Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Cancer Immunosurveillance and Immunotherapy

Robert Emmons, MD FACP

UofL Stem Cell Transplant Program

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CHAMPION OF THE EMERGENCY PHYSICIAN

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Disclosures

- I have no disclosures pertinent to this talk
- I will be discussing non-FDA approved indications during my presentation and will indicate during my talk.

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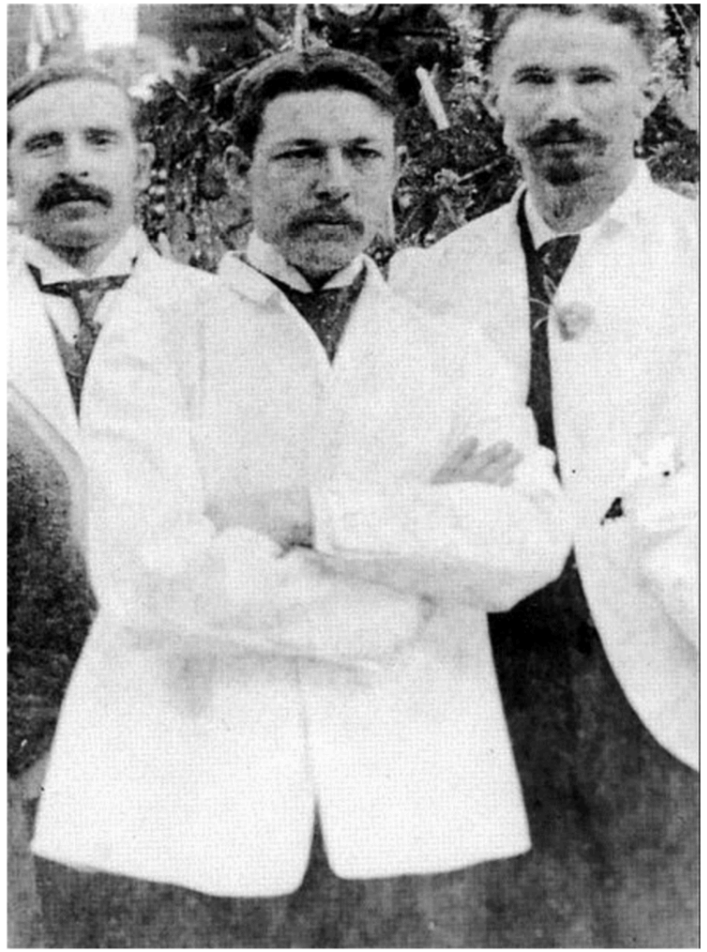
Coley Suggests Cancer Immunotherapy



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

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Cancer Immunity Poorly Understood for a LONG time

- 100 years of evolution
- T cells in cancer patients detect tumor-associated epitopes (Thierry Boon, Brussels)
- Peptide vaccines to boost T cell responses: few clinical responses
- Cytokines to boost T cell responses (IL-2, interferon): few clinical responses and toxicity

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Mice led the way

- First **reproducible immunity to induced tumor in mice** (JNCI 18:769, 1957)
- Tumor removed from mice **induced immune response on reintroduction** (Annu Rev Med 15:167, 1964)
- Nude mice (athymic) did not have significantly increased tumor incidence, **NK cells discovered**
- Subsequent generations of knockout mice had **increased cancer incidence of varying types**:
  - RAG-/-: Lack T, B, NKT
  - Perforin -/- lack cytotoxic T and NK cells
  - Others: Deficient in STAT-1, α/β, γ/δ, IL-12

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Views of immunity

- Self vs Non-self dominated thought in immunology arguing against an important role for the immune system in cancer surveillance (a “self” tissue)
- This changed with the realization that the immune system evolved to recognize “danger” and with mouse system defective in various aspects of immunity with increased susceptibility to cancer

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Immunosurveillance

- Increased cancer incidence noted in patients with inborn errors of immunity and on long term immune suppression (solid organ transplant and GVHD in stem cell transplant)
- The ability to survive in the face of immune attack now recognized as a hallmark of cancer
- Modern understanding of “tumor immunoediting” has three outcomes: tumor elimination, equilibrium or immune escape

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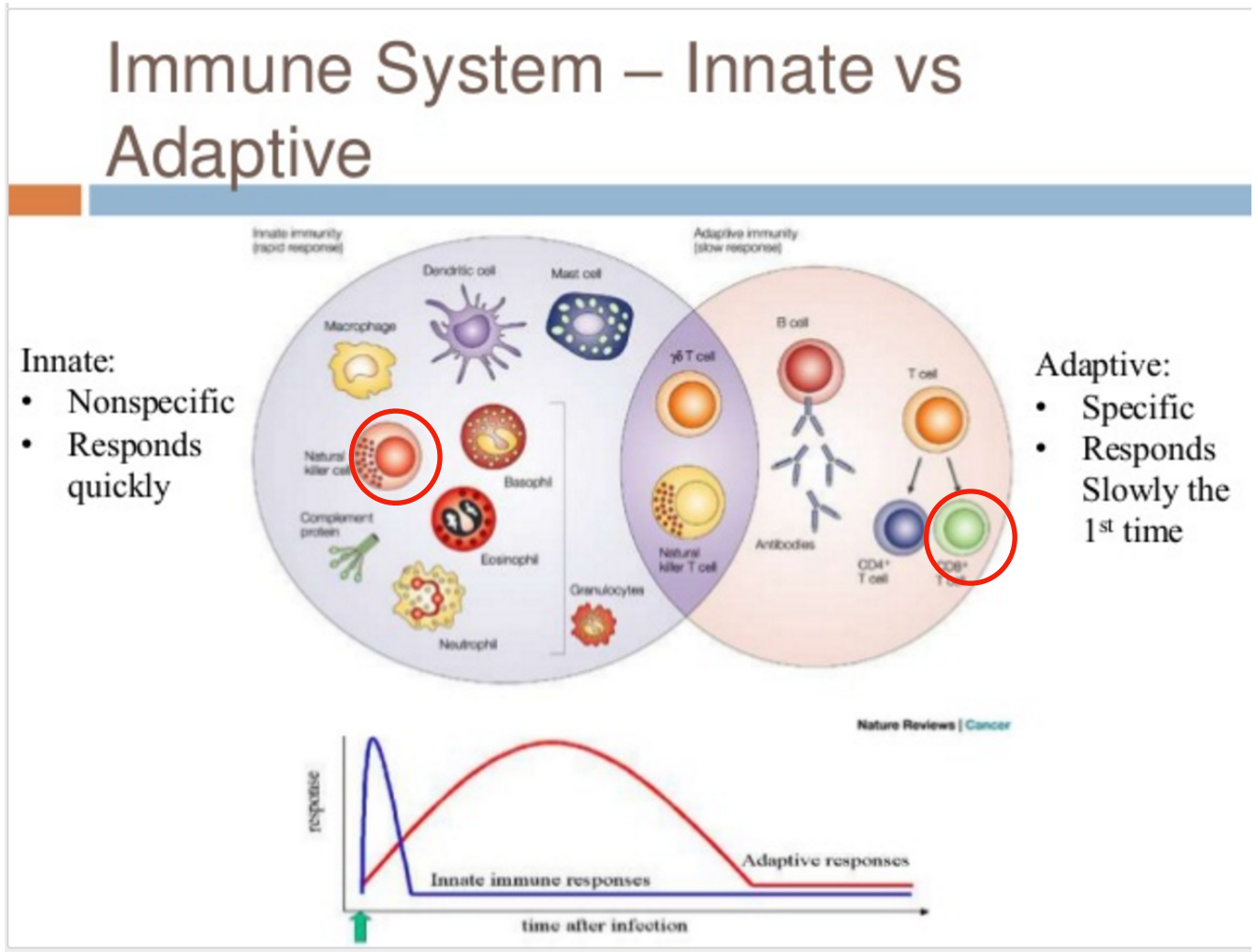
Innate vs Adaptive



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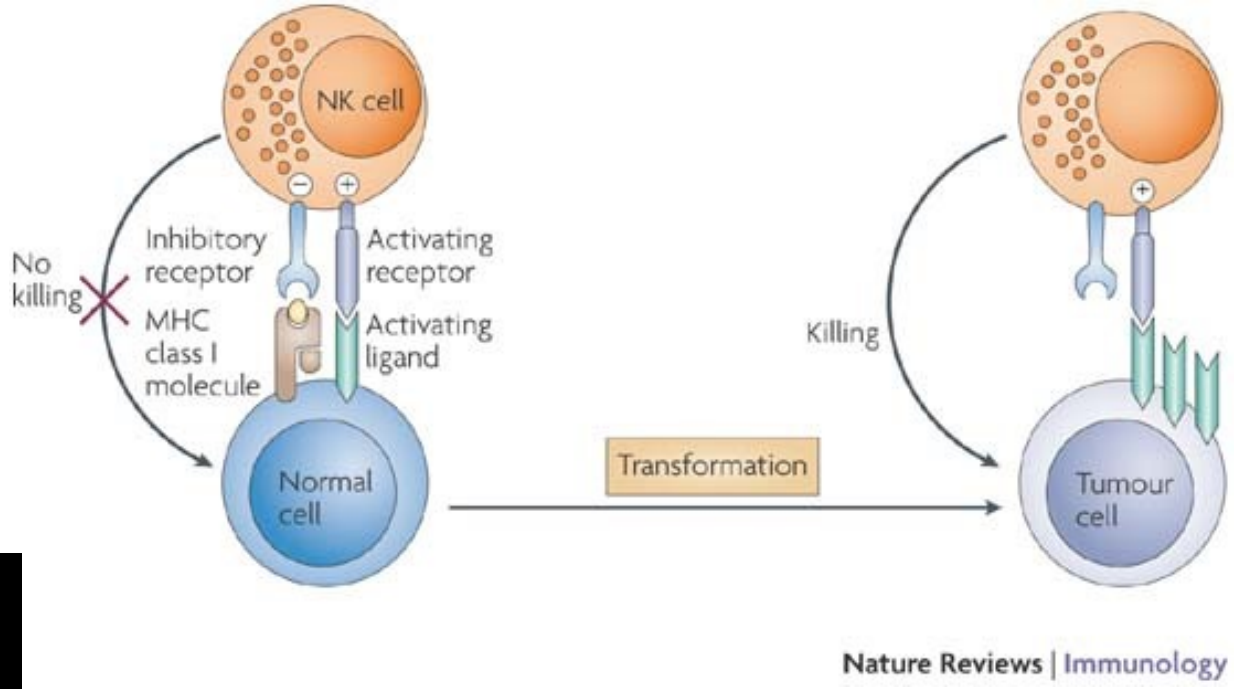

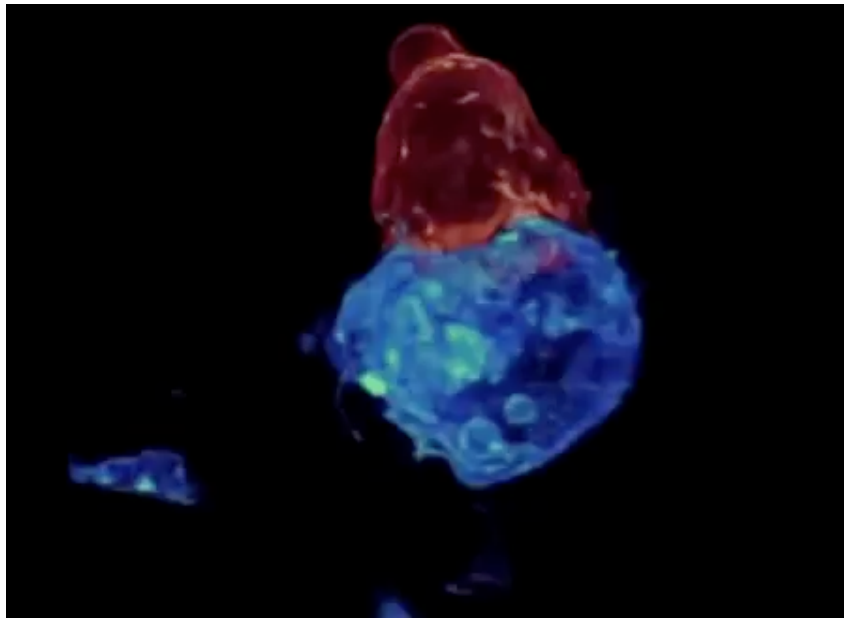

NK cell

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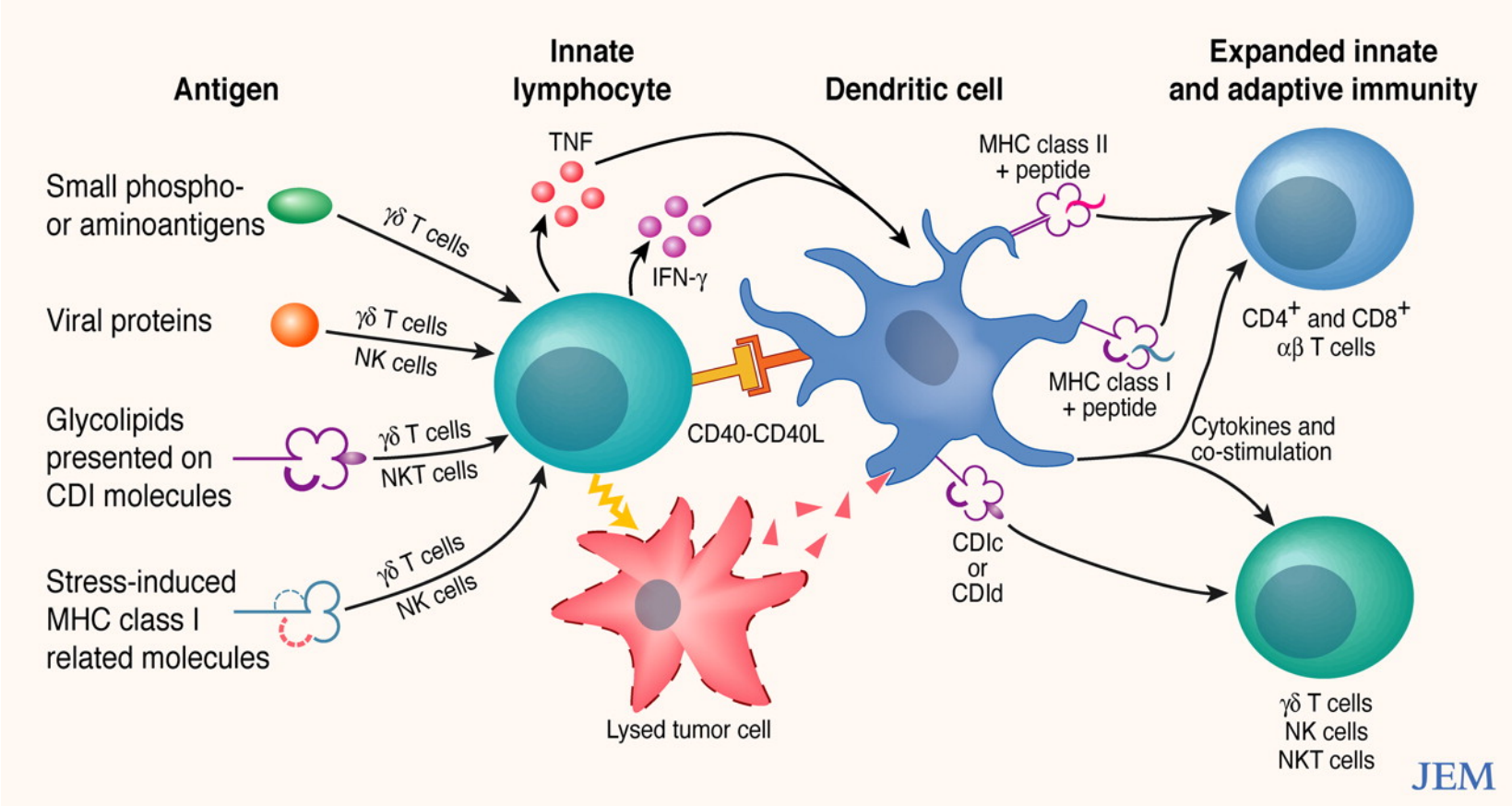
Innate lymphocytes mature DCs. Innate lymphocytes, including γδ T, NKT, and NK cells recognize pathogen-derived and self-antigens on infected cells, tumors, and stressed self-tissues (left).



Christian Münz et al. J Exp Med 2005;202:203-207

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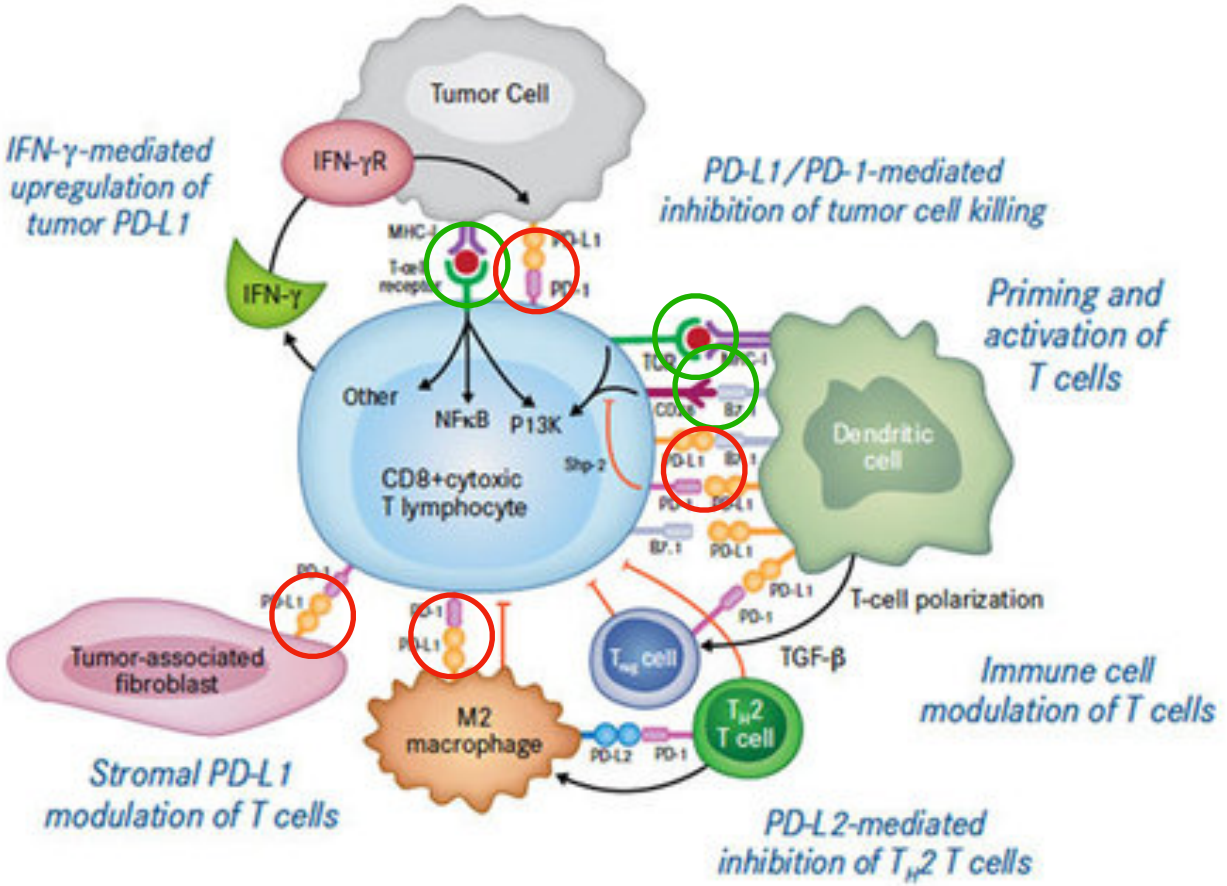
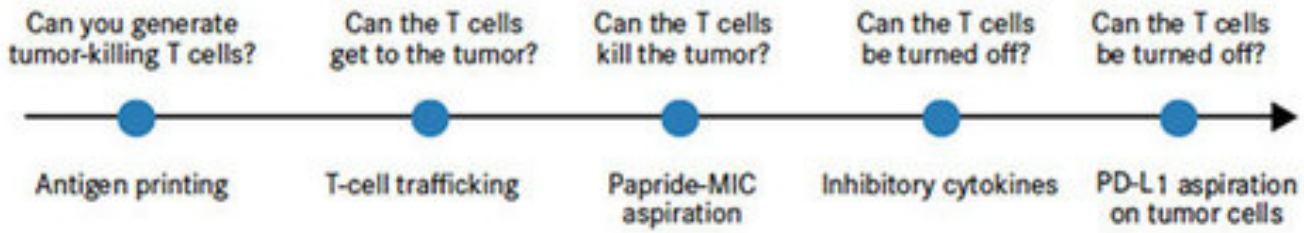
Cytotoxic T cell





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Tumor Antigens

- Epithelial mucin, MUC1, was first tumor antigen shown to be recognized by human CTL from a patient with pancreatic cancer
- Peptides eluted from HLA class I and II molecules on tumor cells, characterization by mass spectroscopy and representation on APC identified more antigens
- Antigens presented on tumors are from mutated AND non-mutated genes

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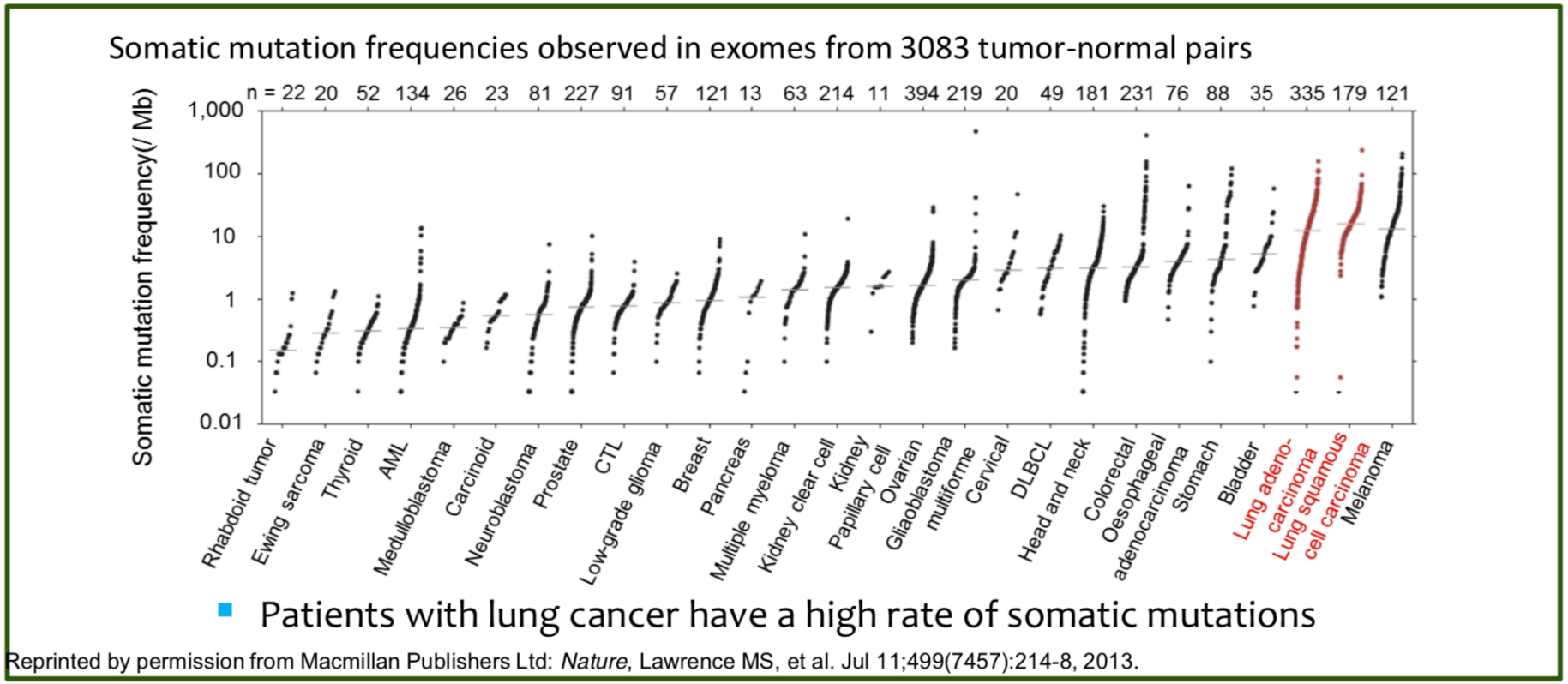
Higher mutation rates and immunogenicity



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Nature 515:572, 2014

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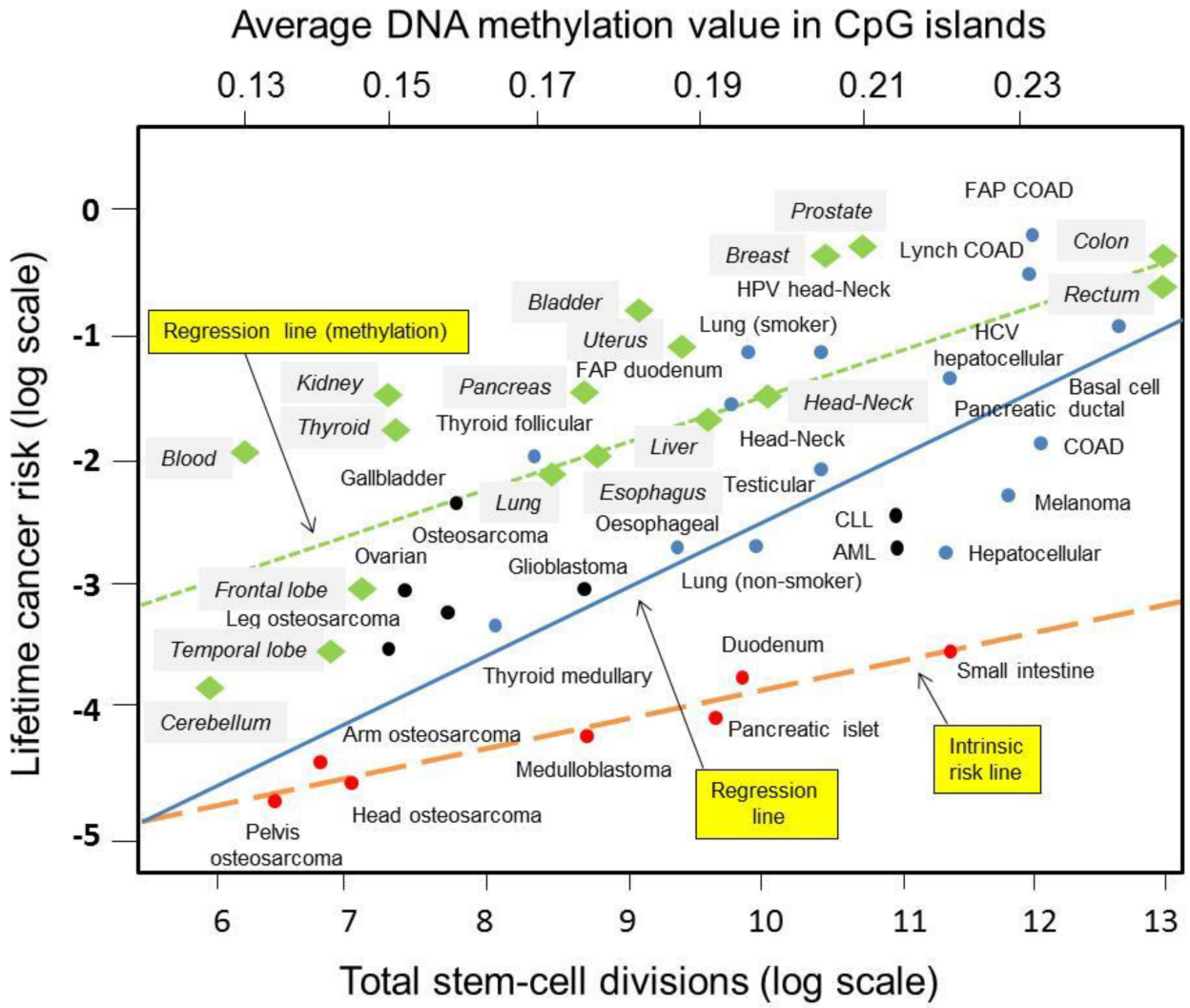
Intrinsic Cancer Rates



Vogelsang et al

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The Benzene Tree

The Atlantic 10/4/17
How the Benzene Tree Polluted the World

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Immune Escape

- Because cancer patients have tumors they have tumors that have by definition escaped immunosurveillance
- Hence, we don't have as much information about when the immune system becomes involved in cancer detection and elimination
- However, we do know there are expressed tumor antigens that can cause an immune response

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Tumor Antigens: Unique!

Mutated Antigens Recognized by TIL from 99 Patients with Epithelial Cancers

Cancer	# of patients screened	# of patients with neoantigen reactivity	Total # of neoantigens recognized
Colorectal	45	39 (87%)	95
Cholangiocarcinoma	12	9 (75%)	20
Pancreatic	6	5 (83%)	7
Esophageal	2	2 (100%)	3
Endometrial	3	3 (100%)	4
Breast	10	7 (70%)	22
NSCLC	11	8 (73%)	34
Ovarian	7	6 (86%)	16
Stomach	3	2 (67%)	5
TOTAL	99	81 (81.8%)	197

All neoantigens were unique except for 2 KRAS antigens.

Rosenberg, ASH Immunotherapy Conference 2018

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Hence, NO general cancer vaccine on the horizon (maybe personalized?)

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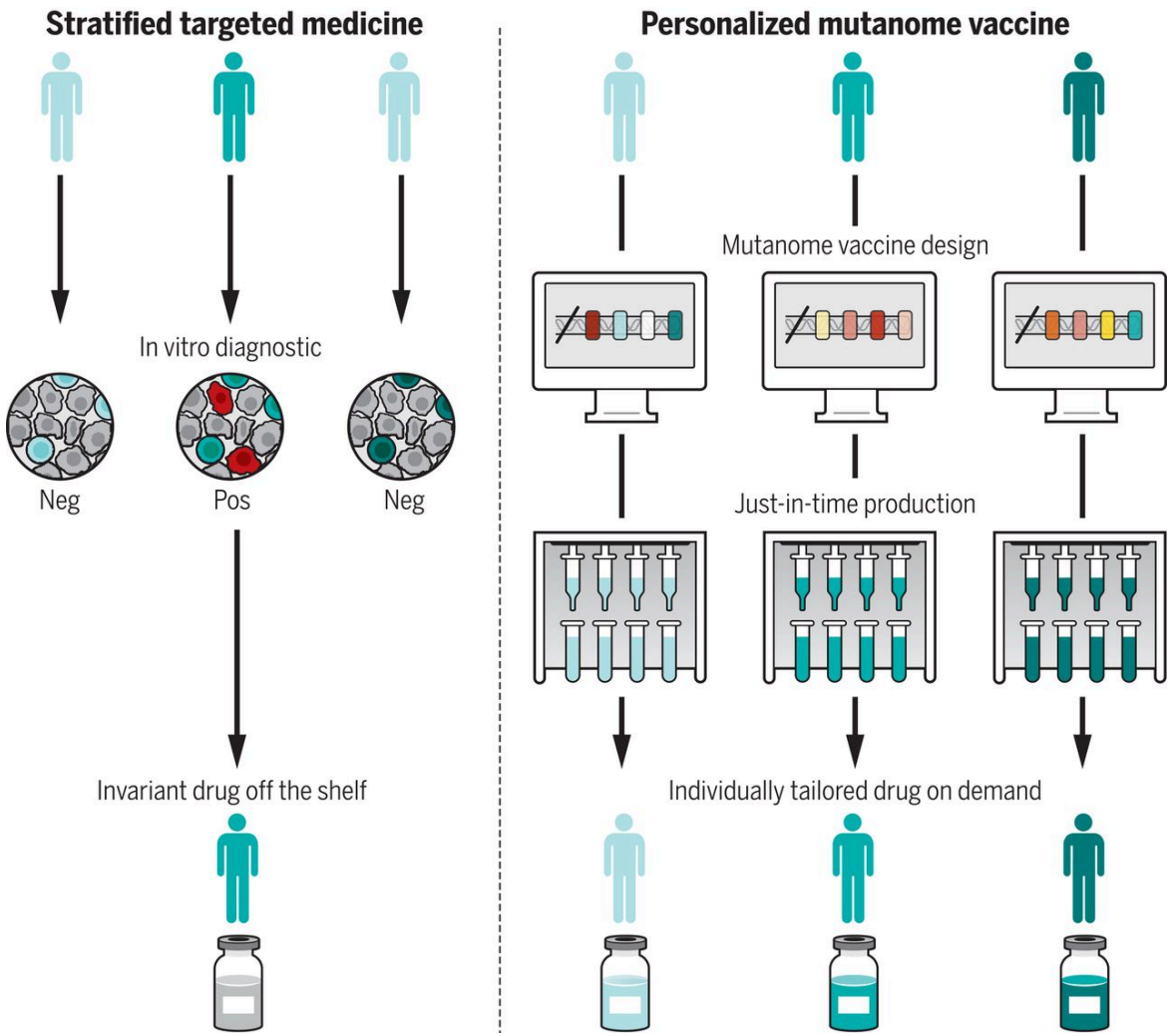
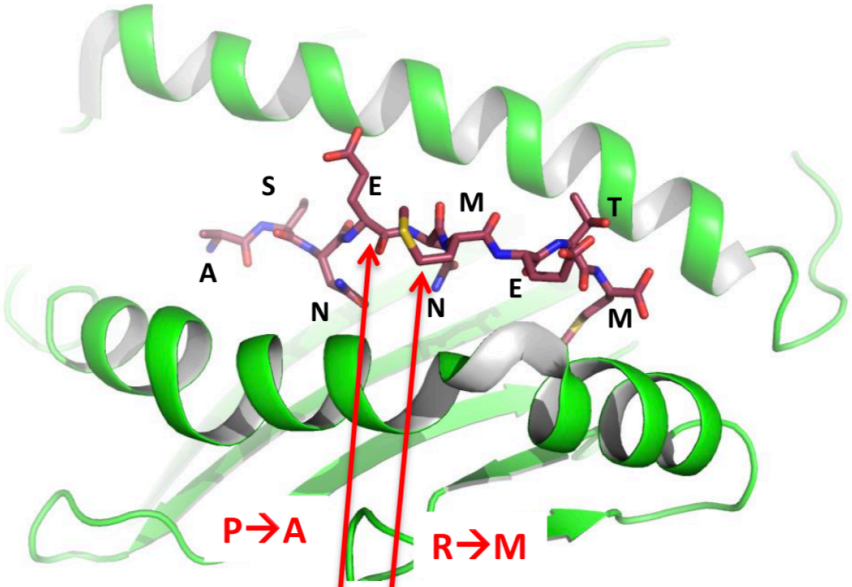
Fig. 3 Personalized cancer medicine.



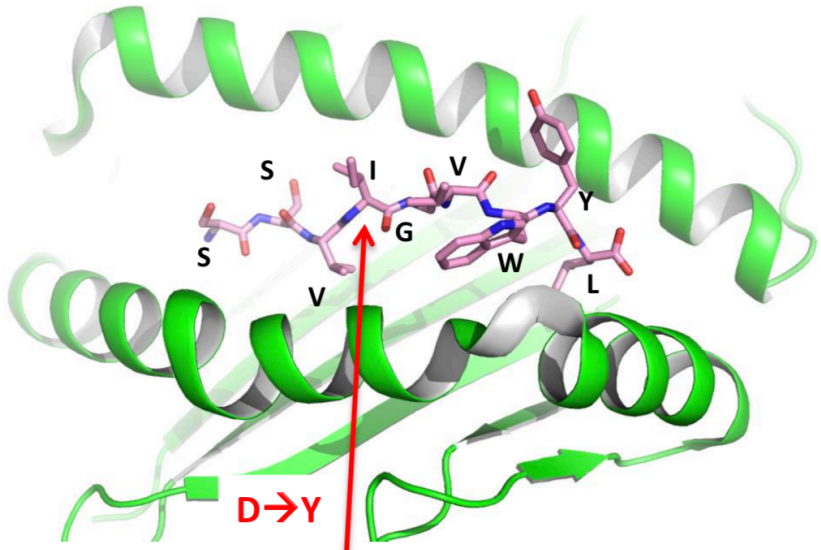
Ugur Sahin, and Özlem Türeci Science 2018;359:1355-1360

Published by AAAS

Cancer mutation immunogenicity variability



REPS1	AQLPNDVVL
ADPGK	ASMTNRELM
FLU-NP	ASNENMETM



Copine-1	SSPDSLHYL
H60	SSVIGVWYL

Nature 515:572, 2014

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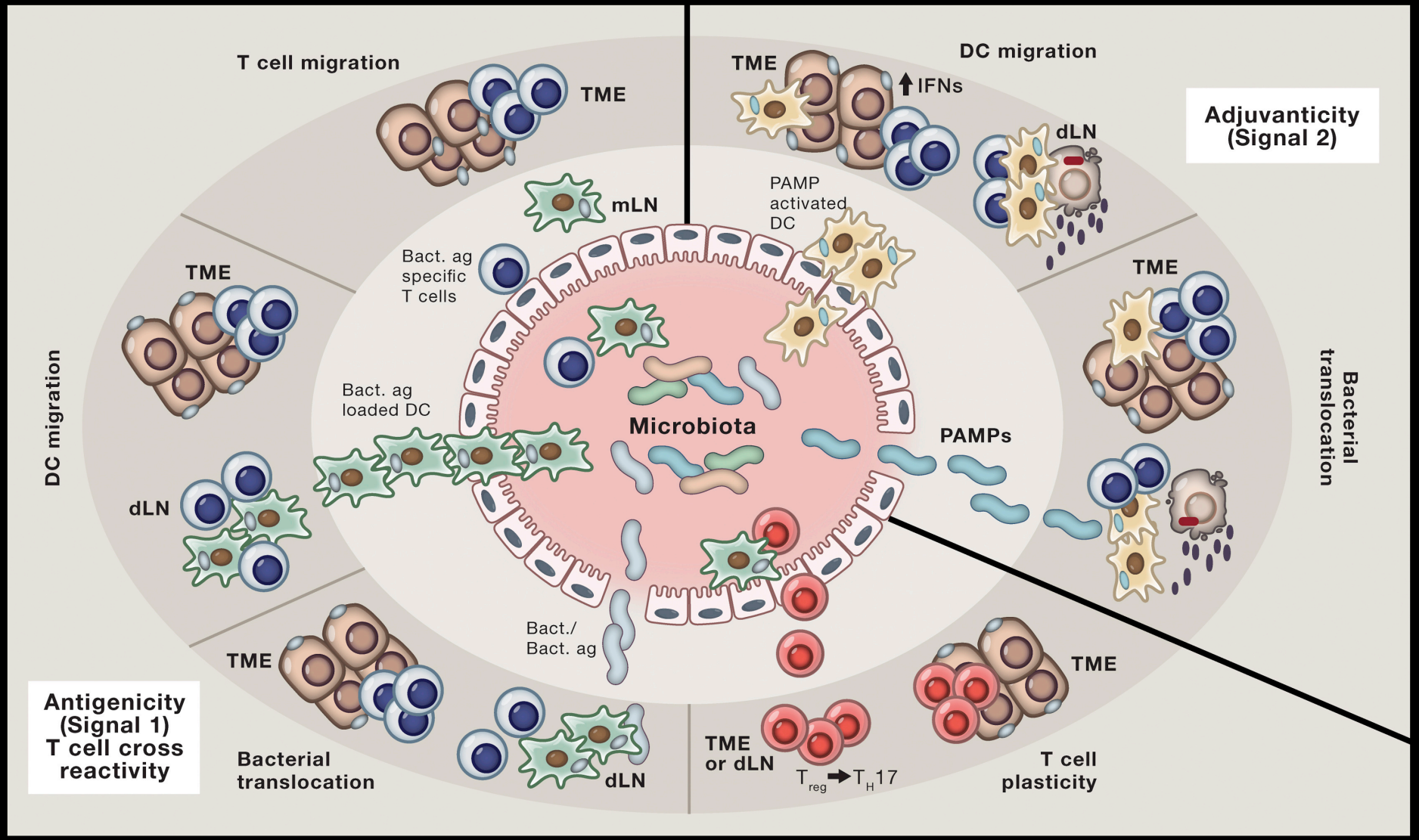

Cell 2016 165, 276-287DOI: (10.1016/j.cell.2016.03.001)
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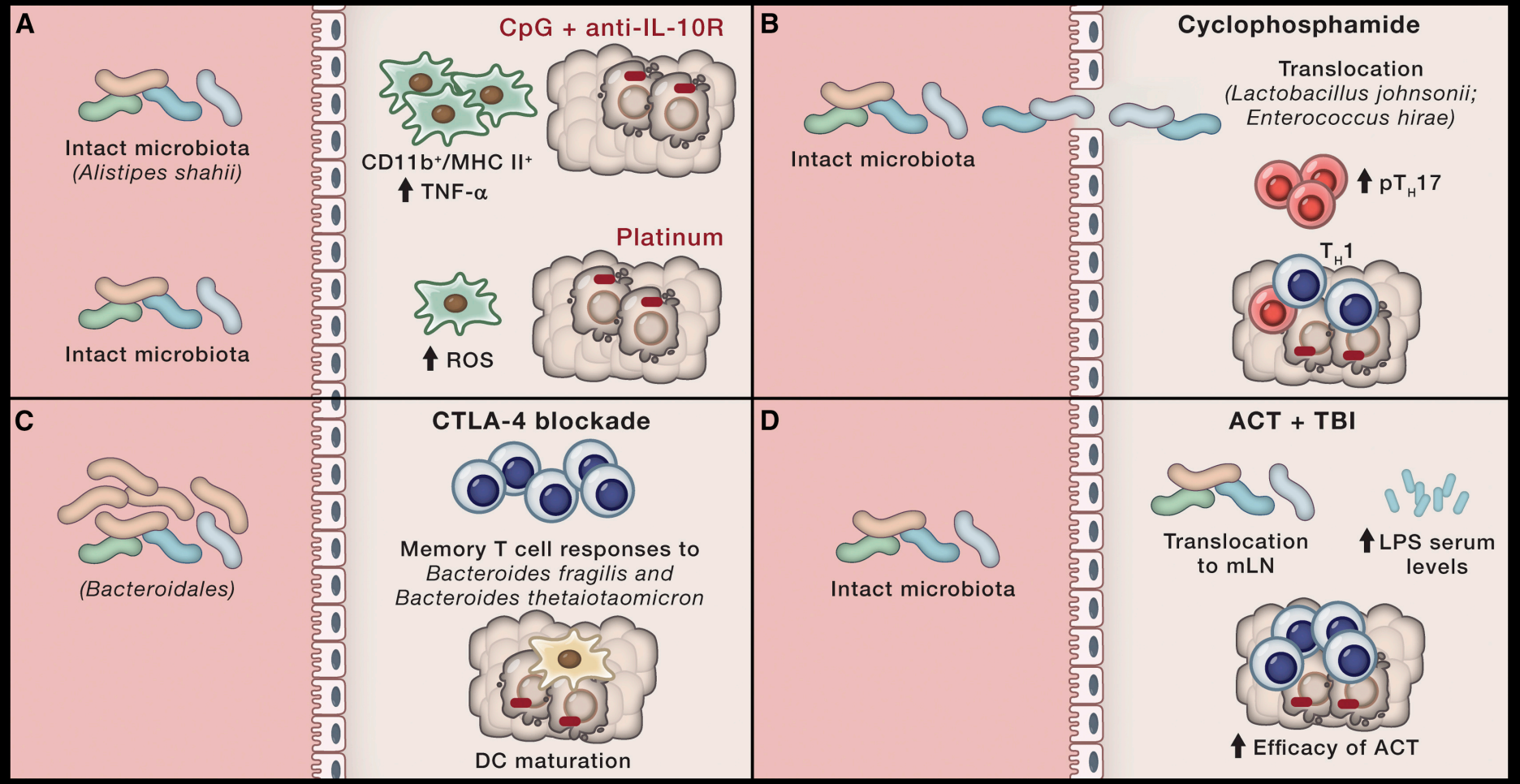

Cell 2016 165, 276-287DOI: (10.1016/j.cell.2016.03.001)
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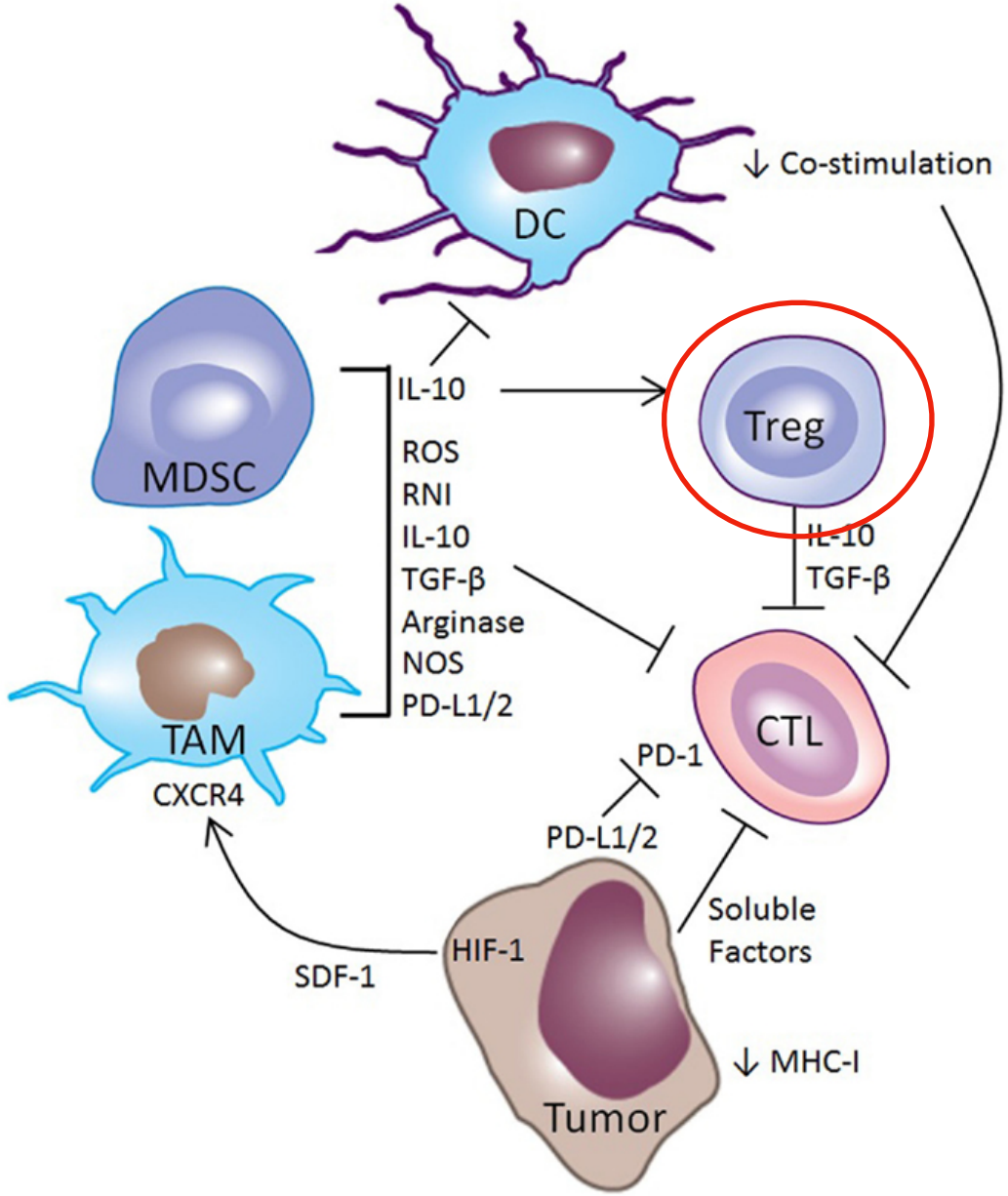
Tumor Immunologic Microenvironment



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Variability: Escape

- Genetic differences affecting the immune response affect immunosurveillance and immunotherapy
- Cancers have varying genetic mutations AND virtually never share the same immunogenic antigens
- Individuals with varying HLA types have varying ability to present various tumor antigens
- Microbiome differences between individuals affect immune response to therapy (and potentially immunosurveillance)
- Differing tumor microenvironment influences retard the immune response

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In many cases, immune escape is accompanied by ongoing immune attack which is too weak to prevail

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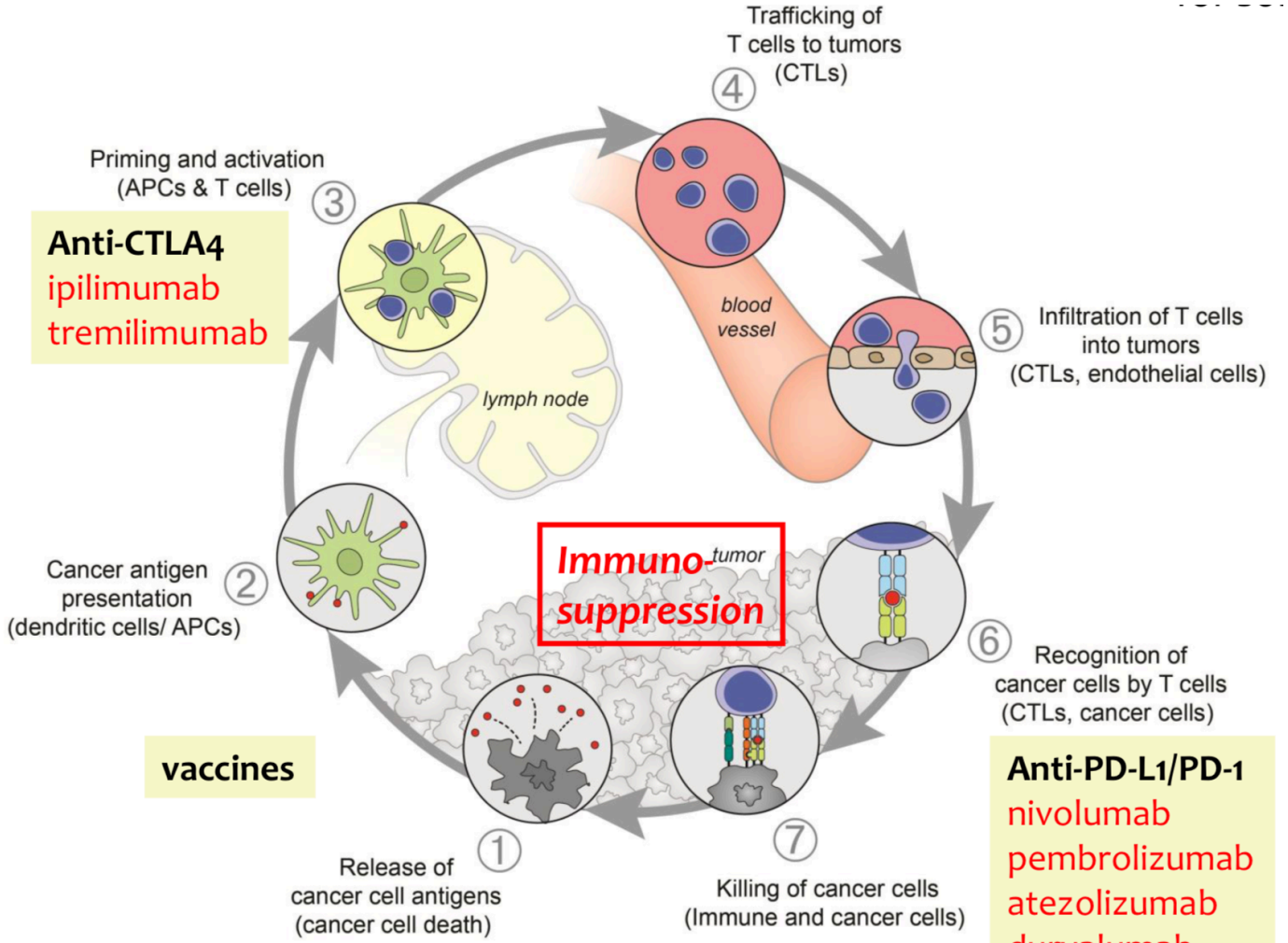
Priming and Killing



Chen & Mellman (2013) Immunity

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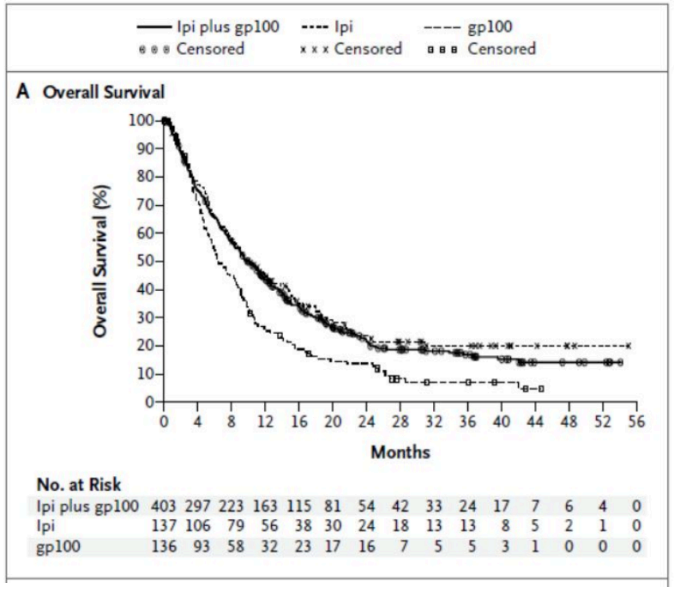
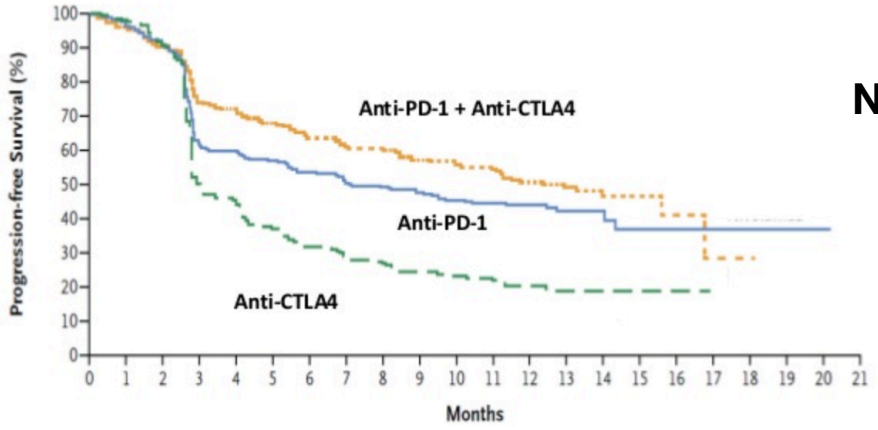
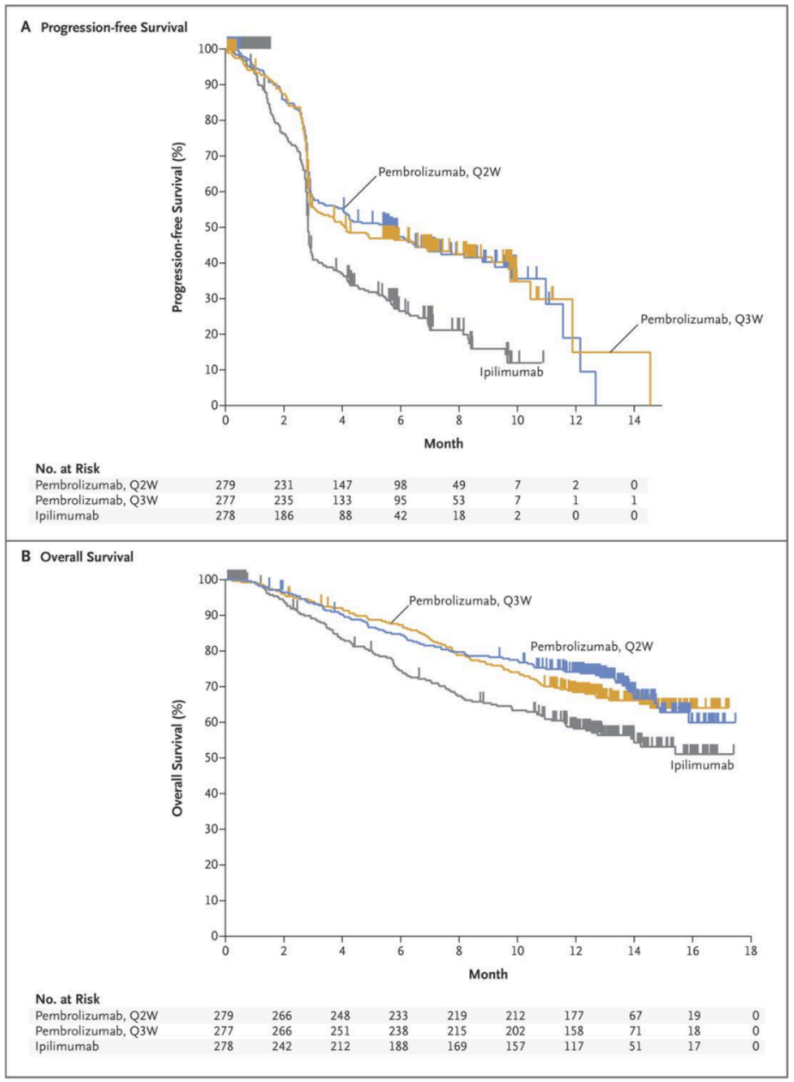
Anti-CTLA4 and Anti-PD1





NEJM 363:8, 2010
NEJM 372:2521, 2015
NEJM 373:23, 2015



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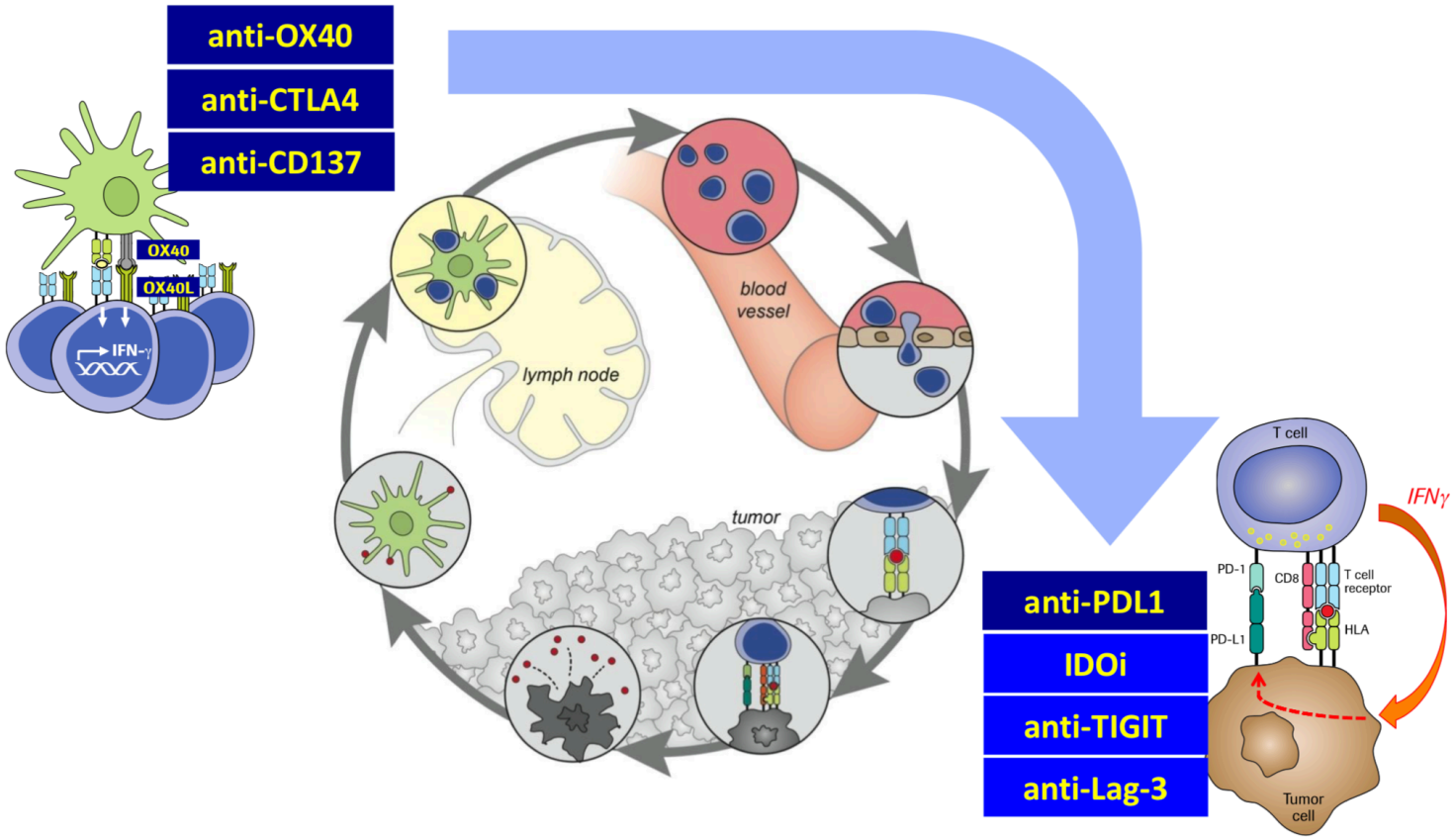
Improvements



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By manipulating inhibitory signals between APC:T and T:Cancer we can optimize antigen presentation to make better cytotoxic T-cells and can help break immune escape

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What if there is an immune response but blocking inhibitors is not enough to overcome immune escape?

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Could we collect tumor infiltrating lymphocytes (TIL), expand them and return them after inhibiting regulatory cells?

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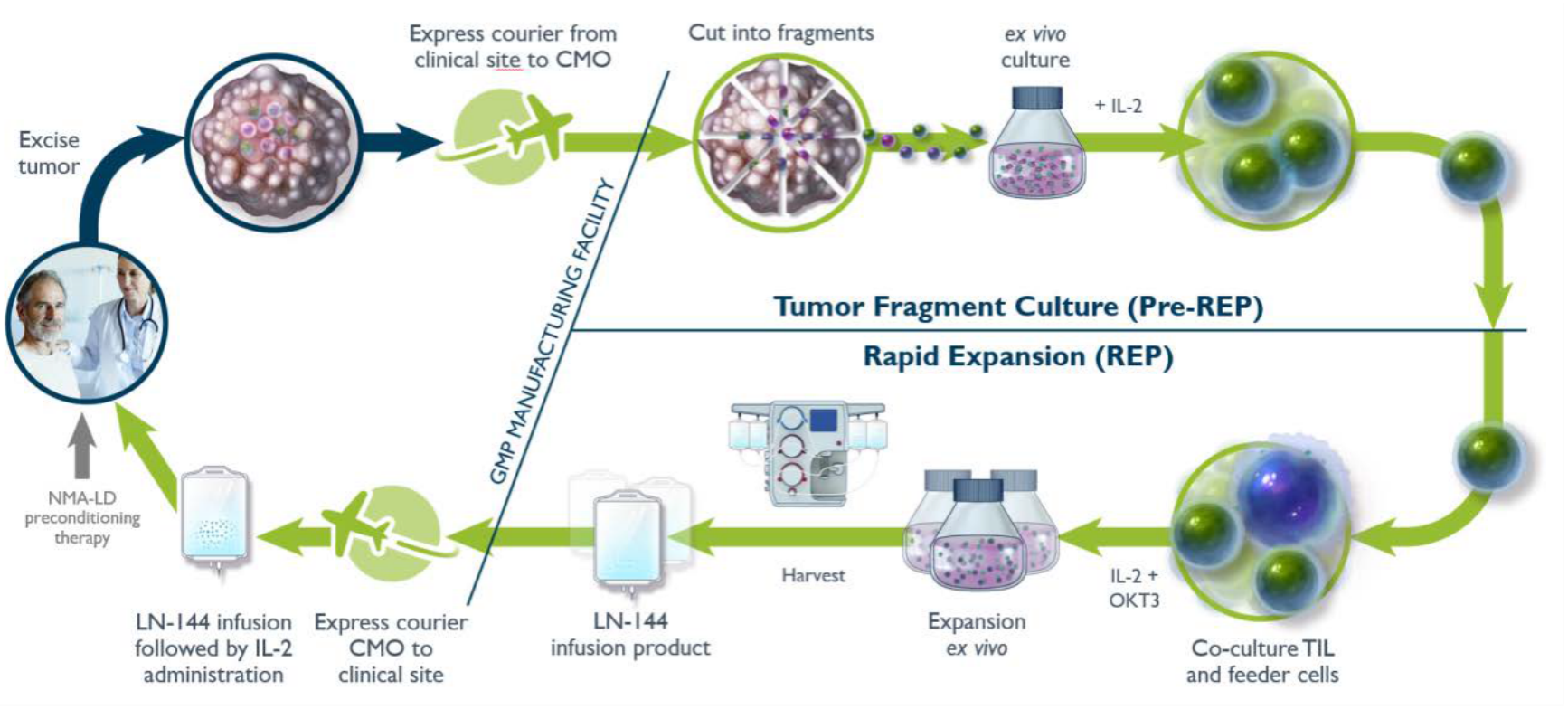
TIL Expansion Therapy



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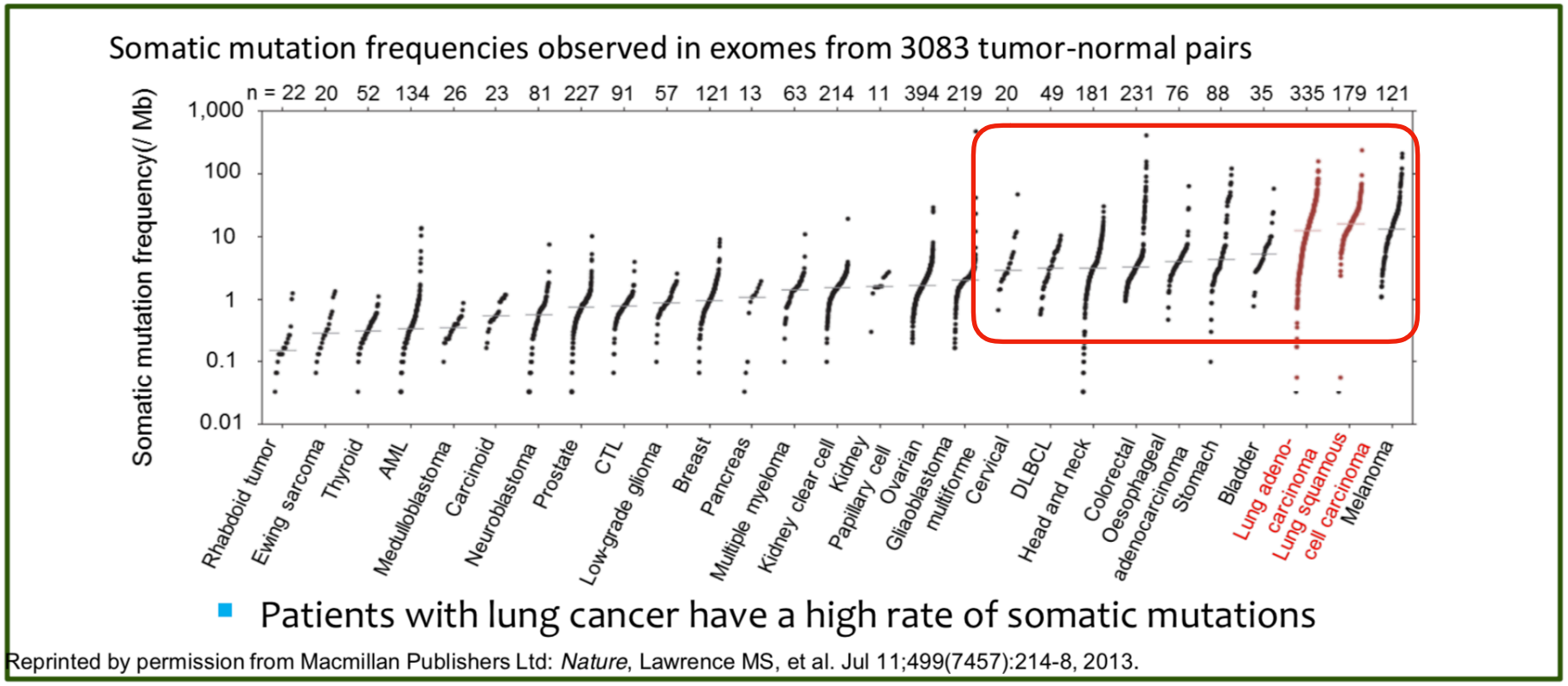
TILs work best when mutation rates high (antigen)



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Nature 515:572, 2014

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What about lower mutation (antigen) situations where manipulation of inhibitory signals or TIL expansion is not enough?

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In the case of many blood cancers (lesser solid tumors) we can replace the immune system with one from and HLA matched donor: Allogeneic transplant

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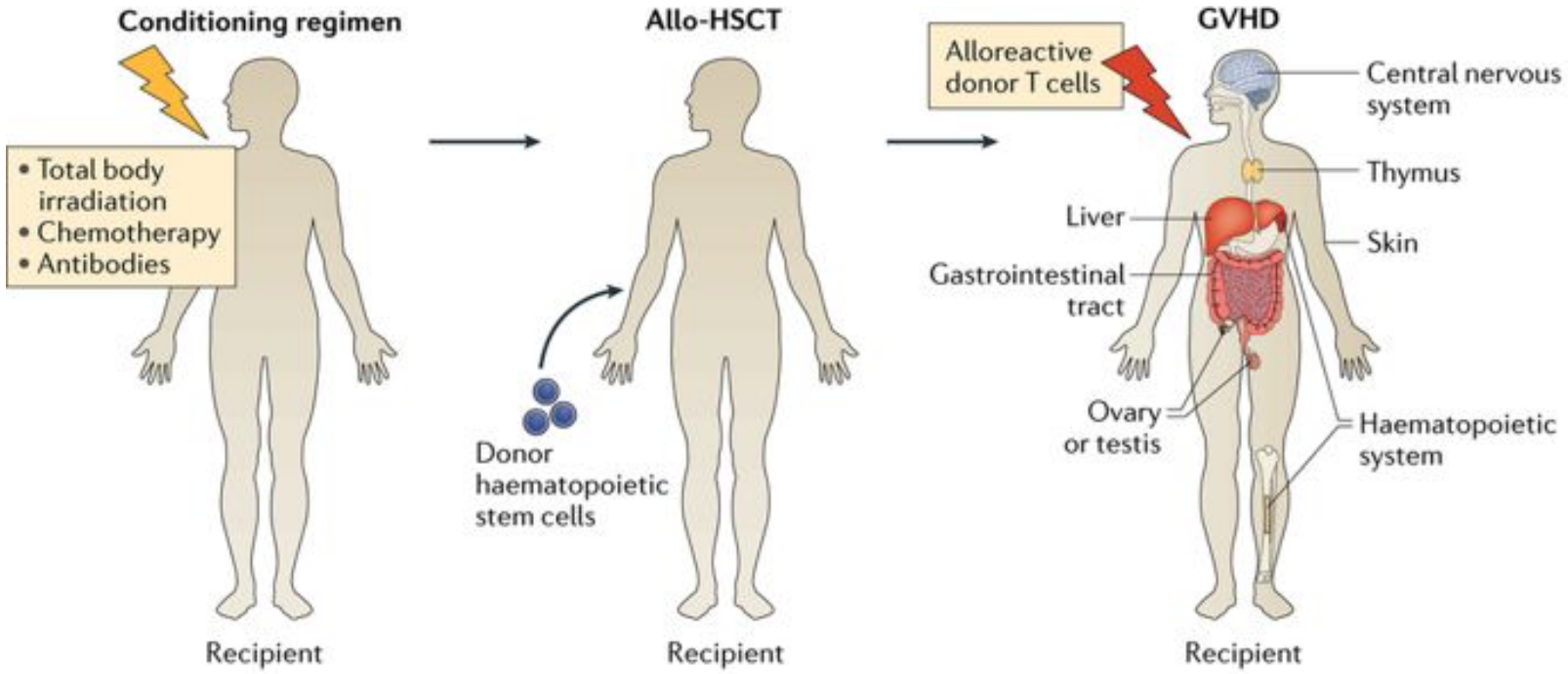
Allogeneic Transplant



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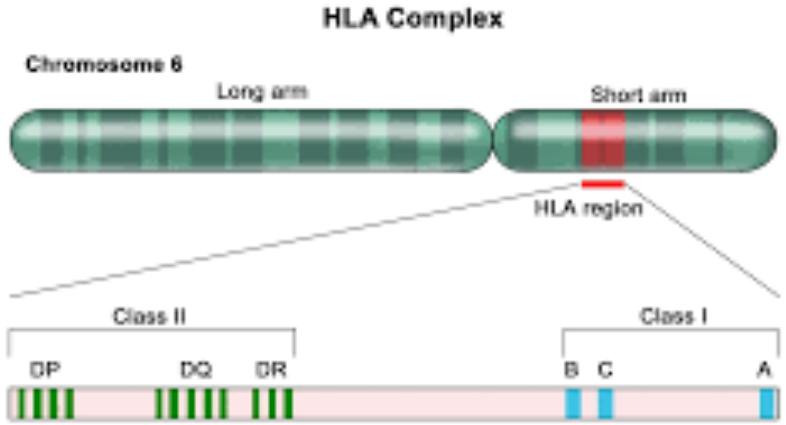
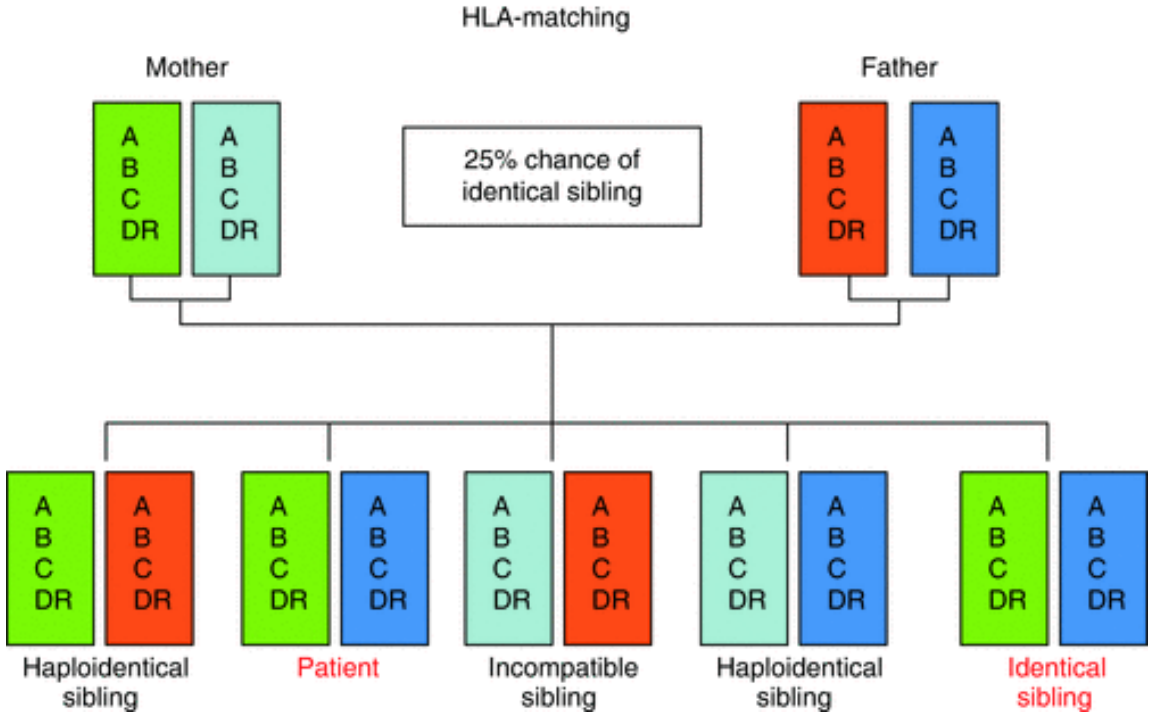


HLA Matching



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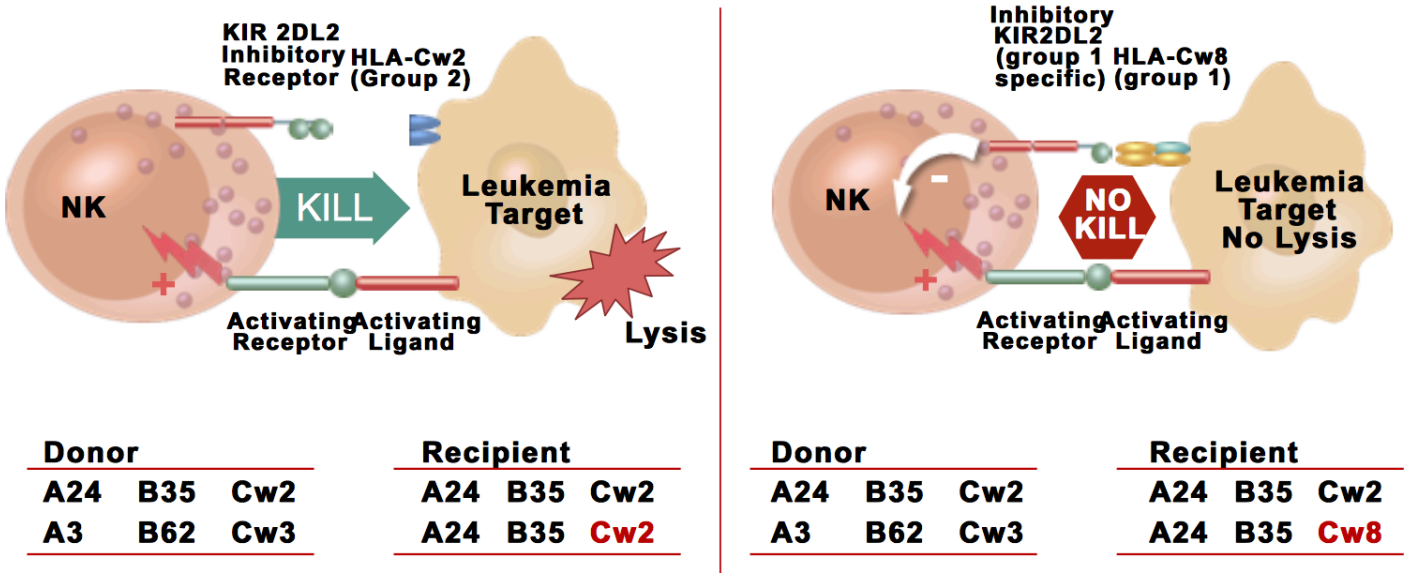
Haplo transplant AML: NK



Donor		
A24	B35	Cw2
A3	B62	Cw3

Recipient		
A24	B35	Cw2
A24	B35	Cw2

Donor		
A24	B35	Cw2
A3	B62	Cw3

Recipient		
A24	B35	Cw2
A24	B35	Cw8

Haplo transplant done with high dose chemotherapy, radiation and ATG; no T-cells in the early phase post transplant, yet AML patients did not relapse

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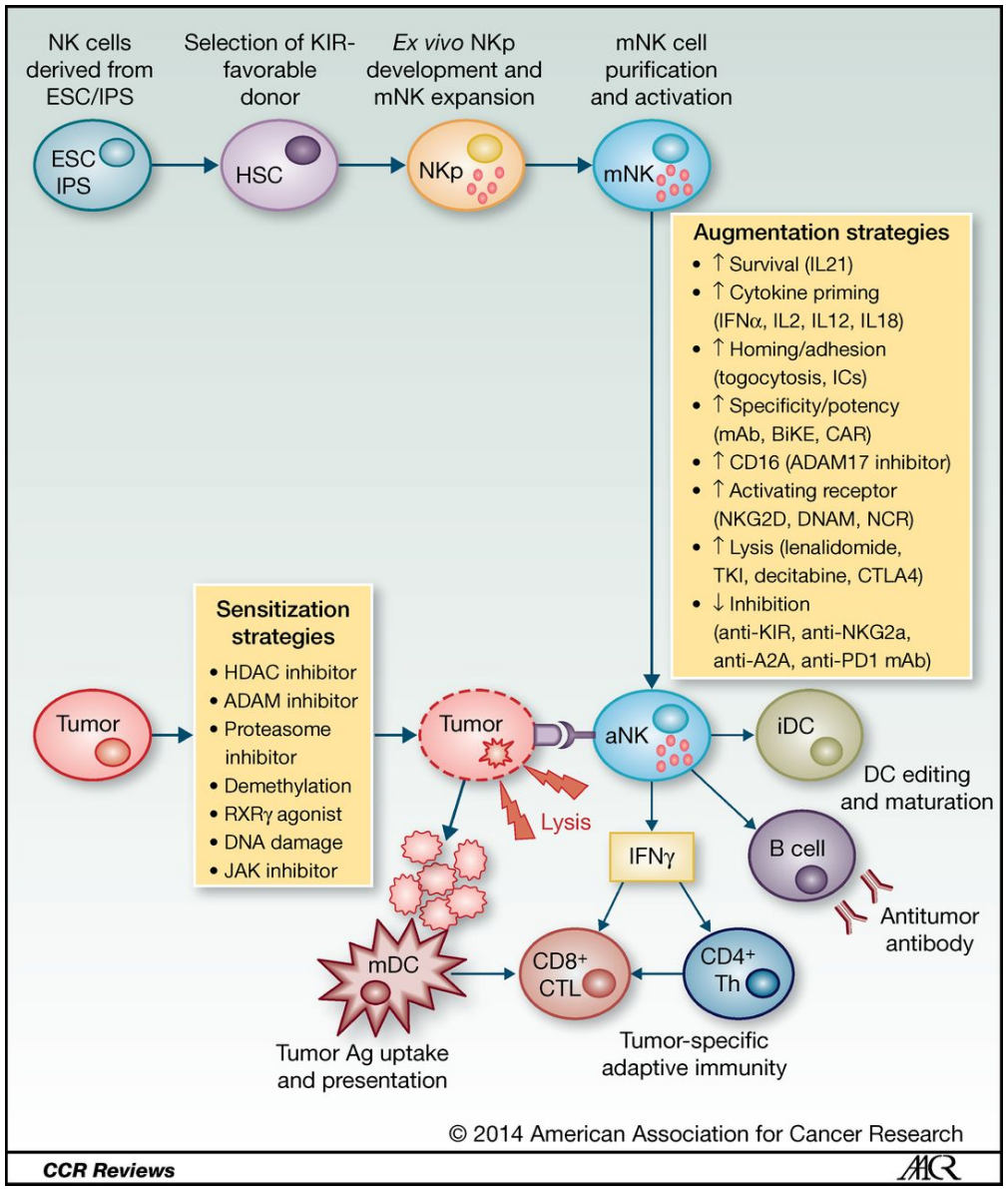
Clinically feasible approaches to optimize NK cell therapy.



©2014 by American Association for Cancer Research

Wing Leung Clin Cancer Res 2014;20:3390-3400

Clinical Cancer Research
AACR American Association for Cancer Research

What about:
Cancers not sensitive to the allo effect?
Cancers growing too fast for allo effect to work?
Cancers not responsive to NK attack or TIL therapy?

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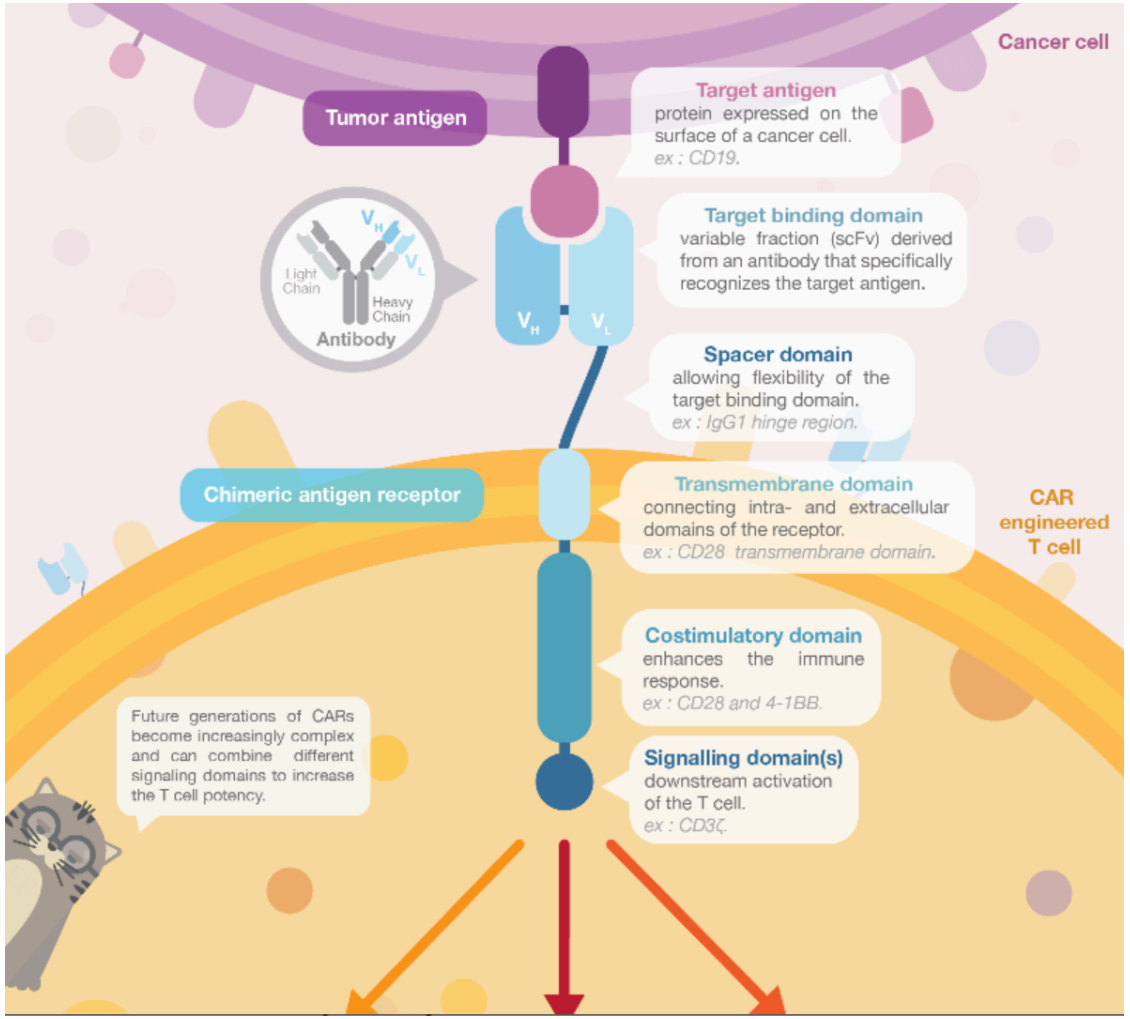
Chimeric Antigen Receptor (CAR) T cells



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3 Technologies have made this possible

- **ScFv:** Single Chain Variable Fragment. Genetic shuffling of heavy and light chain variable regions from an antibody into a single protein combined with bacteriophage expression.
- **T-cell signaling:** Better understanding of how the T-cell receptor works and sends signals to the T-cell when the receptor is activated.
- **Viral vector:** Improved delivery of genes into cells efficiently with high and stable expression over time.

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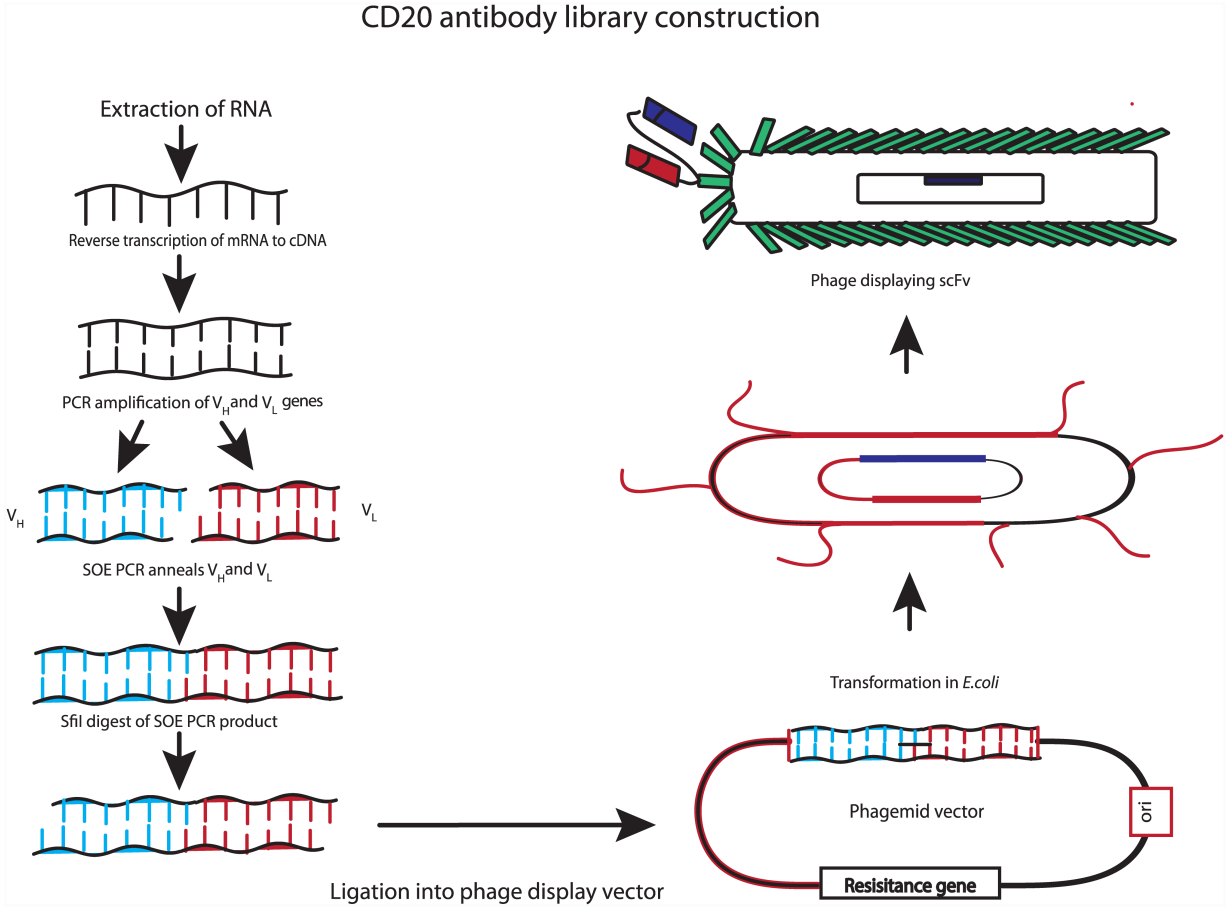
ScFv technology



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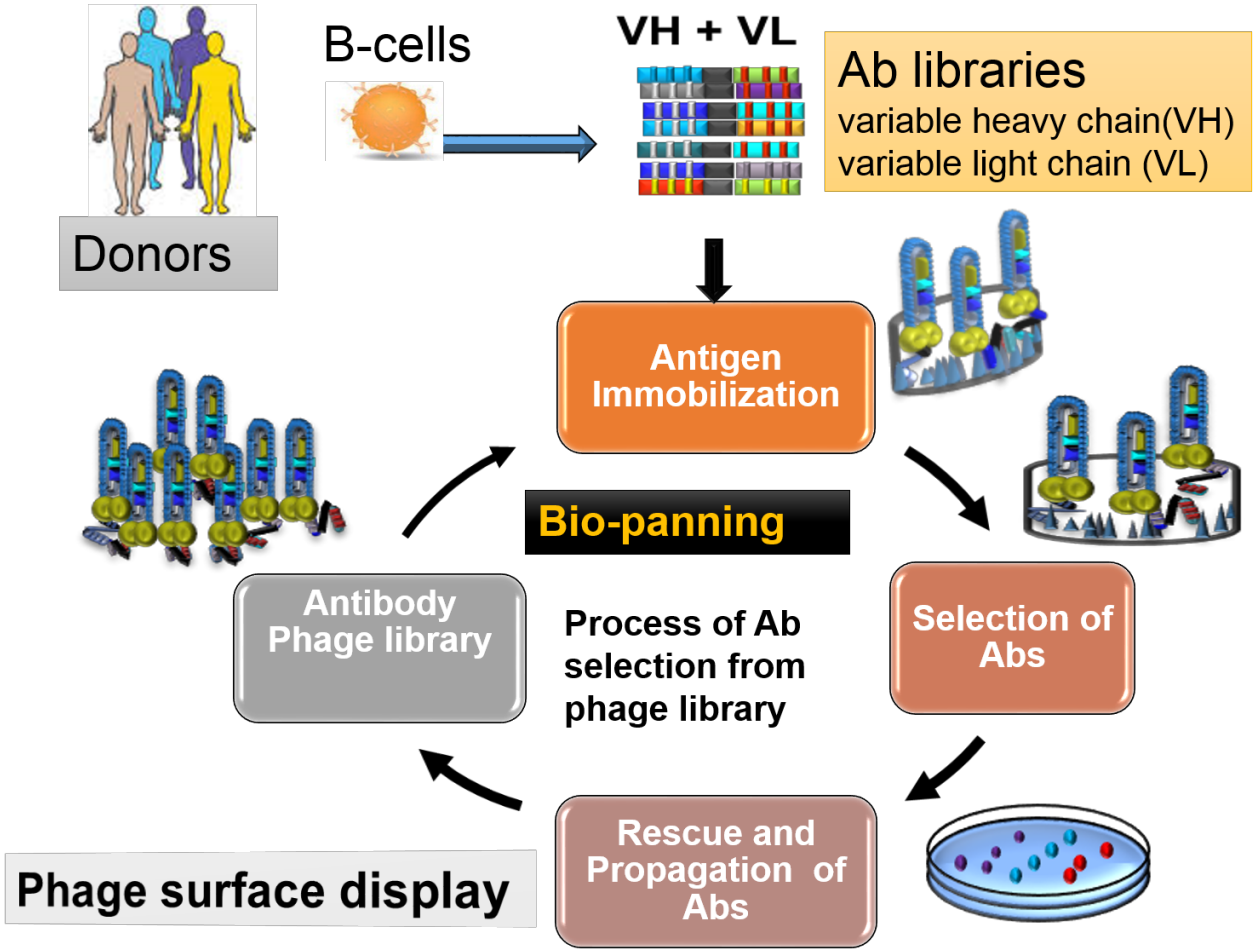
ScFv targeting



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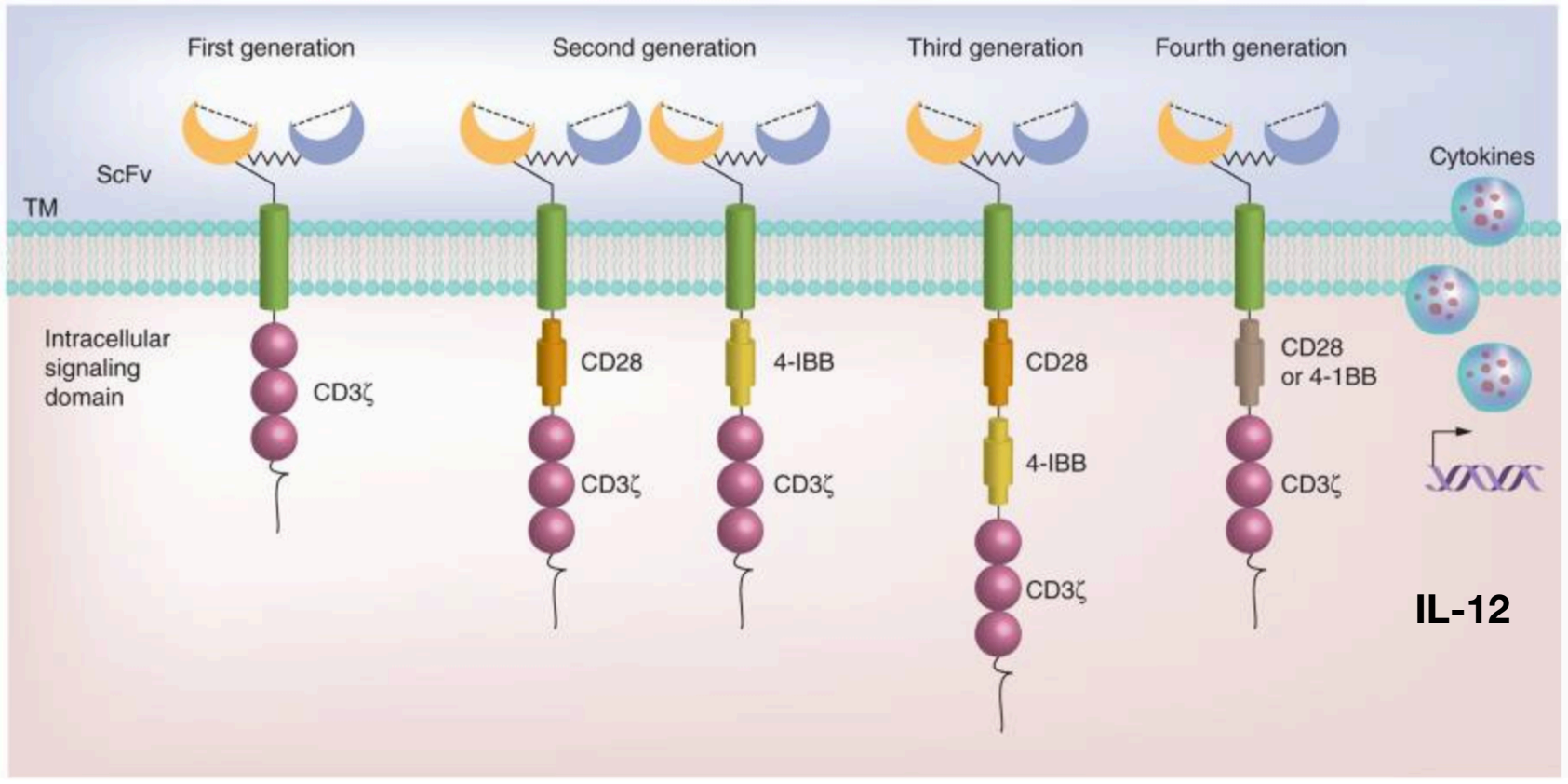
Evolution



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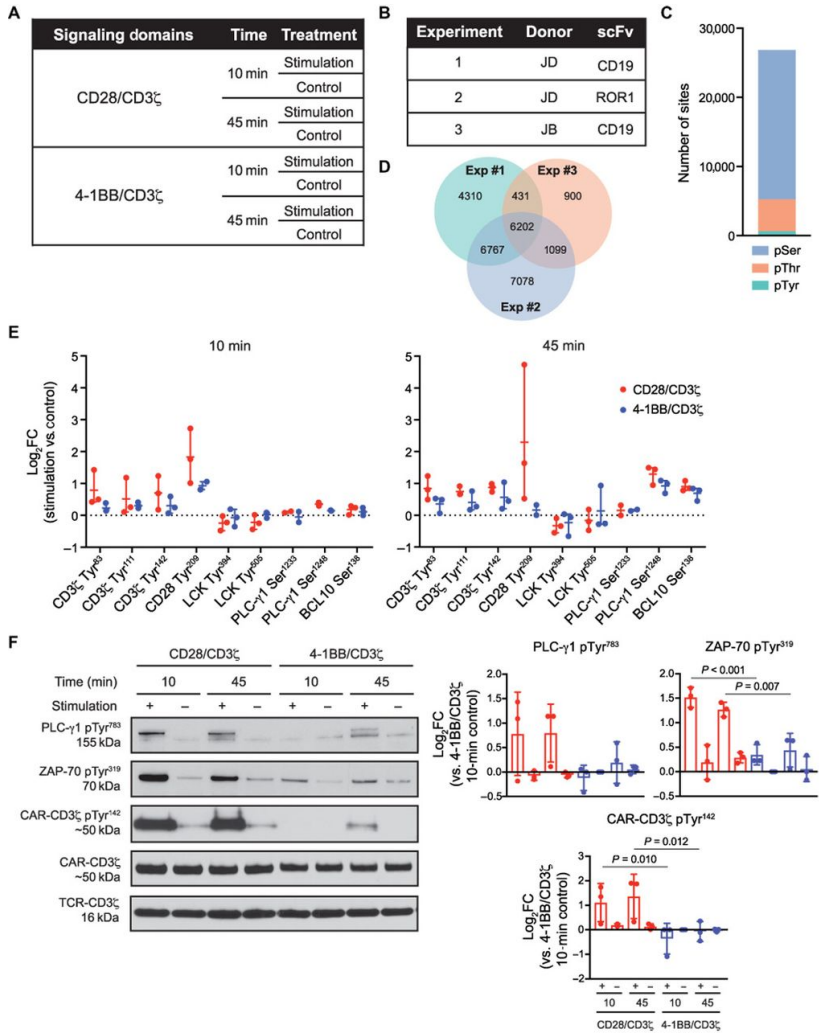
CAR T cells signal through endogenous T cell signaling proteins.



Alexander I. Salter et al., Sci. Signal. 2018;11:eaat6753

Science Signaling
AAAS

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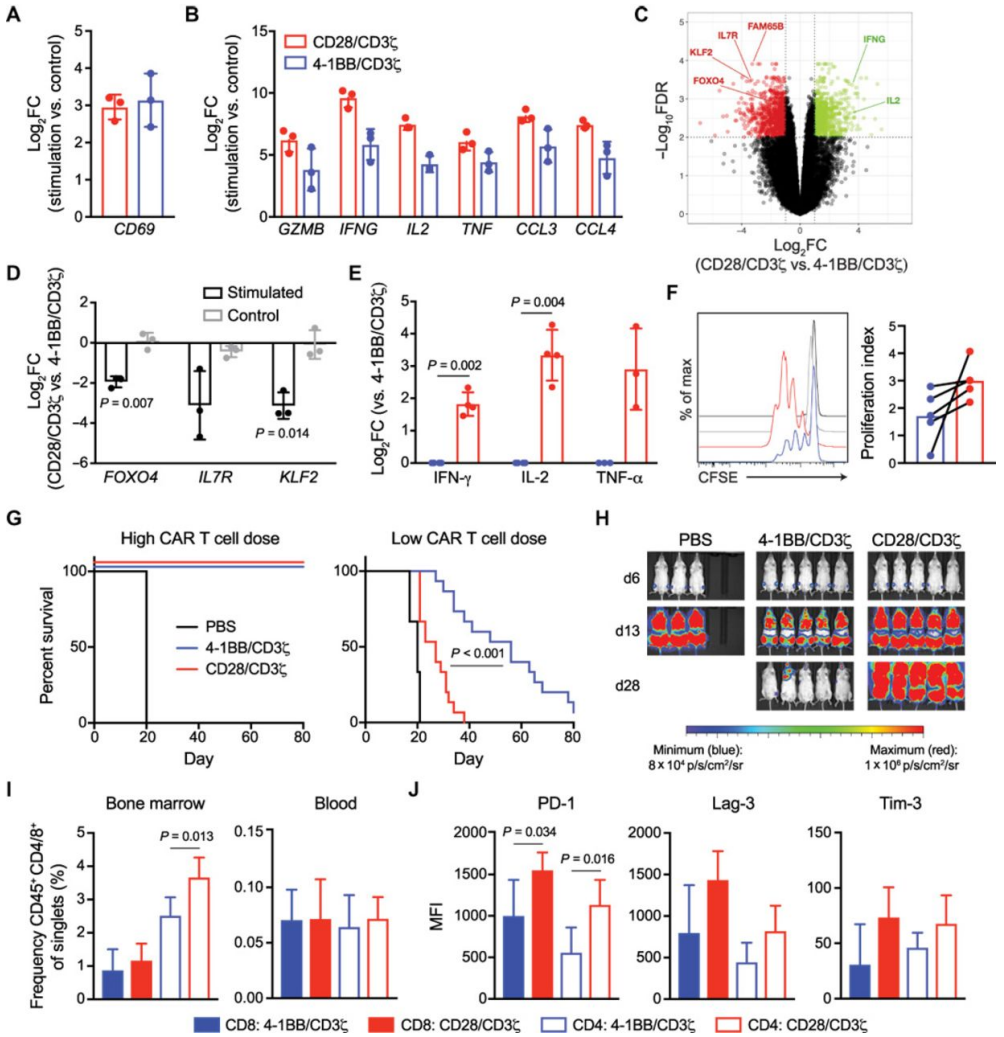
Increased CD28/CD3ζ CAR signal intensity is associated with an effector cell–like phenotype and reduced in vivo antitumor activity.



Alexander I. Salter et al., Sci. Signal. 2018;11:eaat6753

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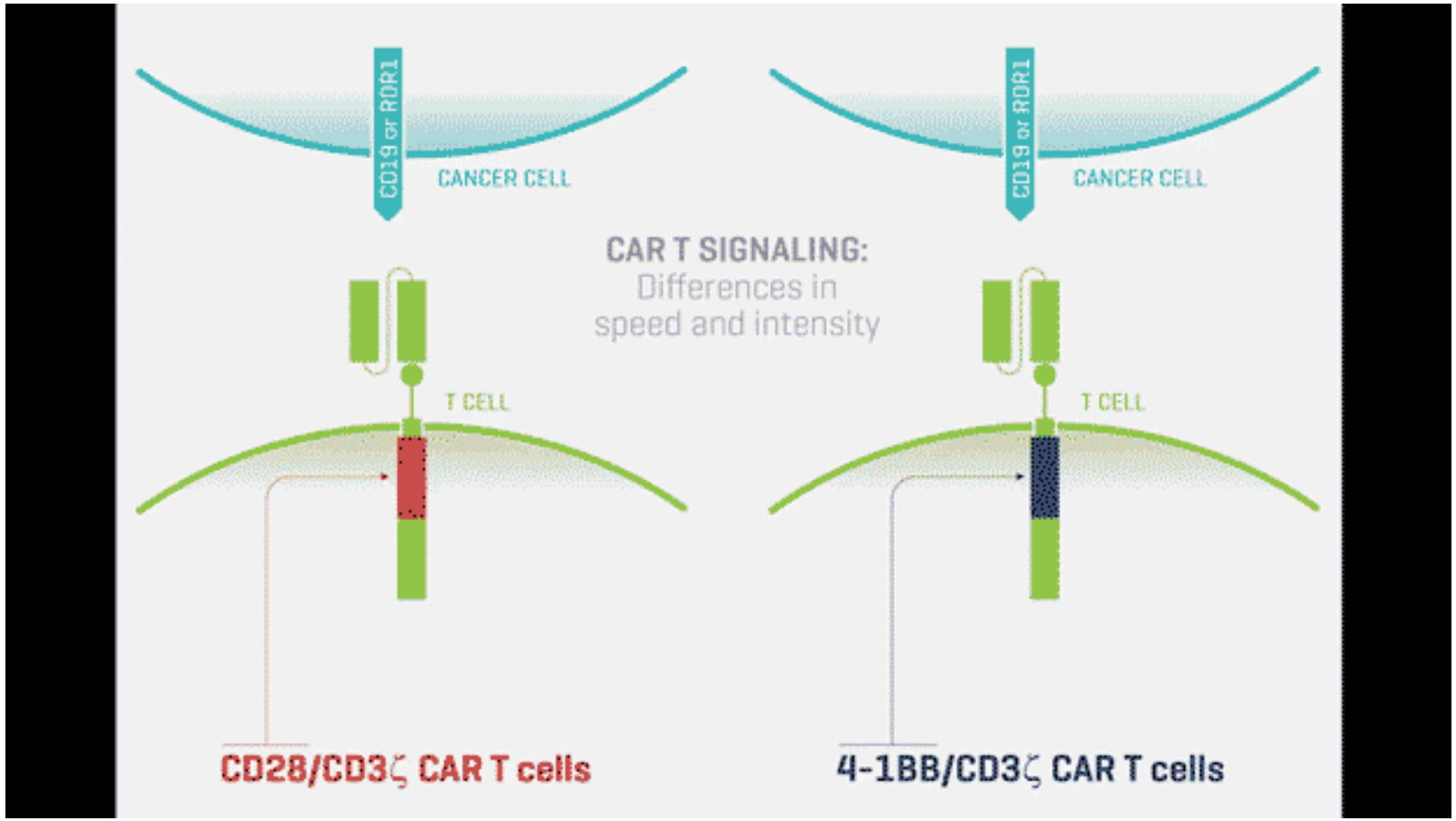
4-1BB Slower-Sustained



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Why IL-12?

- Recruits innate and adaptive effector cells
- Activates T cells, NK cells, CD11b+ myeloid derived cells
- Promotes Th1 cell polarization and reverses TH2 polarization
- Improves MHC class I presentation
- Increases IP-10, MIG chemokine secretion
- Alters extracellular matrix (decreases MMPs, VEGF, endothelial cell adhesion)
- Decreases angiogenesis

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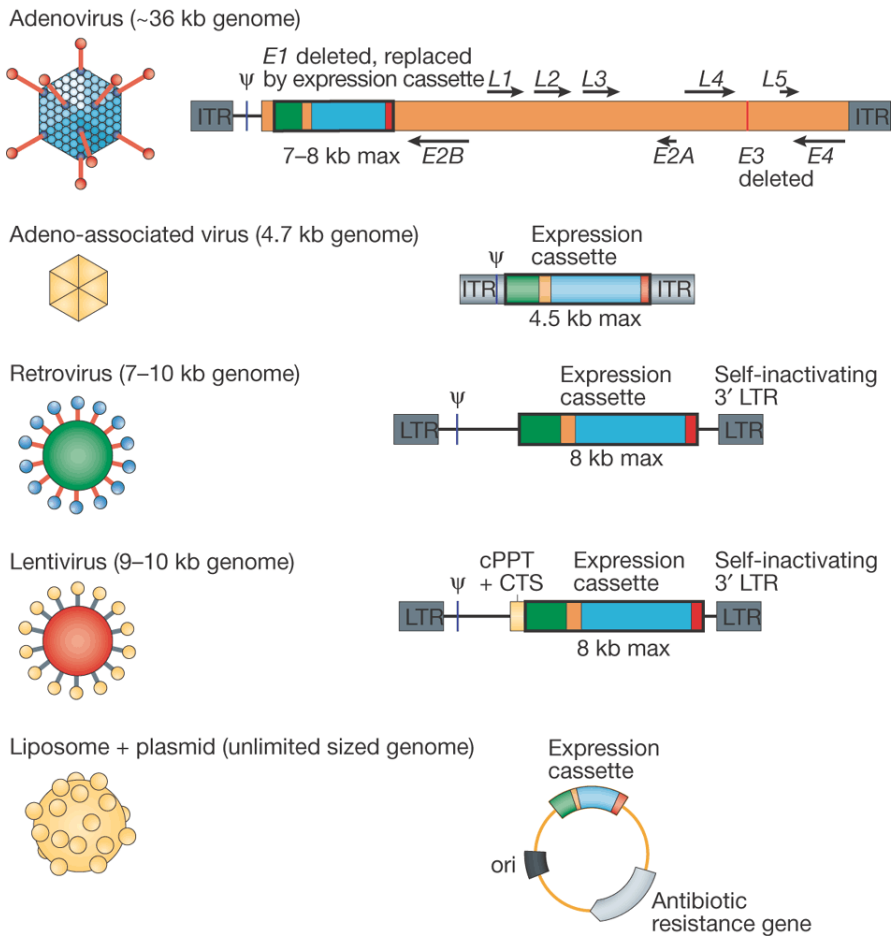
Gene Therapy Vectors

- LV - Lentivirus vectors
- RV - gammaretroviral vectors
- AAV – adeno-associated vectors
- Adenovirus vectors

- **Vectors are replication defective** – so they cannot replicate and spread once they are inside the cells and after delivering the anti-HIV genes



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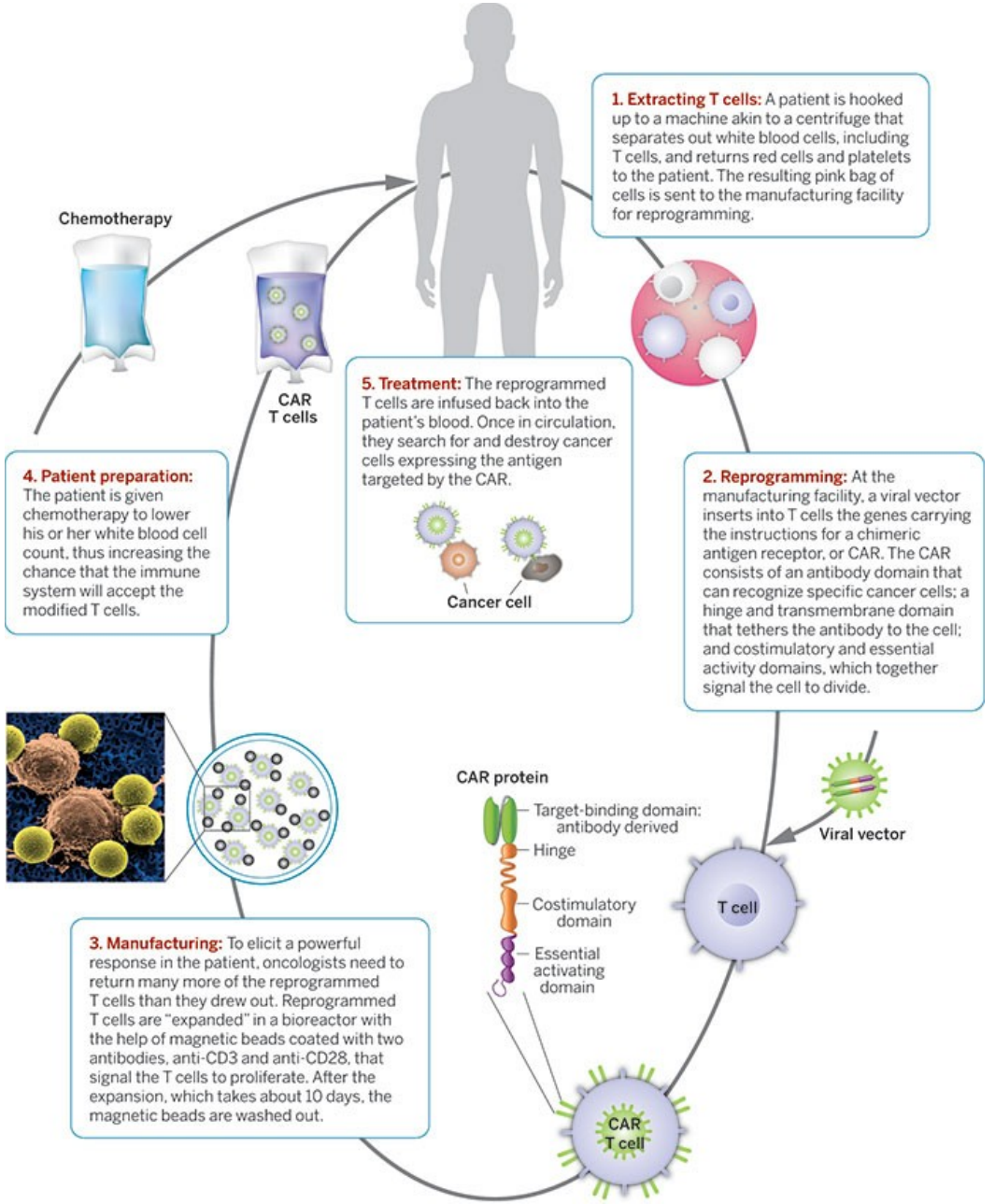

Car-T Therapy: Clinical Protocol

UofL Brown Cancer Center

AAEM American Academy of Emergency Medicine

ACCC Association of Community Cancer Centers

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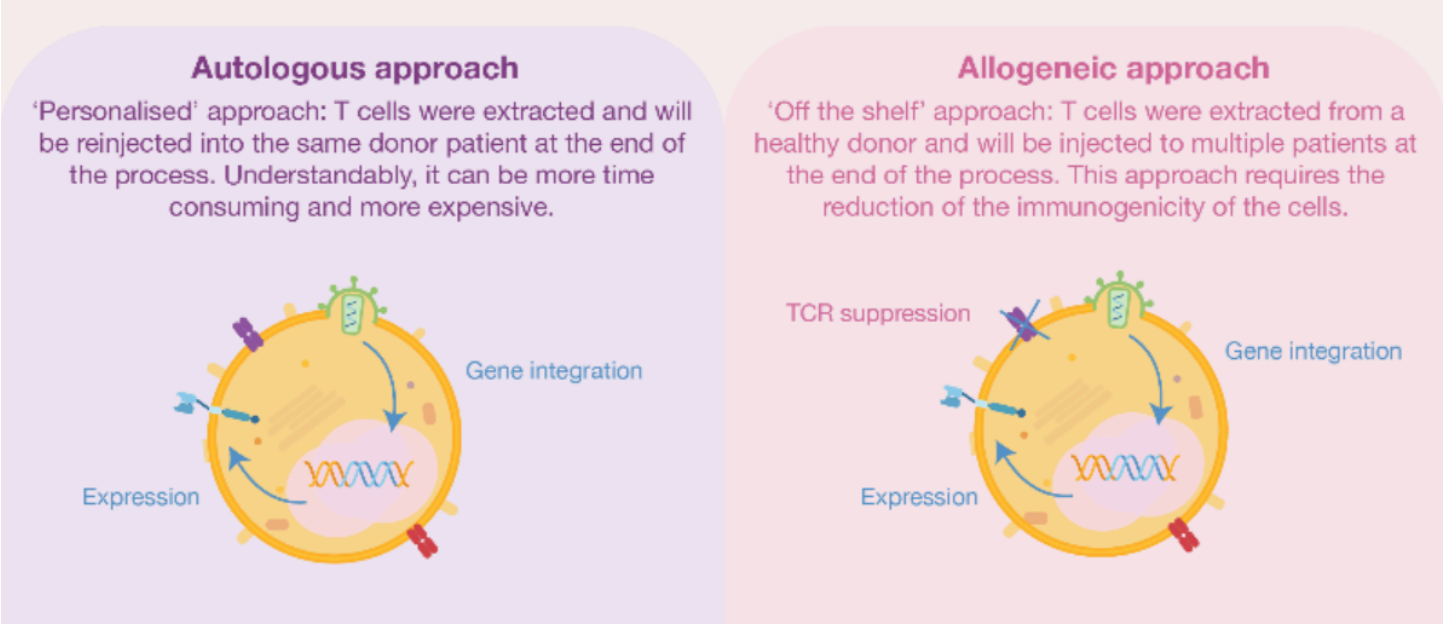
Auto vs Allo



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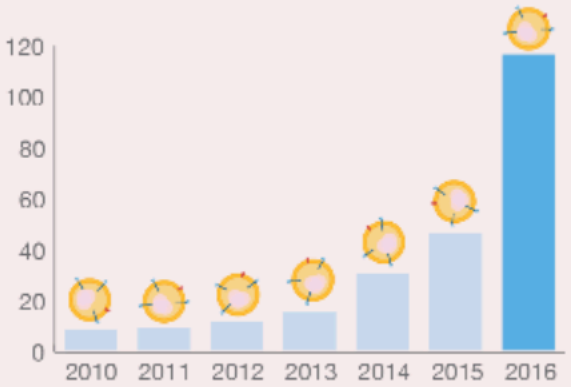
Activity in the USA

CAR-T therapies are generating huge hope and expectations. This can be translated by the number of clinical trials registered : more than 250 since 2004 and 116 for 2016 alone.

Novartis is currently leading the race for the commercialisation of CAR-T therapies. **Kymriah™** was unanimously approved by the FDA for the treatment of children with ALL*. This CAR-T is directed against cancer cells expressing CD19 on their surface.



Number of total CAR-T clinical trials per year
(adapted from celltrial.org)

*ALL or Acute Lymphoblastic Leukemia is the most common cancer among children. Current treatments are limited to chemotherapy and stem cell transplant.

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Kymriah: CD19 Car-T

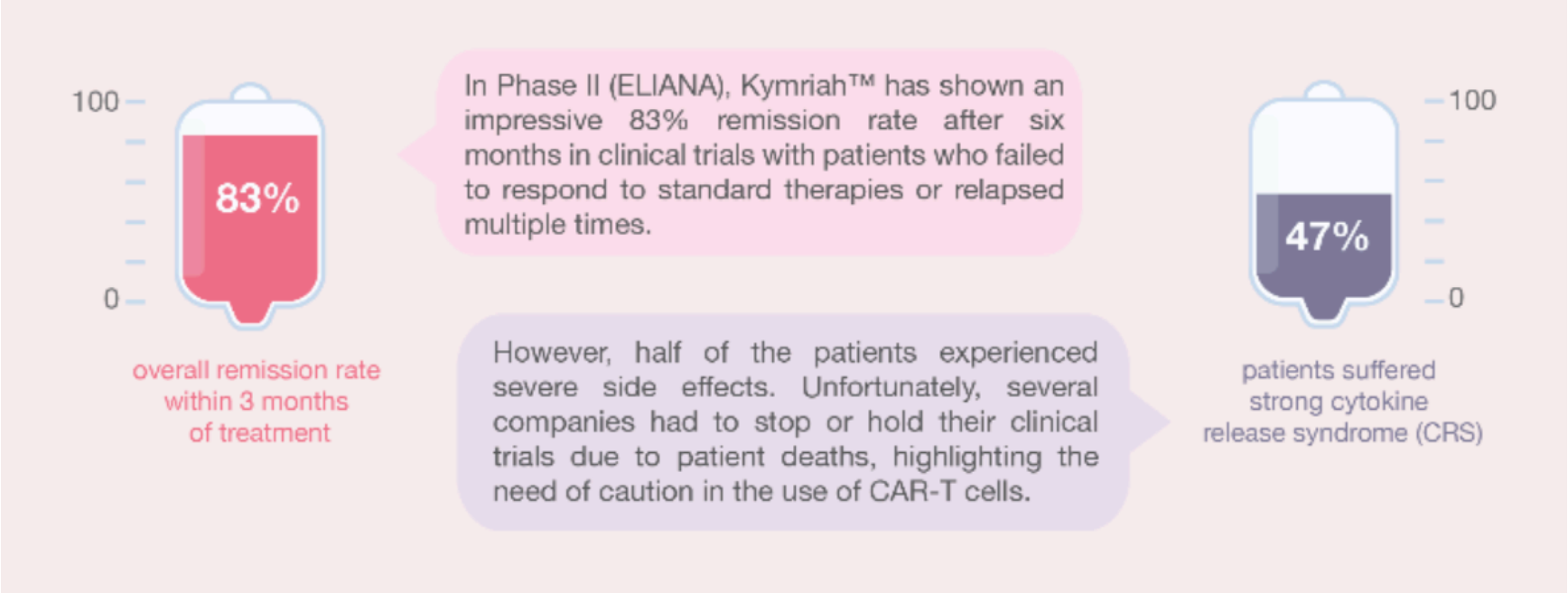

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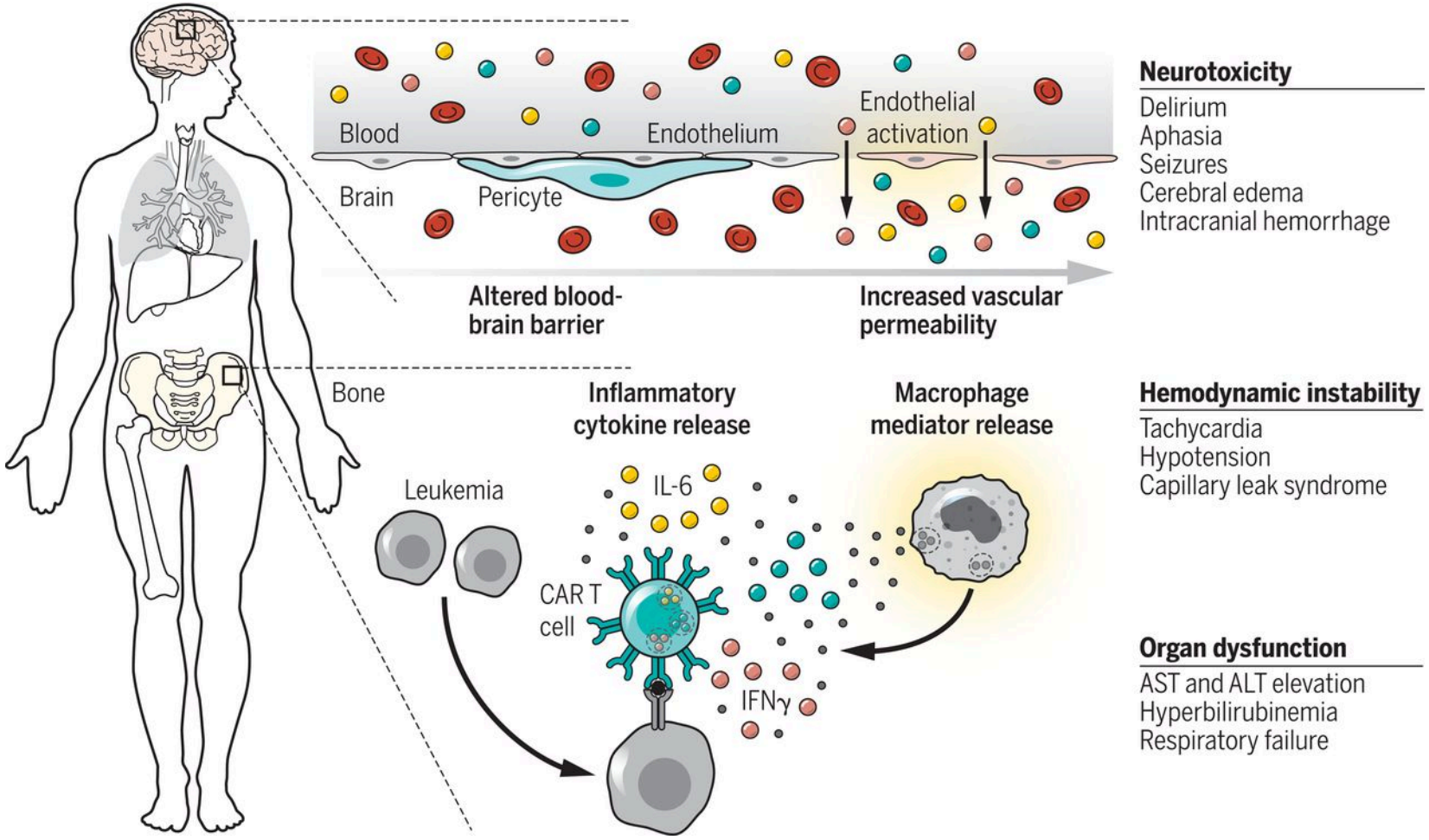
Fig. 2 CAR T cell therapy is associated with cytokine release syndrome and neurotoxicity.



Carl H. June et al. Science 2018;359:1361-1365

Also: Tumor Lysis Sundrome
Long term B-cell aplasia (CD19)

Published by AAAS

CD19 Car-T AE

Institution	Disease	CRS incidence and severity	CRS-specific management	Neurological toxicity
UPenn (CHOP)	Pediatric ALL	25/25 (initial cohort); 8/25 required vasopressors 48/53 with ≥ grade 1 CRS	Tocilizumab (28%) ± corticosteroids (N=9); reversed in all cases	13/25 (initial cohort), delirium to global encephalopathy
NCI	Pediatric ALL	15/20 with ≥ grade 1 CRS (grade 3 N=3, grade 4 N=3); cardiac arrest (N=1)	Tocilizumab alone (N=2); Tocilizumab + corticosteroids (N=2)	6/20, visual hallucinations (N=5) and transient dysphasia
NCI	Adult B-NHL	12/15 fever; 4/15 hypotension	Tocilizumab (N=2)	6/15, confusion, obtundation, aphasia, encephalopathy
MSKCC	Adult ALL	11/46 with severe CRS requiring vasopressors or mechanical ventilation	Not reported	13/46 with ≥ grade 3 neurological toxicity
FHCRC	Adult ALL	7/27 with severe CRS fever and hypotension requiring ICU; death (N=2)	Not reported	13/27 with ≥ grade 3 neurological toxicity
FHCRC	Adult CLL and B-NHL	0/12 with severe CRS; 2/16 dose-limiting toxicity	Not reported	Not reported
UPenn	Adult CLL	9/14 with ≥ grade 1 CRS (grade 3-4 N=6); ICU admission (N=4)	Tocilizumab ± corticosteroids (N=5)	6/14, ≤ grade 2 hallucinations, confusion, delirium
UPenn	Adult CLL	14/26 CRS	Tocilizumab ± corticosteroids (N=3)	Not reported
UPenn	Adult B-NHL	16/24 CRS (grade 2 N=14, grade 3 N=1, grade 4 N=1)	Not reported	3/24, delirium (grade 2 N=1, grade 3 N=1) and encephalitis (grade 5

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Car-T Challenges

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Myeloma Need

- Like ALL and refractory CLL and other B-cell lymphomas, multiple myeloma can be a relentless malignancy with high mortality rates for patients refractory to standard therapy
- For patients with high risk genetics other therapies are desperately needed
- There is no current standard for the treatment of plasma cell leukemia

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Myeloma Target

- Need right antigen: Enough and universal but not too much
- Need specific antigen: Specific to tissue of interest with little if any other tissue expression
- Need stable antigen: Does not fluctuate with time or down regulate with binding
- Need non-soluble antigen: Will not occupy binding sites needlessly

BCMA **CS1**

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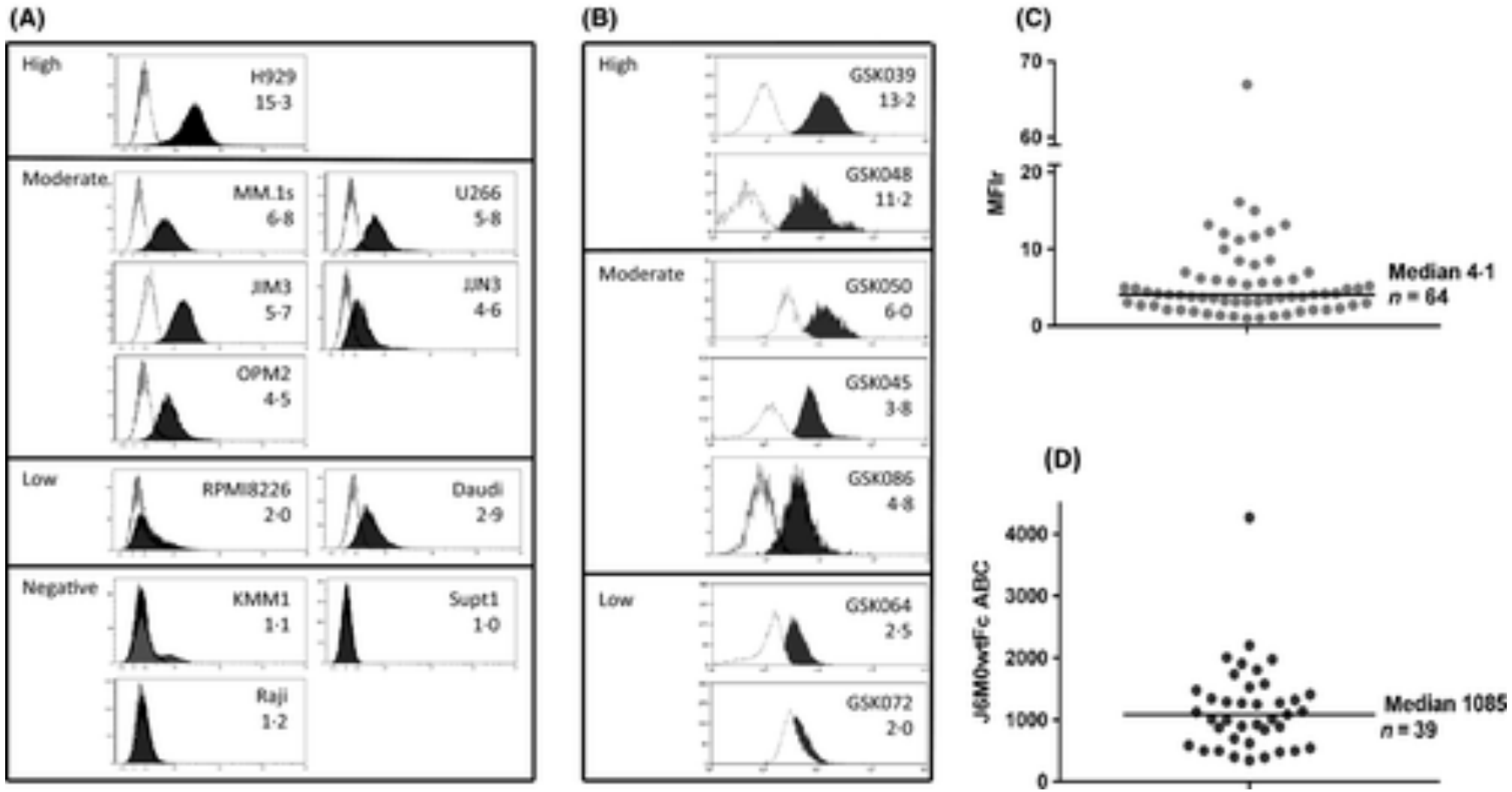
Evaluation of B cell maturation antigen as a target for antibody drug conjugate mediated cytotoxicity in multiple myeloma

BCMA



Evaluation of B cell maturation antigen as a target for antibody drug conjugate mediated cytotoxicity in multiple myeloma, Volume: 174, Issue: 6, Pages: 911-922, First published: 17 June 2016, DOI: (10.1111/bjh.14145)

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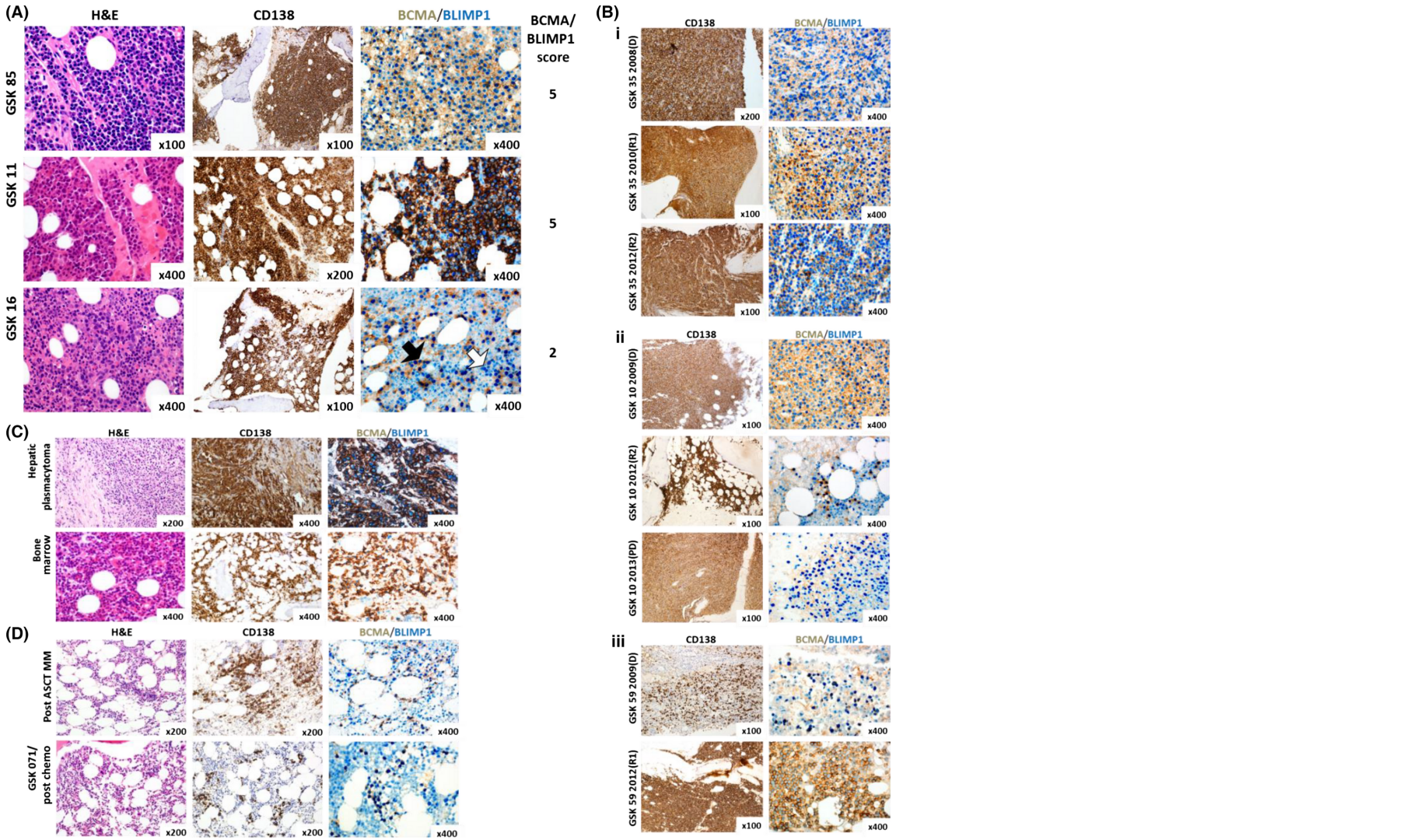

Evaluation of B cell maturation antigen as a target for antibody drug conjugate mediated cytotoxicity in multiple myeloma, Volume: 174, Issue: 6, Pages: 911-922, First published: 17 June 2016, DOI: (10.1111/bjh.14145)

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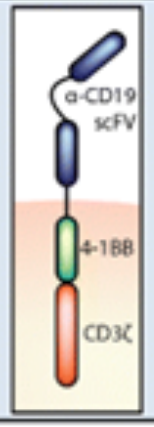
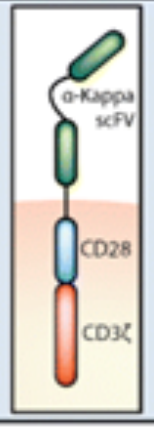
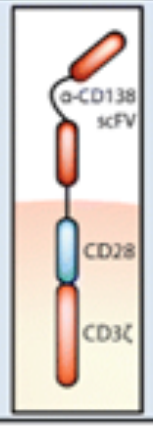
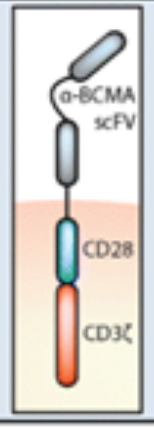
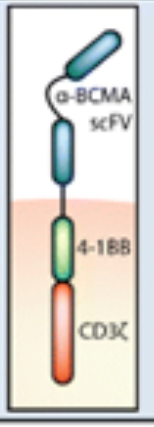
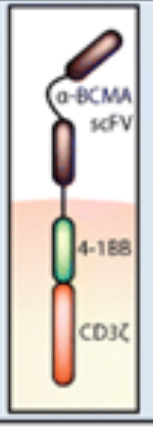
Myeloma BCMA Car-T

	α-CD19-BBz	α-Kappa-28z	α-CD138-28z	α-BCMA-28z	α-BCMA-BBz	α-BCMA-BBz
						
Institution	Penn	Baylor	Chinese PLA General Hospital	NCI	Penn	bluebird bio
scFV Clone	FMC63	CRL-1758	NK-92	11D5-3	ND	bb2121
scFV Origin	Murine	Murine	Murine	Murine	Human	Humanized
Gene Transfer System	Lentivirus	Retrovirus	Lentivirus	Retrovirus	Lentivirus	Lentivirus
Intracellular Domain	4-1BB ICD-CD3zeta	CD28 ICD-CD3zeta	CD28 ICD-CD3zeta	CD28 ICD-CD3zeta	4-1BB ICD-CD3zeta	4-1BB ICD-CD3zeta
Patients Treated	11	8	5	12	6	9
Dose(s)	1-5e7 CARTs/pt	0.2-2e8 CARTs/m2	0.44-1.51e7 CARTs/kg	0.3-9e6 CARTs/kg	1e7-5e8 CARTs/pt	5-80e7 CARTs/pt
Best Response (number of patients)	CR (1), VGRP (6), PR (2), PD (2)	SD (5), NR (3)	SD (4), PD (1)	Stringent CR (1), VGPR (2), PR (1), SD (8)	Stringent CR (1), VGPR (1), SD (1), MR (2), PD (1)	Stringent CR (2), VGPR (1), PR (4), SD (1), PD (1)
Reference(s)	25--	27--	26	28	29	ASH 2016 Abstract

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BCMA Car-T AE

Study/Therapeutic	Reported AEs
Bluebird Bio/Bb2121(Berdeja et al. 2017; Berdeja et al. 2017)	Favorable safety profile with no dose-limiting toxicity even at 800x10^6 CART doses: primarily grade 1 or 2 CRS reported in 73% of patients, no >grade 2 CRS observed.
Novartis/UPenn/CART BCMA(Cohen et al. 2016)	3/8 patients with grade 3-4 CRS and reversible neurotoxicity in 2/8 managed without long-term neurological dysfunction. 33% of patients in later cohorts with grade 3, else lower, and no unexpected/dose-limiting toxicities were observed.
National Cancer Institute/anti-BCMA CAR(Ali et al. 2016)	Mild toxicities in patients receiving lower doses: (0.3 – 3.0 x10^6 CARTs/kg). Two patients treated at highest dose level: (9 x 10^6 CART/kg) experienced grade 3 and 4 toxicities that were managed without long-lasting complications.
Nanjing Legend/LCAR-B38(Fan et al. 2017)	CRS occurred in 74% (14 patients) of patients but was mild in most patients, 1 case of grade 3, 1 case of grade 4 both of whom recovered.

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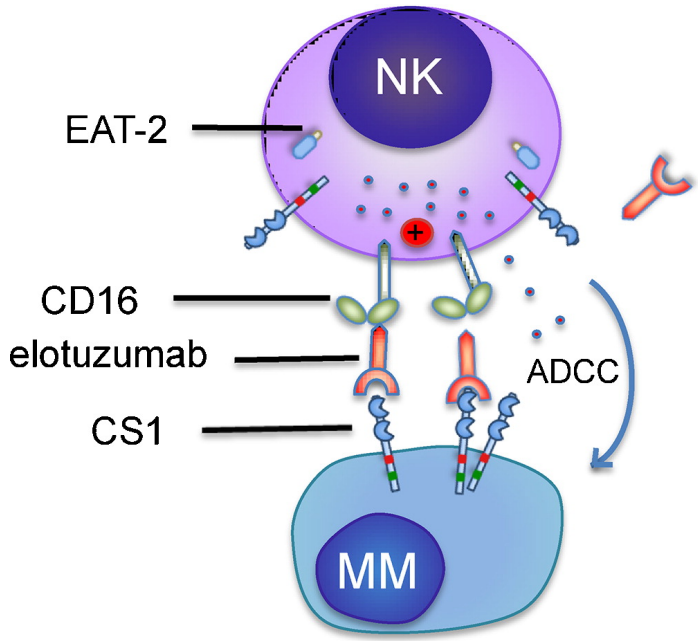
Elotuzumab

- Elotuzumab is a humanized IgG1 mAb targeting human CS1, a cell surface glycoprotein (*Clin Cancer Res* 2008;14:2775; *Blood* 2008;112:1329).
- CS1 is highly expressed on >95% of MM cells (*Blood* 2008;112:1329; *Mol Cancer Ther* 2009;8:2616).
- The mechanism of action of elotuzumab is primarily through **NK cell-mediated ADCC against myeloma cells** (*Clin Cancer Res* 2008;14:2775; *Blood* 2008;112:1329).
- In an MM xenograft mouse model, the combination of elotuzumab and lenalidomide significantly reduced tumor volume compared to either agent alone (*Mol Cancer Ther* 2009;8:2616).



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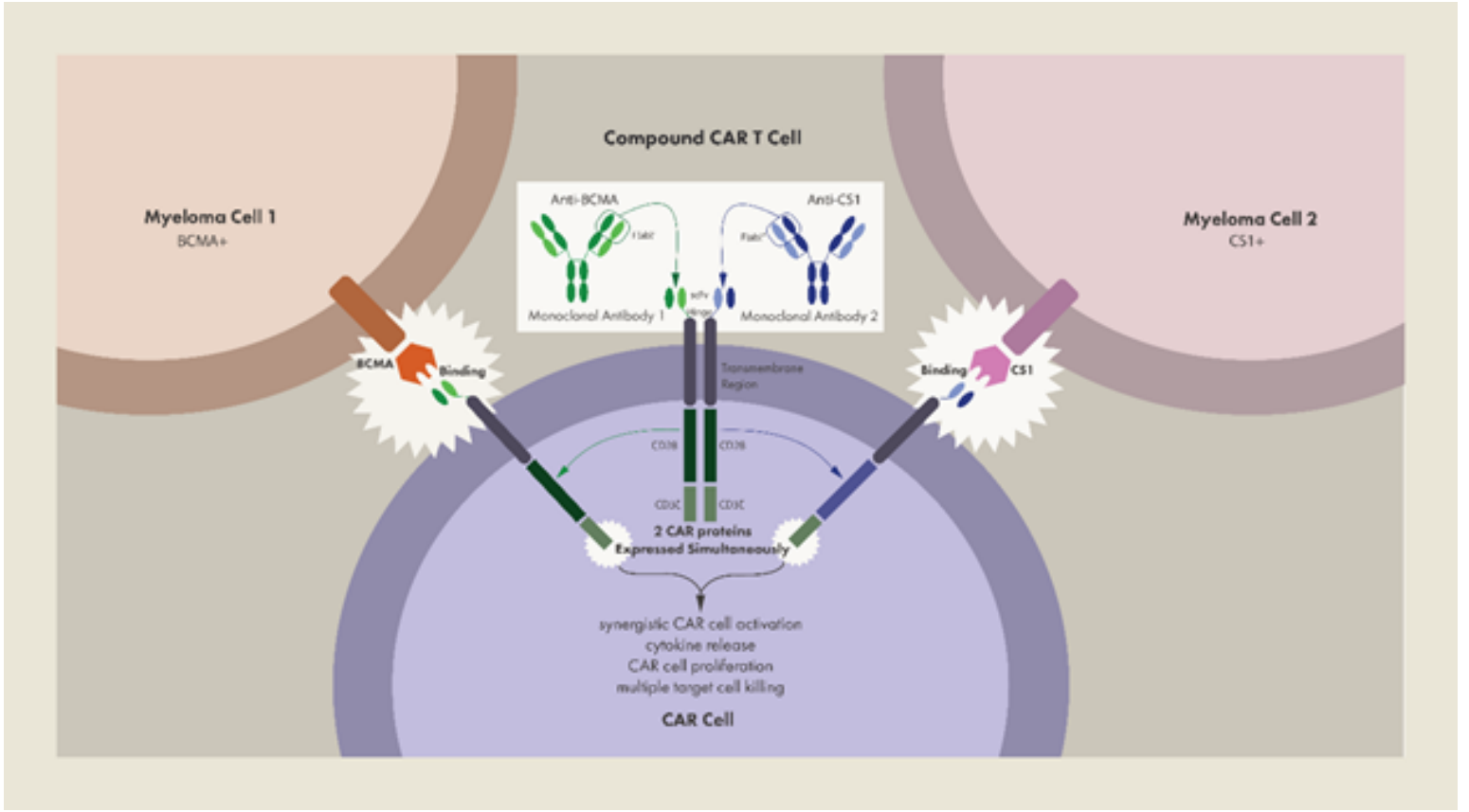
Myeloma Compound Car-T



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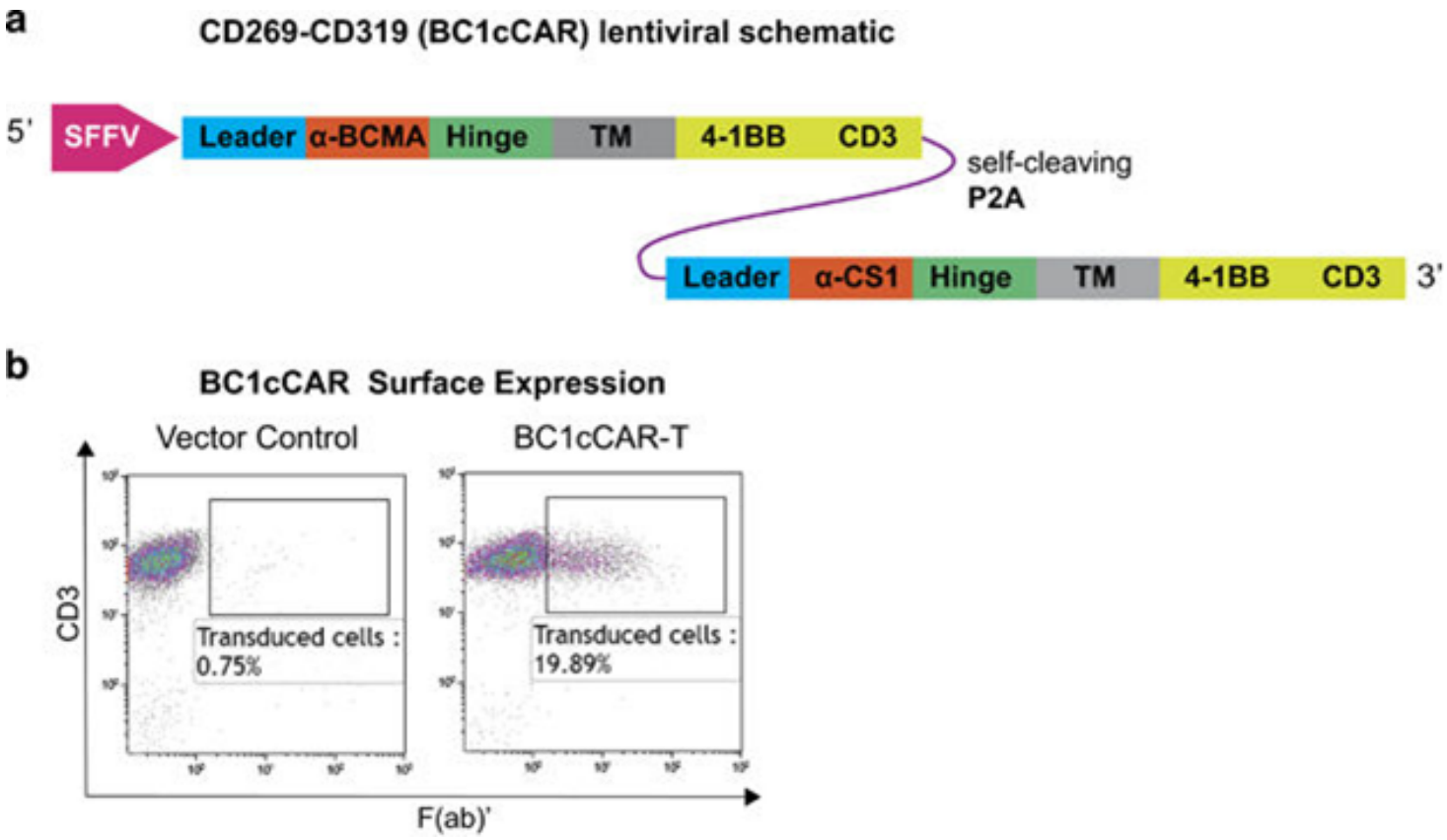
Compound Construct



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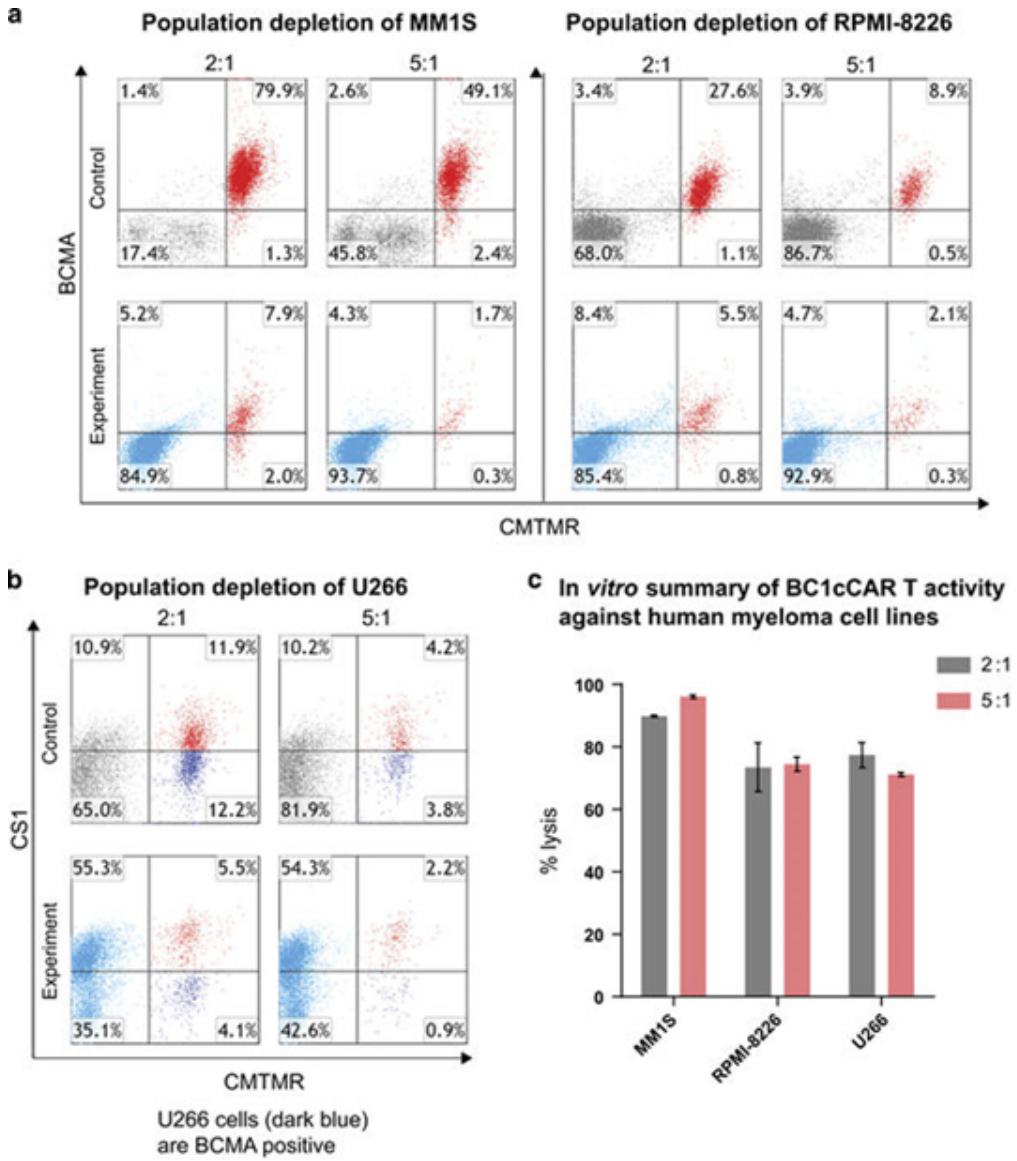
Killing: Ex Vivo



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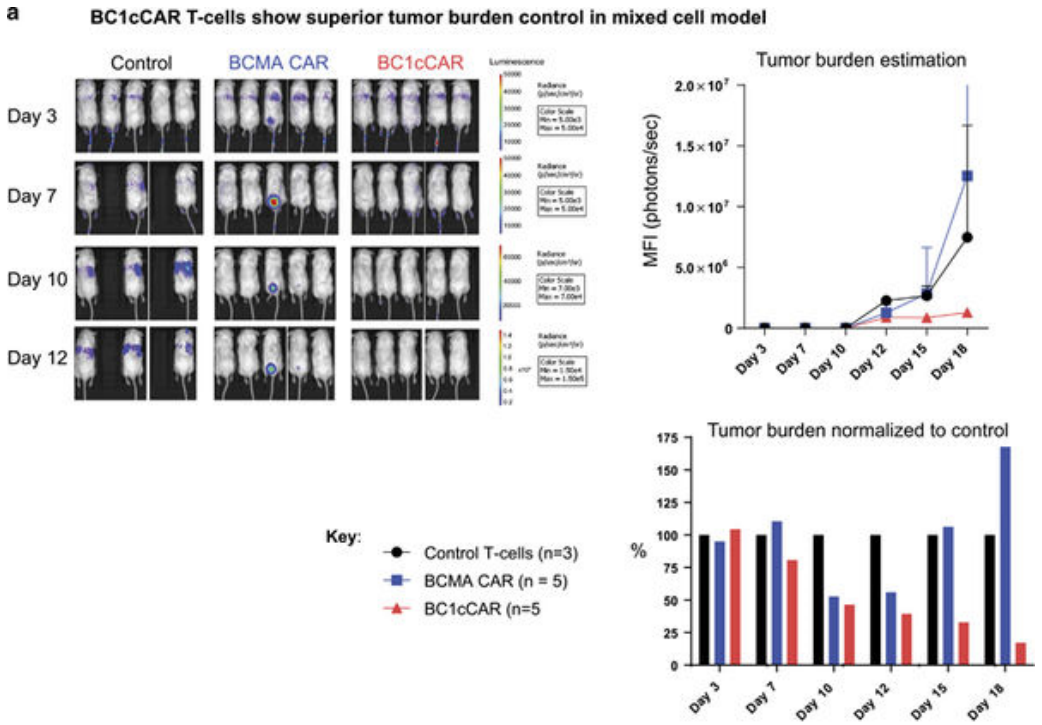
Killing: In Vivo



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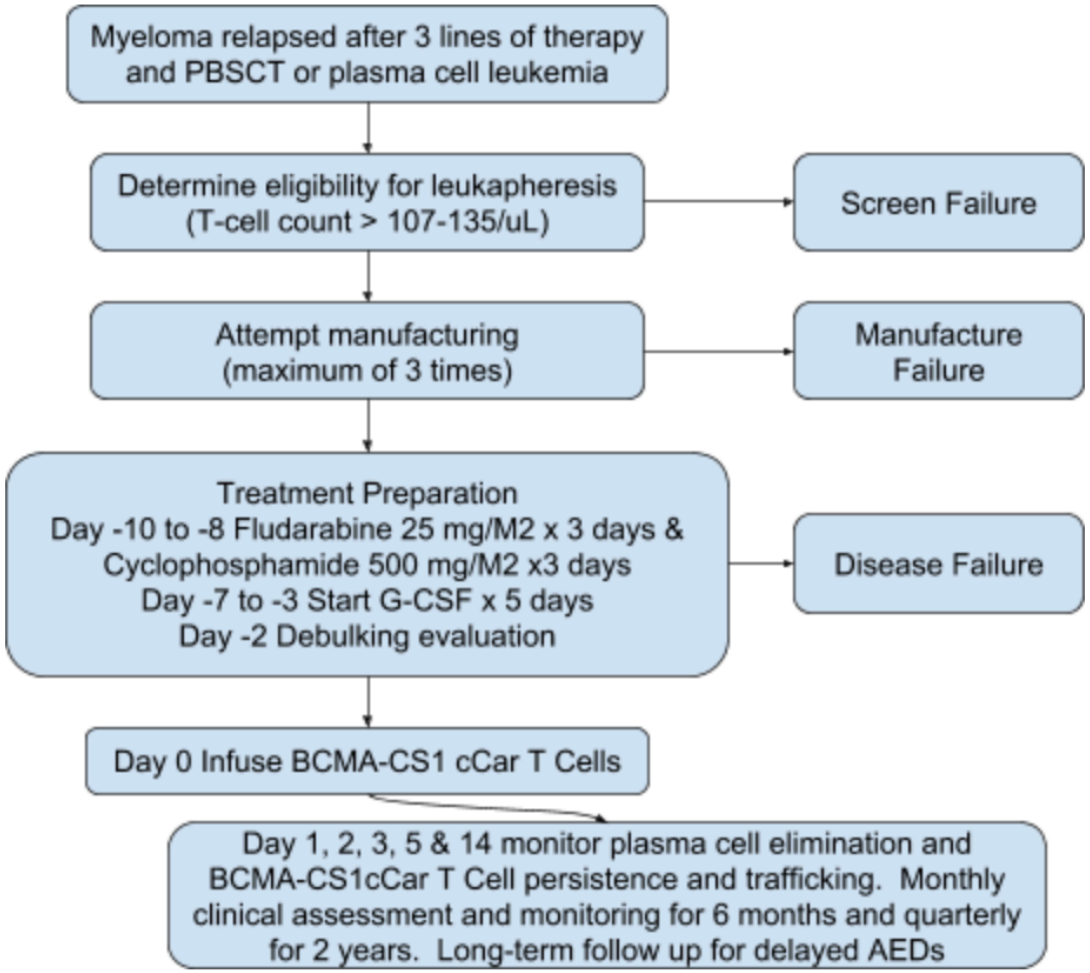
Phase I Myeloma



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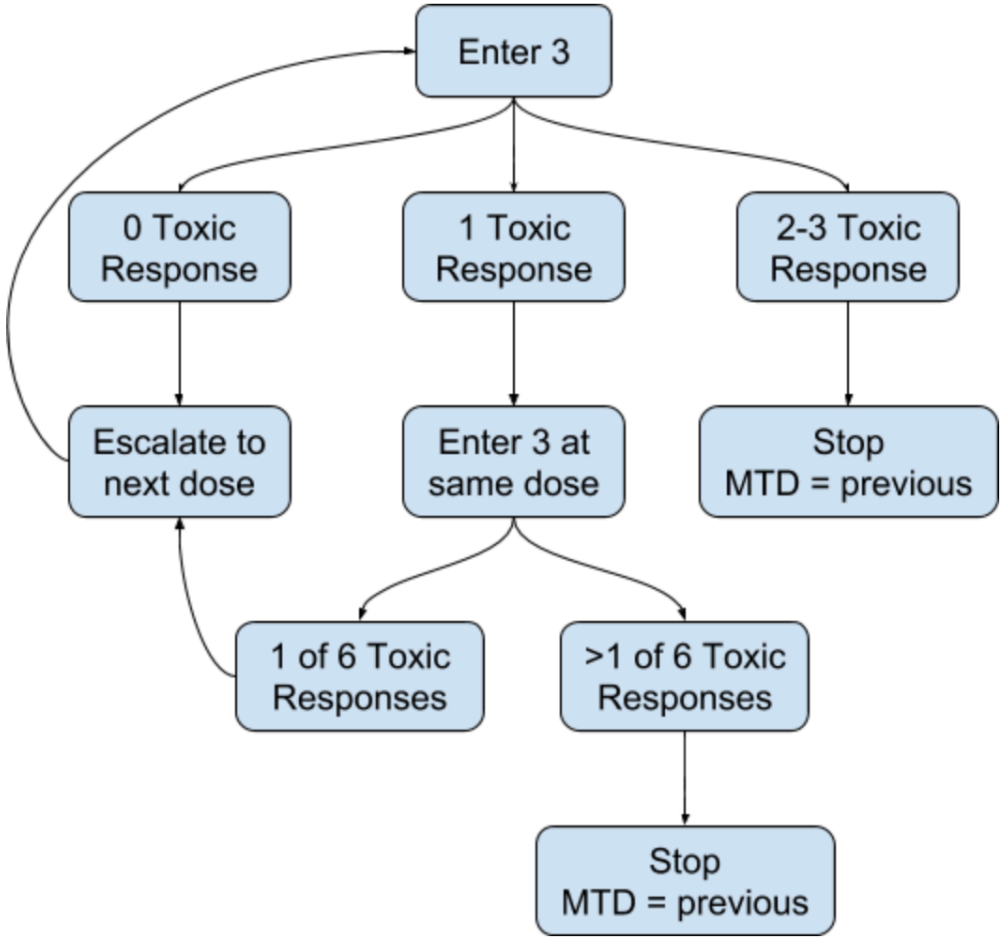
Phase I Myeloma



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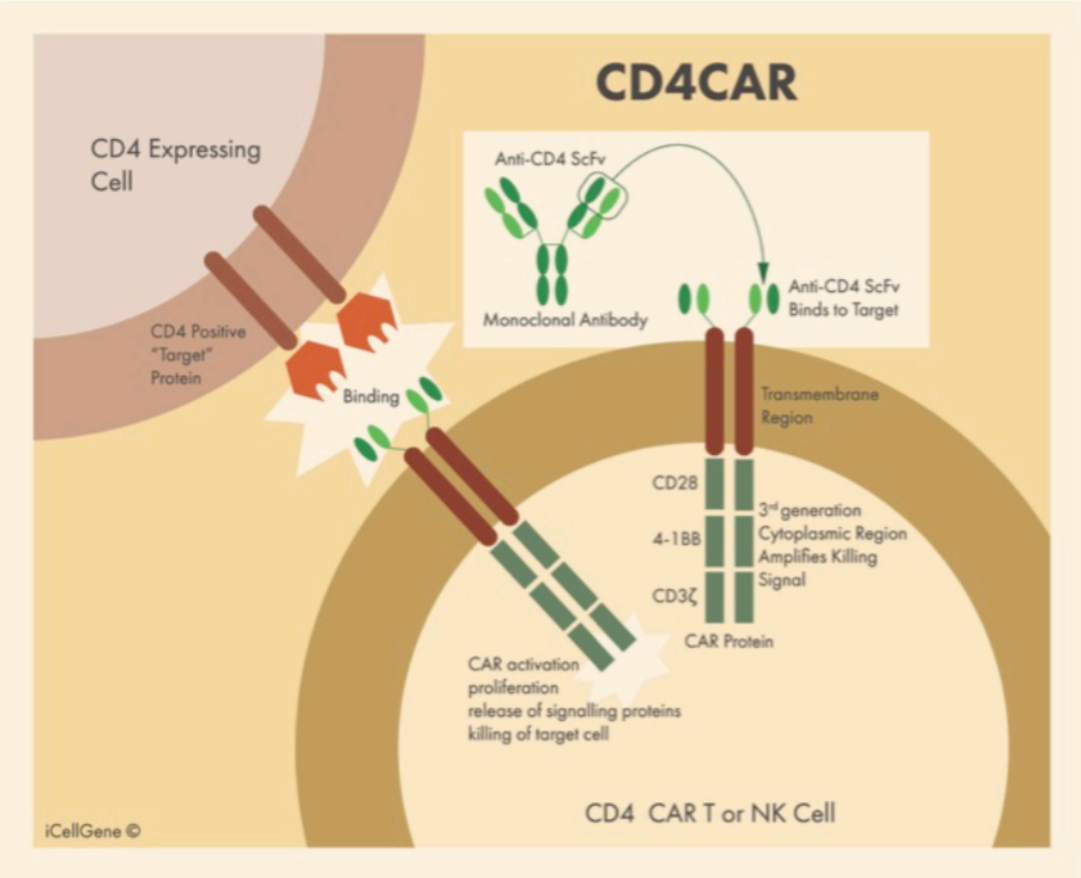
CD4 CarT



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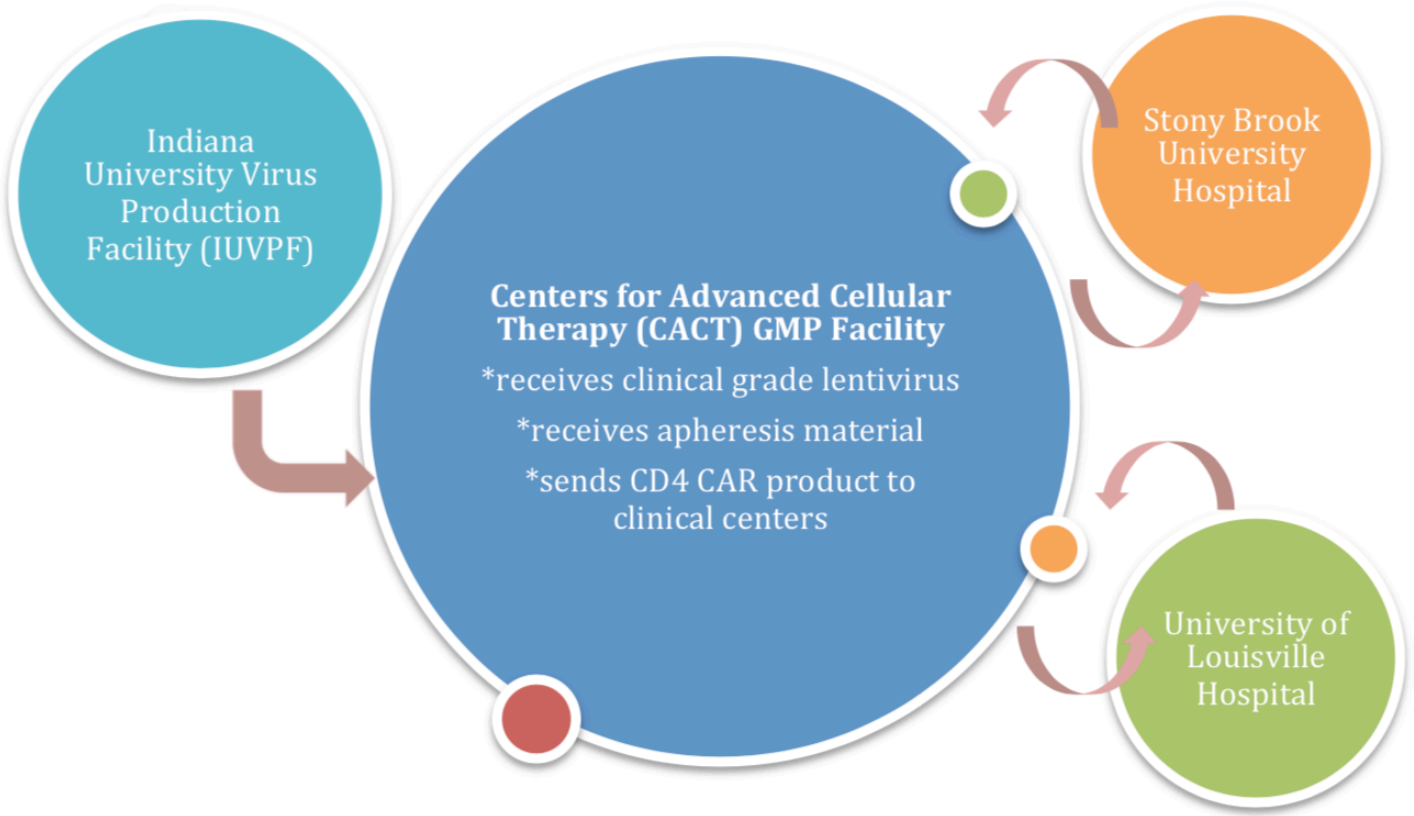
Production: CD4



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UofL Roadmap

- Lymphoid: CD4: Stony Brook PI, FDA approved
- Plasma cell: BCMA-CS1: FDA submission next month, UofL only site
- AML: CD33-CD133: FDA submission late 2018, UofL only site
- Future?

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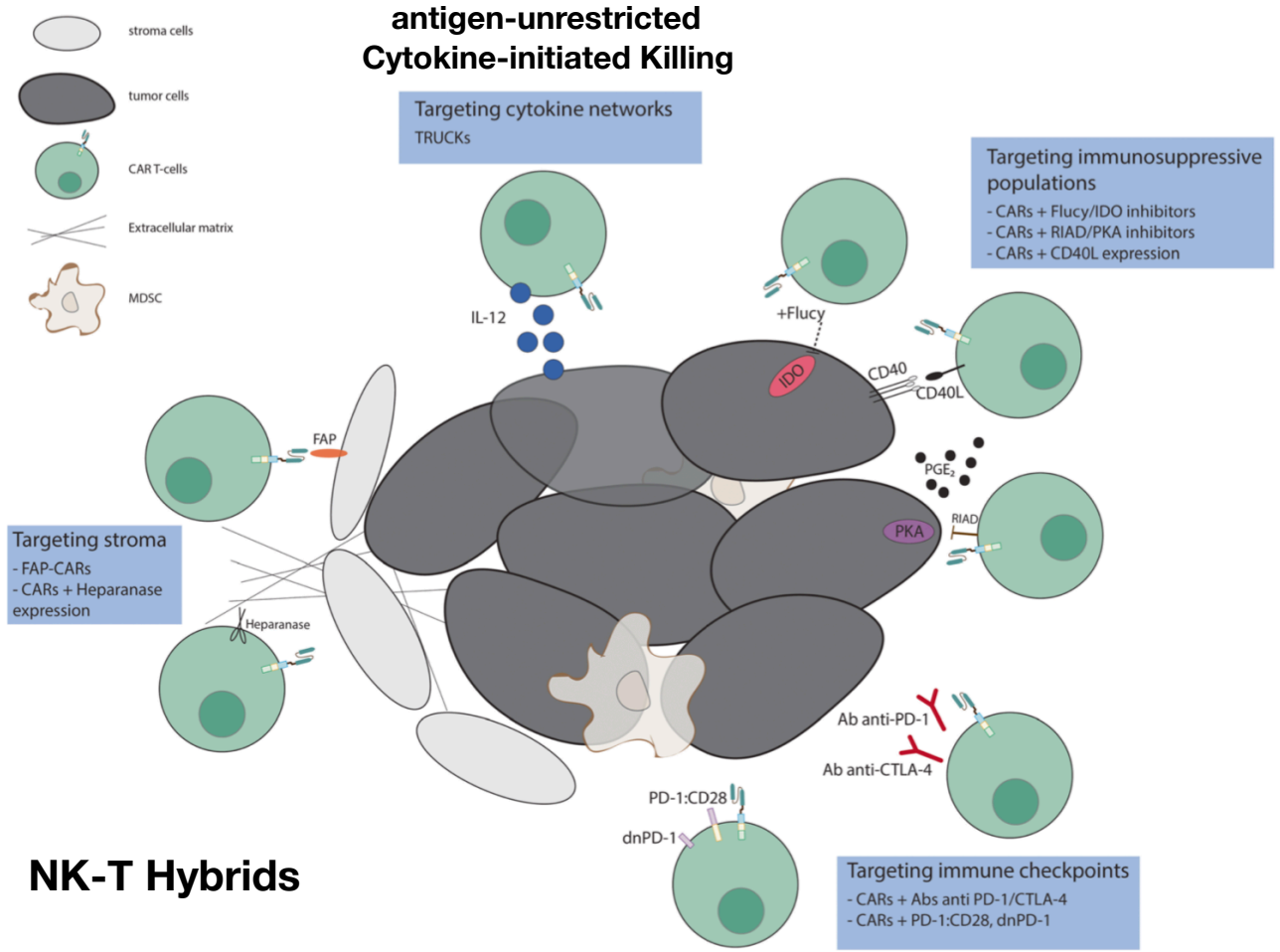
Future CarT Strategy

T cells Redirected for antigen-unrestricted Cytokine-initiated Killing



NK-T Hybrids

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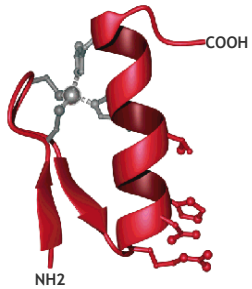
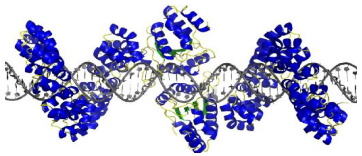
Next Generation Gene Editing

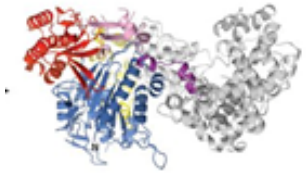
Genome editing

- Zinc finger

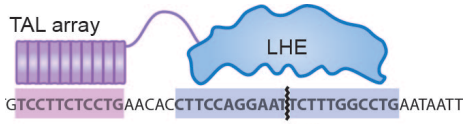


- TAL Effector Nuclease





- CRISPR/Cas9



- MegaTals

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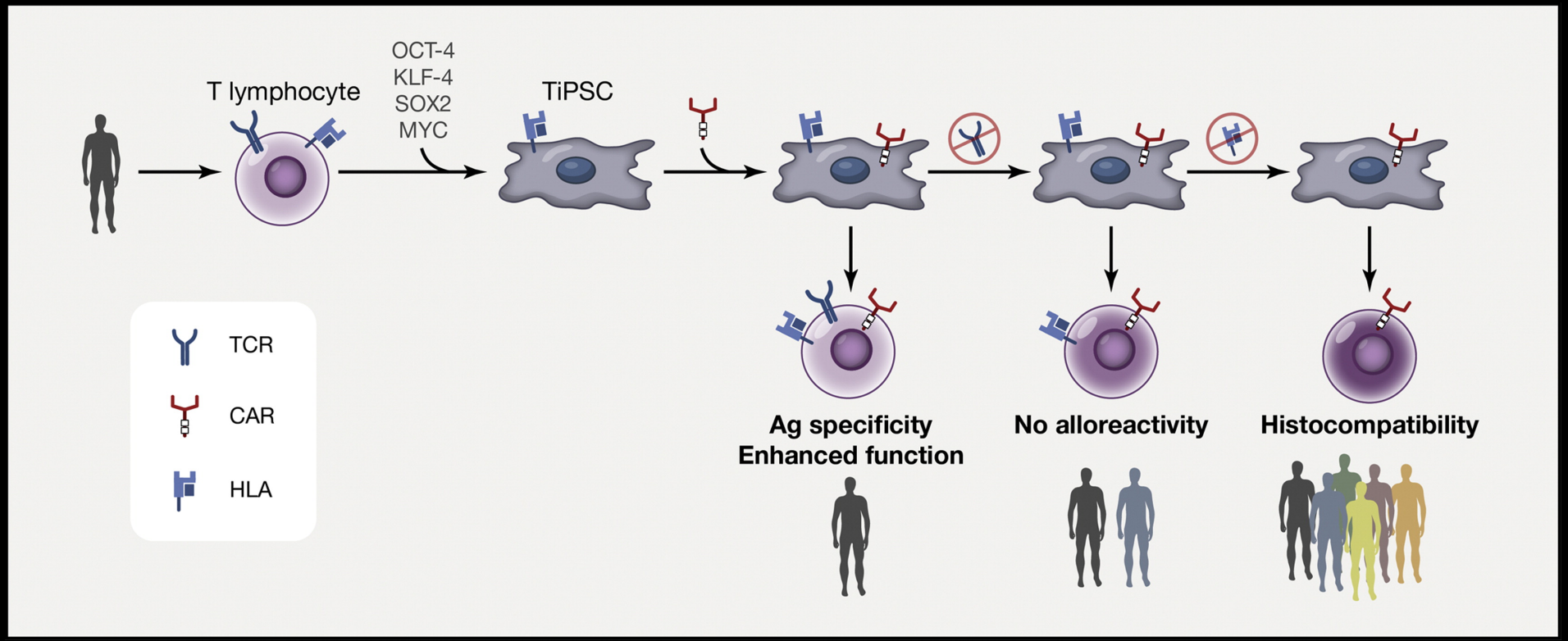
Gene Editing for "Off the Shelf" CarT



Cell Stem Cell 2015 16, 357-366DOI: (10.1016/j.stem.2015.03.011)
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Unintended Consequences

- Retrovirally transduced cells can have insertional mutagenesis from interruption or activation of off target genes
- Gene edited cells (CRISPR) from recent technology results in double strand breaks in DNA. Most cells die when such breaks are detected by the actions of p53. Hence, surviving cells gene corrected by CRISPR have higher likelihood of p53 deletion or other problems with DNA error detection and malignant transformation. Advanced forms of CRISPR have been developed to don't completely sever DNA.

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Conclusions I

- Immunsurveillance of cancer is critical for complex life
- Our understanding immunosurveillance prior to escape is poor
- Immune escape is the hallmark of clinically important cancer
- CTL and NK cells are the key cells in immune surveillance and immune therapy of cancer
- NK cells recognize “missing self” and augment other immune response

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Conclusions II

- CTL are the most targeted and powerful immune cells
- Blocking inhibitory signals at APC:CTL and CTL:Cancer has improved clinical outcomes in some cancers
- Different cancers have varying degrees of mutation and neoantigens BUT antigens DIFFERENT across cancers
- Variability between individuals (antigen, HLA presentation, other immune genes, microbiome) helps explain differing cancer predispositions and responses

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Conclusions III

- TIL therapy may work well for certain high mutation (antigen) cancers UofL Research
- Allogeneic transplant can cure many hematologic malignancy patients
- CarT therapy is a very powerful experimental strategy for immune targeting cancers but expense, safety and side effects are important limitations UofL Research
- Next generation gene editing opens new worlds for out understanding of cancer immunity and immunotherapy

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Questions?

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