Immunotherapy on the Horizon

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UNIVERSITY of VIRGINIA HEALTH SYSTEM

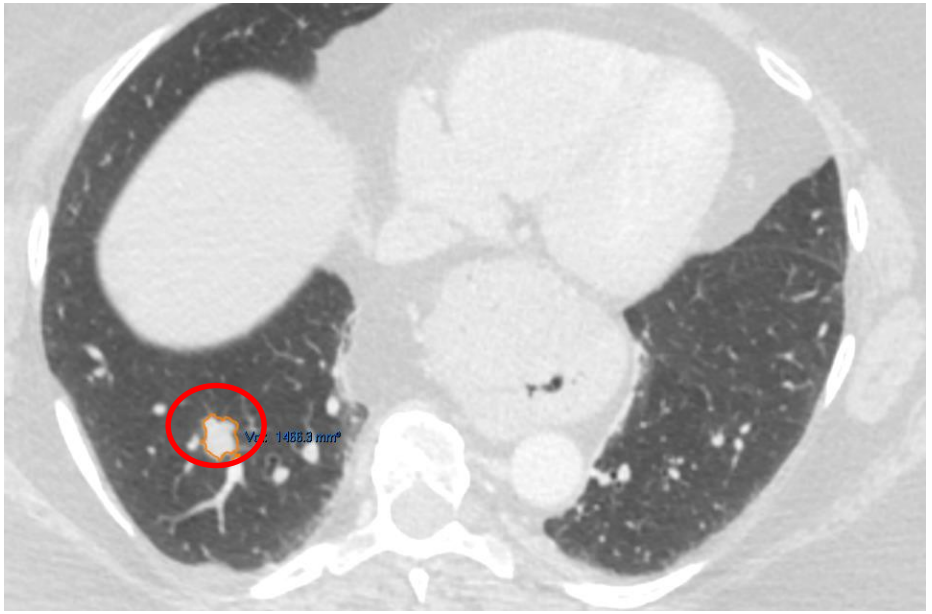
Disclosures

Institutional funding: Pfizer, Novartis, AbbVie, Newlink Genetics, BMS, Eli Lilly

I will be discussing non-FDA approved treatments in this talk

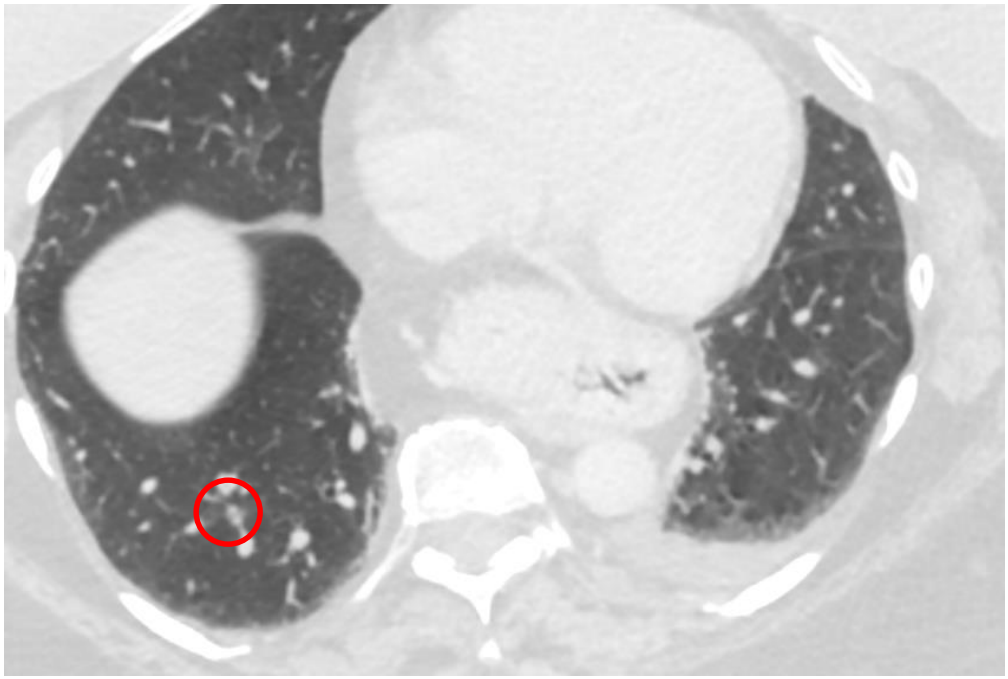
Case

- 67yo woman with metastatic breast cancer.
- Triple negative, grade 3.
- Progressive disease (lung) after 1 prior line of chemo.
- Not in visceral crisis.
- Panel testing revealed:
  - Mutations: TSC2, ATM, TP53, APC.
  - Amplification: CDK12, FGF19, FGF4, PRSS8



Outcome

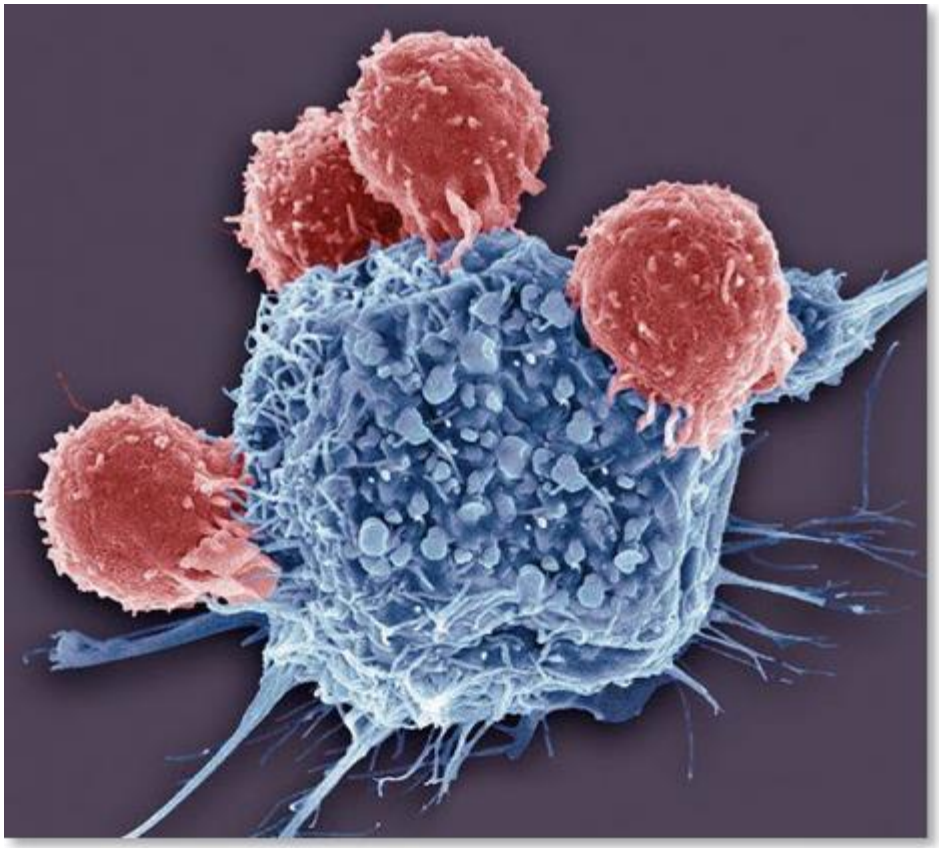
- Referred for IDO inhibitor trial
- Excellent partial response in lung at 4months on trial
- Grade 2 colitis on cycle 2. Treated with prednisone 0.5mg/kg, then tapered over 6 weeks – recovered.
- Now on chemo holiday at 2 years.



On The Horizon:

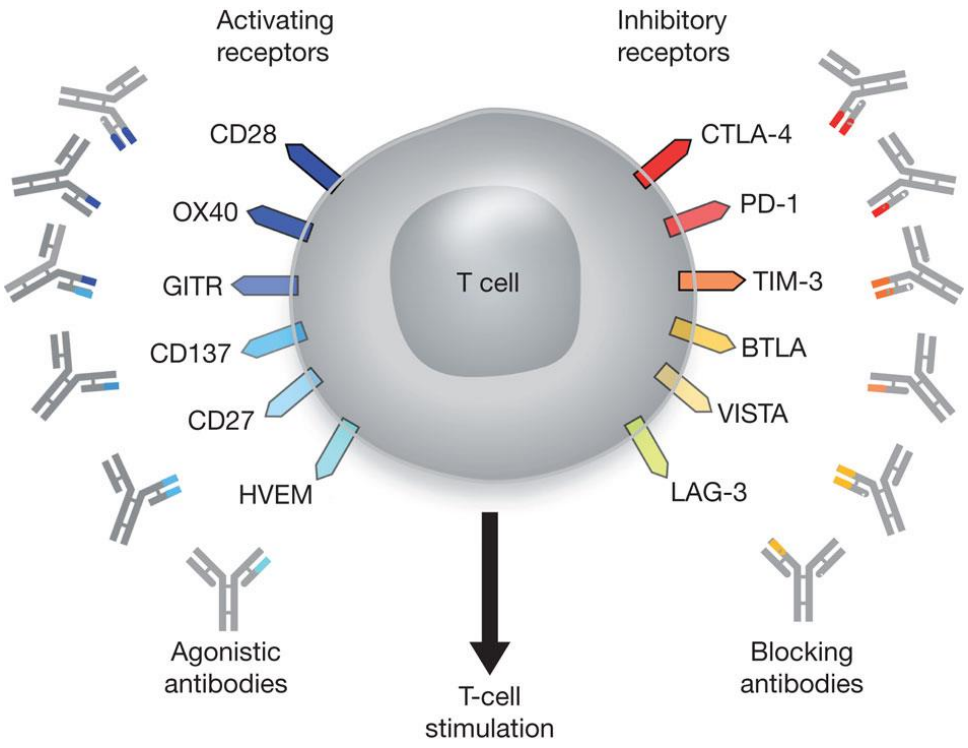
- Checkpoints: OX-40, LAG-3, TIM-3, TIGIT, CEACAM1
- CD-28 agonists, CD-40 agonists
- IDO inhibitors
- CAR-T cells
- Novel Vaccines
- Myeloid agents
- Intra-tumoral therapy
- BATs

Goal of Immunotherapy:



T-cells (red) attacking a cancer cell (blue)
SCIENCEphotoLIBRARY

T-Cell Signaling is Complex

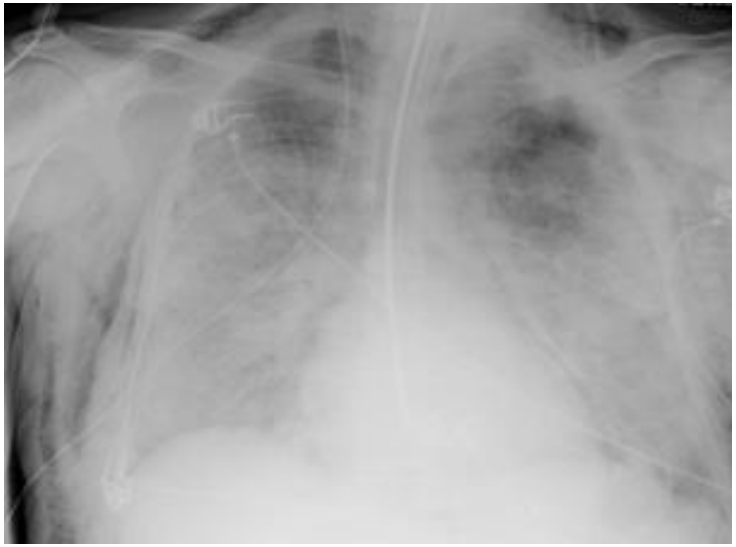


I Mellman *et al. Nature* 480, 480-489 (2011) doi:10.1038/nature10673

nature

Too much T-Cell Signaling is Dangerous

- Pandemic Influenza (H1N1) example:



Courtesy Andrew Mihalek. University of Virginia.

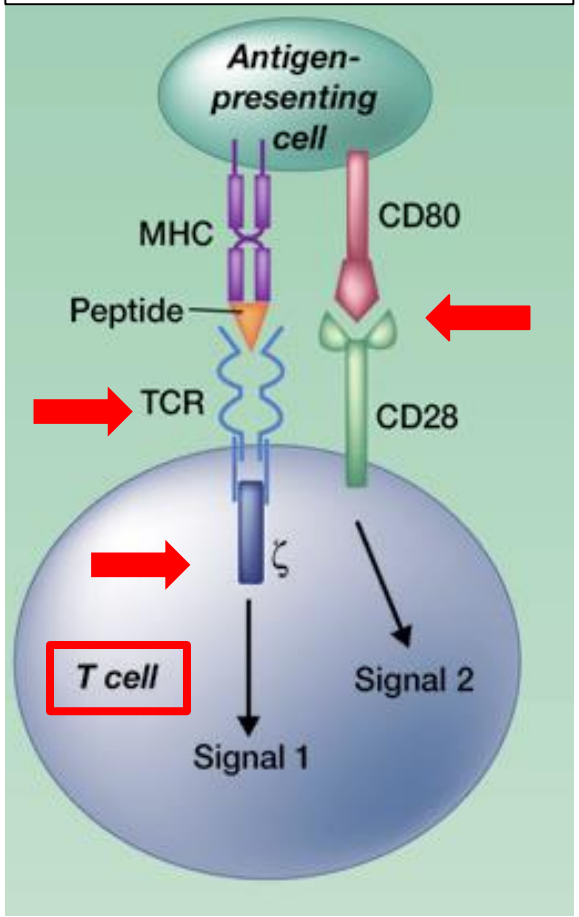
- CD28 Example:
  - 6 young, healthy male patients were treated with THG1412 (CD28 agonist)
  - Severe inflammatory symptoms required ICU admissions and immunosuppression
  - Fortunately no one died.

Suntharalingam G el al. *N Engl J Med.* 2006;355:1018-1028

Engineered T Cells

Mechanisms for T cell Response to Cancer

T Cell Receptor Signaling

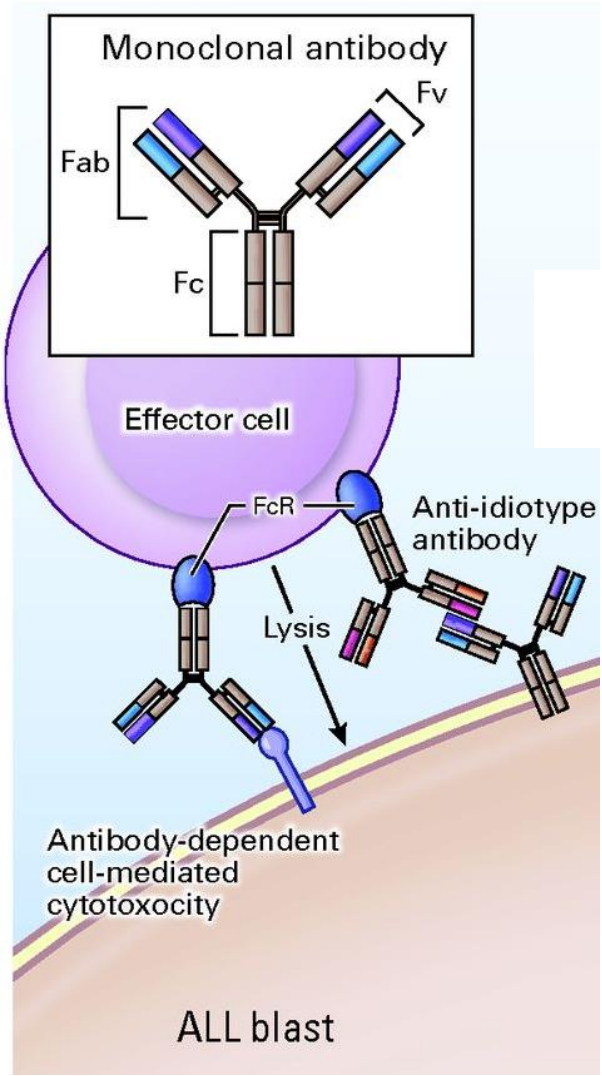


T Cell Receptor responses:

- Can recognize intracellular peptides
- Are not universal
- Restricted by MHC
  - Often downregulated
- Require additional stimulation

Antibody responses:

- Universally recognize cognate antigen
- Relies principally on intact effector cell function



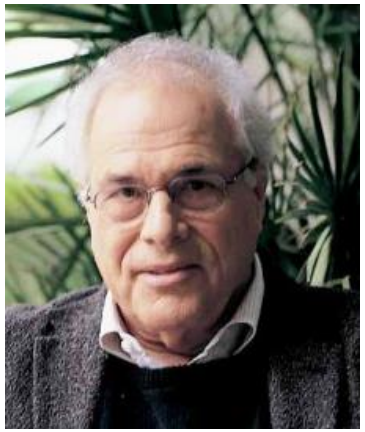
Adapted from Lee DW et al, *Clin Can Res* 2012

Kantarjian H et al. JCO 2012;30:3876-3883

Best of Both:
Genetically Engineered T Cells to Attack Leukemia

Chimeric Antigen Receptors:

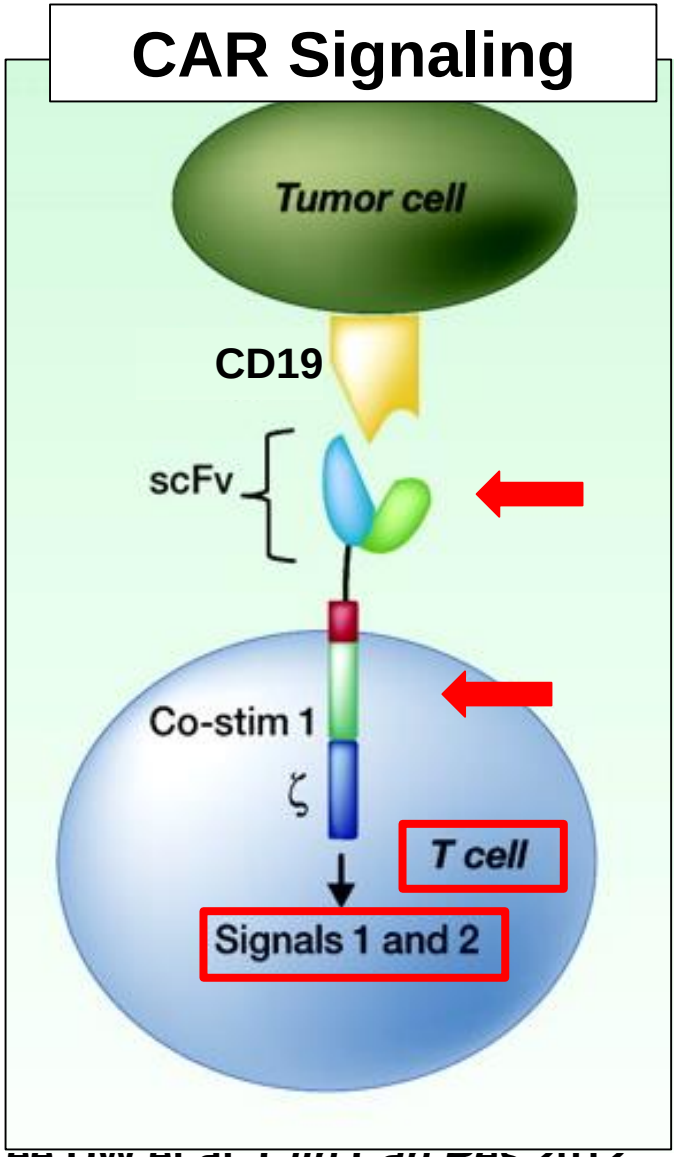
- **Specific for a surface protein**
- **Free of MHC restriction - can be used in any patient**
- **Signals for full activation are self-contained**



Zelig Eshhar

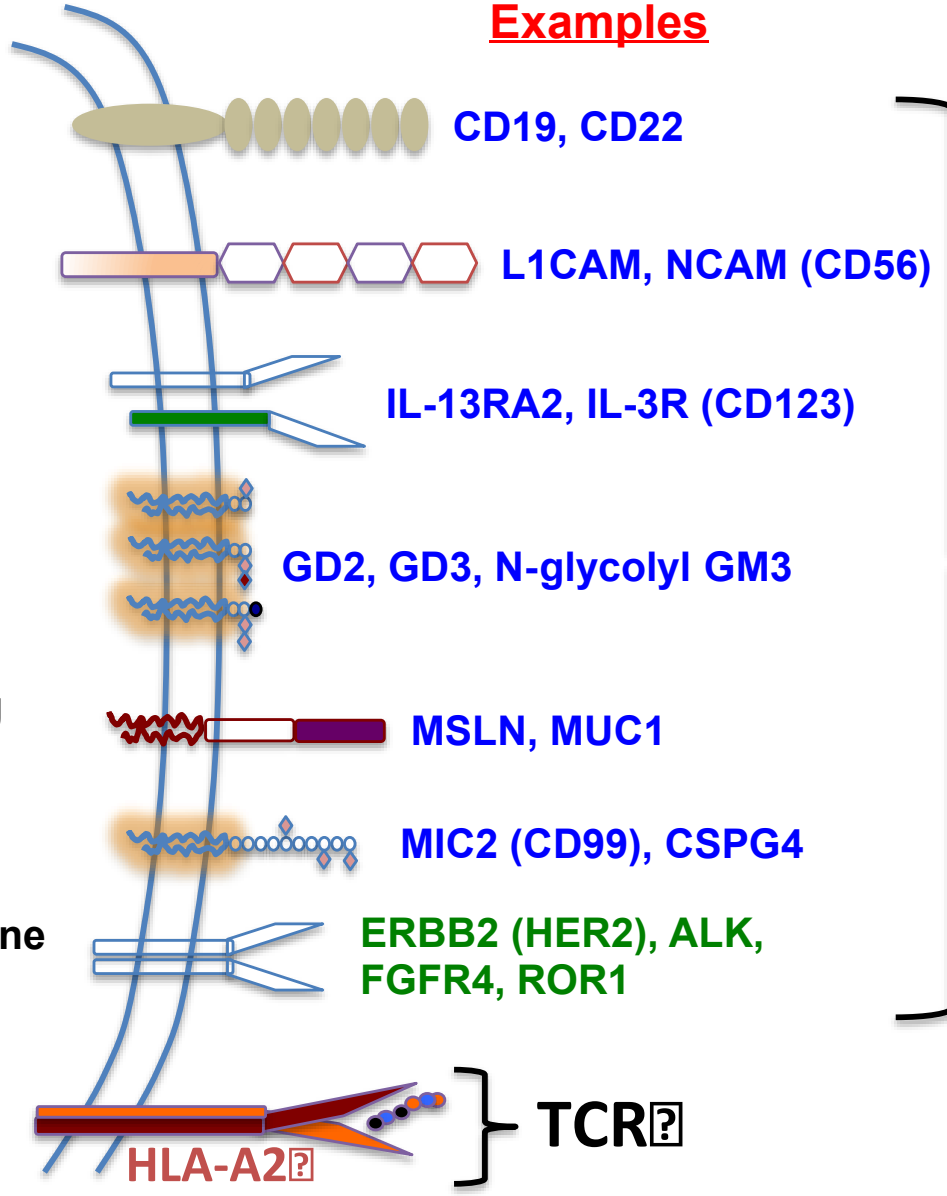
Activated CAR T Cells:

- **Kill the target**
- **Produce inflammatory cytokines**
- **Proliferate daughter CAR T cells**



Adapted from Lee DW et al, *Clin Can Res* 2012

Beyond CD19 – Diversity of CAR Targets



Adapted from Orentas, et al Frontiers in Oncology, 2012

CD19 CAR T Cells are Manufactured in 11 Days

Day -11

24-28

-4 ~~3~~ 7 -2 0

Apheresis

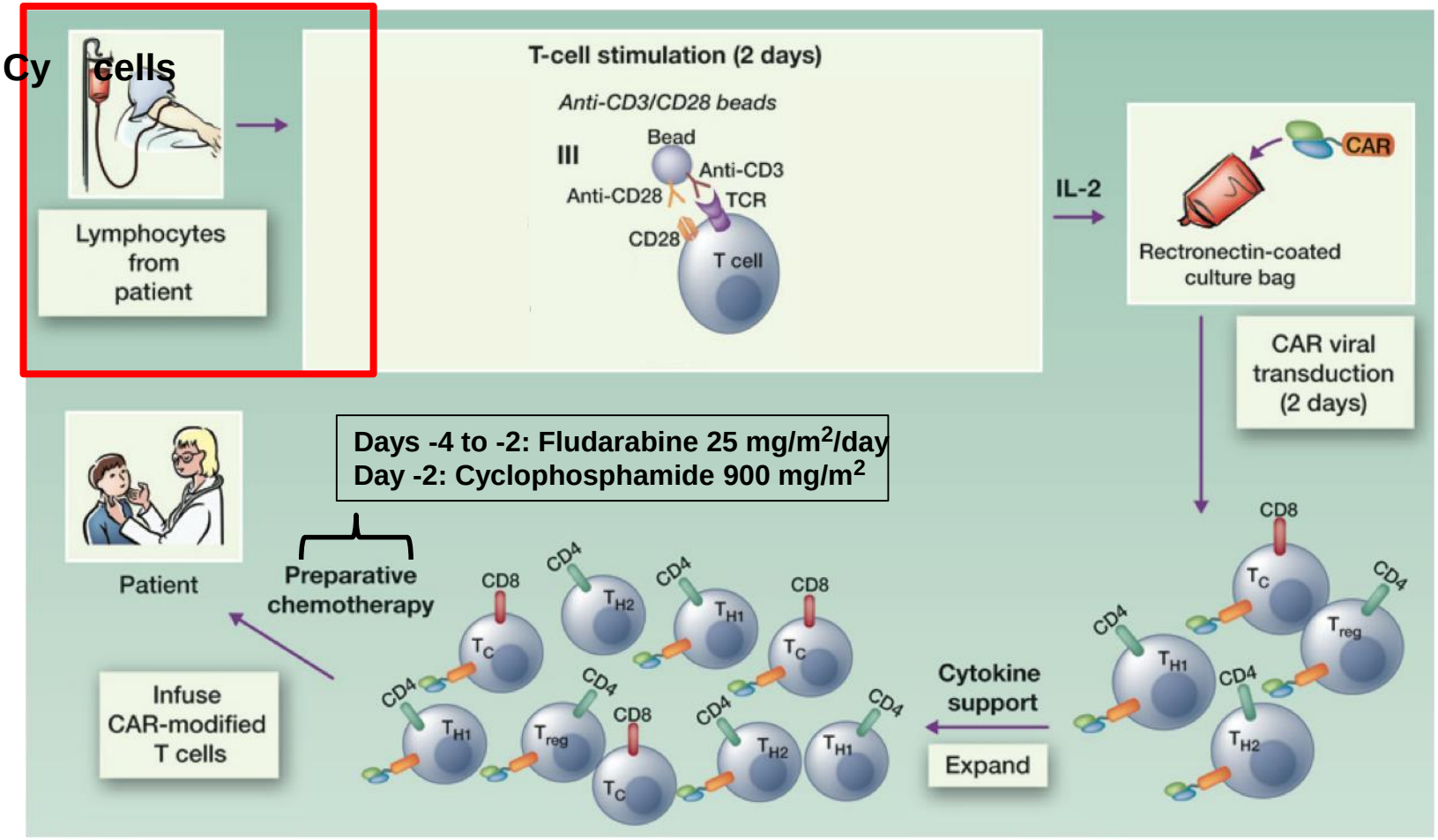
CAR T

- Genetically engineered to express the CD19 CAR
- Expanded *ex vivo* before infusion

Restage

Flu Flu Flu

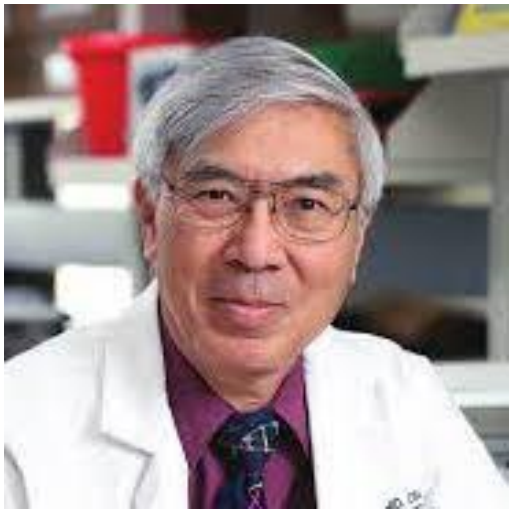
Cy cells



Adapted from Lee DW et al, *Clinical Cancer Research* 2012

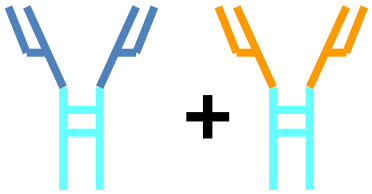
More T cell engineering: BATS

BATs = Bispecific Antibody Armed T-cells



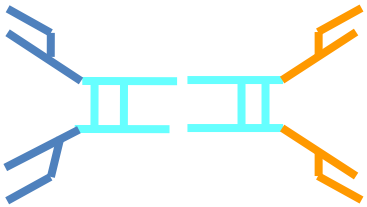
Bispecific Ab Armed T cells (BATs)

Chemical Heteroconjugation

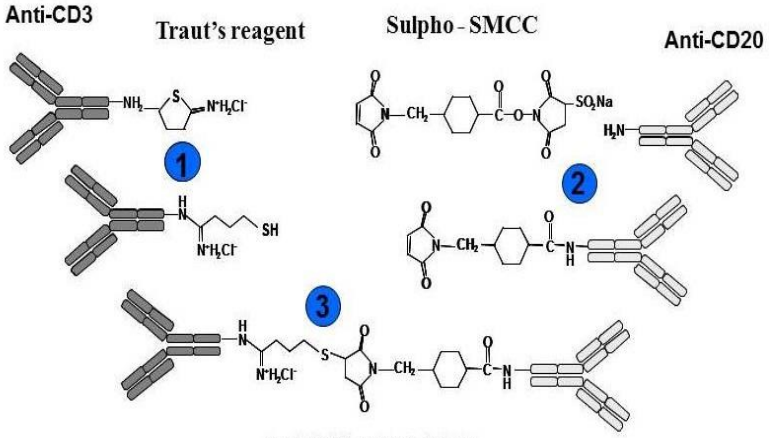


Anti-CD3 Anti-TAA

Anti-CD3



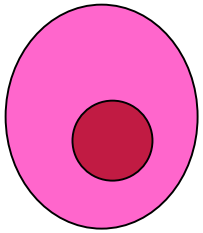
Anti-CD3 x Anti-TAA



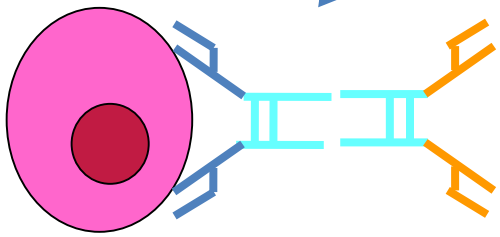
Anti-CD3 x Anti-CD20

Sen et al JStem Cell Res 2001

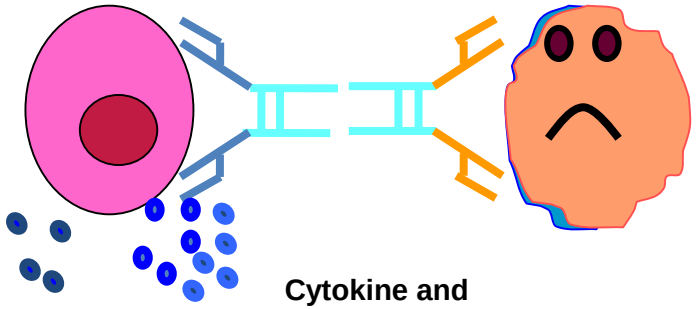
+



14 d T cell Expansion



Arming of T Cells



T Cell

Cytokine and ChemokineSecretion

Tumor Kill

Production of Armed T cells

PBMC from Pheresis

↓

OKT3 (20 ng/ml) + 100 IU/ml of IL-2

↓

ATC are split every other day

↓

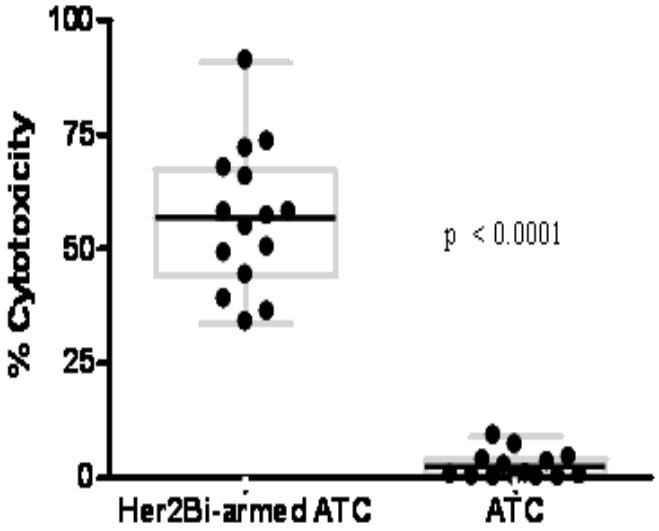
Harvest, Arm with BiAb (HER2) and Cryopreserve after 10-14 days

↓

Quality Control Release (Bacteria, fungal, and Mycoplasma stain) 7 days

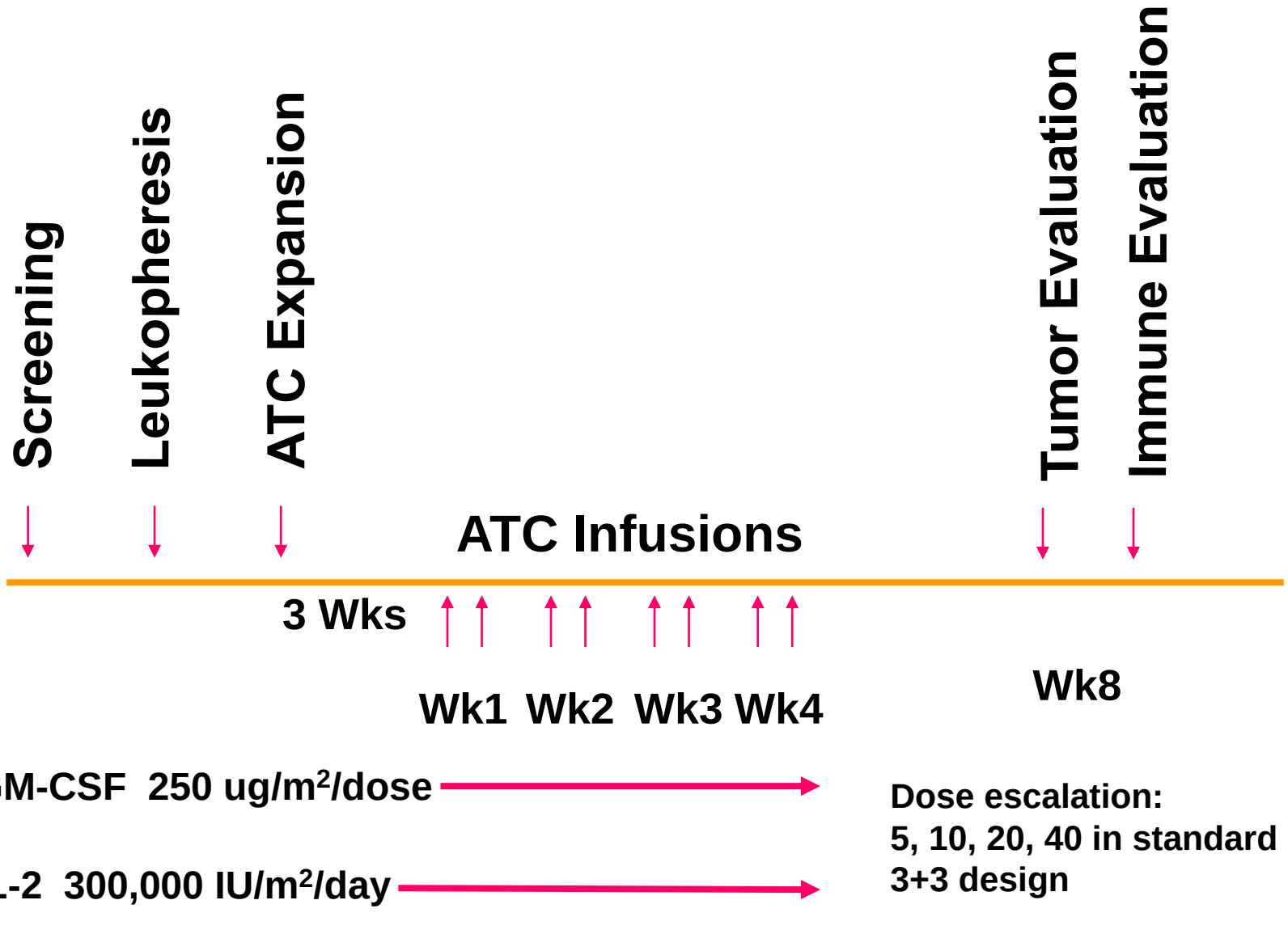
↓

Testing for cytotoxicity and cytokine production



Lum et al. *Clin Cancer Res*. 2015 May 15; 21(10): 2305–2314. doi:10.1158/1078-0432.

Treatment Schema for Stage IV Breast

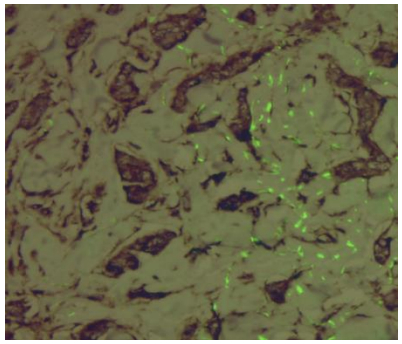


Stage IV Breast Cancer Patients

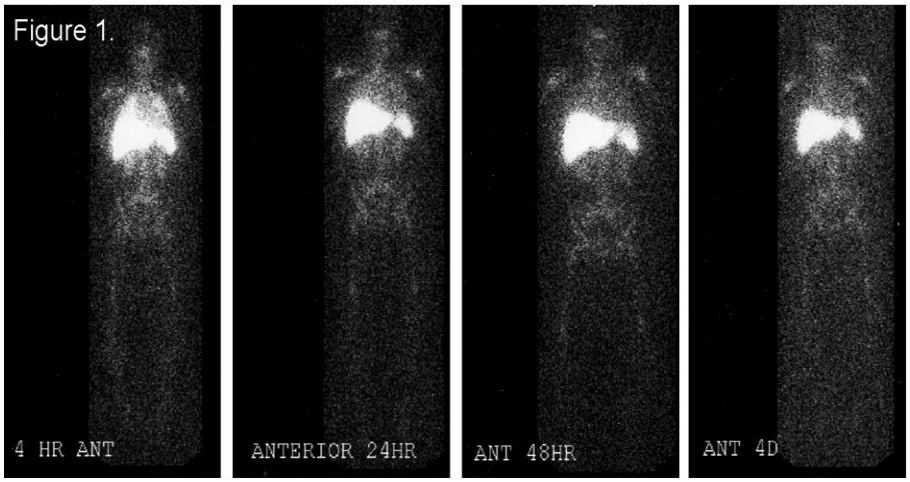
Table 1: Patient Characteristics		
	No.	**%**
Age < 50 ≥ 50	 **14** **9**	 **60.9** **39.1**
Cancer Stage Stage IV	**23**	**100**
Performance Status (ECOG) 0 1 2	 **18** **5** **0**	 **78.3** **21.7** **0**
ER/PR Status Positive Negative Unknown	 **14** **8** **1**	 **60.9** **34.8** **4.3**
HER2/neu Status 0 1+ 2+ 3+ Unknown	 **10** **2** **2** **8** **1**	 **43.5** **8.7** **8.7** **34.8** **4.3**
Prior Treatment w/ Herceptin Yes No	 **8** **15**	 **26.0** **74.0**

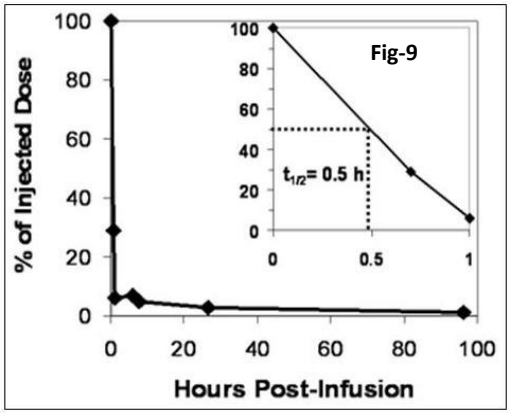
Lum et al. *Clin Cancer Res*. 2015 May 15; 21(10): 2305–2314. doi:10.1158/1078-0432.

Trafficking of BATs to Breast CA



Her2 1+: 80 x 10^9 Her2Bi-armed ATC. Sternal tumor biopsy 1 week post treatment





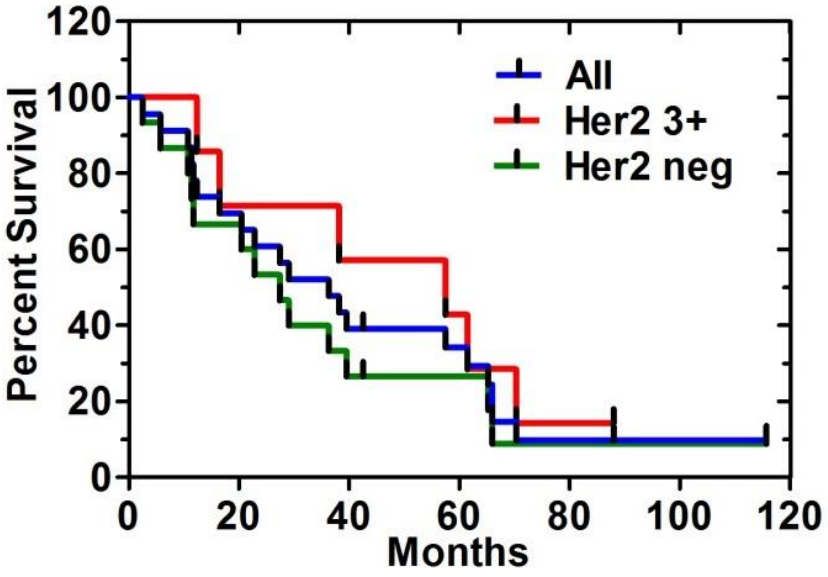
Lum et al. *Clin Cancer Res*. 2015 May 15; 21(10): 2305–2314. doi:10.1158/1078-0432.

Partial Response 7mo post BAT therapy: Her2 negative

Lum et al. *Clin Cancer Res*. 2015 May 15; 21(10): 2305–2314. doi:10.1158/1078-0432.

Stage IV Breast Cancer: Phase I Clinical Responses

Phase I Metastatic Breast Cancer (Her2/neu 0-3+)		
Status	**Pt #**	**Stable or Better at 14.5 weeks after last tx**
NED	**1**	
PR	**1**	
SD	**9**	**52%**
PD	**10**	**48%**
NE	**2**	
Total	**23**	**100%**
Median OS = 57.9mo (HER2+ patients)		



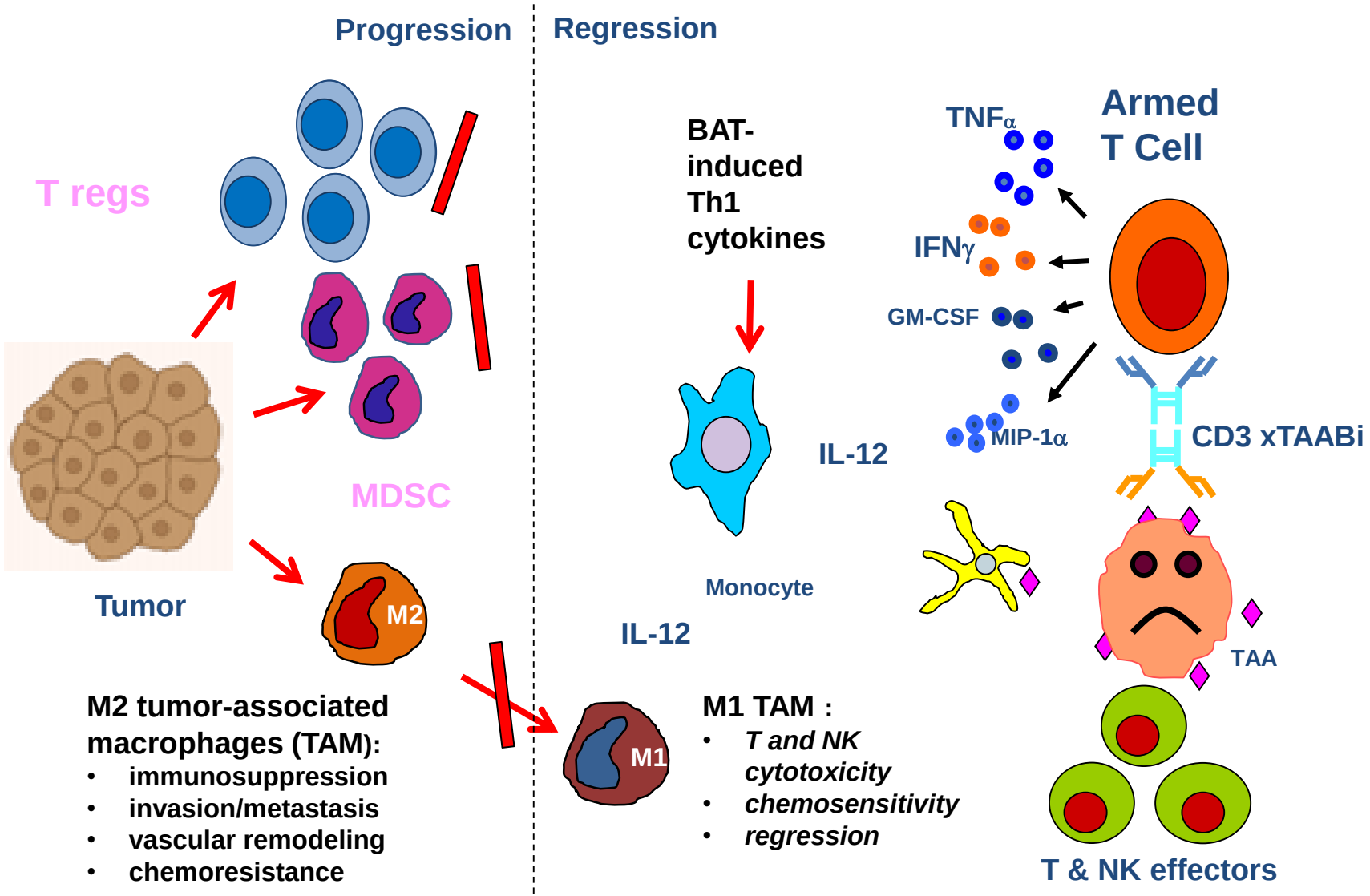
Lum et al. *Clin Cancer Res*. 2015 May 15; 21(10): 2305–2314. doi:10.1158/1078-0432.

HER2 Bispecific T cells - Phase I Toxicities

Toxicity Grade	Grade 1	Grade 2	Grade 3	Grade 4	Total Episodes	% of Total
Chills	0	4	36	0	40	51
Headache	0	3	14	0	17	22
N/V	8	1	2	0	11	14
Fever	3	1	0	0	4	5
Hypotension	1	3	0	0	4	5
Hypertension	0	0	0	1	1	1.3
SOB	0	1	0	0	1	1.3
Total	12	14	52	1	77	

Lum et al. *Clin Cancer Res*. 2015 May 15; 21(10): 2305–2314. doi:10.1158/1078-0432.

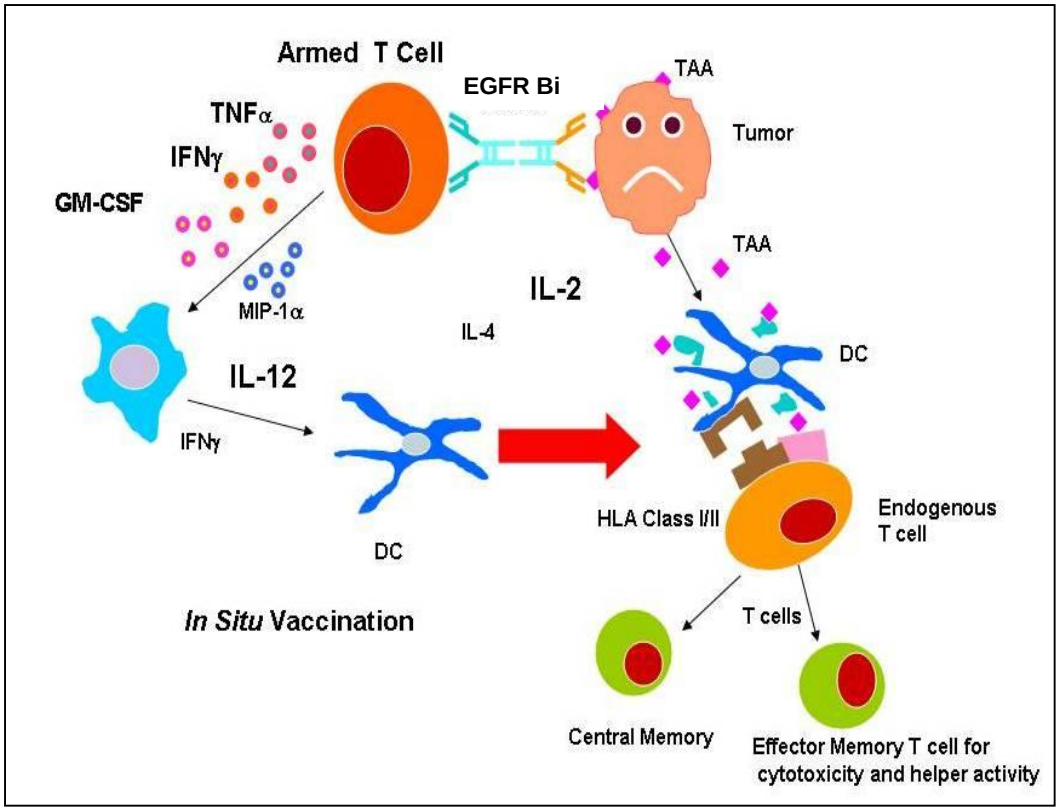
Mechanism for BATs Overcoming Tumor Induced Suppression



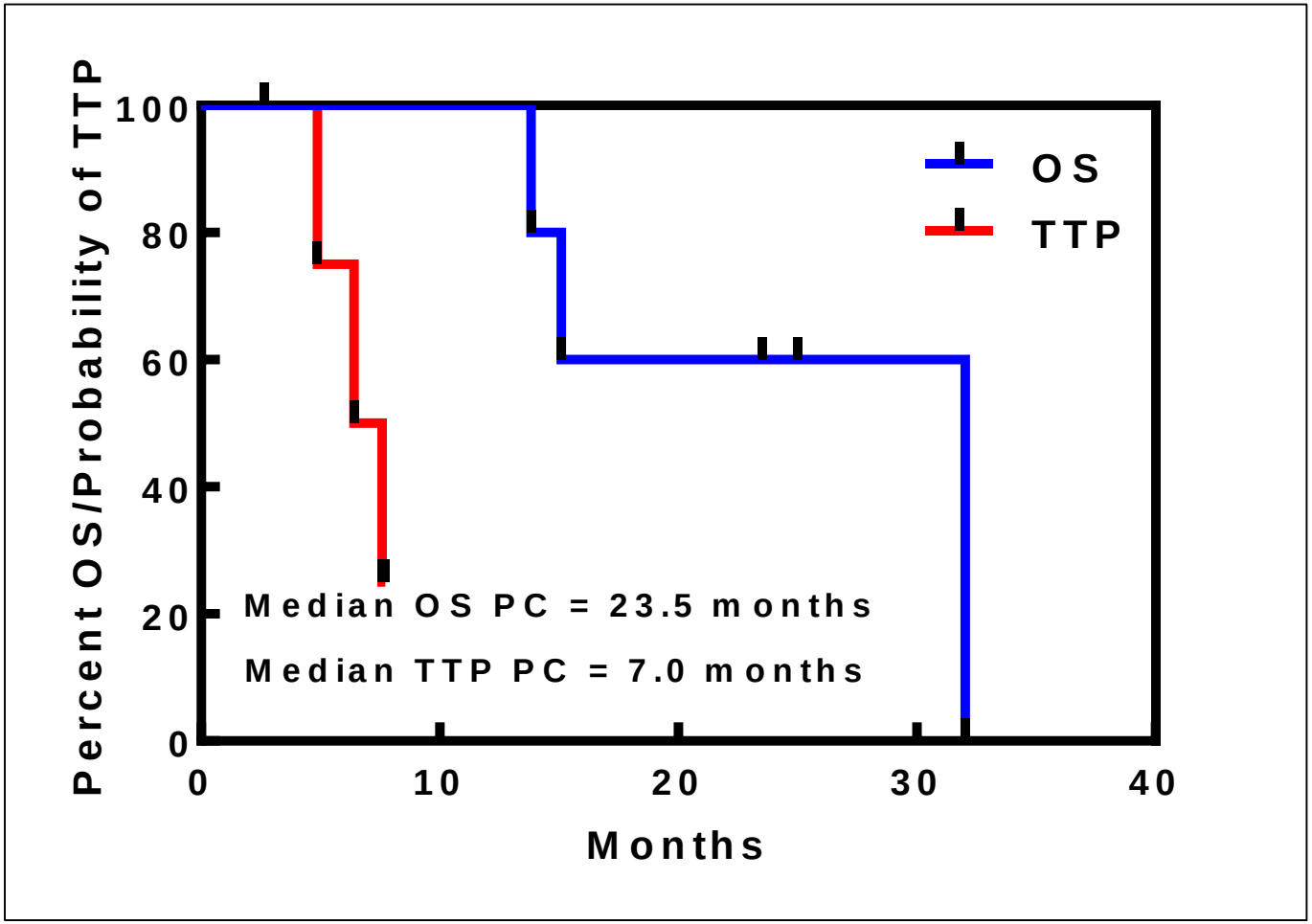
Thakur. J Transl Med. 2013;11:35.

Lum et al. *Clin Cancer Res*. 2015 May 15; 21(10): 2305–2314.

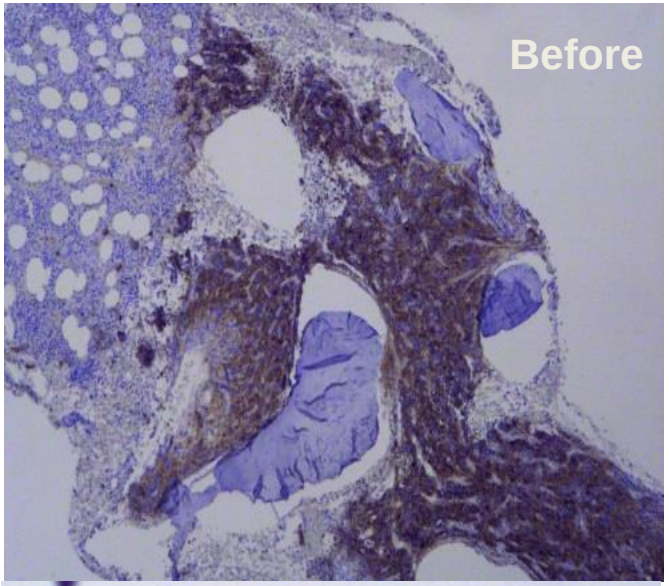
CD3-EGFR BiAntibody Armed T cells

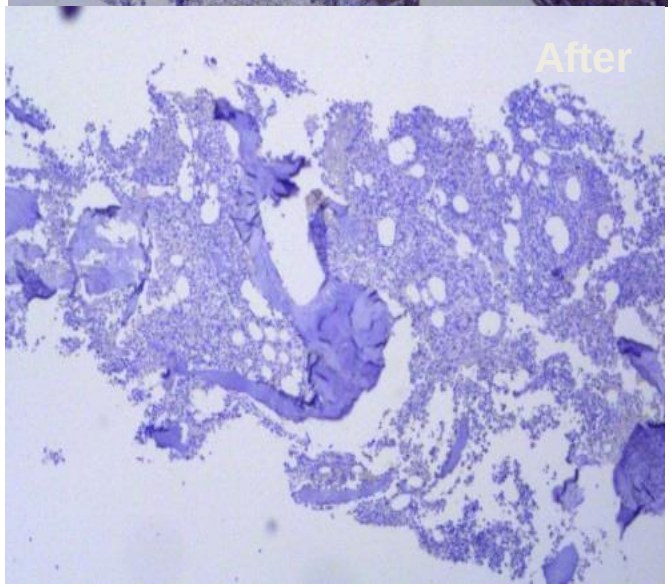


CD3-EGFR BATs Phase I for Pancreatic Cancer



BATs Trial for Neuroblastoma

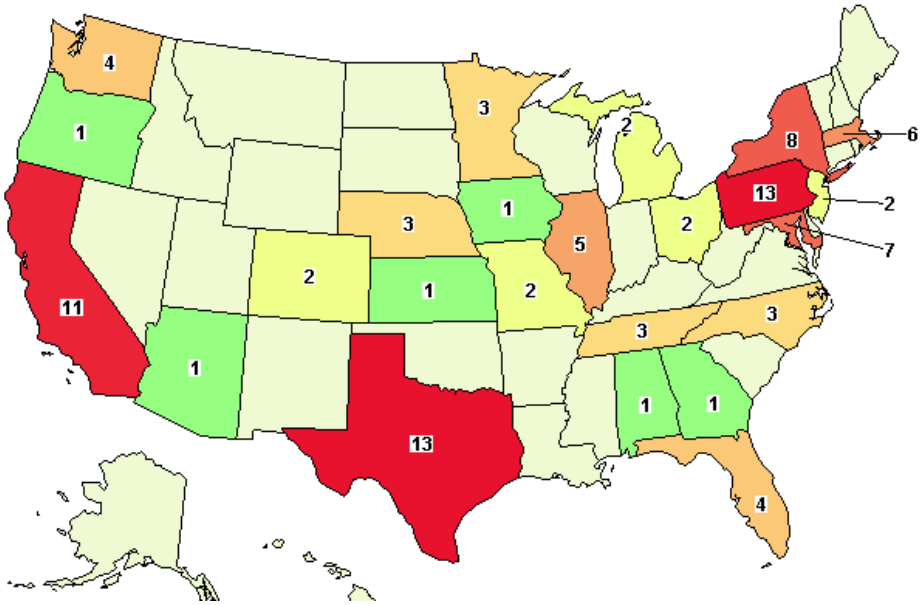




Yankelevich et al Ped Blood Cancer 2012

Summary

- BATs show evidence of anti-tumor activity in breast, pancreatic, neuroblastoma (and several other cancers)
- CAR-T cell therapy for several tumor types are either available or opening soon in Mid-Atlantic Region.



MAP of CAR-T studies open (per clinicaltrials.gov 8/18/2016)

The IDO Pathway

A key immune checkpoint mediating immunosuppression in cancer

Indoleamine 2,3-dioxygenase (IDO) Pathway

A Key Immune Checkpoint

- Regulates innate and adaptive immune response
  - Is counter-regulatory (induced by inflammation)
  - Inhibits effector T-cells, activates suppressive Tregs
  - Can create peripheral tolerance de novo
- Predominant role
  - Maternal tolerance, Autoimmune disorders, Transplant tolerance
  - Tumor induced immunosuppression
- Overexpressed
  - Within tumor cells to directly suppress T-cells
  - Within antigen presenting cells resulting in peripheral tolerance to tumor associated antigens (TAAs)

IDO and Metabolic control of Immune Responses

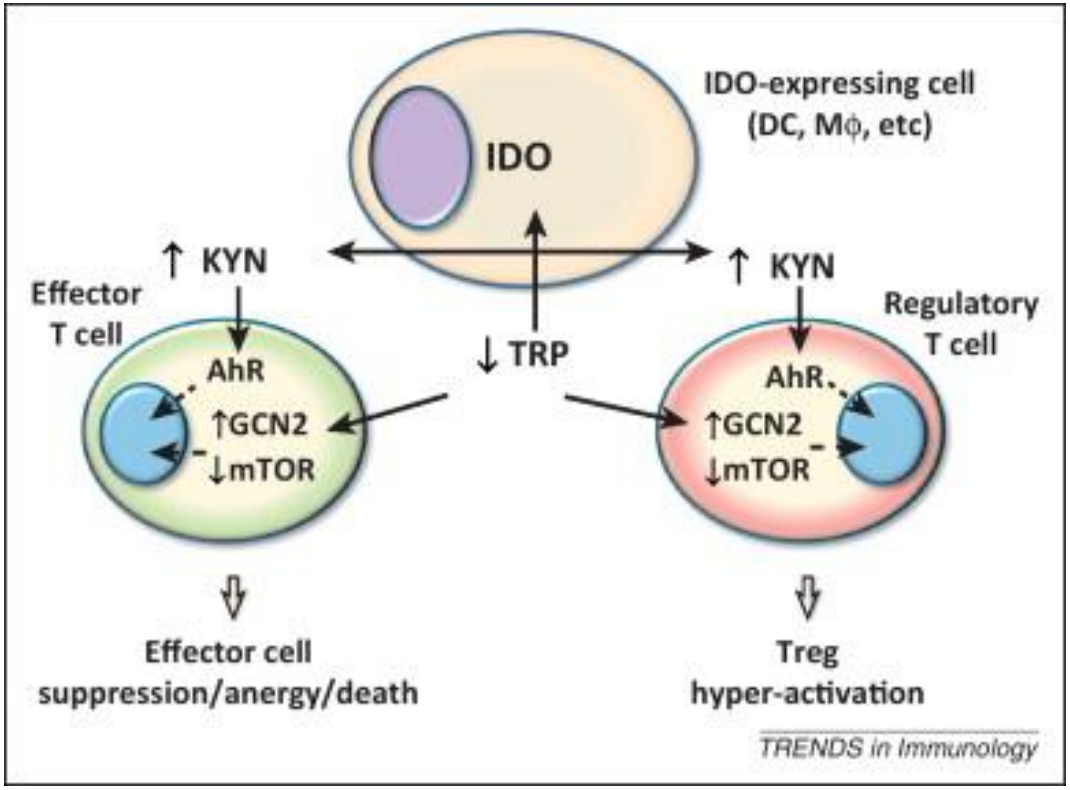
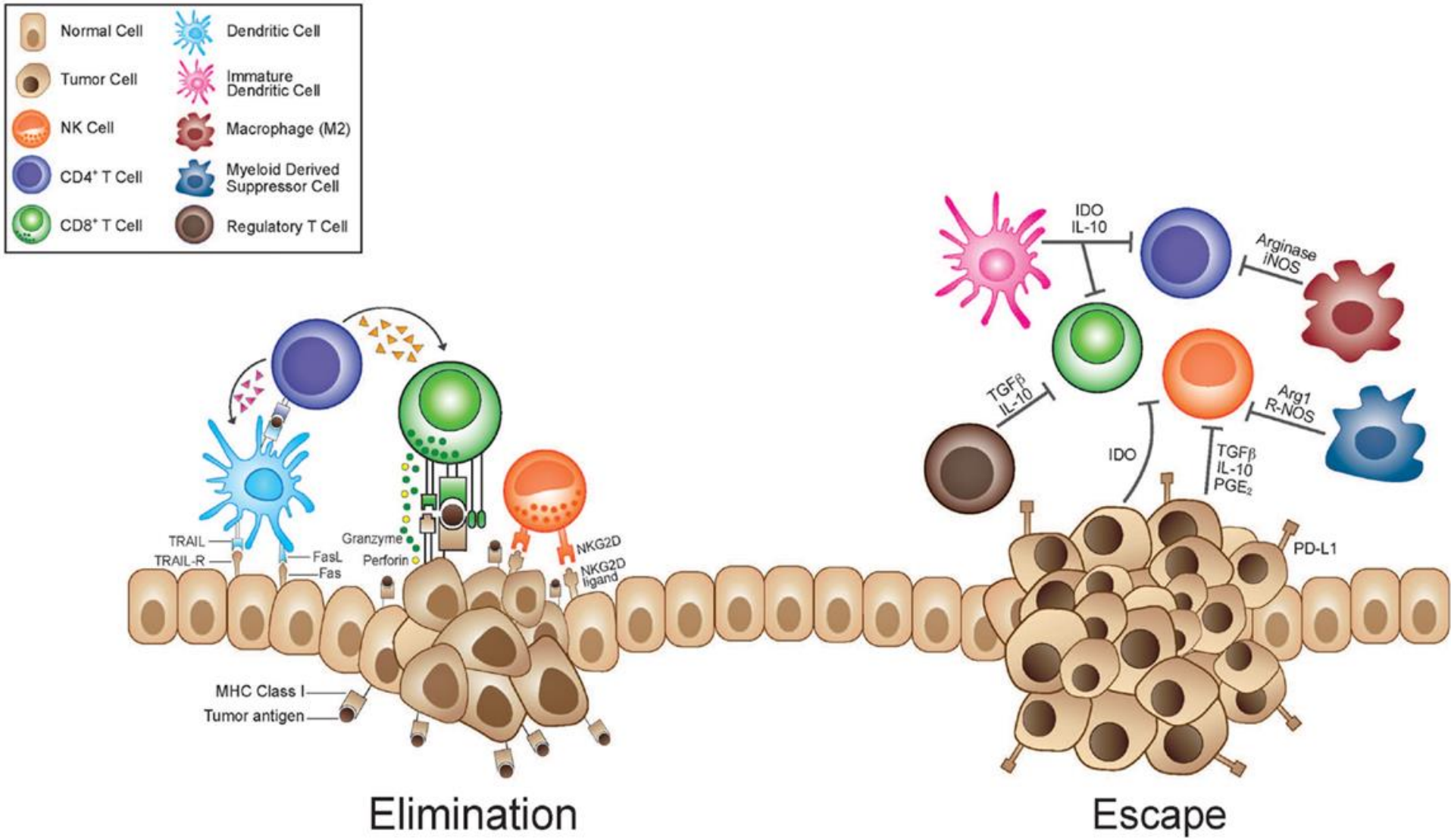


Figure 1 Metabolic control of T cell and Treg responses via IDO. KYN release and TRP consumption by accessory cells expressing IDO generates signals via AhR and amino-acid sensors (GCN2, mTOR), respectively, that have profound effects on T cell and Treg responses to inflammatory and antigenic signals. IDO activity in APCs also enhances Treg differentiation from naïve CD4 T cells via these metabolic pathways (not shown).

David H. Munn , Andrew L. Mellor. Trends in Immunology, Volume 34, Issue 3, 2013, 137 - 143

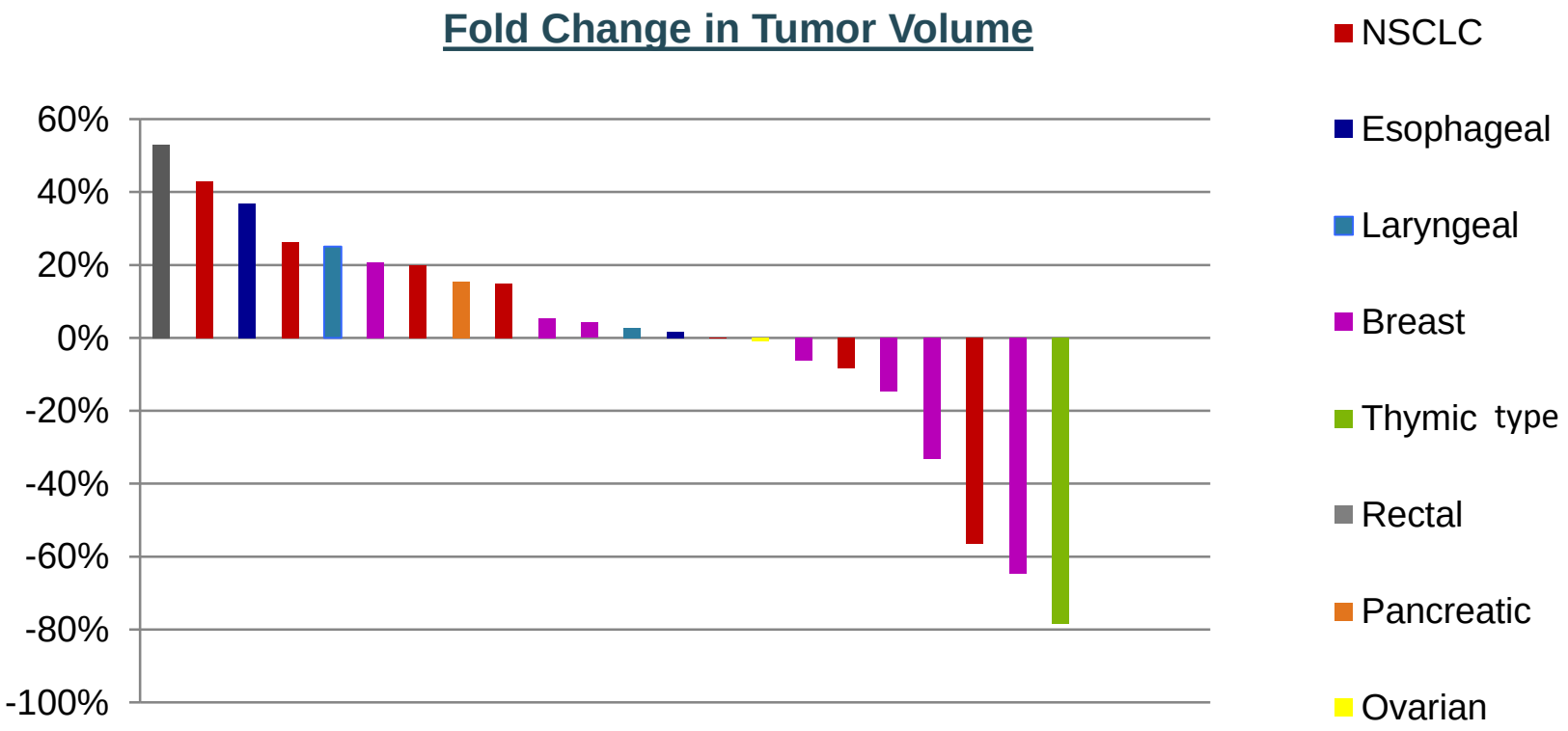
IDO in the Tumor Microenvironment



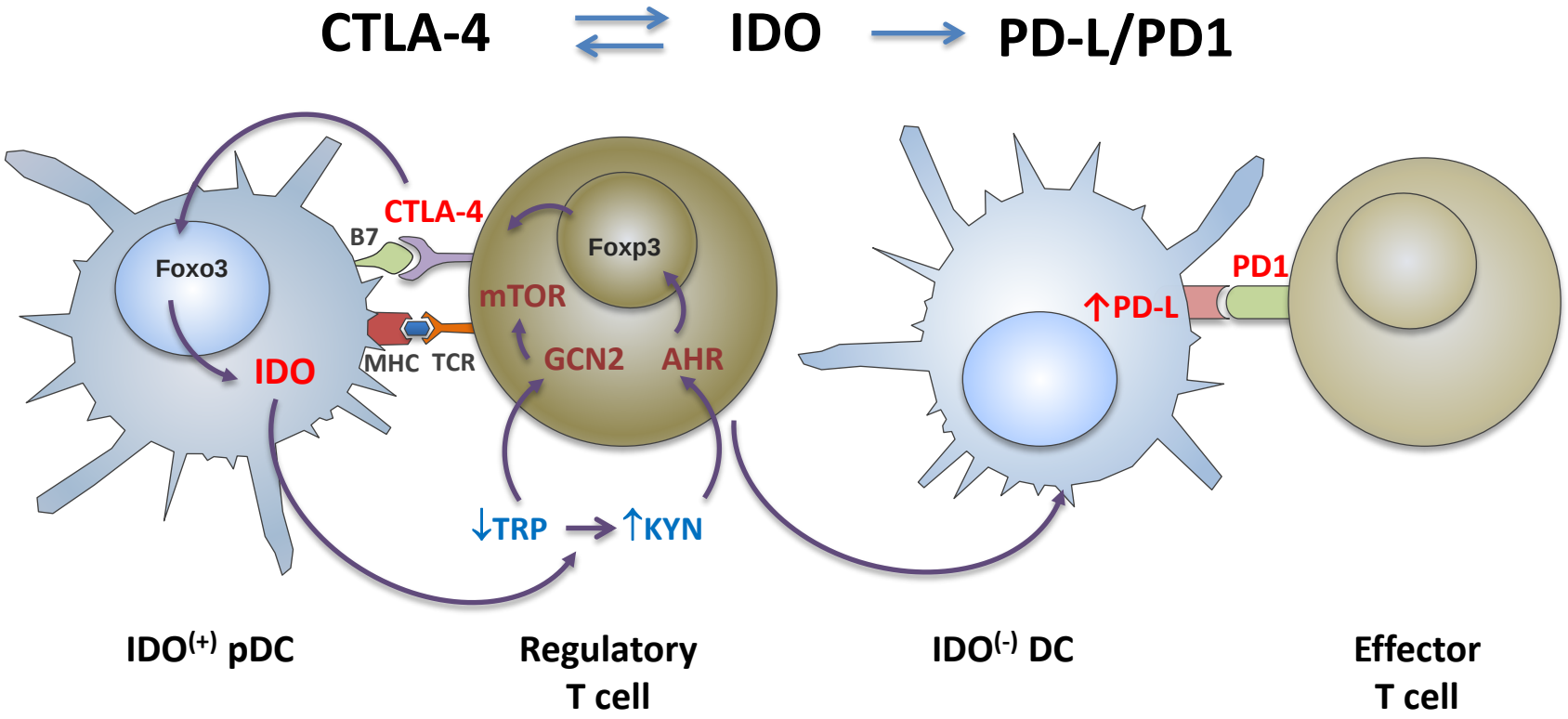
Monjazeb AM. Immunoediting and antigen loss: overcoming the Achilles heel of immunotherapy with antigen non-specific therapies. Front. Oncol. 2013; 3:197.

Indoximod + Docetaxel Combination

- ***Phase 1: Efficacy Results***
- **18% (4/22) partial response rate (2 breast, 1 lung, 1 thymic)**
- **41% (9/22) rate of stable disease**



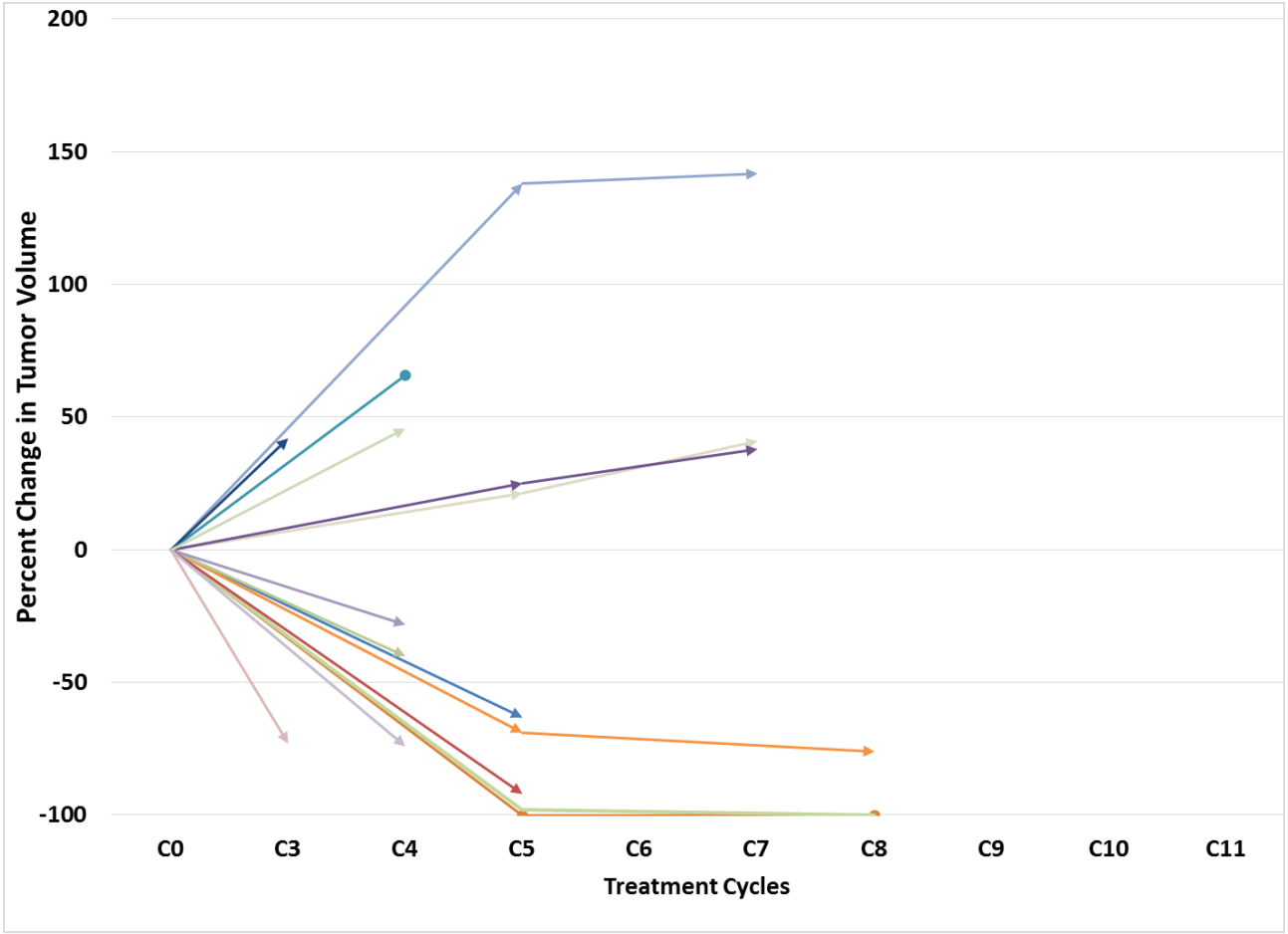
Interrelations of CTLA-4, IDO and PD-1 pathways



CTLA-4 and IDO participate in a self-maintained loop
IDO activated Tregs up-regulate PD-ligands on dendritic cells

DH Munn *J. Clin. Invest.*, 2007

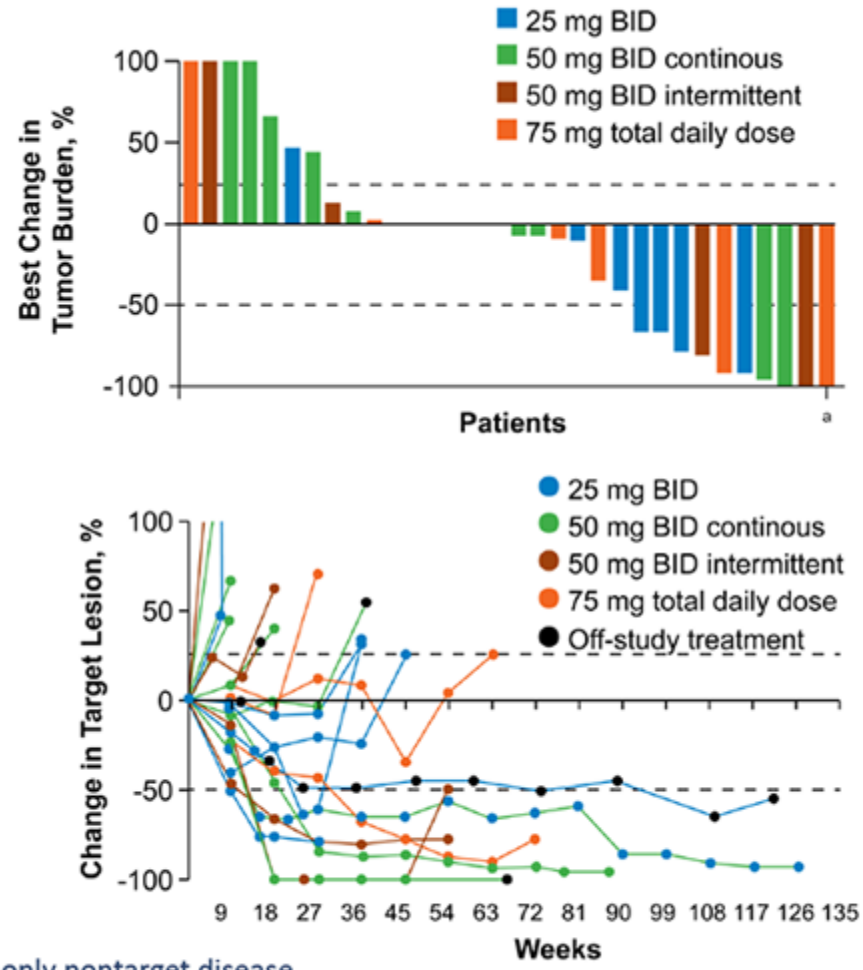
Indoximod + Pembrolizumab in Melanoma (ASCO 2016)



- 15 evaluable pts
- 53% response rate
- 2 CR's

Zakharia et al. ASCO 2016, abstract #3075

Epacadostat + Ipilimumab

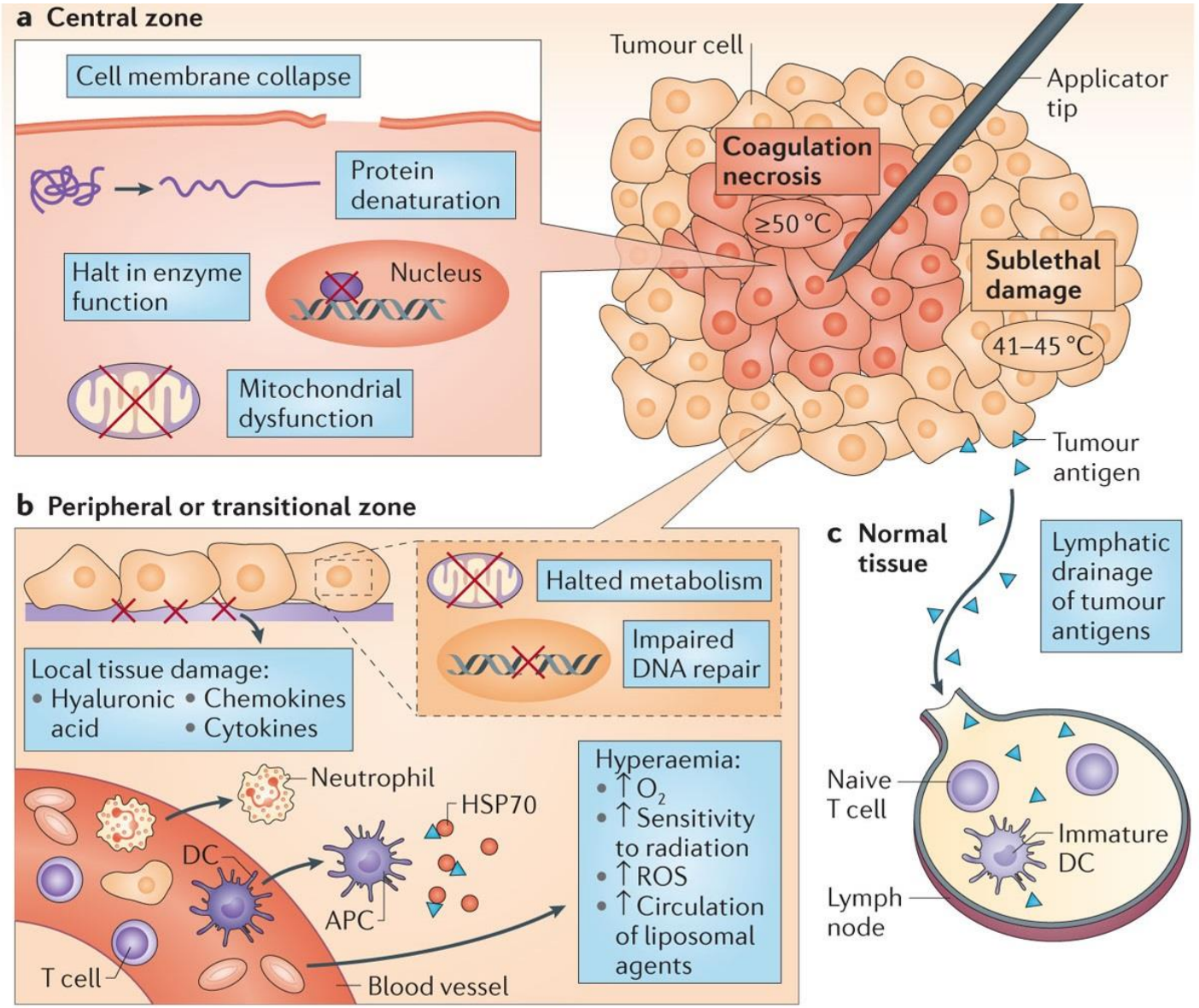


In immunotherapy-naïve patients (n = 32)

[a] Patient had only nontarget disease.

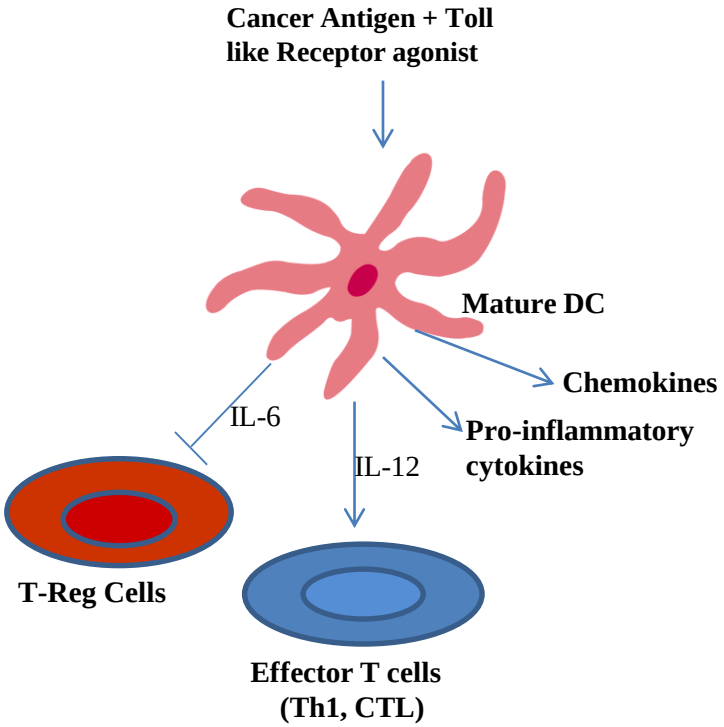
1. Gibney GT et al. European Cancer Congress 2015. Abstract 511.

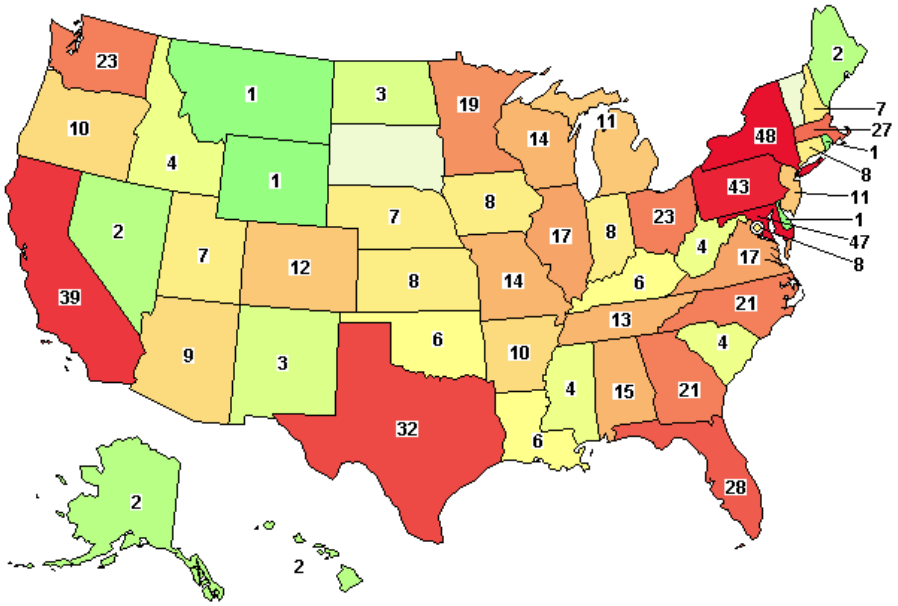
Immune Effects of Thermal ablation



Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. Nature Reviews Cancer 2014; 14: 199–208

Cancer Vaccines





Open Vaccine trials (clinicaltrials.gov 8/19/16)

Combination Strategies:

Checkpoint inhibitors plus :

- **IDO**
- **anti-CD47**
- **HDAC's**
- **small molecule inhibitors**
- **cytokine Rx / modified cytokines**
- **Adenosine 2R inhibs**
- **STING agonists**
- **CAR-T/ BAT's**
- **Other adoptive T cell transfer**
- **Anti-CD40**
- **CSF-1Ri**
- **Vaccines**
- **TLR agonists**
- **Cox2 inhibitors**
- **Chemotherapy**

ALSO: Nanoparticle delivery, intratumor delivery, etc