VANDERBILT-INGRAM CANCER CENTER

Immunotherapy in Malignancies of the Immune System – Early Lessons for a New Age

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October 2, 2015

NCI CCC A Comprehensive Cancer Center Designated by the National Cancer Institute

Relevant Disclosures

Advisory Committee or Board

Celgene, Incyte, Novartis, TG Therapeutics, Karyopharm

Consultancy

Celgene, Incyte, Gilead

Research Funding

TG Therapeutics, Sunesis, Incyte, Karyopharm, Astex, Bayer

Equity

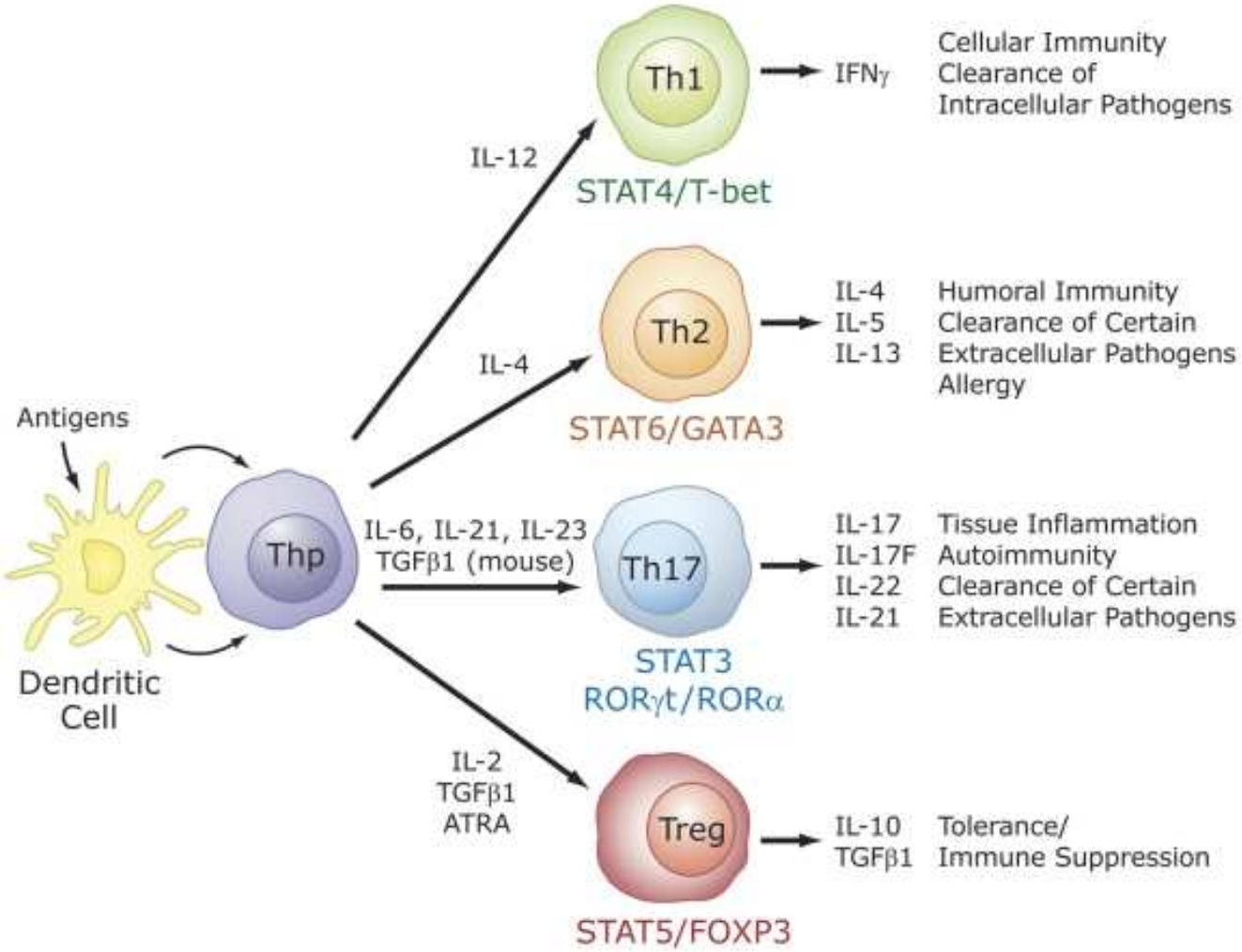
Karyopharm

I will be discussing investigational/non-FDA approved treatments and will make note of this as they are presented.

Blood Cancers – Immunotherapy for the Rogue Immune System

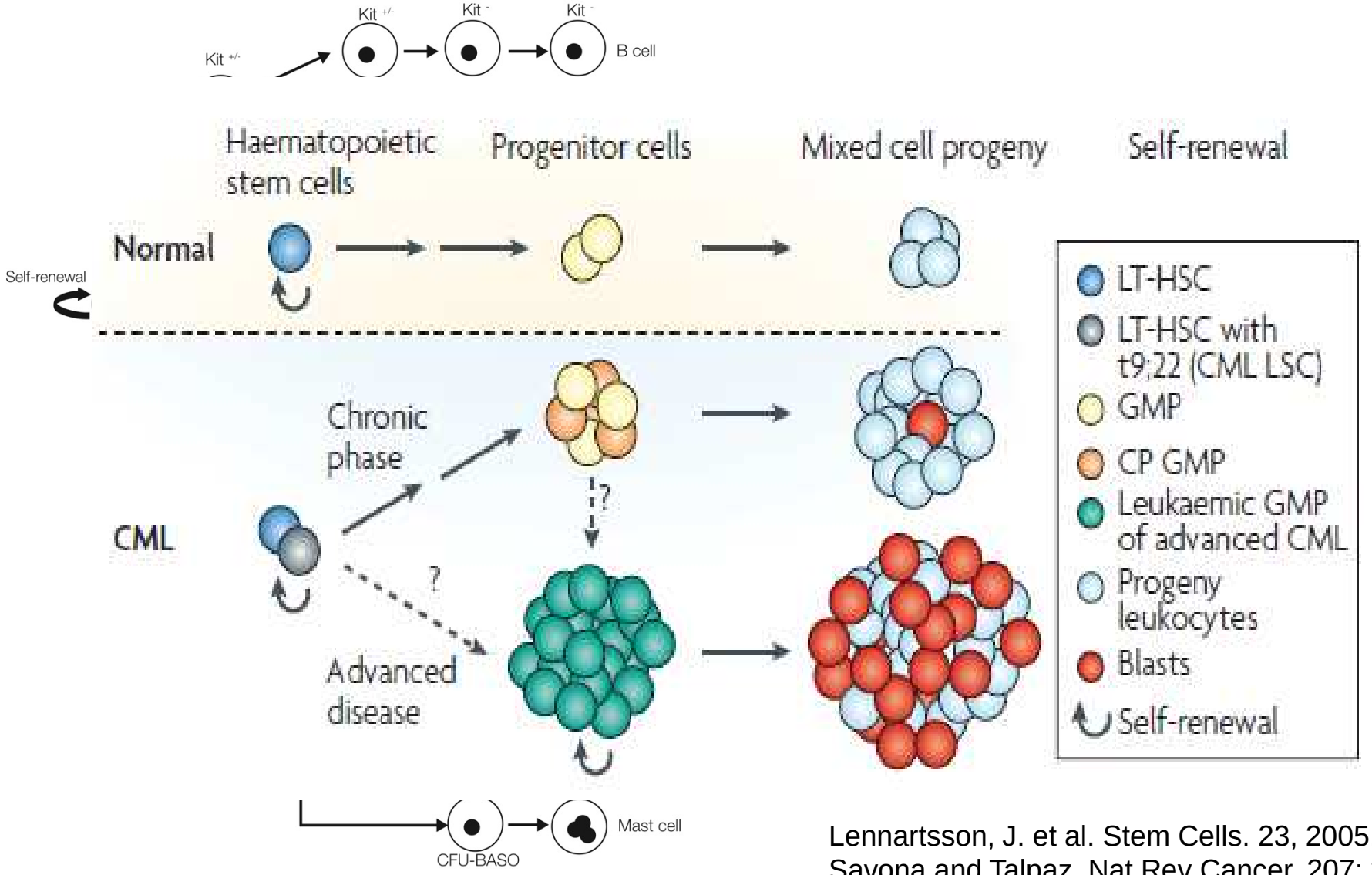
- Easy access of tissue for sampling
- Cellular origins as antigen-presenting cells for most heme malignancies
- Unique and clear delineation of hierarchy and discrimination of disease and normal tissue
  - To survey
  - To separate (purging or treatment)
- Unique scenario of generation of tumor *within* the immune bed – and manipulation of the leukemia-immune system interaction

Cytokine Drivers are Influenced by Tumor



Jetten. Nucl Recept Signal, 7, 2009.

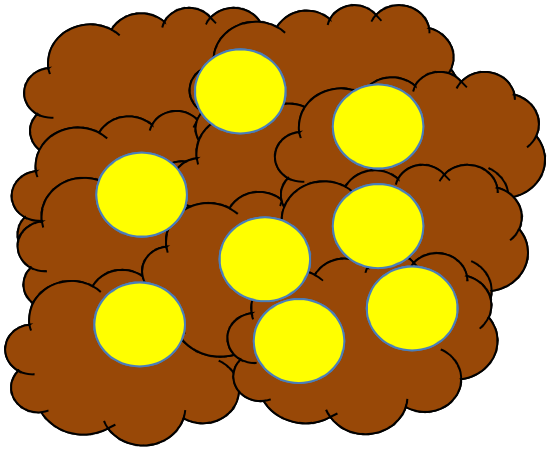
Hematopoietic Hierarchy



Lennartsson, J. et al. Stem Cells. 23, 2005.
Savona and Talpaz. Nat Rev Cancer. 207; 2008.

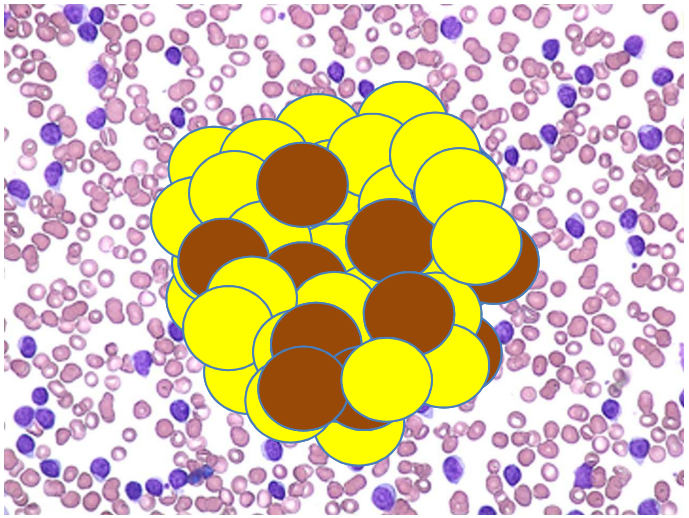
Invasion / Corruption

Tumor Infiltrating Lymphocytes



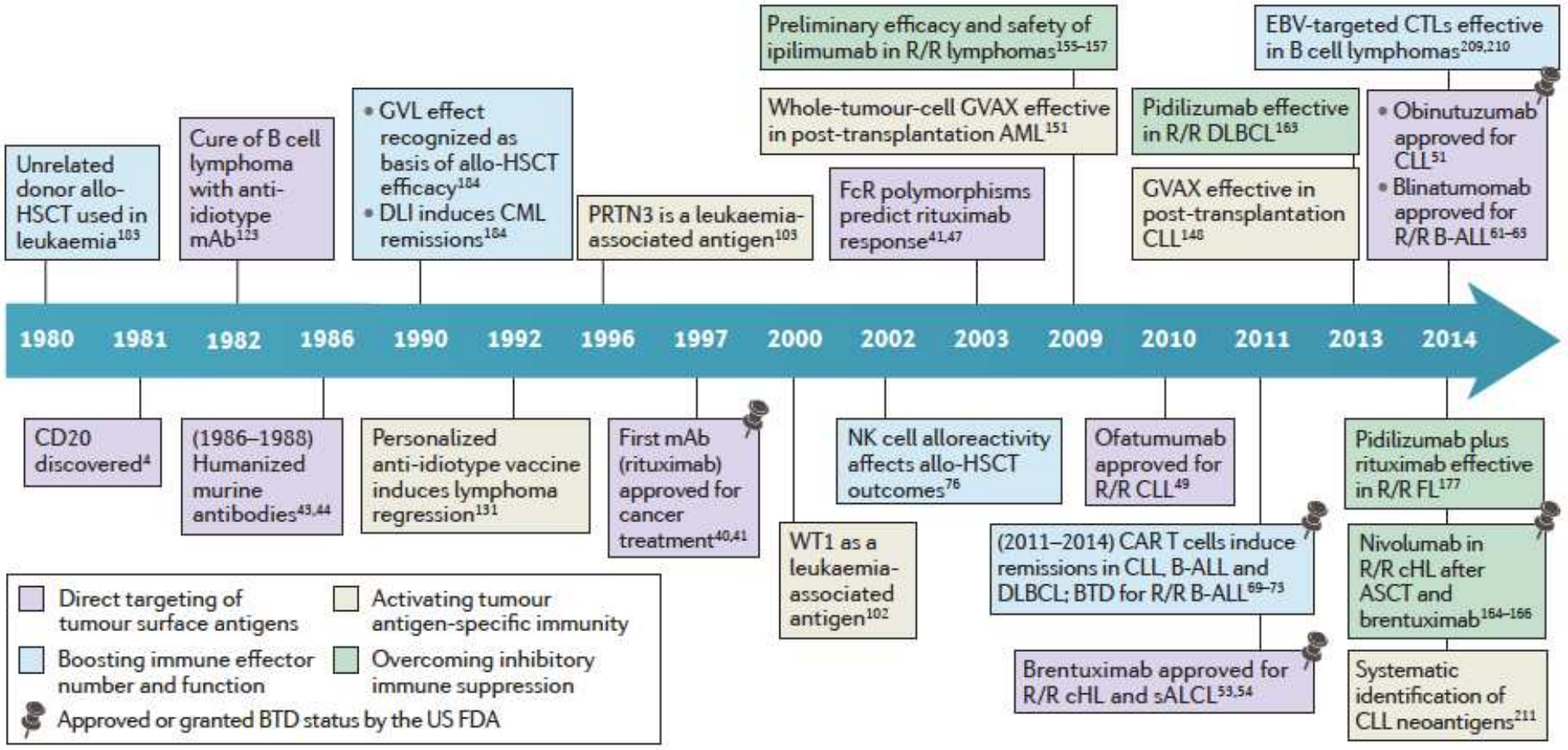
Epithelial Tumor Bed:
Lymphocytes within the tumor

Clonal lymphocytes



Blood Cancer in Lymph Node:
Immune Tumor within the
Immune Organ

Immunotherapy in Hematology

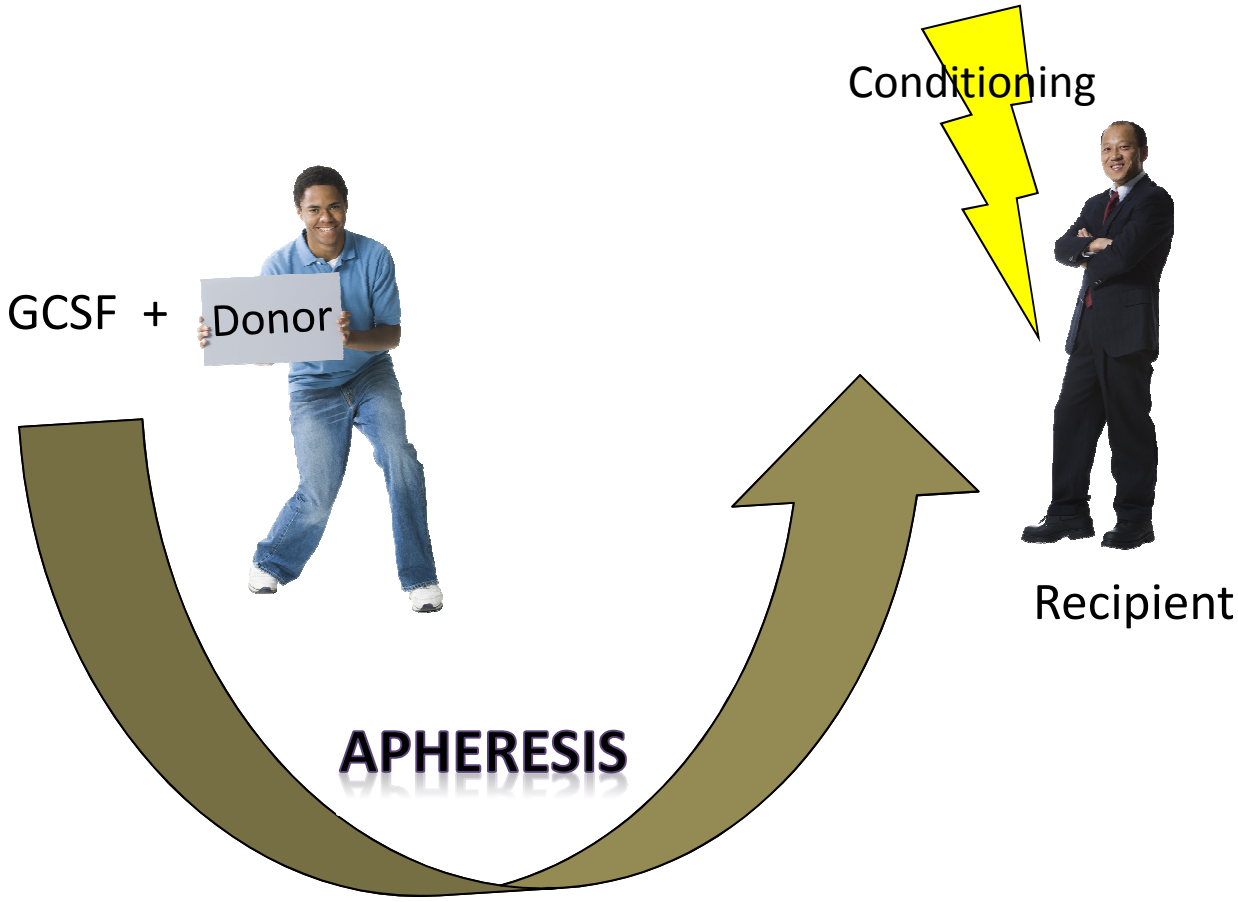


Bachireddy et al, Nature Rev Can, 15, 2015.

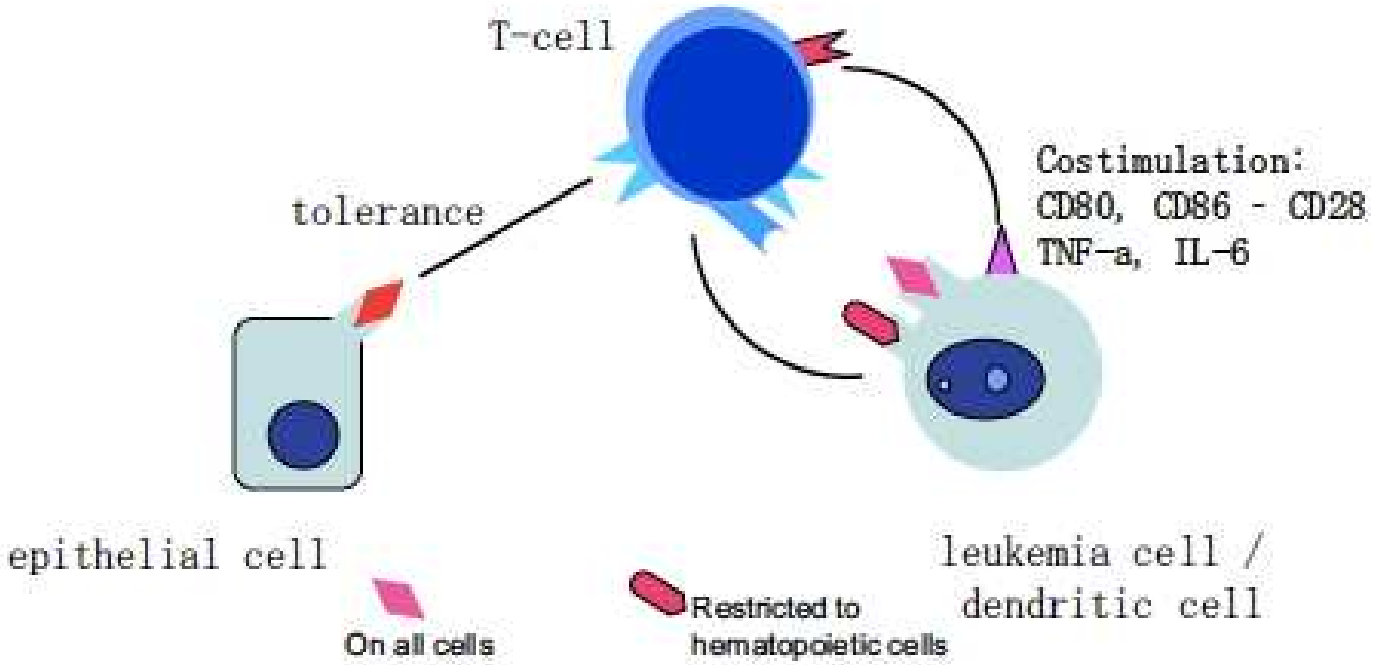
Immunologic treatment of Hematologic Malignancies

1. Direct targeting of tumor surface antigens
2. Stimulating immune effector cells
3. *Activation of tumor antigens/vaccines*
4. *Overcoming inhibitory immune signal from tumor*
5. Small molecules or TKIs which accomplish above via ‘pro-immunoactive’ cytokine signaling

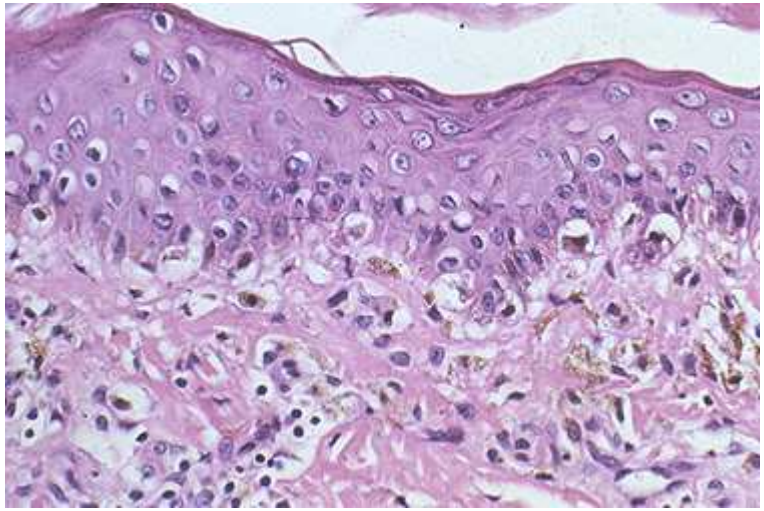
Stimulating immune effector cells: Allogeneic Stem Cell Transplant is an Immune System Transplant



Adoptive Immunotherapy in Chimerism GVL-Reaction



Kolb. Blood 112 (12), 2009.

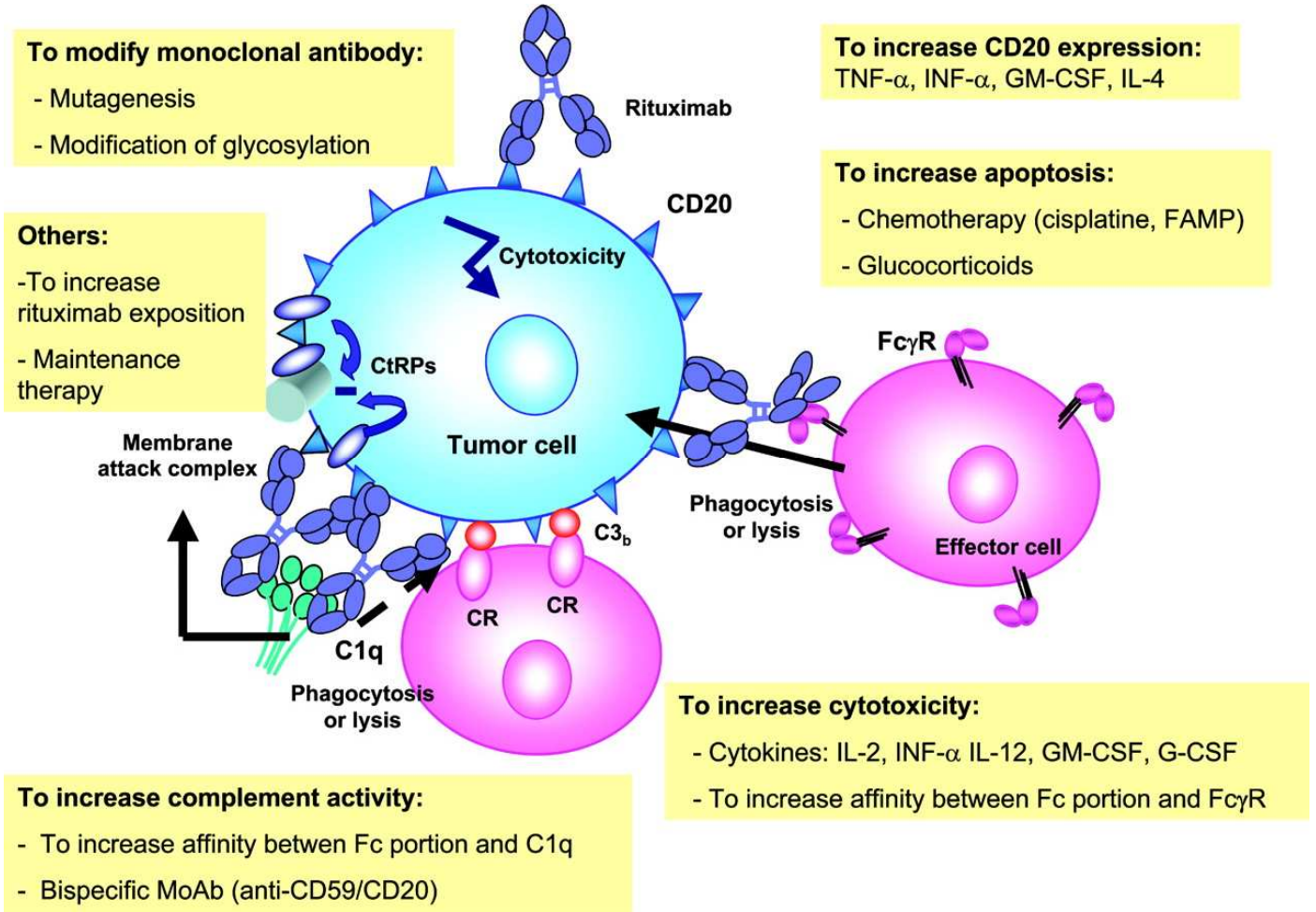


Skin Biopsy in Acute GVHD

Disease/study cohorts	No. of patients responding/no. treated	% CCR (y)
CML molecular/cytogenetic relapse		
EBMT study	40/50	80% (4 y)
North American	3/3	
Chronic phase		
EBMT	88/114	60% (4 y)
North American	25/34	
Japan	11/12	82% (3 y)
Transformed phase		
EBMT	13/36	20% (4 y)
North American	5/18	
Japan	3/11	0% (3 y)
AML/MDS		
EBMT	15/58	15% (4 y)
North American	8/44	
Prospective US study	25/51	19% (2 y)
Japan	13/32	7% (2/3 y)
		33% (2/3 y)
Korean	10/17	31% (2 y)
Lille, France	2/14	2/14 (4 y)
ALL		
EBMT	3/20	0% (4 y)
North American	2/11	ND
IBMTR	11/44	13% (3 y)
Japan	6/23	0% (3 y)
Korean	7/10	10% (2 y)
CLL		
German Multicenter trial on molecular relapse and persistence	7/9 molecular remission	7/9 (> 2 y)
Bristol multicenter	1/7	0
DFCI	6/7	NK
NHL		
North American study	0/6	NK
EBMT study	10/14 OR	NK
Progressive and refractory	6/14 CR	
UC London	LG-NHL 6/10	NK
Relapsed and refractory	HG-NHL 3/9	
Myeloma		
EBMT study	5/17	45% (2 y)
Relapse/progression		
North American Study relapse/progression	2/4	
US multicenter study persistent/progressive	7/22	4/7 (> 1 y)
Dutch multicenter study relapse and progression	14/27 OR	5/27 (> 2.5 y)
	10/27 CR	
Preemptive in chemosensitive MMY	6/20 CR/PR	30% (2 y)
	→ 7/14 CR/PR	
Relapse/progression	24/63	
	12 CR	~ 45% (3 y)
	12 PR	
Relapse/progression Johns Hopkins Hospital	8/16	5 > 2 y
	6 CR 2PR	

Donor lymphocyte infusion

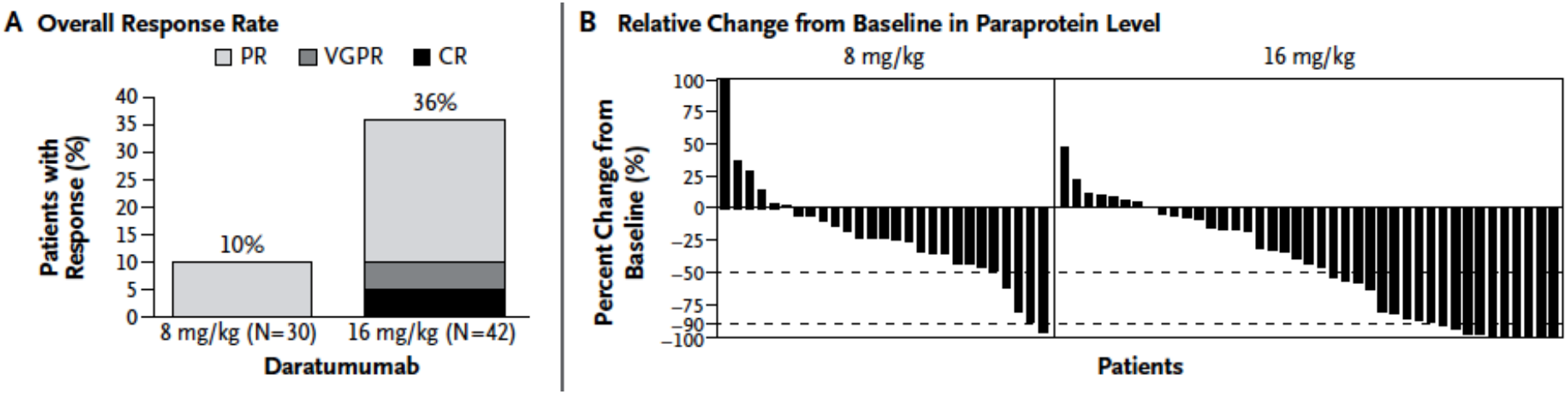
Directly Targeting Tumor Specific Antigens: Maximizing Efficacy of Rituximab



Cartron. *Blood.* 2004;104:2635.

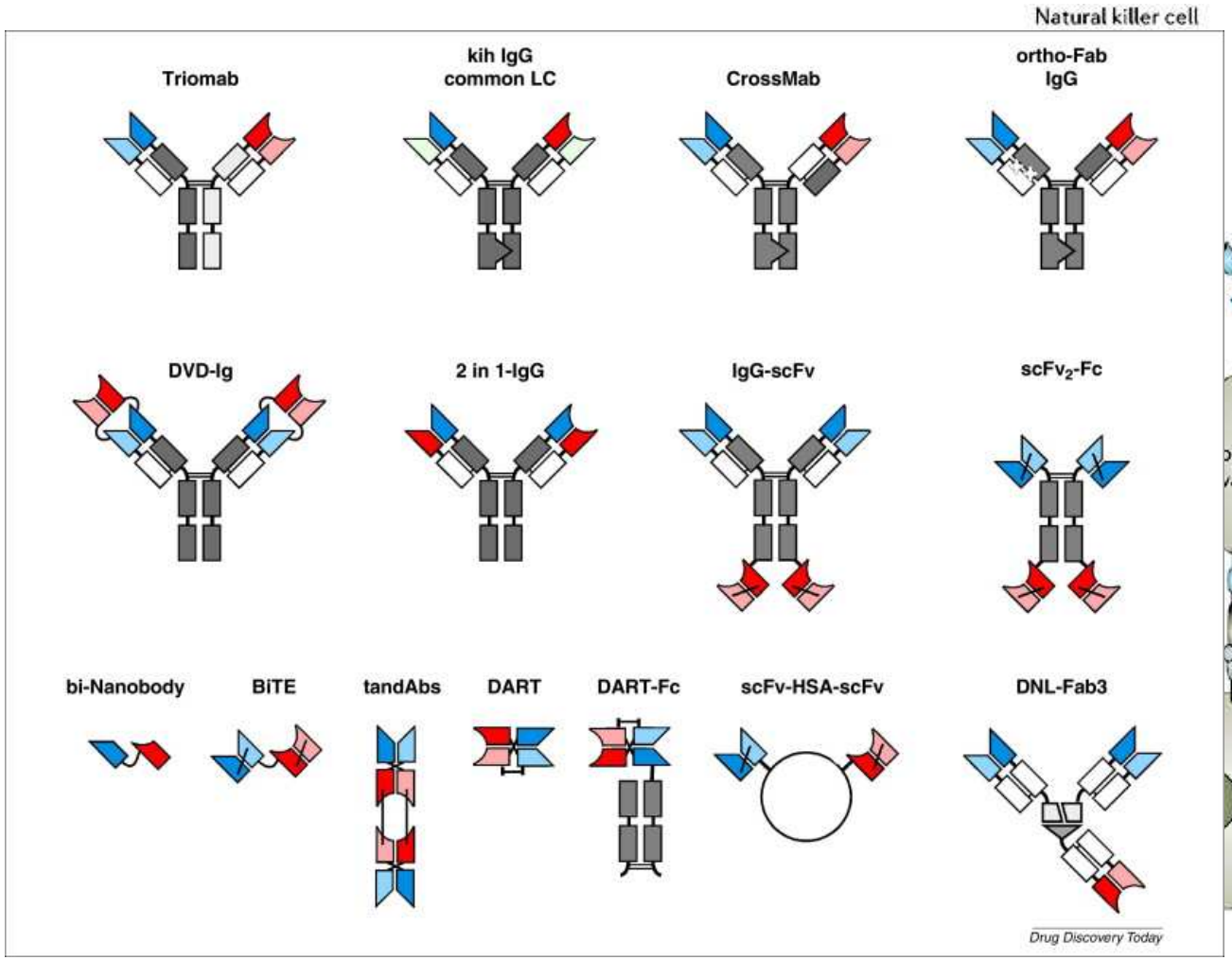
Daratumumab in Mulitple Myeloma

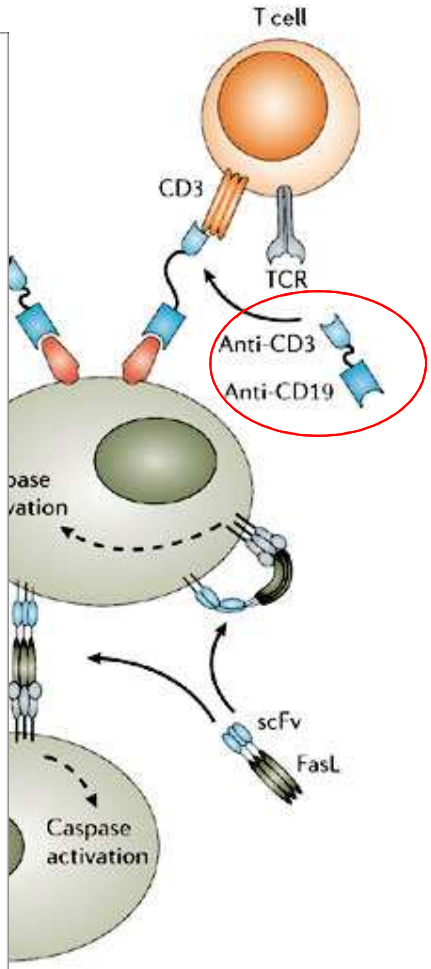
Targeting CD38 in patients with highly refractory multidrug resistant disease



Lokhorst et al, NEJM, 373, 2015.

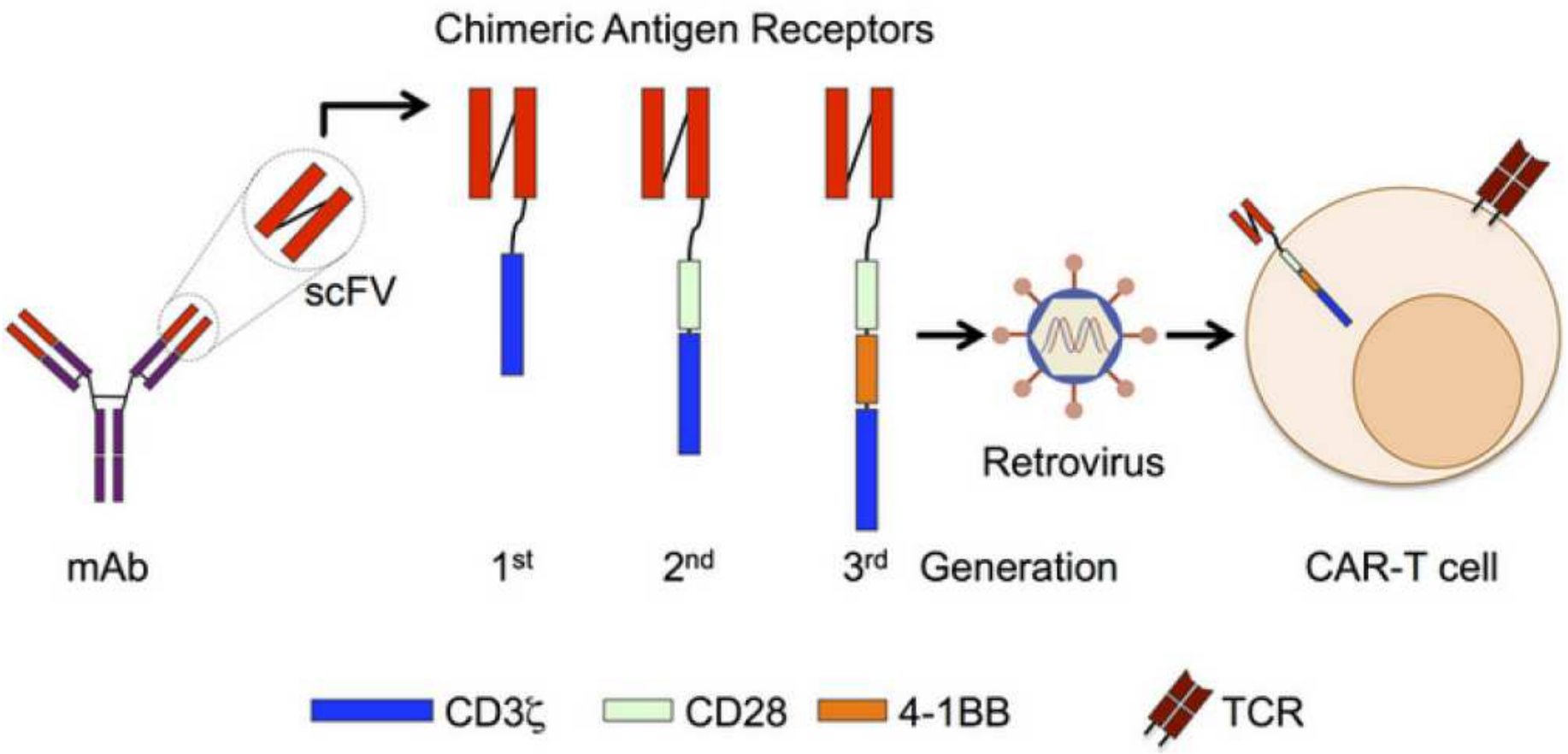
Bi-Specific Antibodies





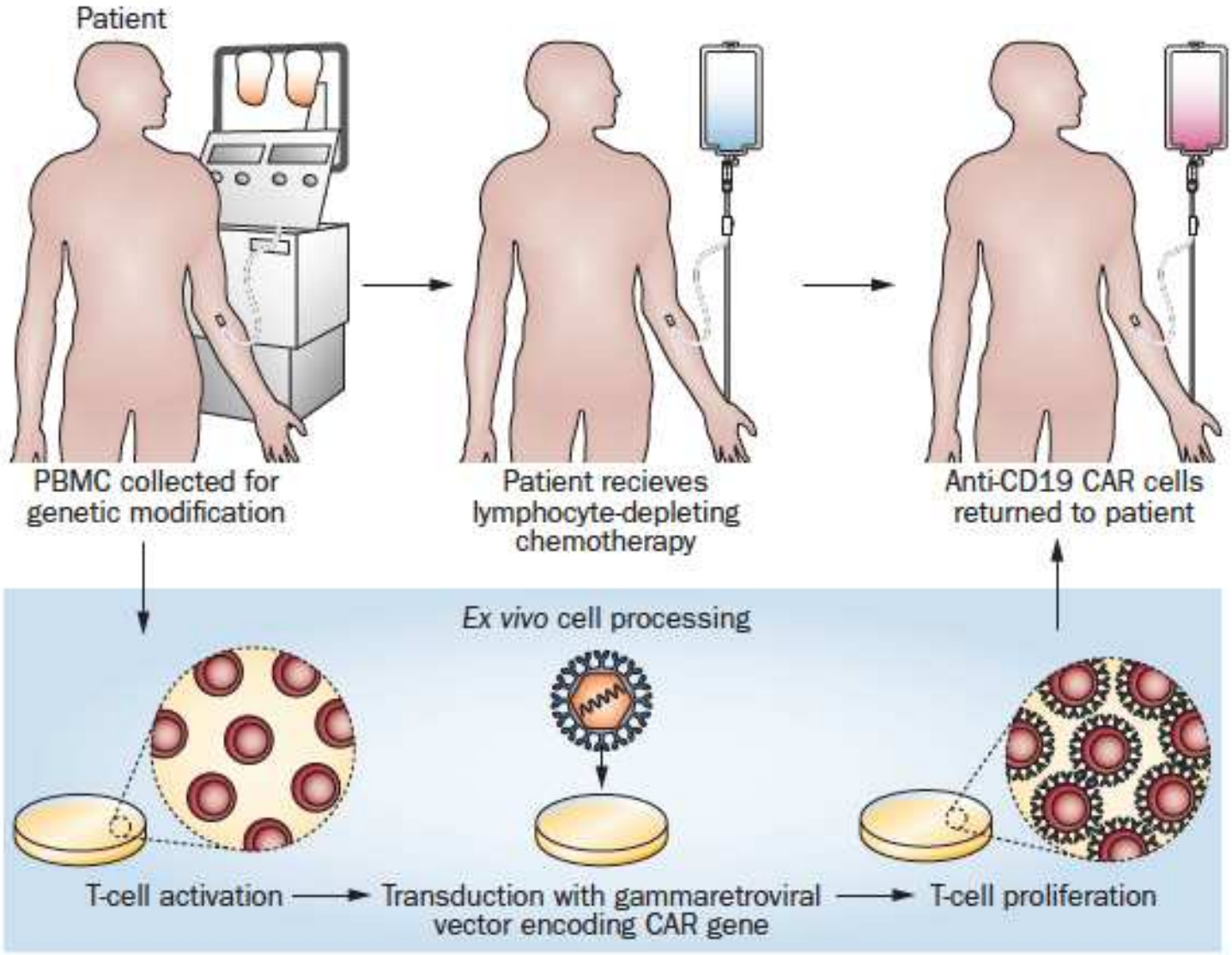
Konterman and Brinkman. Drug Dis Today, 20(7), 2015.
Scharma et al, Nature Reviews Drug Dis, 5, 2006.

Chimeric Antibody Receptor T-Cell



Magee and Snook. Disc Med, 20(108), 2014.

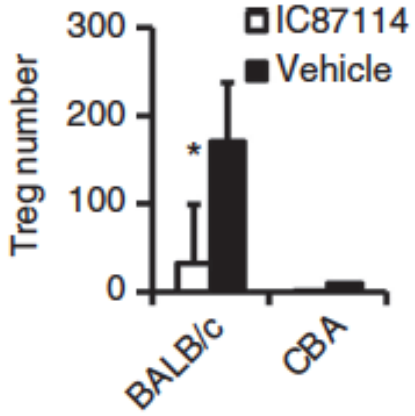
CAR-T Process – B-ALL

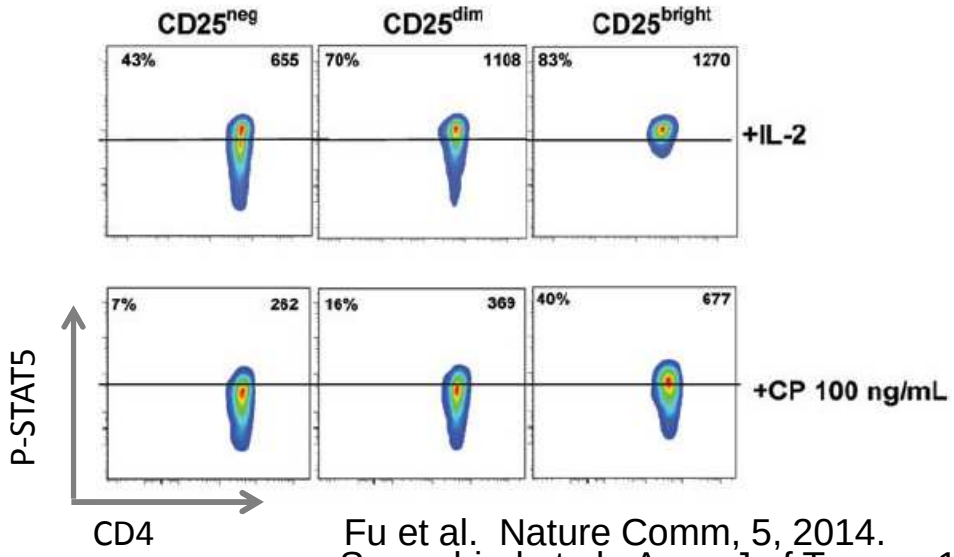


Kochenderfer and Rosenberget al, Nat Rev Clin Oncol. 10, 2013.

Blood Tumors Hijack Intracellular Signaling which Promotes Tolerance

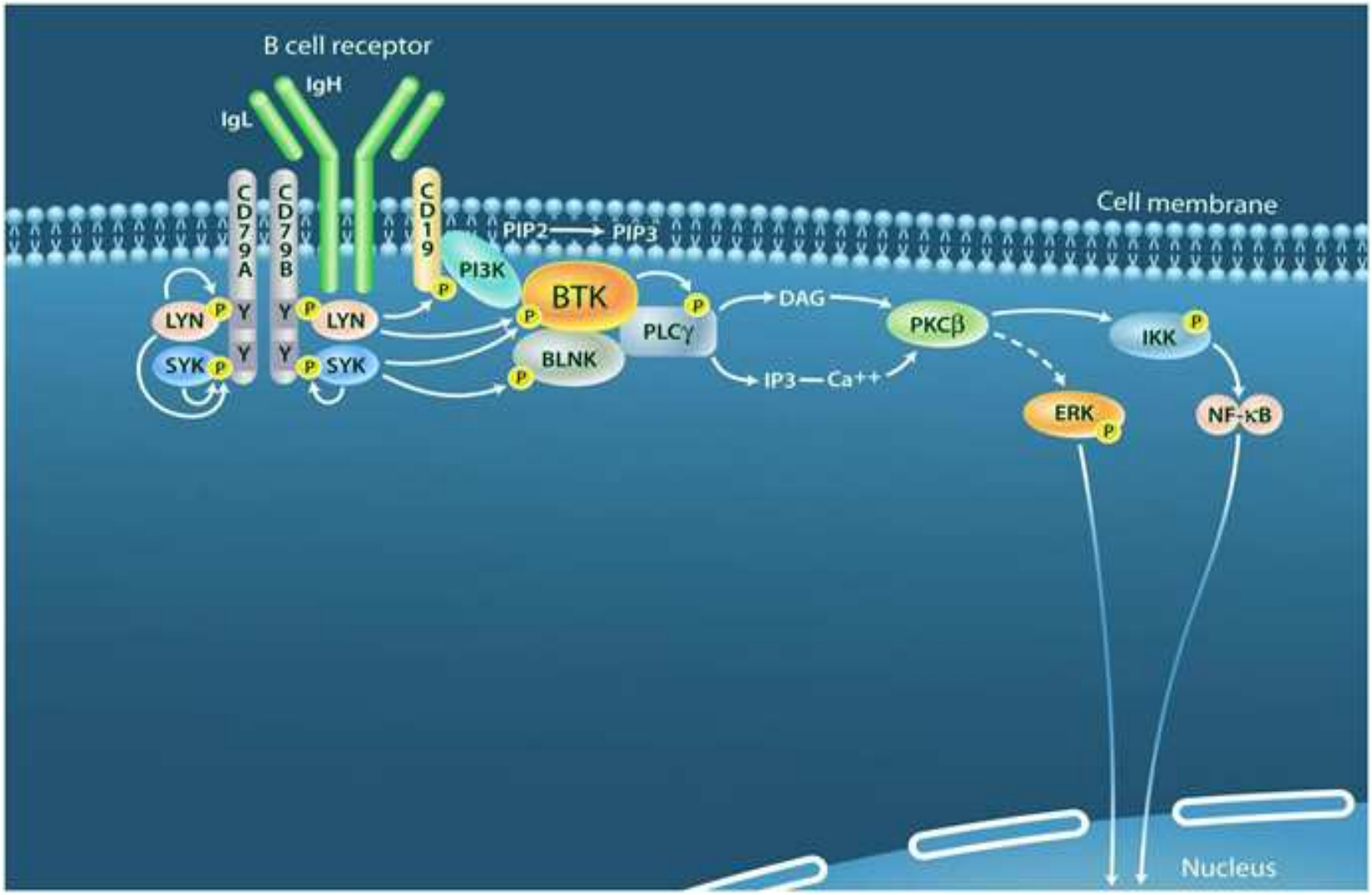
- BCR/PI3K delta signaling stimulates T-regs, MDSCs and TAMs
- JAK-STAT signaling blocks T-effs



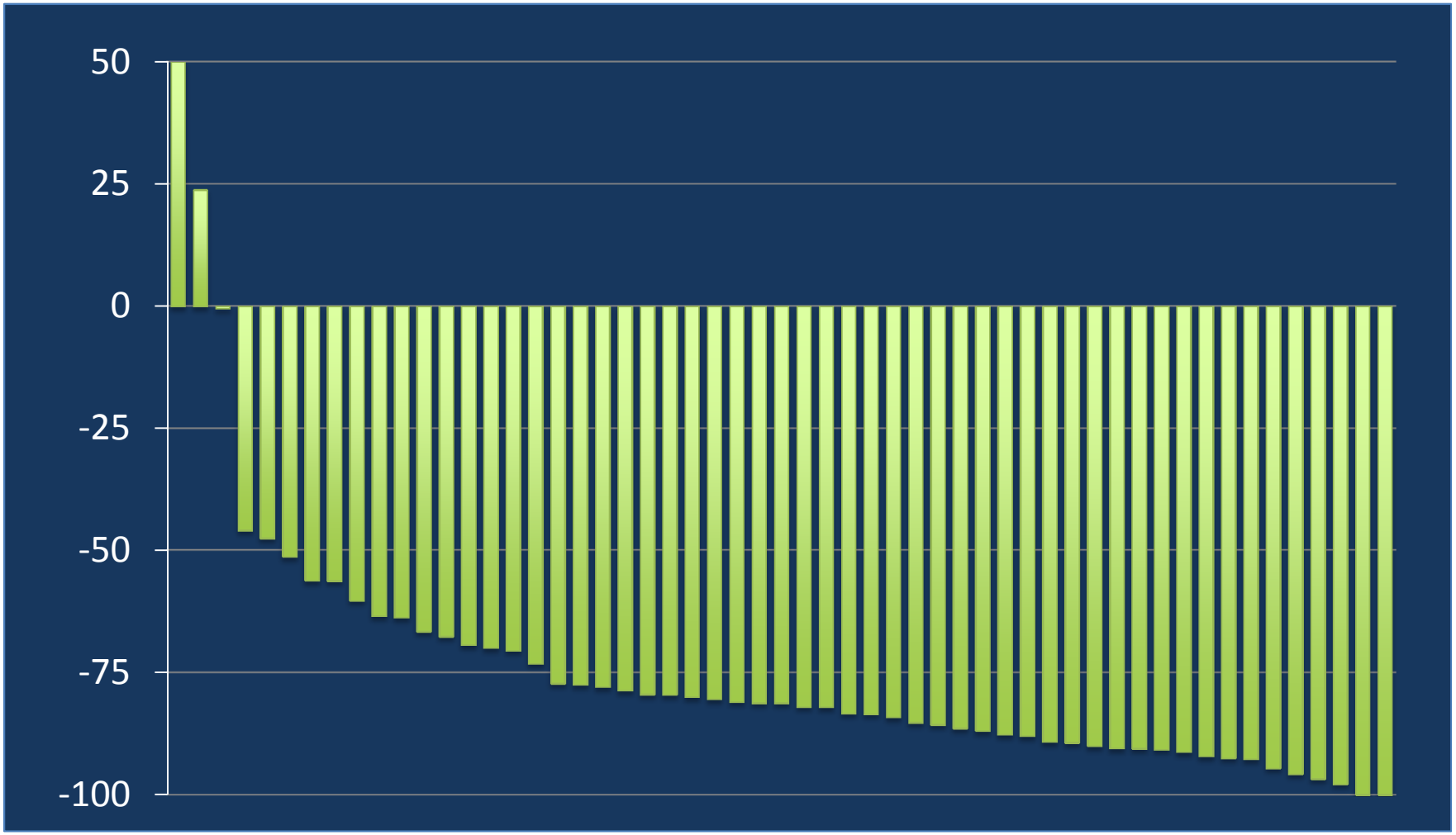


Fu et al. Nature Comm, 5, 2014.
Sewgobind et al. Amer J of Transp, 10, 2010.

Subversion of Physiologic Pathways and Treatment with B Cell Receptor Antagonists

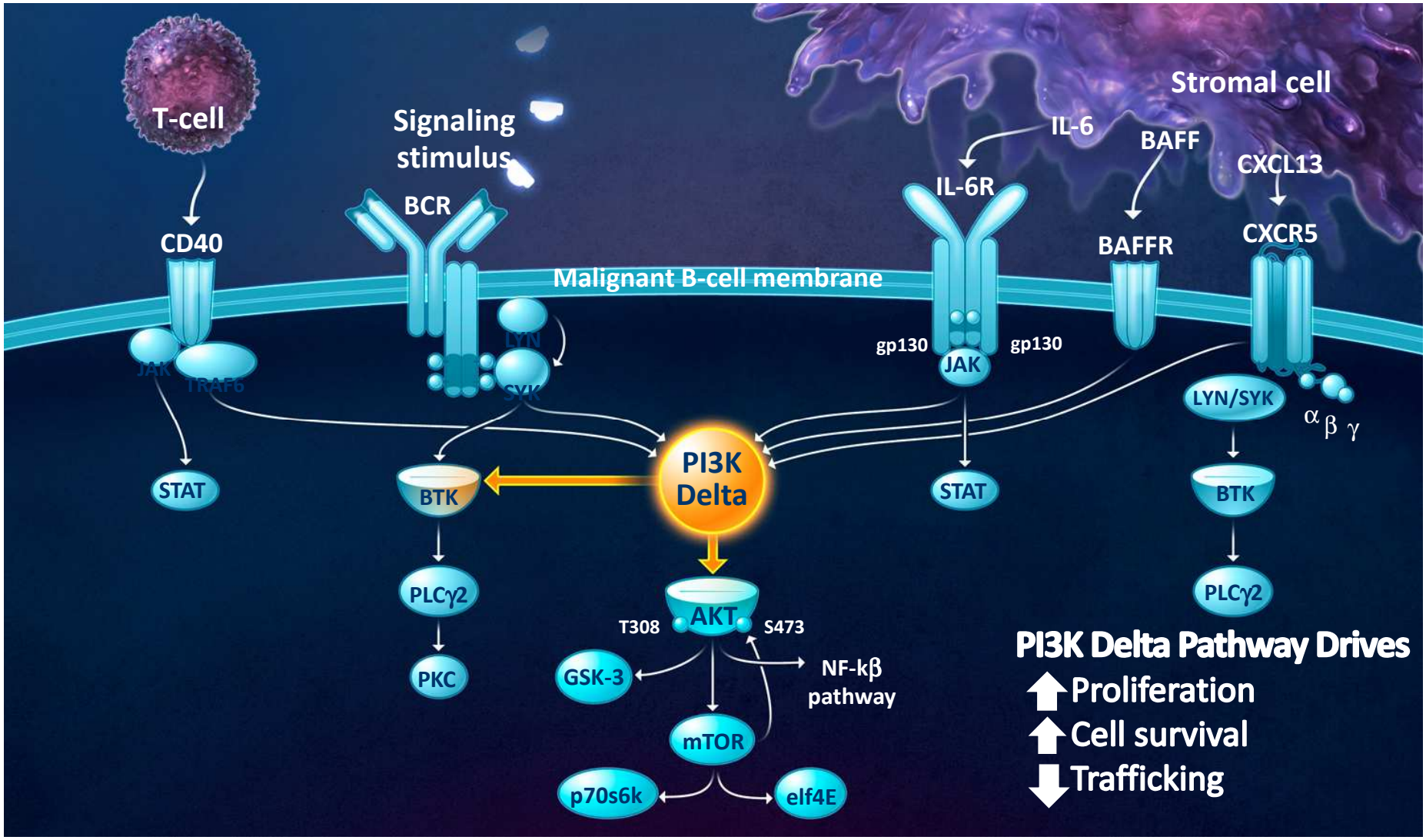


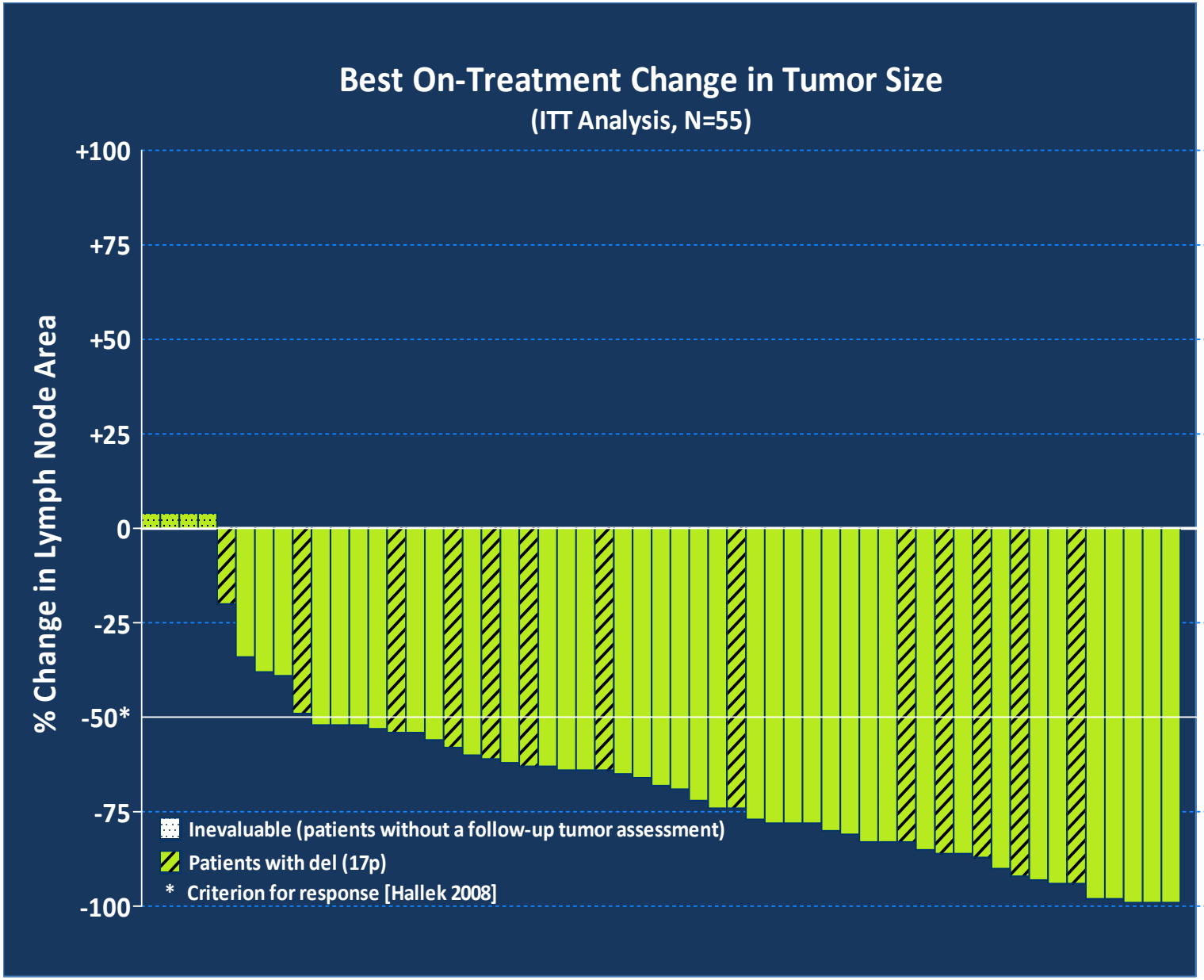
BTK Inhibitor – Ibrutinib in CLL



Bryd et al, Blood 2013.

PI3-K at the Crossroads





Single-Agent CAL-101 (Idelalesib) Resulted in Tumor Shrinkage in CLL, Including del(17p)

Kahl et al, Blood 123(22) 2014.

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