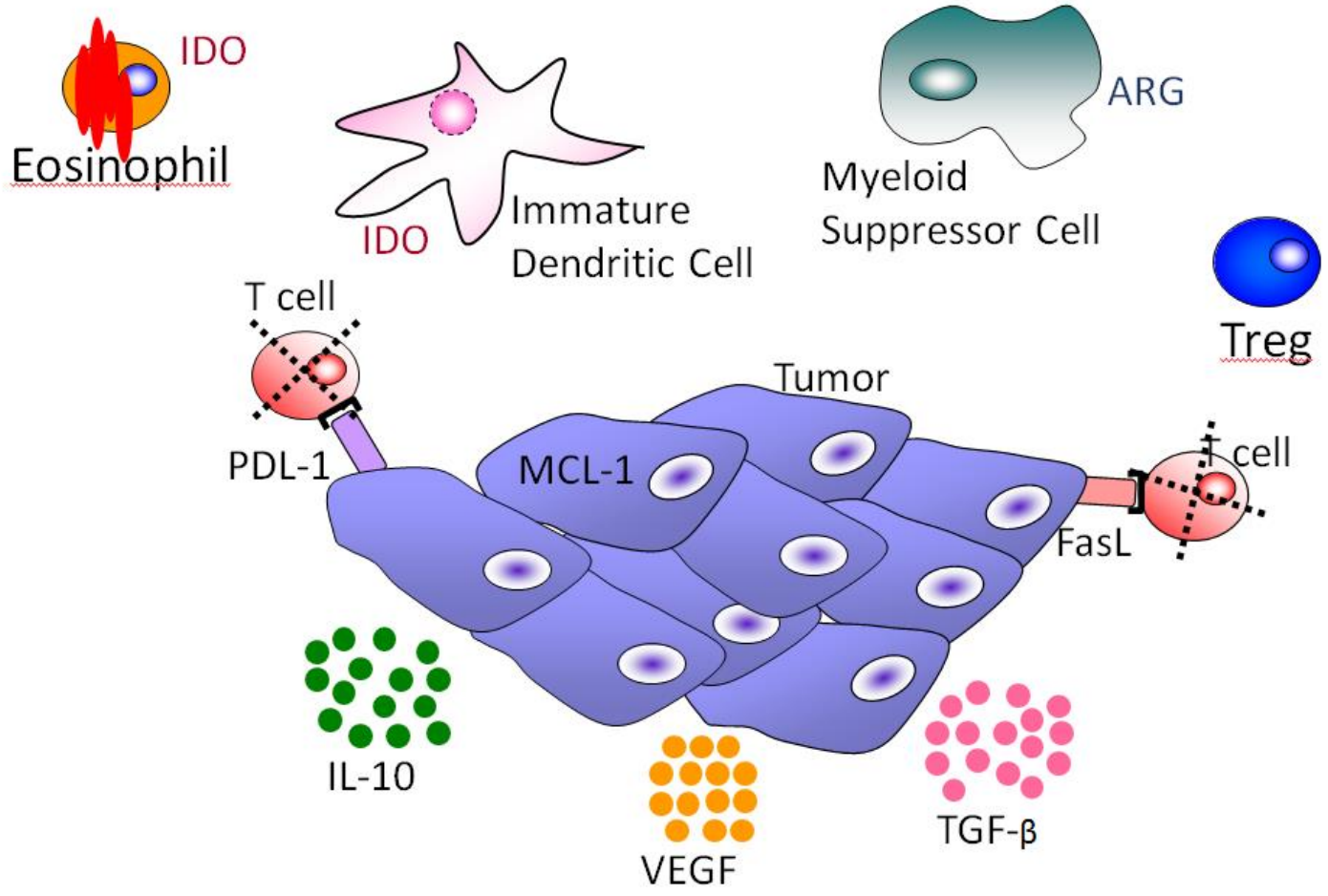
Tumors Actively Inhibit Immune Responses



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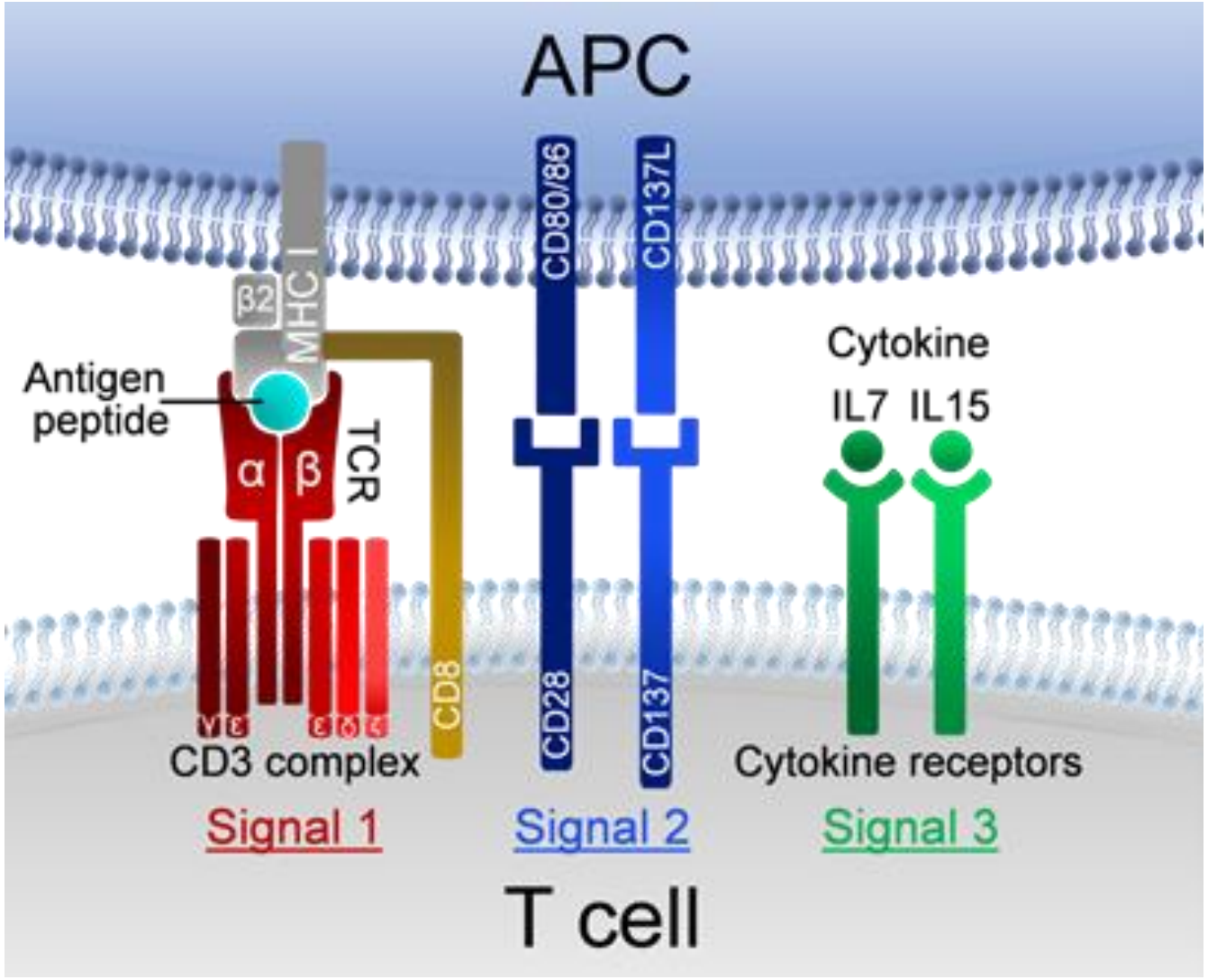
T Cell Activation



Complex process regulated by stimulatory and inhibitory signals

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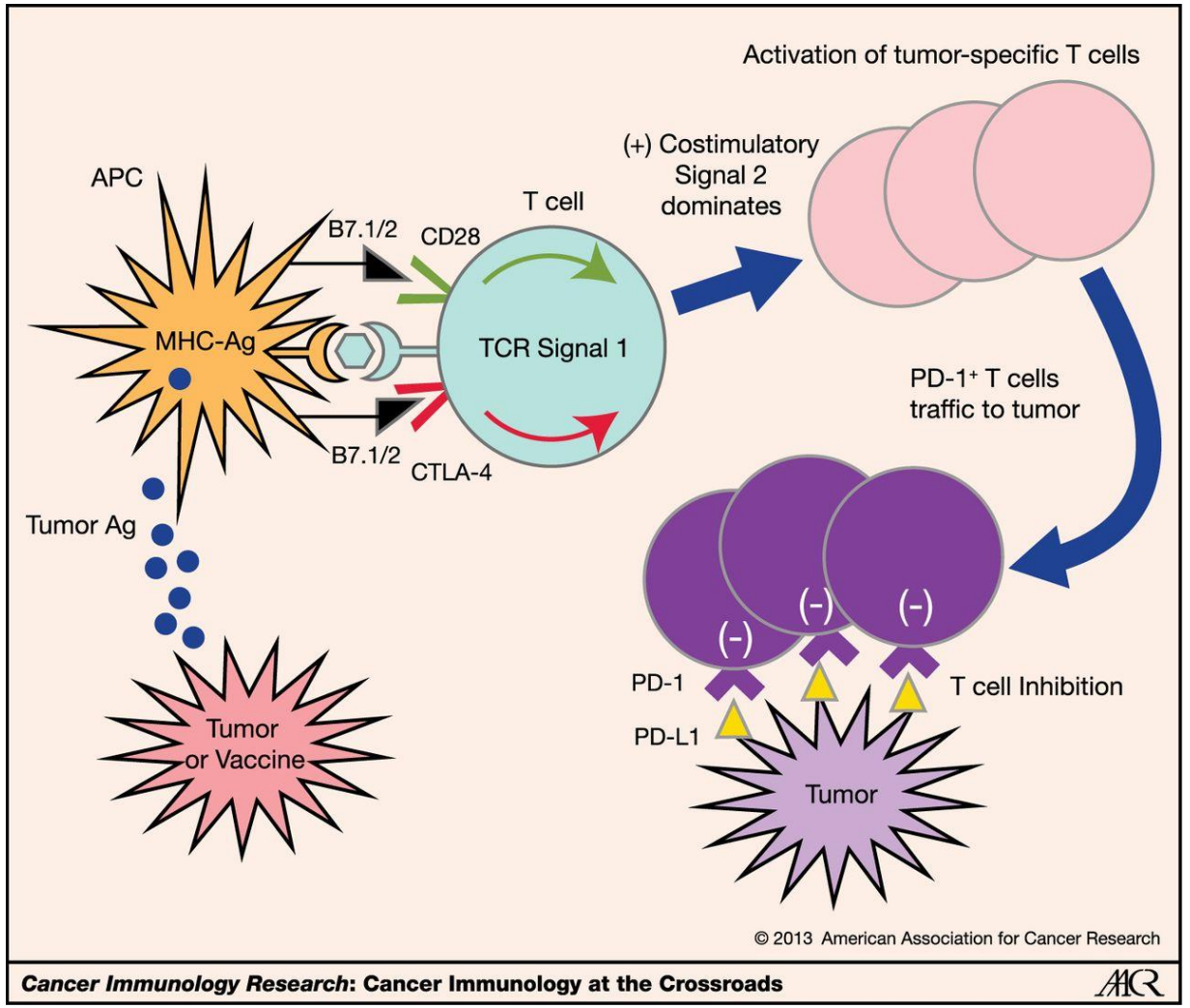
CTLA-4 and PD-1 as Regulators of Antitumor T-cell Responses

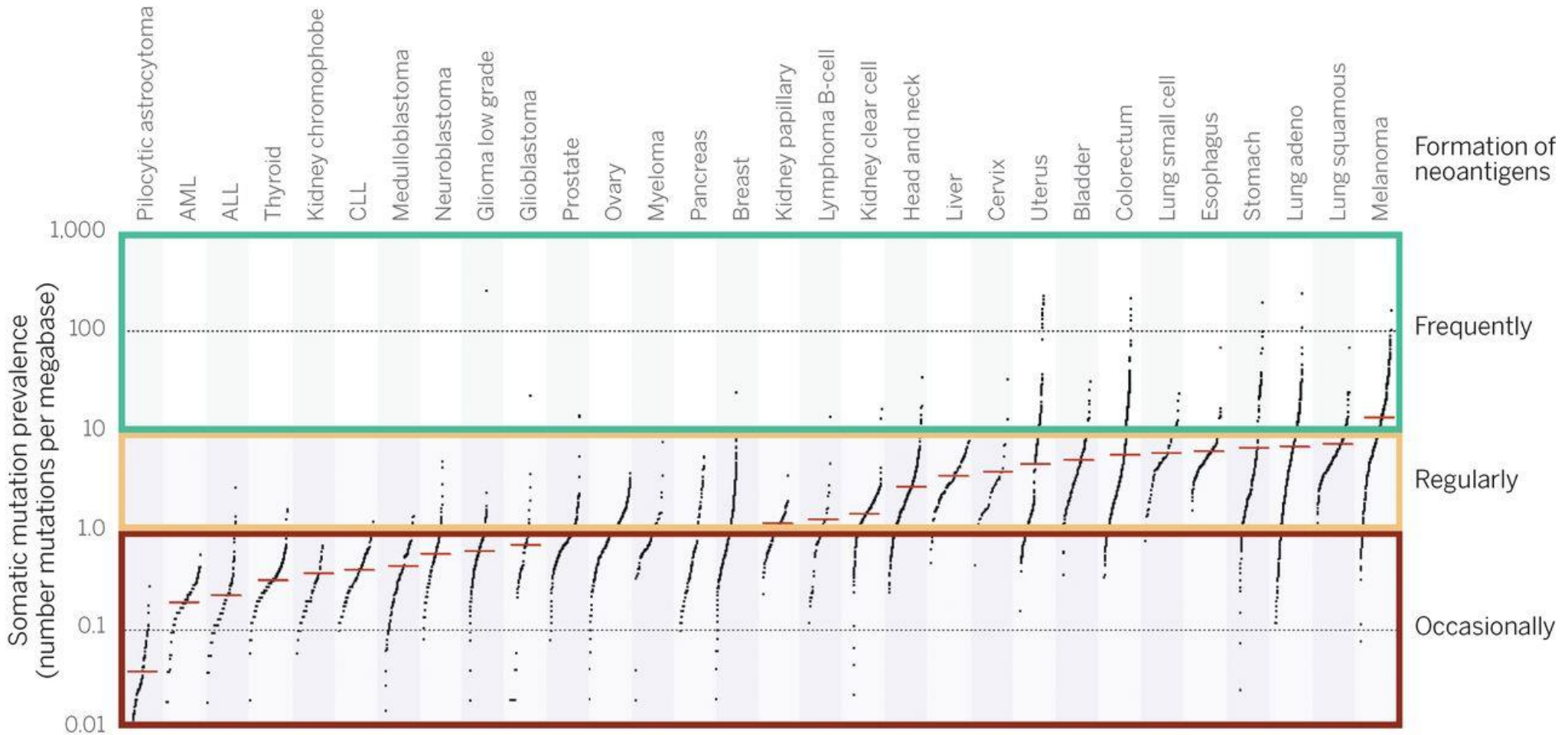


Cancer Immunology Research

AACR American Association for Cancer Research

Brahmer JR, et al. *Cancer Immunol Res.* 2013;1(2):85-91.

Neoantigen Repertoire in Human Cancer



Schumacher TN, et al. *Science*. 2015;348(6230):69-74.

Science
AAAS

Published by AAAS

Checkpoint Inhibition in Hodgkin Lymphoma

- Classical Hodgkin lymphoma has chromosome 9p24.1 alterations
  - Leads to overexpression of the PD-L1 and PD-L2 immune checkpoint ligands
- Suggests RS cells are genetically dependent on the PD-1 pathway to evade T-cell attacks

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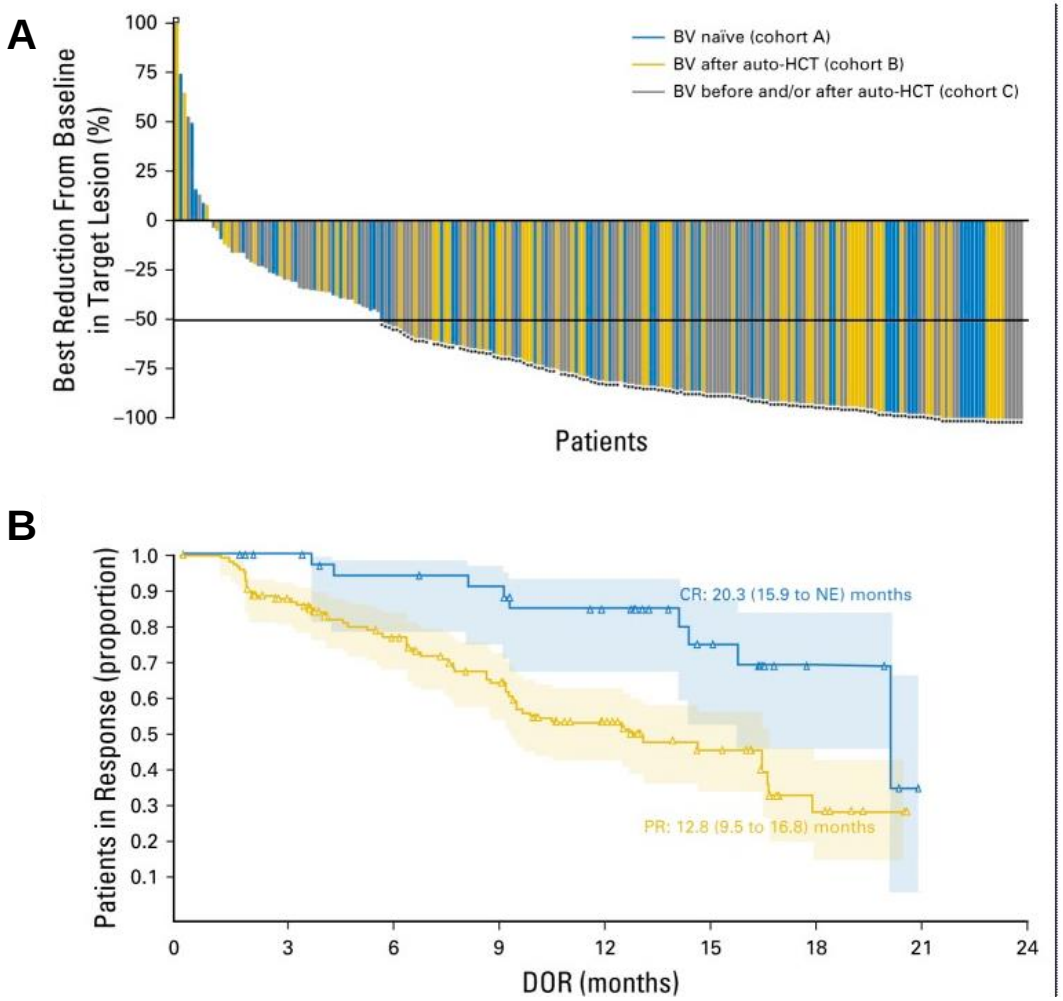
Checkpoint Inhibition in Hodgkin Lymphoma



- Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation
- Objective response rate was 69% overall
- Median duration of response was 16.6 months
- Median progression-free survival was 14.7 months

Armand P, et al. *J Clin Oncol.* 2018;36(14):1428-1439.

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Checkpoint Inhibition in Other Hematologic Malignancies

- NK-T and other lymphoma (Ron Levy)
- Myeloma (Yi Lin)
- Acute myeloid leukemia (Hagop Kantarjian)

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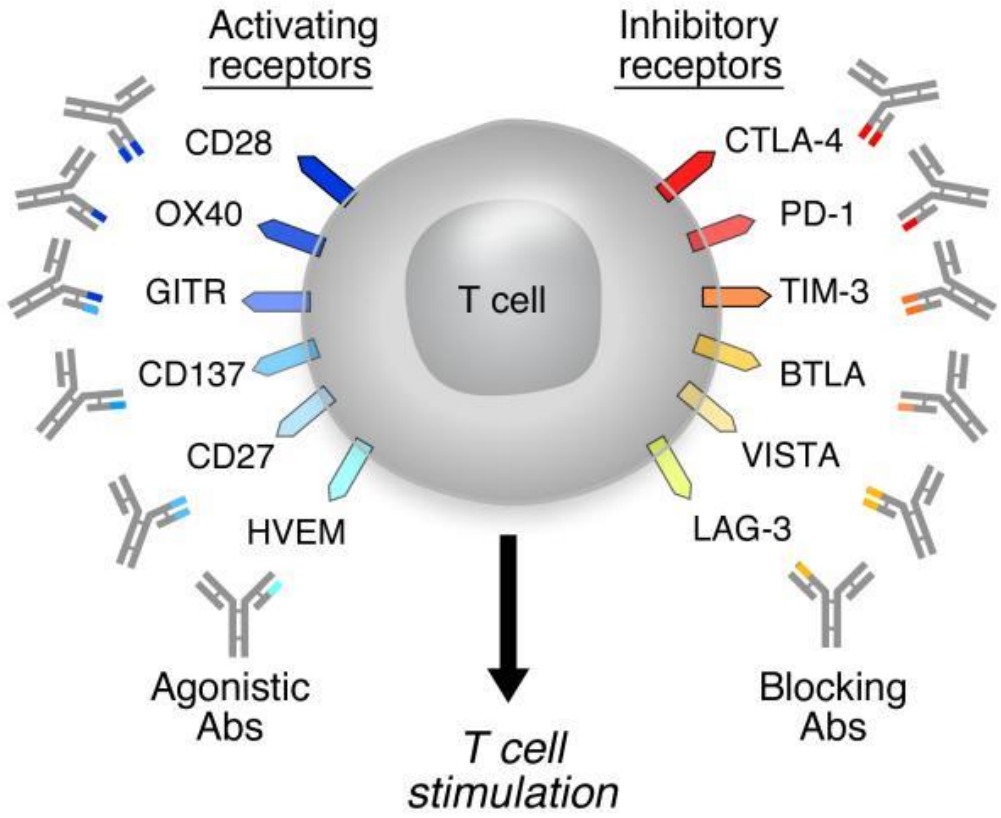
Future Directions



- Blocking other checkpoints
- Combinations
  - Radiotherapy
  - Other immune modulators
  - Cellular immunotherapies

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Benefits of T Cells

- Specific receptors give high targeting ability
- Recognize internal antigens (if processed)
- Good bio-distribution
  - Traffic through multiple tissue planes
- Multiple effector mechanisms
- Self amplifying

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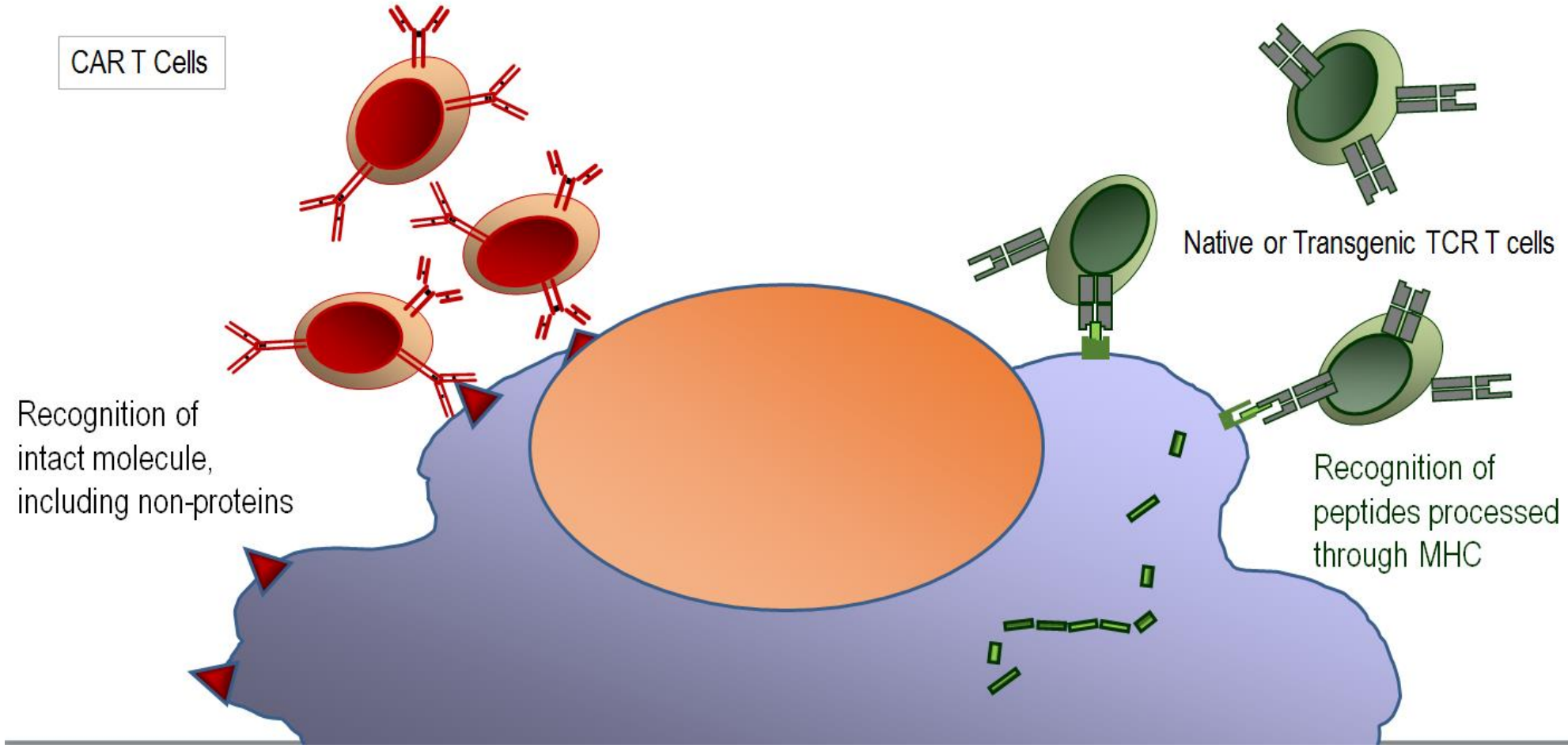
Chimeric versus Native Receptors



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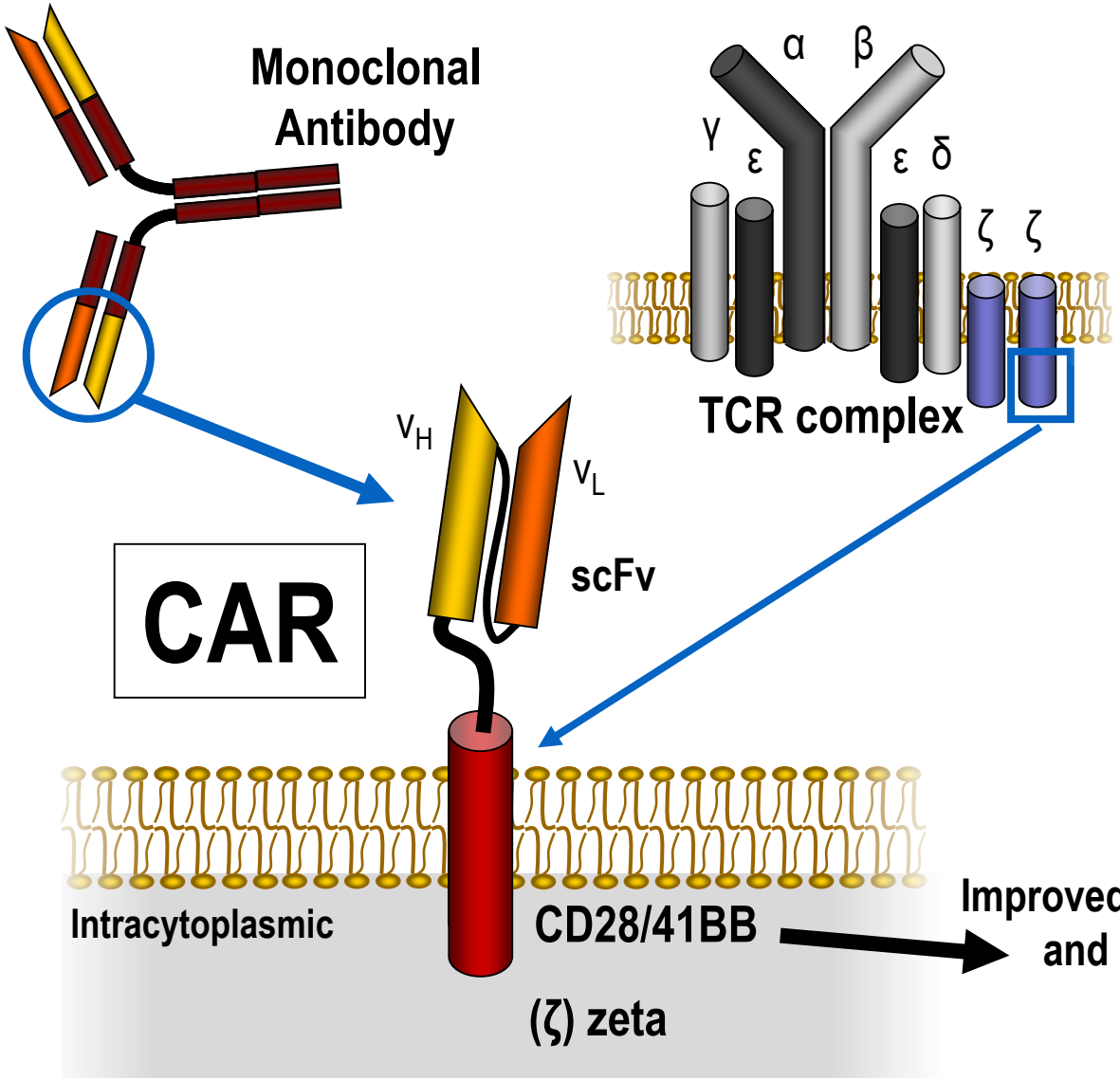
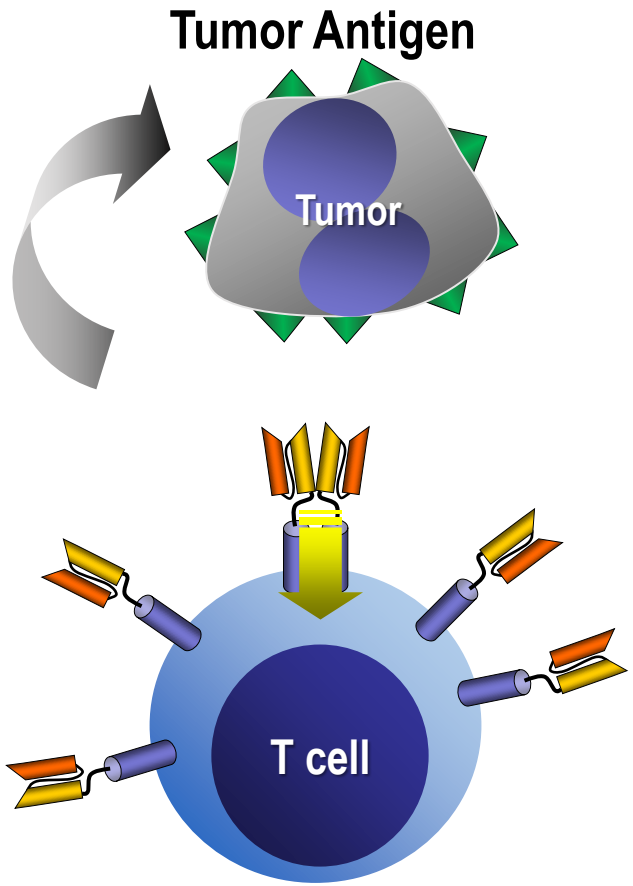
Chimeric Antigen Receptors





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Ramos CA, et al. *Expert Opin Biol Ther*. 2011;11(7):855-873; Gross G, et al. *Proc Natl Acad Sci USA*. 1989;86(24)0024-10028.

CAR-T Cells in Hematologic Malignancies

- Encouraging response rates with CD19 CARs in ALL and NHL in studies by many groups
- Approvals in 2017/2018
  - Tisagenlecleucel (Kymriah) for relapsed/refractory pediatric ALL and later for DLBCL
  - Axicabtagene ciloleucel (Yescarta) for relapsed DLBCL
- Late phase trials with BCMA

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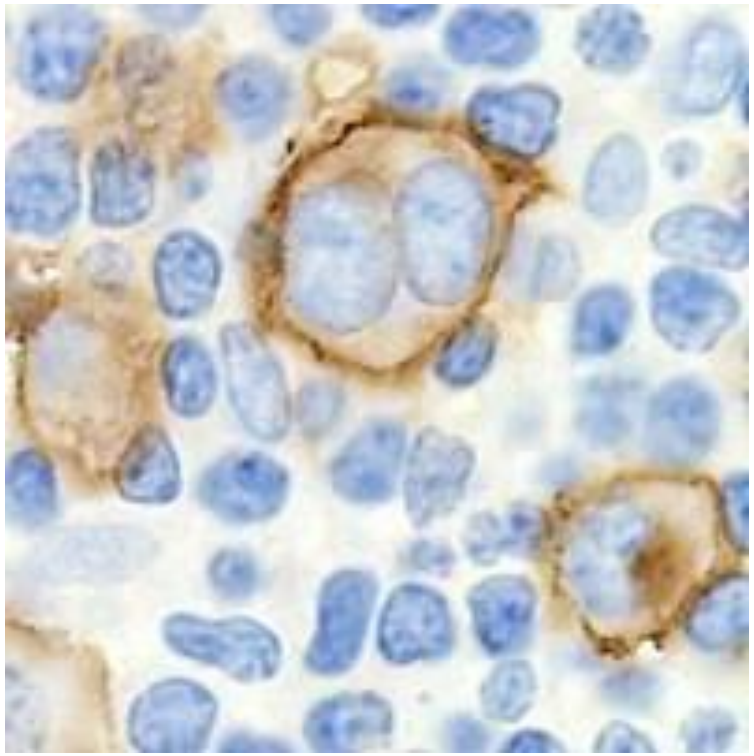
CD30 as a Target

- Expressed by all HRS cells
- Antibody-based immunotherapy
  - *Brentuximab vedotin*



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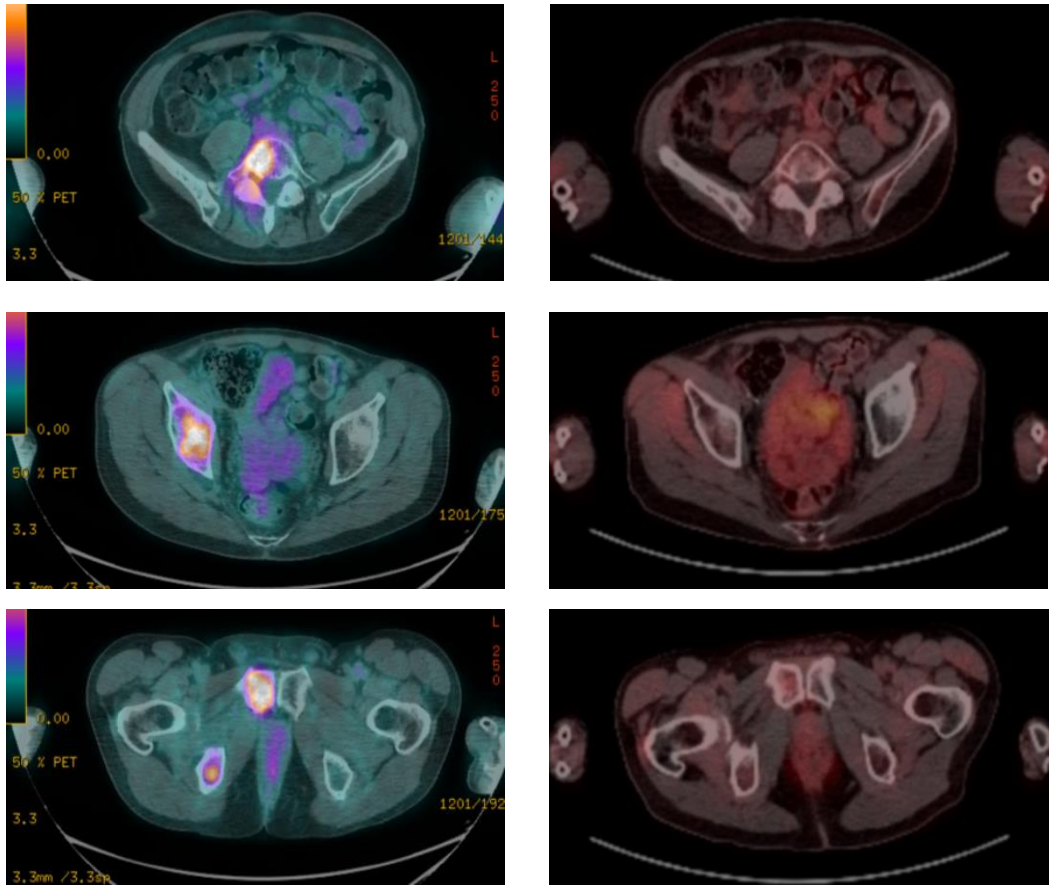
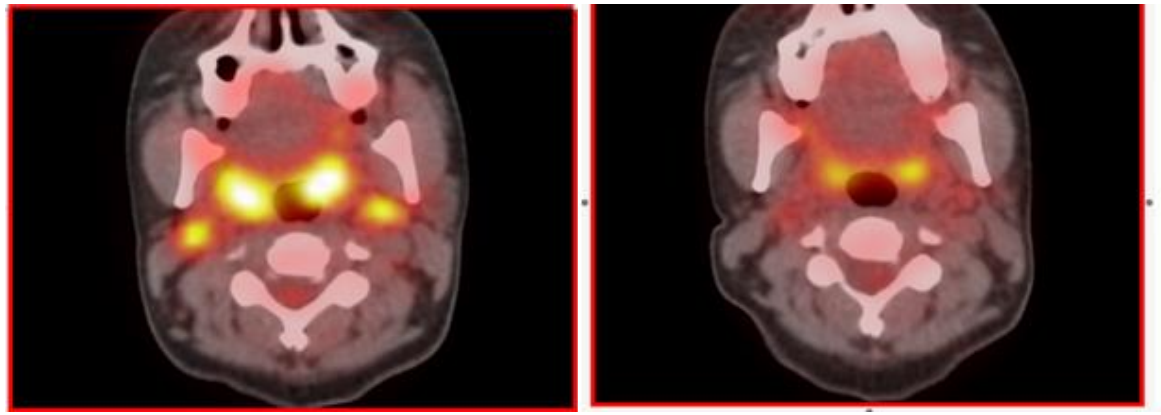
CRs After CD30 CAR-T Cells After Flu/CY





>70% response rates in trials at Baylor and UNC

Ramos CA, et al. ASH 2018, Grover et al ASH 2018.

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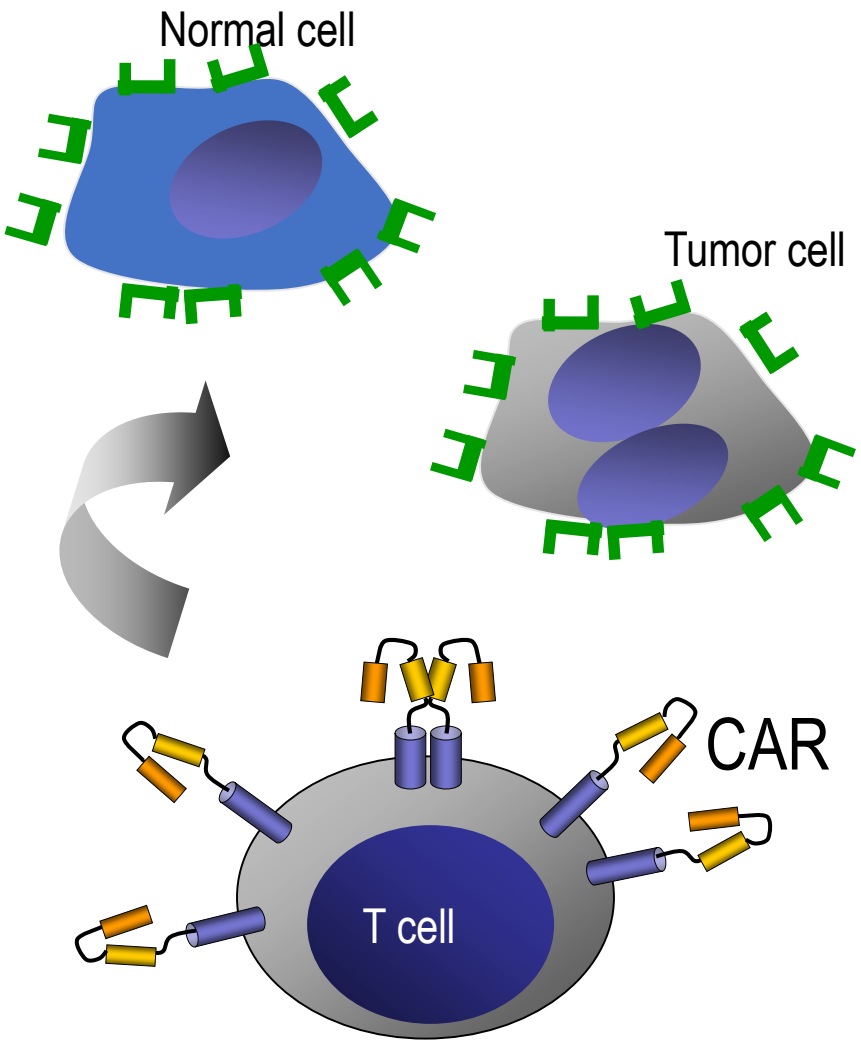
Extending CAR Strategies to T and Myeloid Cells



Myeloid Cells
CD33
CLL-1
CD123
CLEC12A

T Cells
CD5
CD7
CD4

All targets also expressed on normal myeloid or T cells

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Potential Mitigation Strategies

- CAR T cells as a bridge to transplant
- Incorporate suicide genes or activation switches
- Target T cell receptor β-chain constant region
  - Mutually exclusive expression of T cell receptor β-chain constant domains 1 and 2 (TRBC1 and TRBC2)
  - Targeting variant in malignant clone will spare T cells expressing the other one

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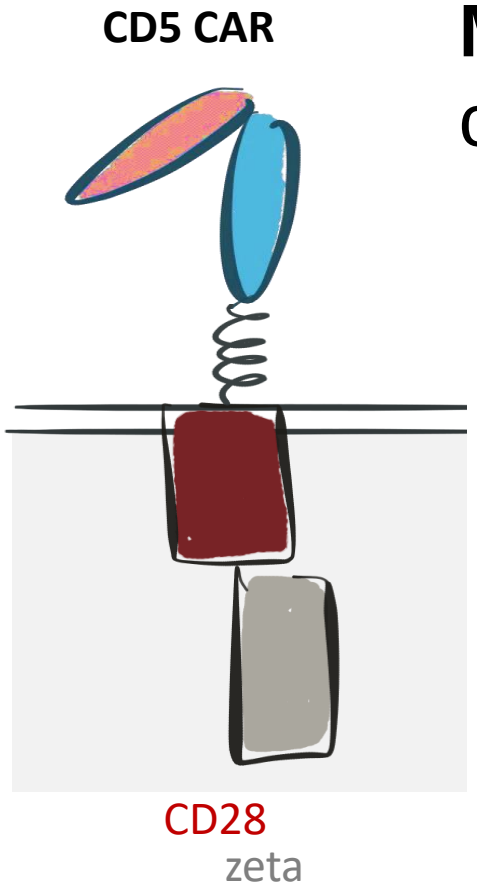
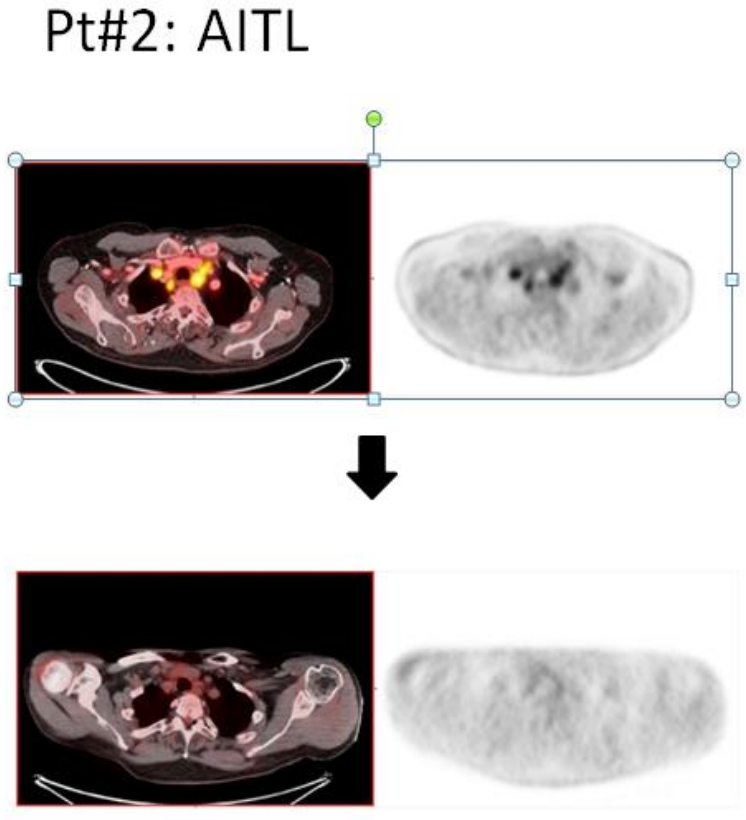
Maciocia PM, et al. *Nat Med*. 2017;23(12):1416-1423.

Clinical Study of CD5 CAR T Cells



MAGENTA: Clinical trial of CD28.zeta CD5 CAR T cells in patients with r/r T-ALL or T-NHL (NCT03081910).



- Bridge to allo-transplant for adult and pediatric patients with CD5+ disease
- Single infusion of CAR T cells after Cy/Flu lymphodepletion

Mamonkin M, et al. *Blood.* 2015;126(8):983-992.

Rayne Rouce and LaQuisa Hill

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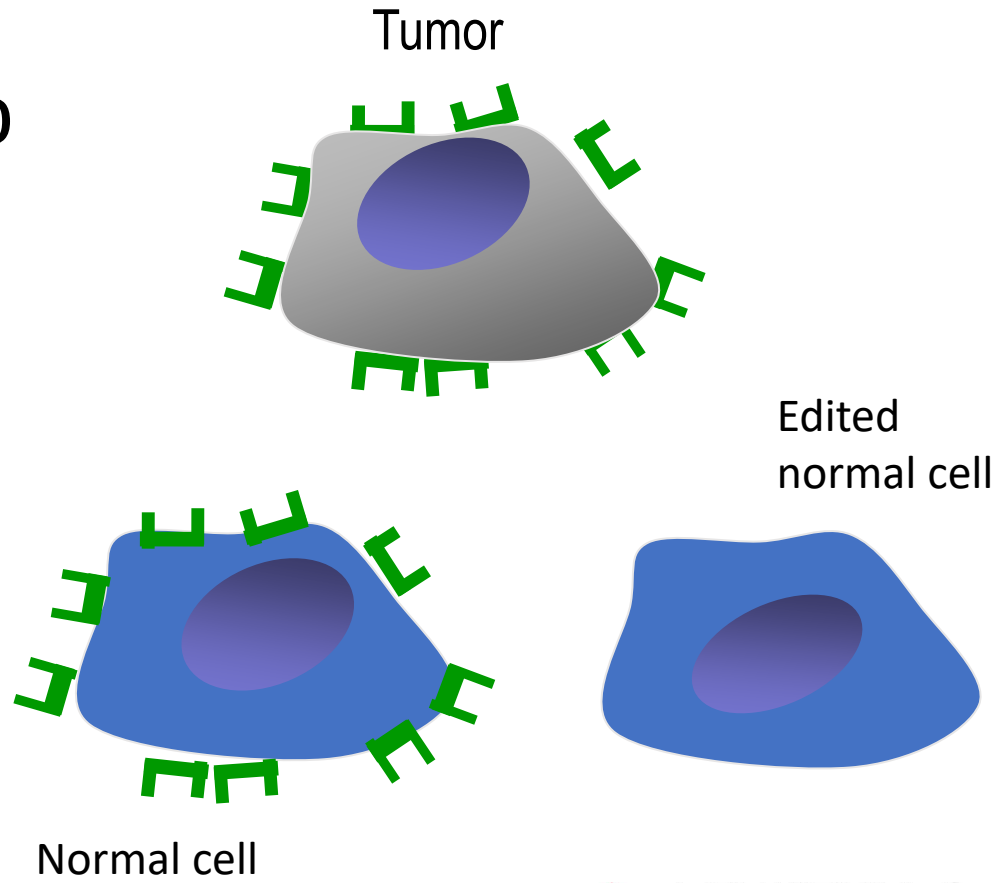
Potential Mitigation Strategies

- Render normal cells resistant to CAR by gene editing with CRISPR/Cas9
  - CD7[1]
  - CD33[2]



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1. Gomes-Silva D, et al. *Blood.* 2017;130(3):285-296.
2. Kim MY, et al. *Cell.* 173(6):1439-1453.

CAR T Cells: Summary

- 2nd generation CD19 CARTs can have remarkable activity against B-cell malignancies (Carl June)
- CARs can successfully travel beyond CD19
  - BCMA in myeloma (Yi Lin)
  - CD30 in Hodgkin lymphoma (Ramos et al, Grover et al ASH 2018)
- Extension to myeloid and T cell disease requires strategy to mitigate effects on normal progenitors

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T Cells Transduced with TCRs

- Autologous T cells expressing an affinity-enhanced TCR recognizing a peptide shared by NY-ESO-1 and LAGE-1 infused to 20 patients post autograft for myeloma
- Expansion and persistence
- Median progression-free survival of 19.1 months
- Disease progression was associated with loss of T cell persistence or antigen escape

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Rapoport AP, et al. *Nature Med.* 2015;21(8):914-921.

Requirements for T Cell Targets

- Possess target antigens
  - Viral antigens, eg, EBV, CMV, HPV
  - Tumor-associated antigens, eg, survivin, PRAME
  - Neoantigens (Cathy Wu)

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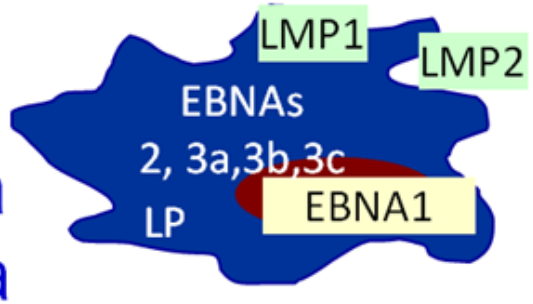
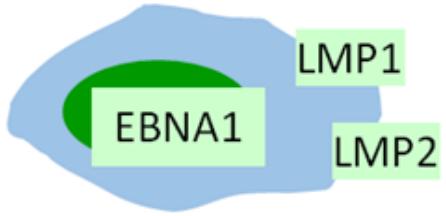
EBV-Associated Malignancies

Latent Malignancy	Latent Gene Expression	Immunogenicity
Type 3 Post transplant lymphoma HIV-associated lymphoma		
Type 2 Hodgkin's lymphoma NHL		
Type 1 Burkitt's lymphoma		

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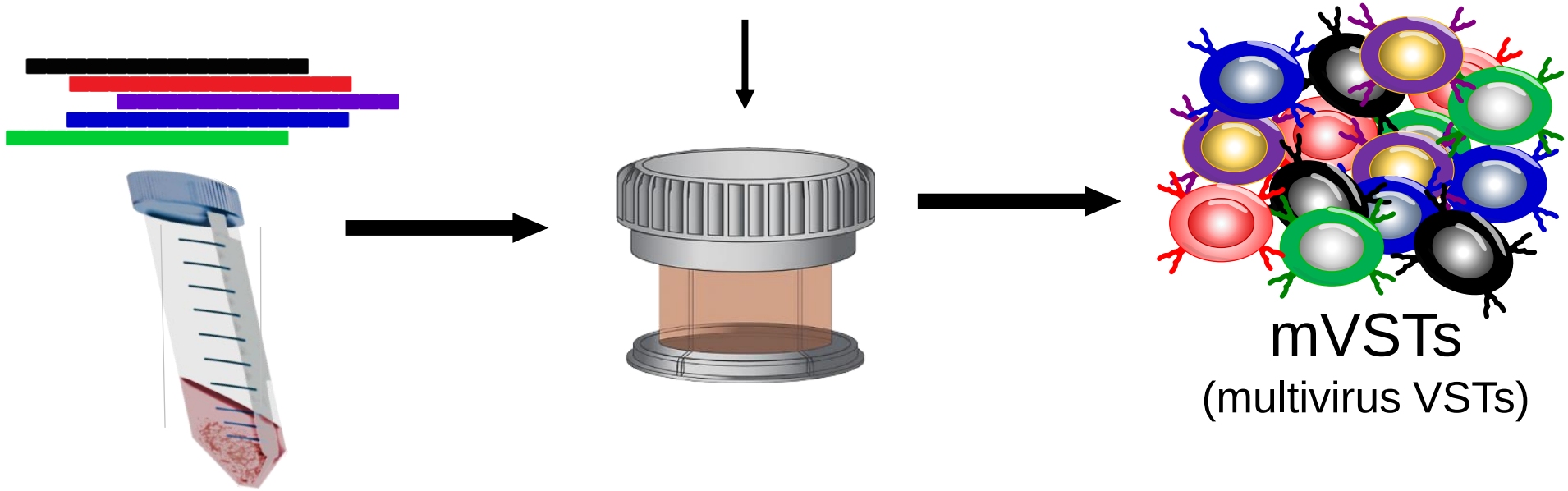
VST Manufacture

AdV – Hexon, Penton
EBV – EBNA1, LMP2, BZLF1
CMV – IE1, pp65
BKV – LT, VP1
HHV6 – U11, U14, U90

Ulrike Gerdemann
Ann Leen



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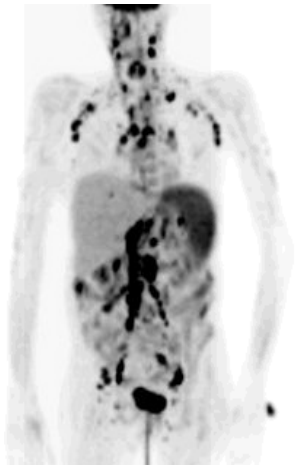
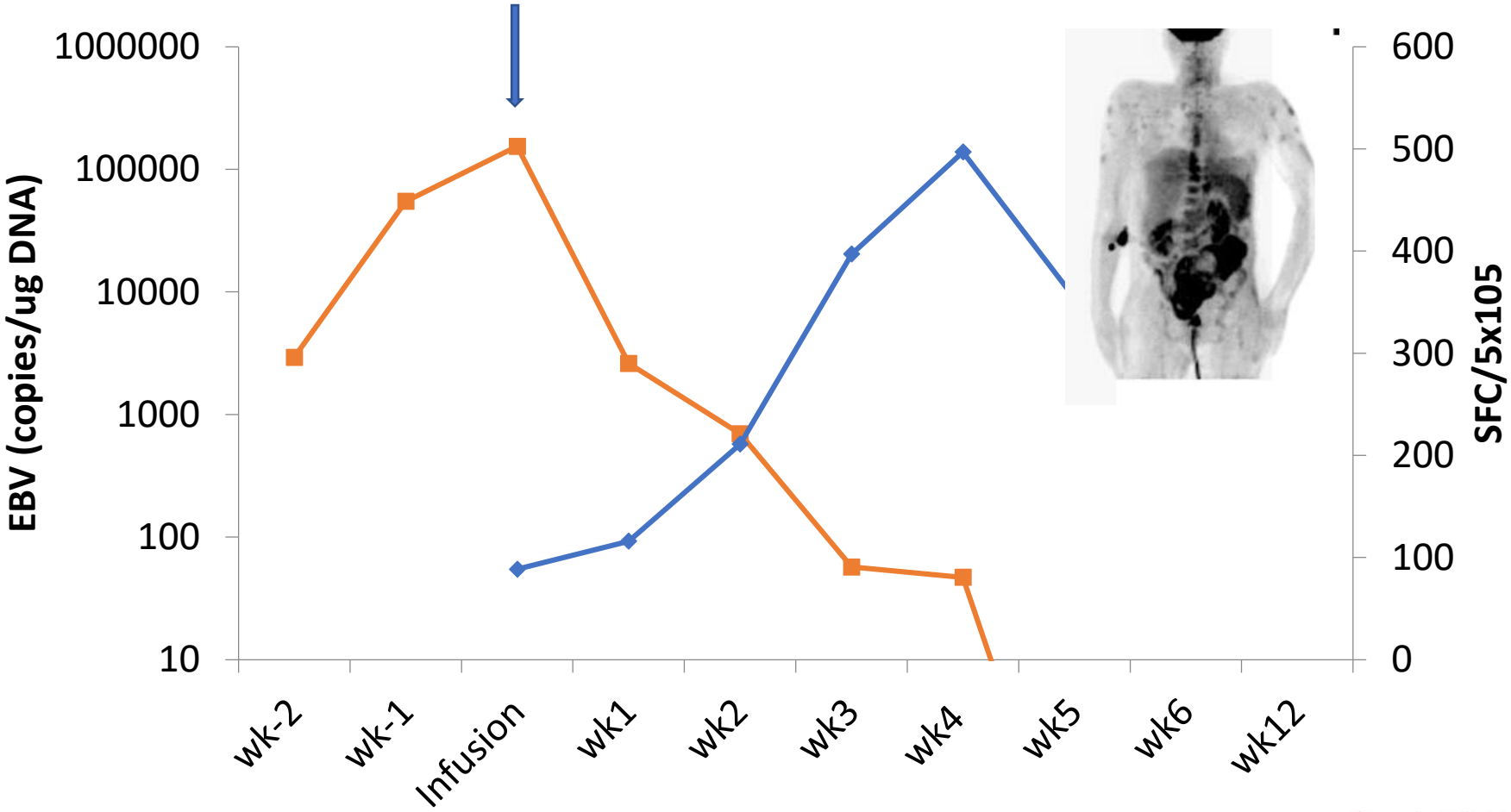
Activity in EBV-PTLD





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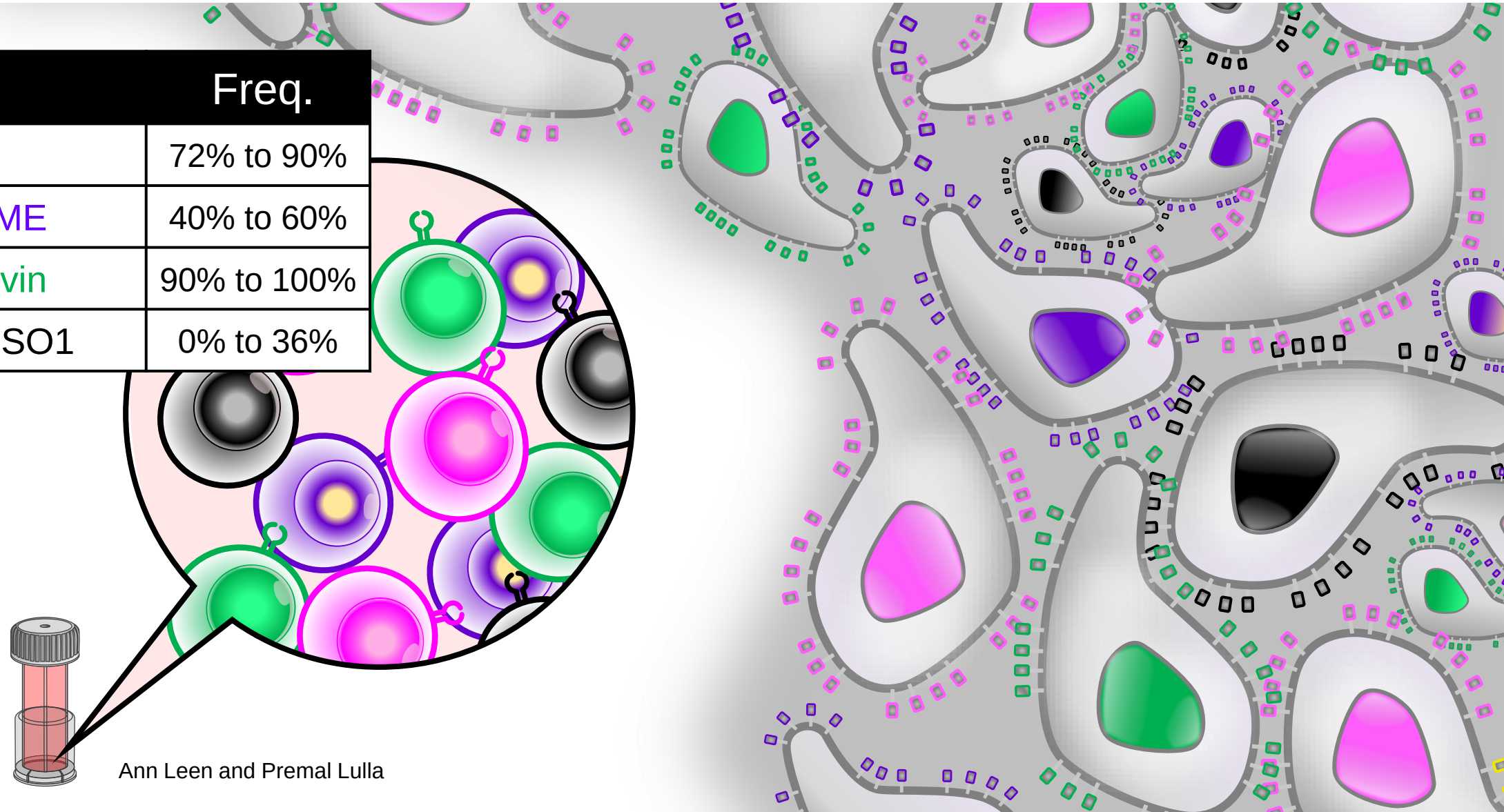
MultiTAA T Cell Therapy for AML

TAA	Freq.
WT1	72% to 90%
PRAME	40% to 60%
Survivin	90% to 100%
NY-ESO1	0% to 36%



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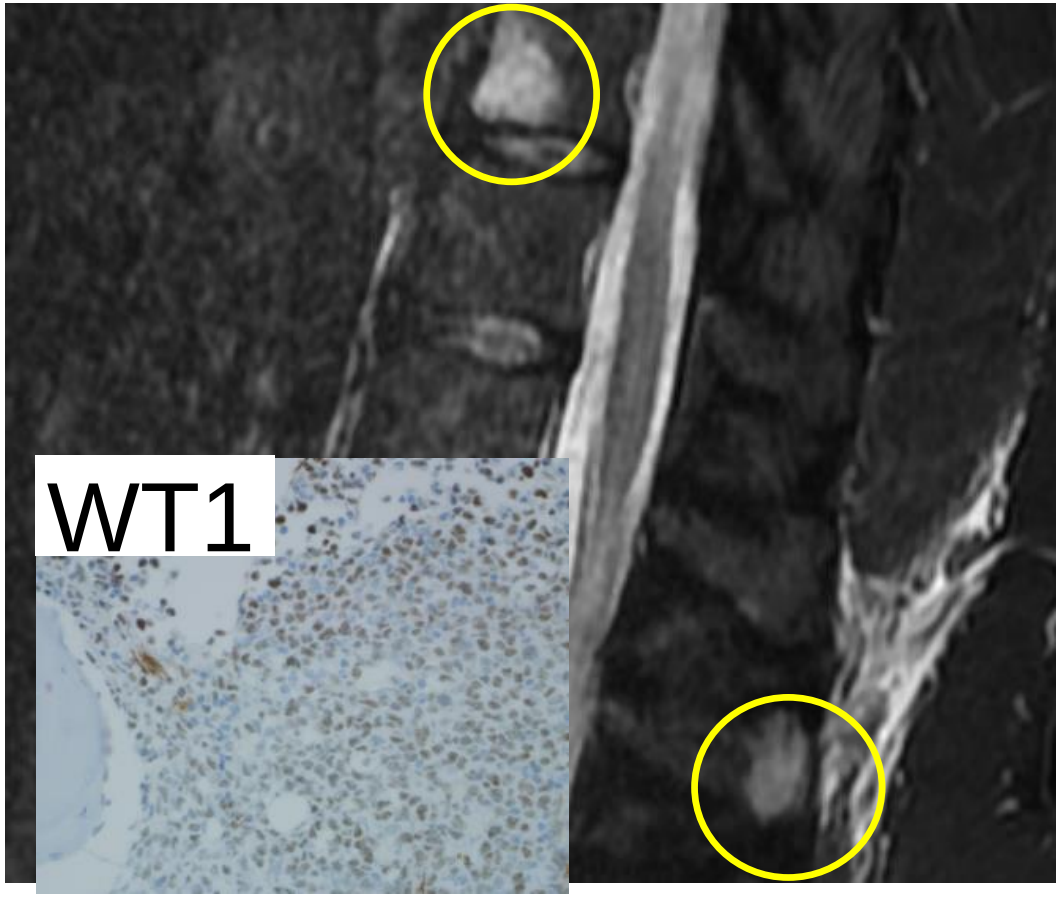
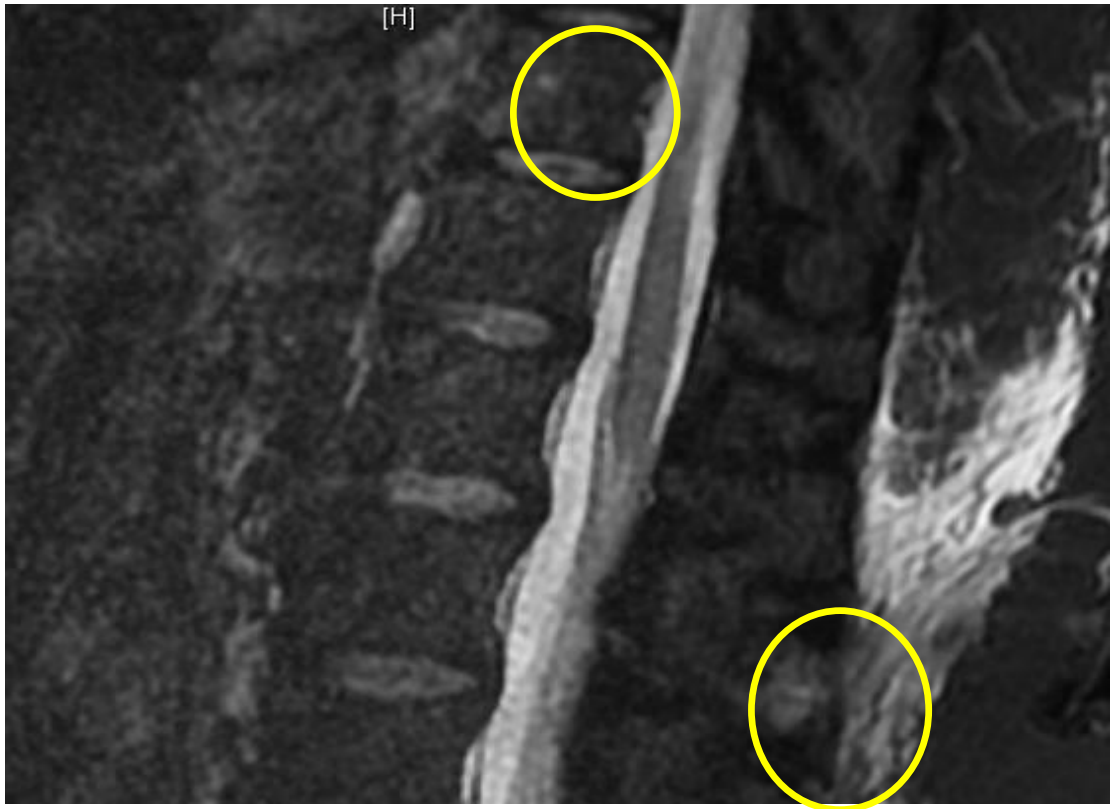
Relapse of AML

Disease Relapse



Resolution



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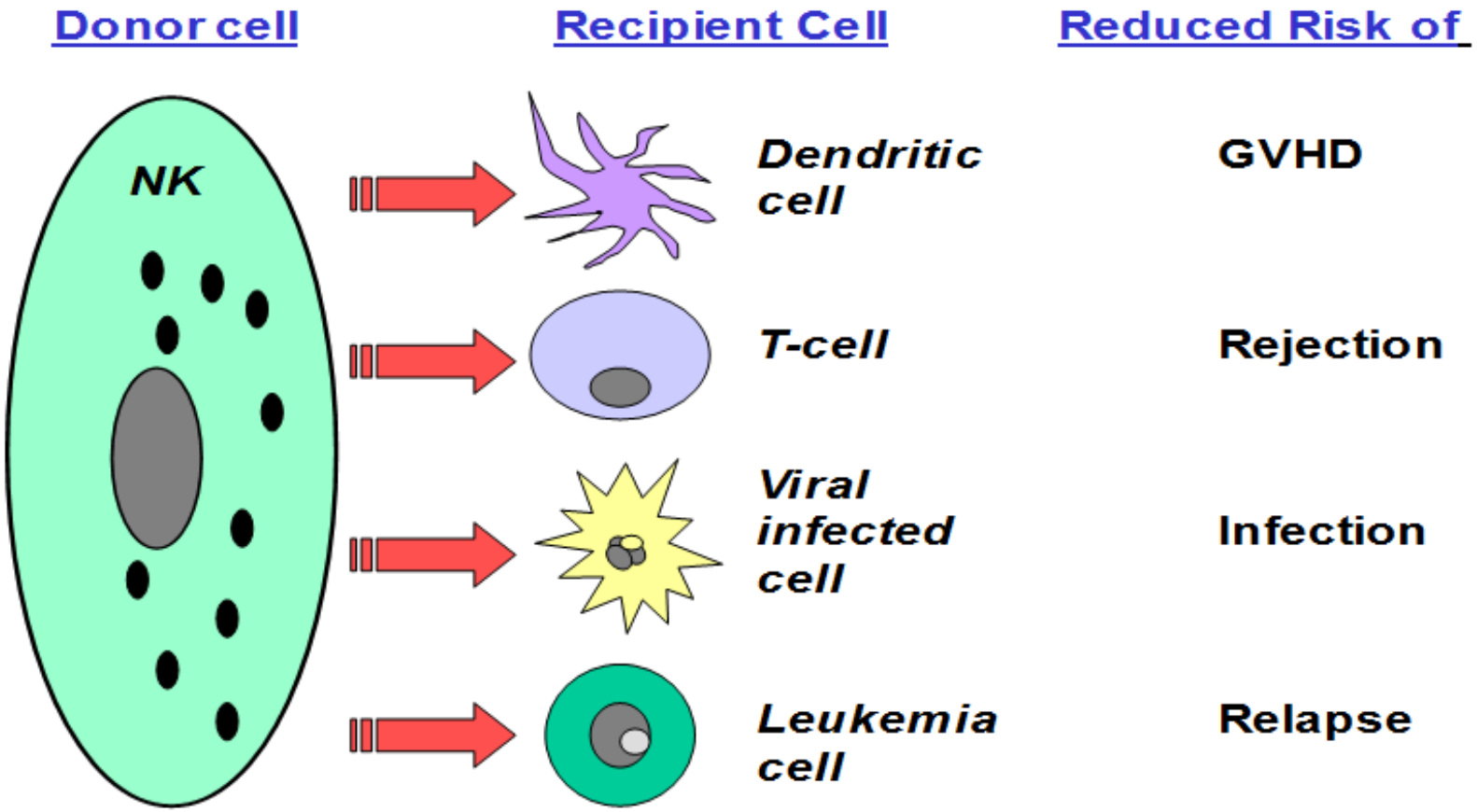
NK Cell Infusions



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How Can Immune Effector Therapies be More Broadly Available?

- “Off-the-shelf” products
- Immediately available
- Lower cost of goods

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Requirements for an "Off-the-Shelf" Product

- Not alloreactive
- Can be cryopreserved
- Candidates
  - Gene edited normal cells
  - Closely matched VSTs
  - NK cells
  - NK-T cells
  - γδ T cells

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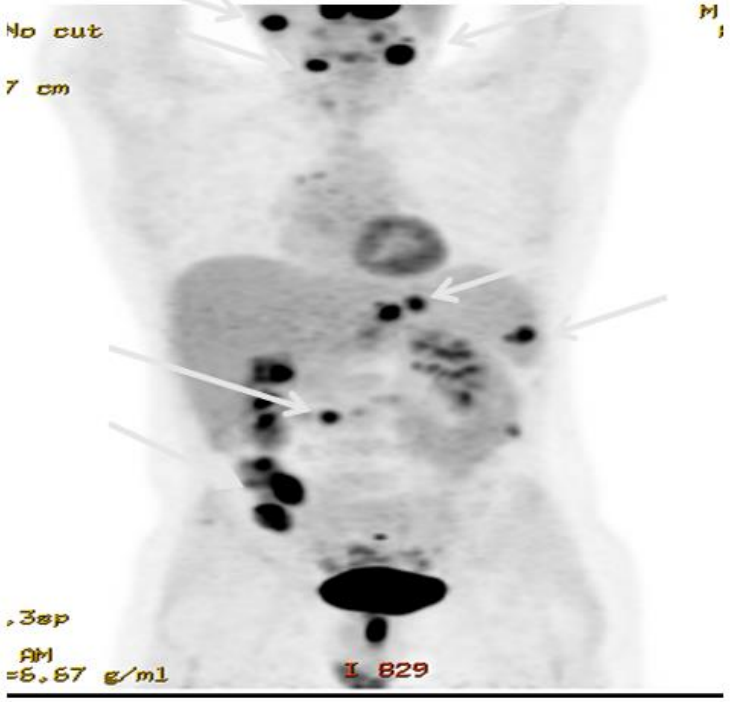
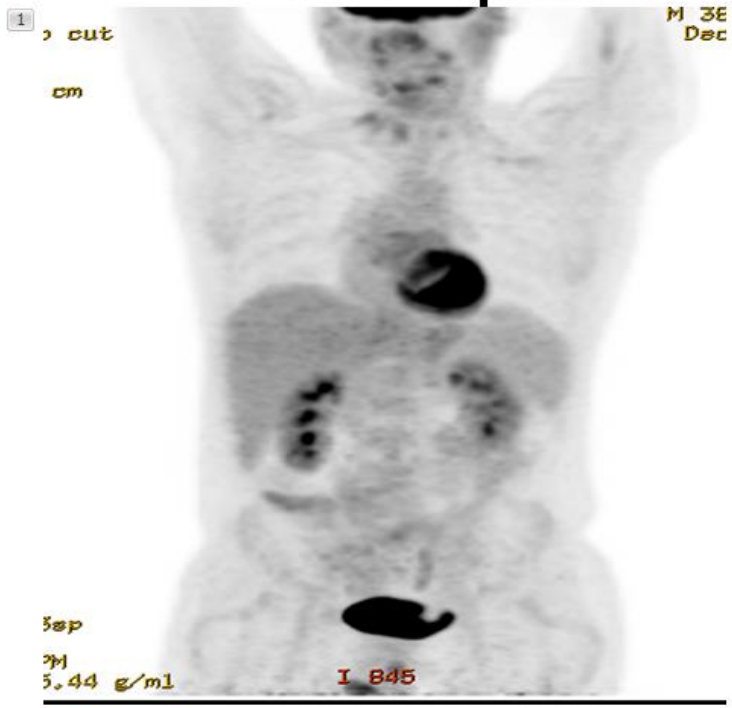
Clinical Responses: EBV

Pre VSTs



1 month post VSTs



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Future Directions

- Combination expanded ± transduced cells, and
  - Checkpoint inhibitors
  - Other immunomodulatory agents
  - Oncolytic viruses
- Genetic strategies to enhance function and overcome tumor evasion mechanisms
- Targeting multiple antigens

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