Le terapie cellulari post allotrapianto

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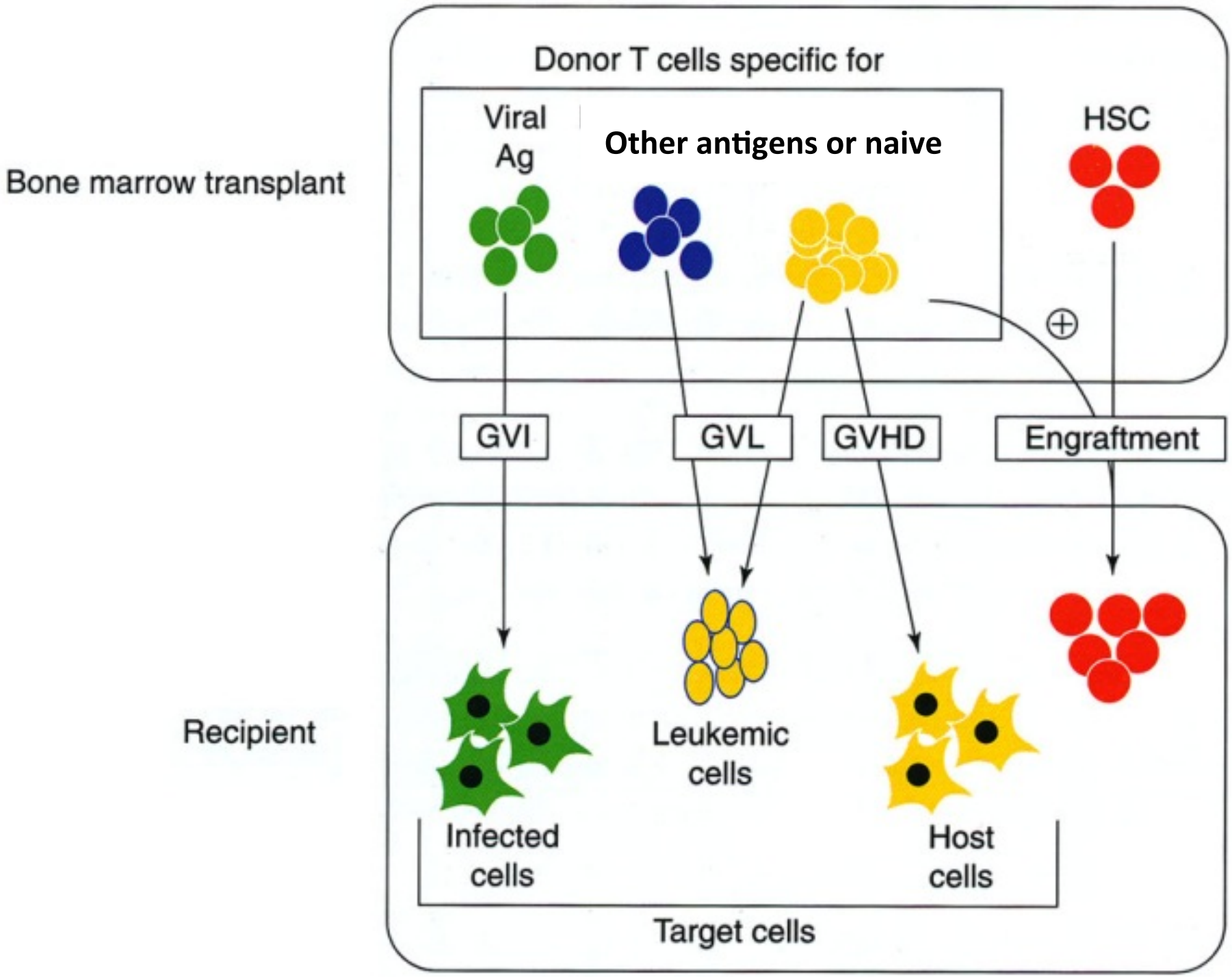
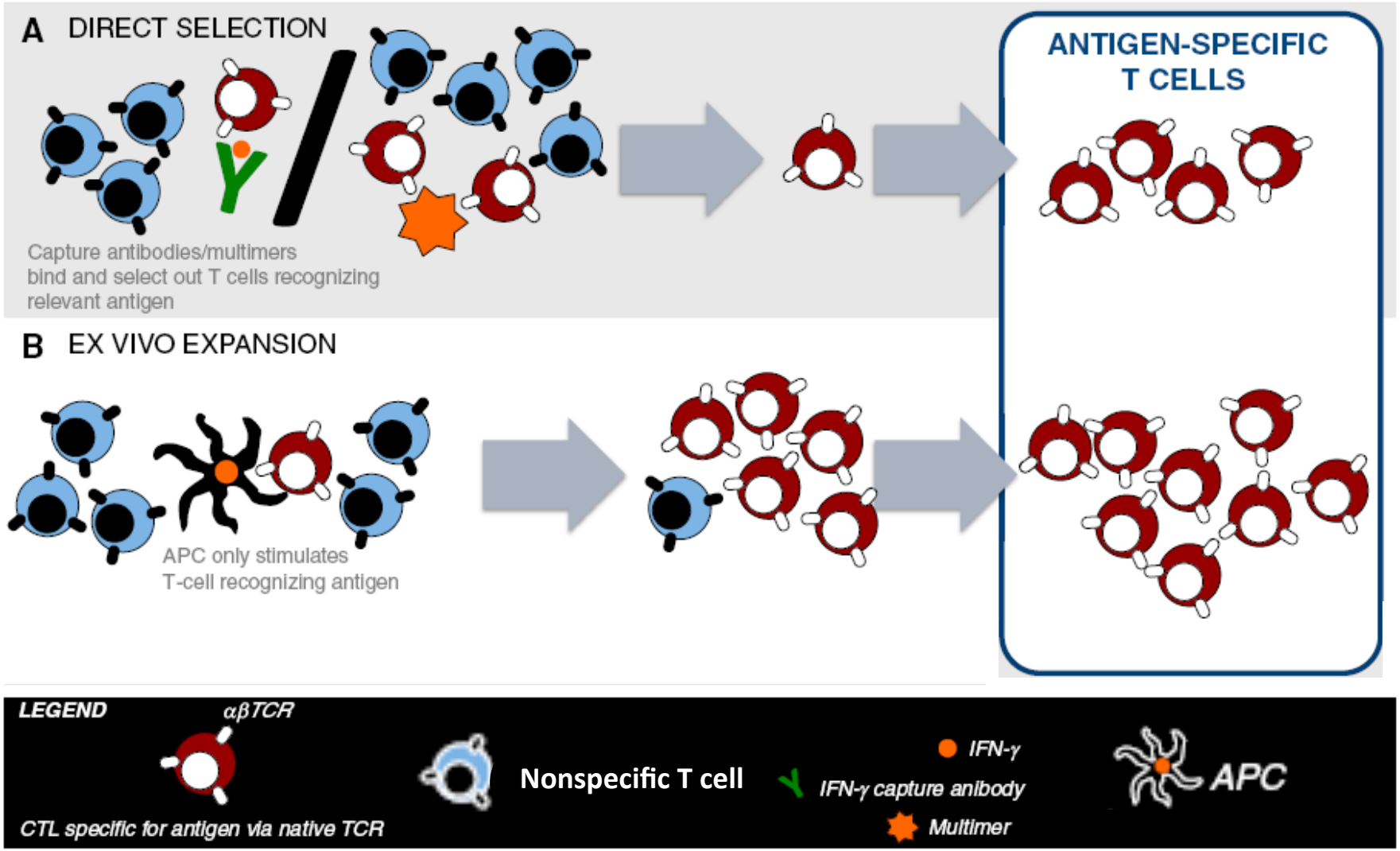
- Nothing in biology makes sense except in the light of evolution (1973)

- Theodosius Dobzansky (1900-1975)

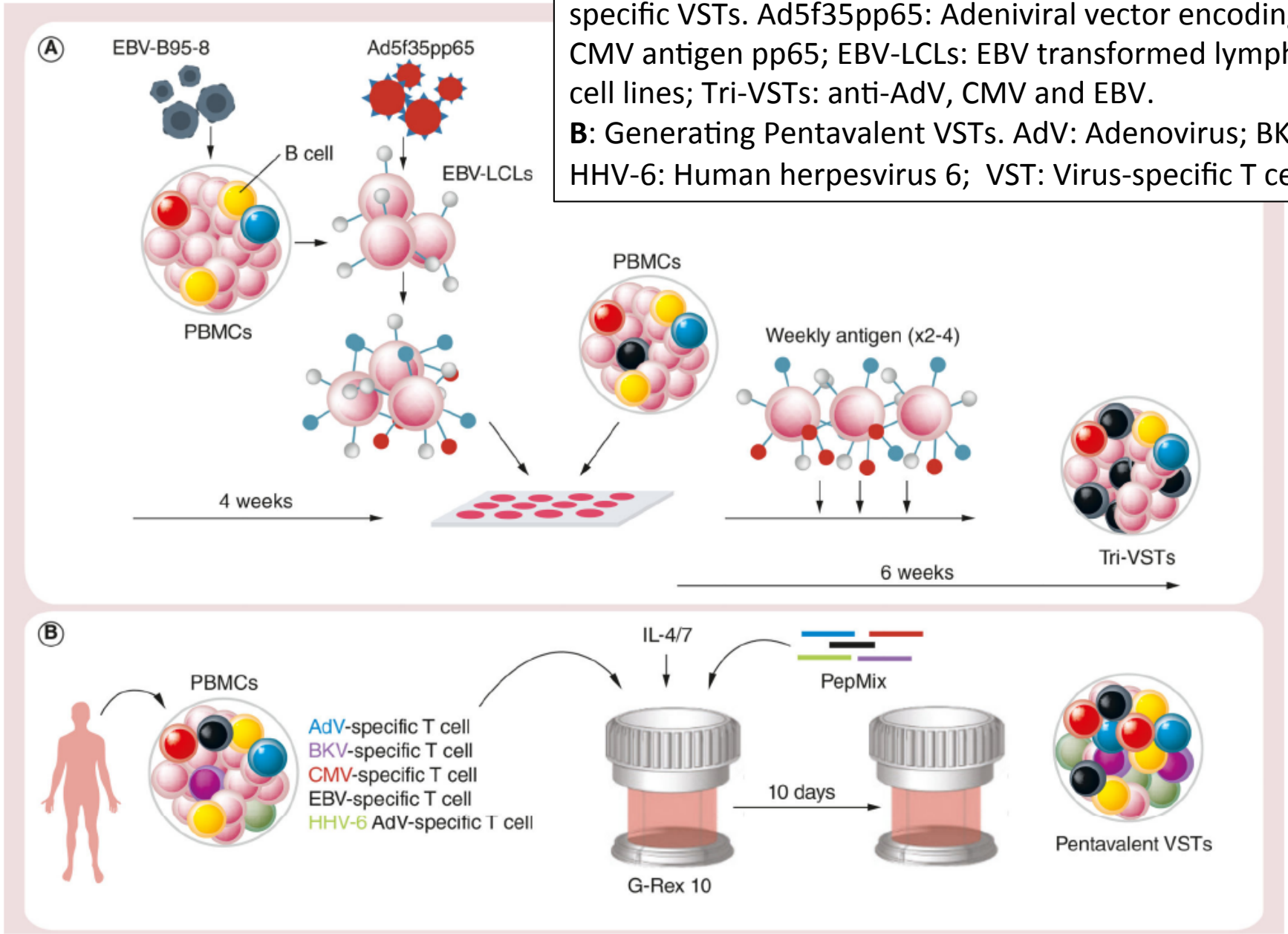

Bone marrow transplant
Donor T cells specific for
Viral Ag
Other antigens or naive
HSC
GVI
GVL
GVHD
Engraftment
Recipient
Leukemic cells
Infected cells
Host cells
Target cells



Adapted from Bollard C. et al, Blood, 2017

Generation of *ex vivo* expanded virus-specific T cells

A: Manufacturing procedure for generating AdV, EBV and CMV-specific VSTs. Ad5f35pp65: Adeniviral vector encoding for the CMV antigen pp65; EBV-LCLs: EBV transformed lymphoblastoid cell lines; Tri-VSTs: anti-AdV, CMV and EBV.
B: Generating Pentavalent VSTs. AdV: Adenovirus; BKV:BK virus; HHV-6: Human herpesvirus 6; VST: Virus-specific T cell.



Tzannou I. et al, Immunotherapy, 2015

A total of 32 lines were produced and characterized, 18 of which were administered to the 50 study patients (Baylor College, Houston, Texas, US). The selection of lines for infusion was based on the specificity of the line for the target virus through a shared HLA allele, as well as the overall level of HLA match.

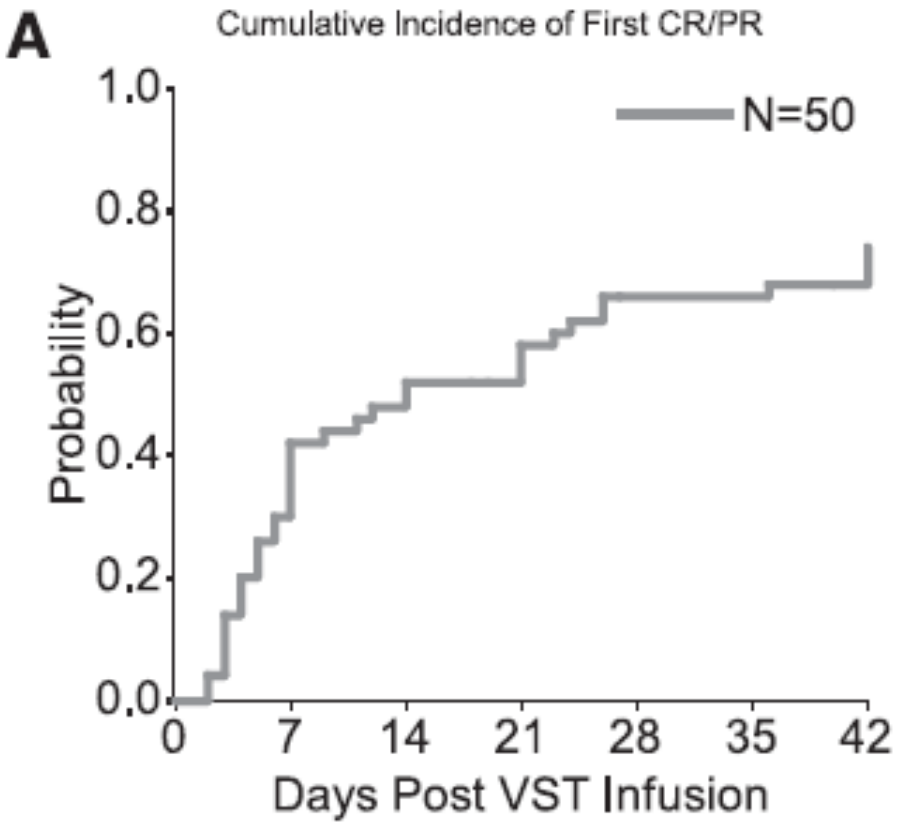
Leen A. et al, Blood, 2013

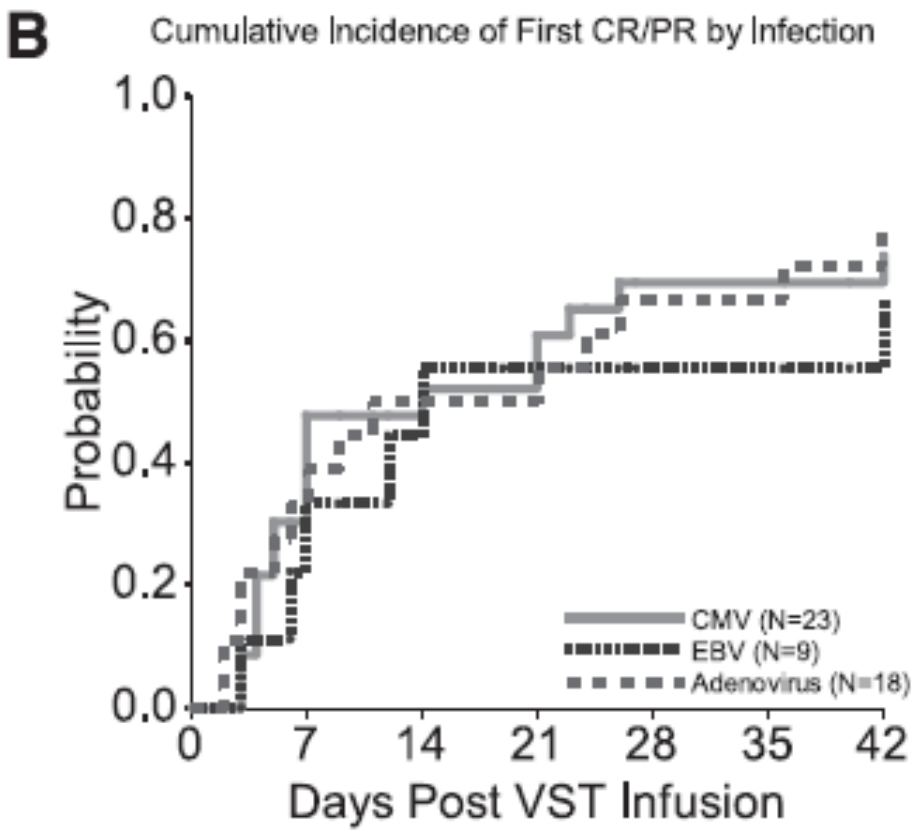
Banked third-party VST to treat severe viral infections

	Infection cohort			
	AdV (n=18)	CMV (n=23)	EBV (n=9)	Total (n=50)
HLA match (recipient to first VST line) (n, %)*				
1/6	5 (27.8)	4 (17.4)	3 (33.3)	12 (24.0)
2/6	9 (50.0)	12 (52.2)	3 (33.3)	24 (48.0)
3/6	3 (16.7)	6 (26.1)	3 (33.3)	12 (24.0)
4/6	1 (5.6)	1 (4.3)	0 (0.0)	2 (4.0)
Number of infusions (n, %)				
1	15 (83.3)	17 (73.9)	4 (44.4)	36 (72.0)
2	2 (11.1)	4 (17.4)	1 (11.1)	7 (14.0)
3	1 (5.6)	2 (8.7)	3 (33.3)	6 (12.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6	0 (0.0)	0 (0.0)	1 (11.1)	1 (2.0)

Leen A. et al, Blood, 2013

Banked third-party VST to treat severe viral infections





At day 42: Overall

74.0 (95% CI: 58.5-89.5)

At day 42:

CMV 73.9 (95% CI: 51.2-96.6)

EBV 66.7 (95% CI: 36.9-96.5)

AdV 77.8 (95% CI: 53.7-100)

Leen A. et al, Blood, 2013

Table 5. Maximal acute GVHD grade within 45 days of first infusion

	Maximum acute GVHD grade									
	0		I		II		III		IV	
Virus	n	%	n	%	n	%	n	%	n	%
CMV (n = 23)	19	(82.6)	3	(13.0)	1	(4.4)	0	(0.0)	0	(0.0)
EBV (n = 9)	8	(88.9)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
AdV (n = 18)	15	(83.3)	2	(11.1)	0	(0.0)	1	(5.6)	0	(0.0)
Total (n = 50)	42	(84.0)	6	(12.0)	1	(2.0)	1	(2.0)	0	(0.0)

Leen A. et al, Blood, 2013

Allogeneic virus-specific T cells with HLA alloreactivity do not produce GVHD in human subjects

The authors reviewed their clinical experience with adoptive transfer of allogeneic HSCT donor derived virus specific CTLs in 153 recipients, including 73 where there was an HLA mismatch.

Table 1. Overall incidence of acute GVHD

Study	Donor/recipient matching	No. of patients	Acute GVHD
EBV-specific CTLs	Haploidentical family member	13	1 grade 1 (preexisting)
	Mismatched unrelated donor	34	2 grade 1
			1 grade 2
	Matched donor	67	3 grade 1
			1 grade 2
Bivirus-specific CTLs	Haploidentical family member	6	None
	Mismatched unrelated donor	5	None
	Matched donor	3	None
Trivirus-specific CTLs	Haploidentical family member	9	None
	Mismatched unrelated donor	6	1 grade 1
	Matched donor	10	1 grade 1

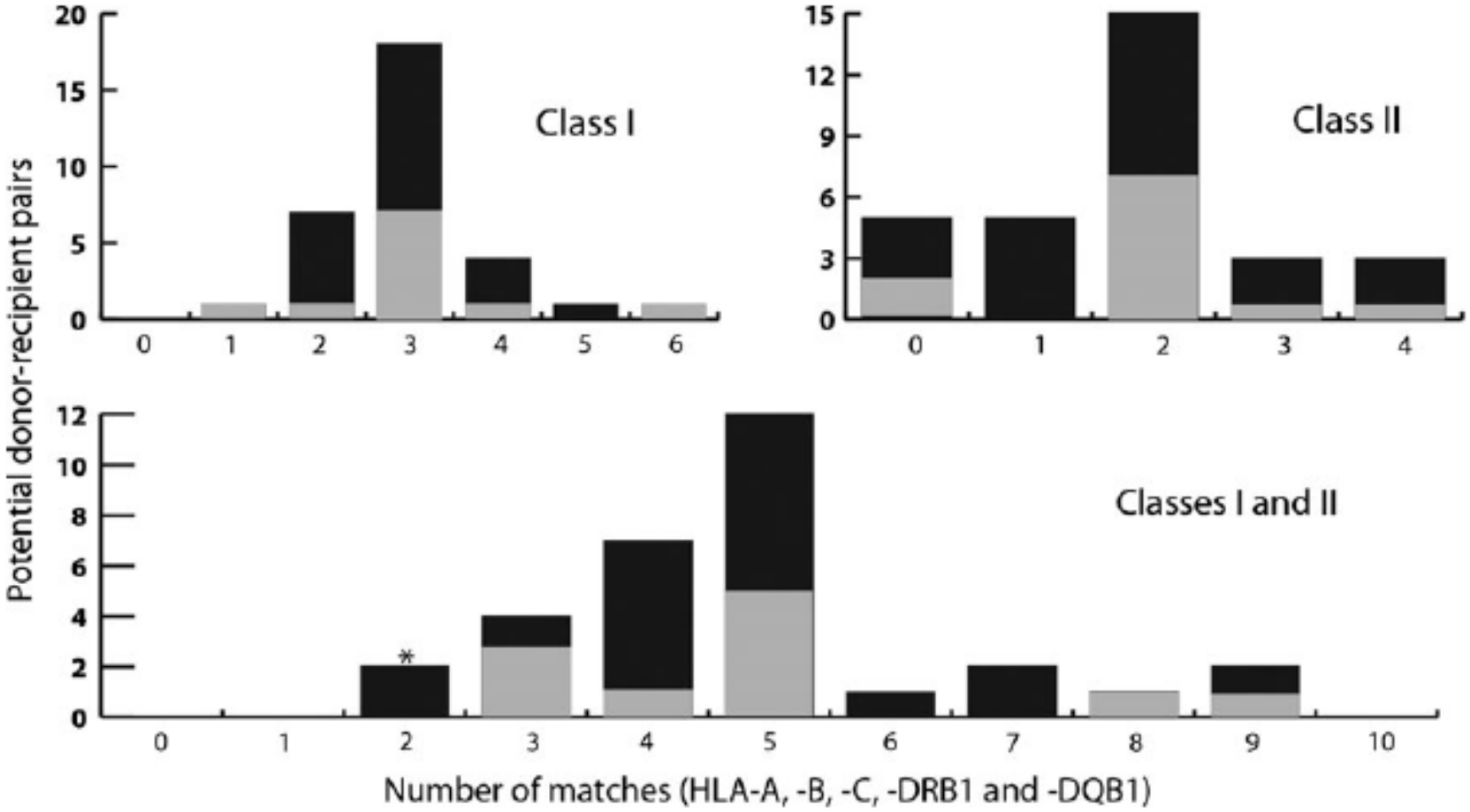
Melenhorst J. et al, Blood, 2010


AIG
adidas

15 well-selected New Zealand donors could cover 57% of the Scottish patient population. This rose to 85% with 25 donors. 25–50 x 10^9 mononuclear cells (MNCs) were collected from each of 25 donors into 10 bags by apheresis, cryopreserved in 10% dimethyl sulfoxide (DMSO), then shipped to the UK in vapour phase liquid nitrogen (Scottish National Blood Transfusion Service)..

Vickers M. et al, British Journal of Haematology, 2014

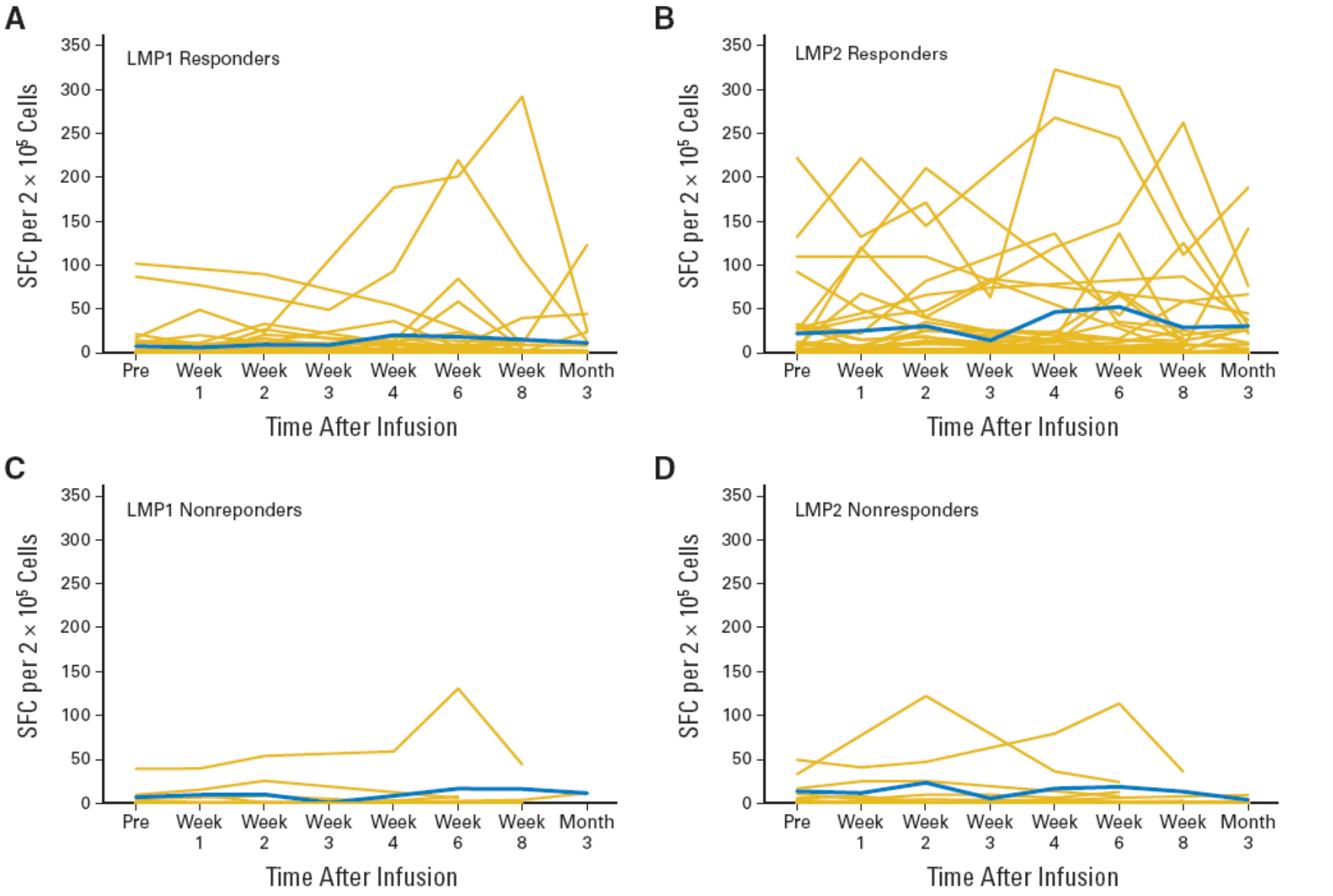
EBV specific banks to treat EBV associated lymphoproliferative disease



Human leucocyte antigen matching of donors with recipients. The number of matches at five human leucocyte antigen (HLA) loci are shown as histograms of the best matched prospective recipient–donor pairs. Matches that resulted in cytotoxic T lymphocyte infusions are shown in grey, those that did not in black. For two pairs, information was only available at HLA class I.

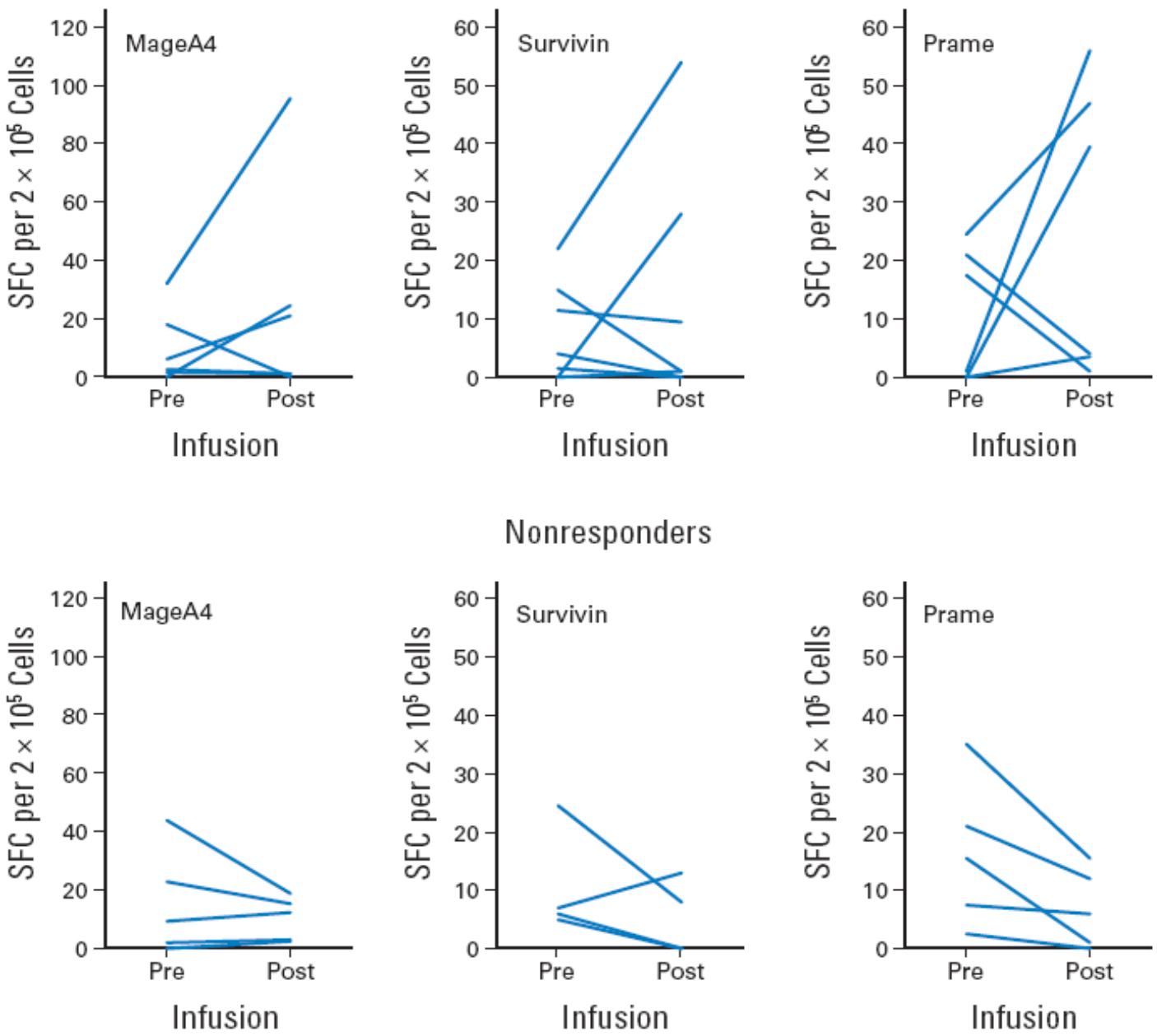
Vickers M. et al, British Journal of Haematology, 2014

Type II or III EBV positive lymphoma treated with autologus LMP CTL
Frequency of LMP specific and tumor antigen specific T cells



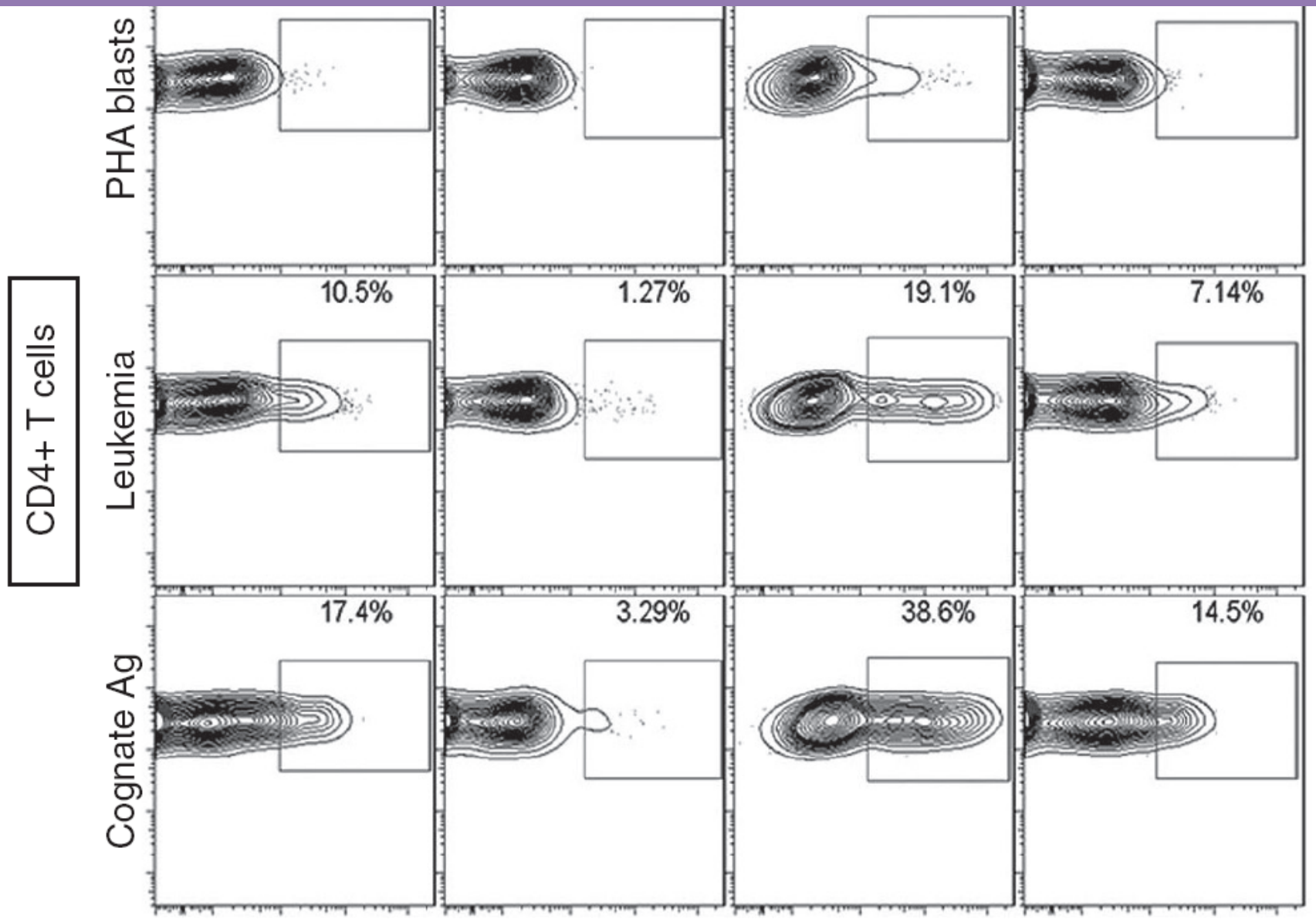
Bollard C. et al, Journal of Clinical Oncology, 2014

Type II or III EBV positive lymphoma treated with autologus LMP CTL
Evidence for epitope spreading in 12 patients with lymphoma



Bollard C. et al, Journal of Clinical Oncology, 2014

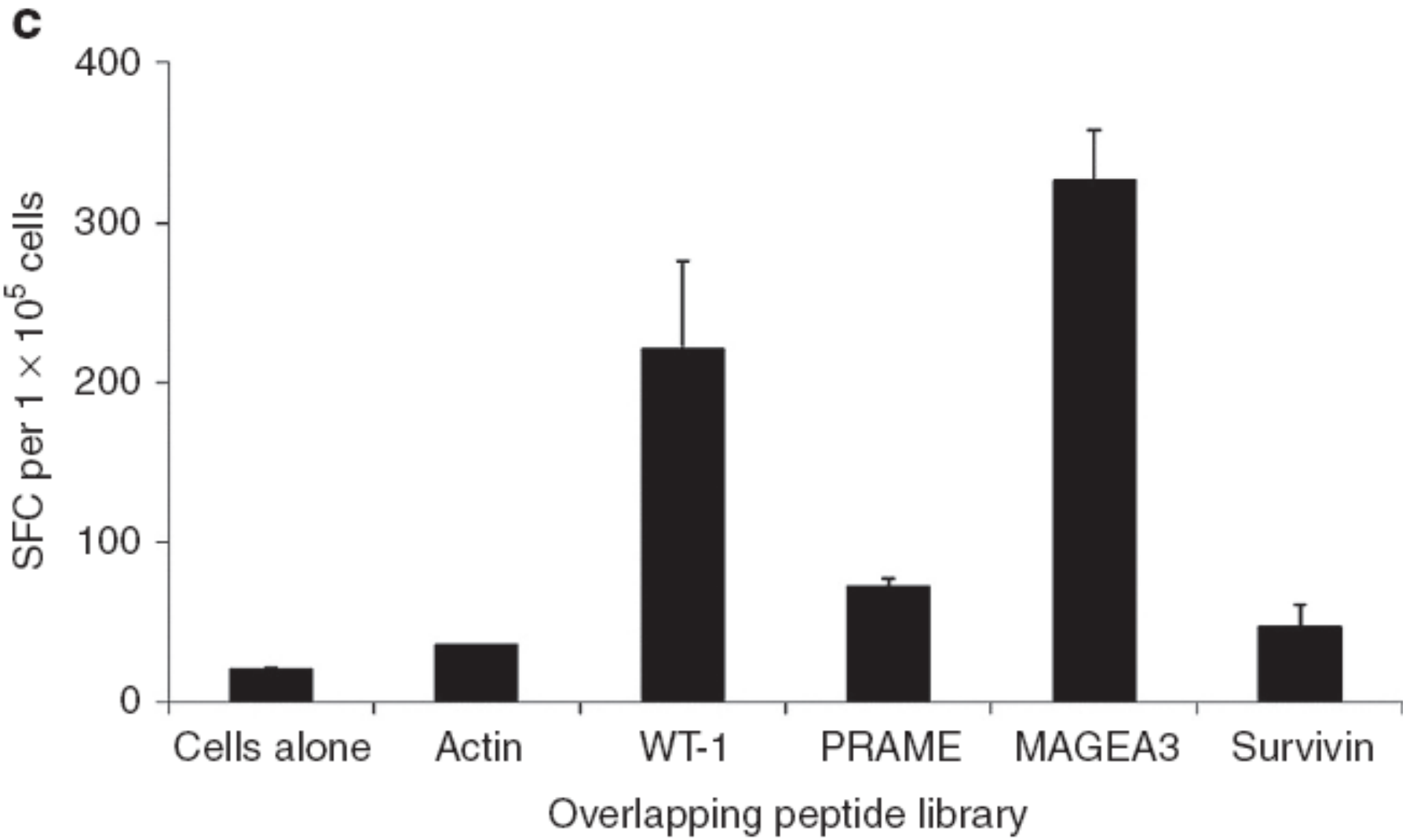
GVL without GVH by Multivirus specific T cells



12 yrs boy with RR-ALL haplotransplanted from the mother

Melenhorst J. et al, Molecular Therapy, 2015

GVL without GVH by Multivirus specific T cells



Melenhorst J. et al, Molecular Therapy, 2015

Generation and administration of HA-1-specific T-cell lines for the treatment of patients with relapsed leukemia after allogeneic stem cell transplantation

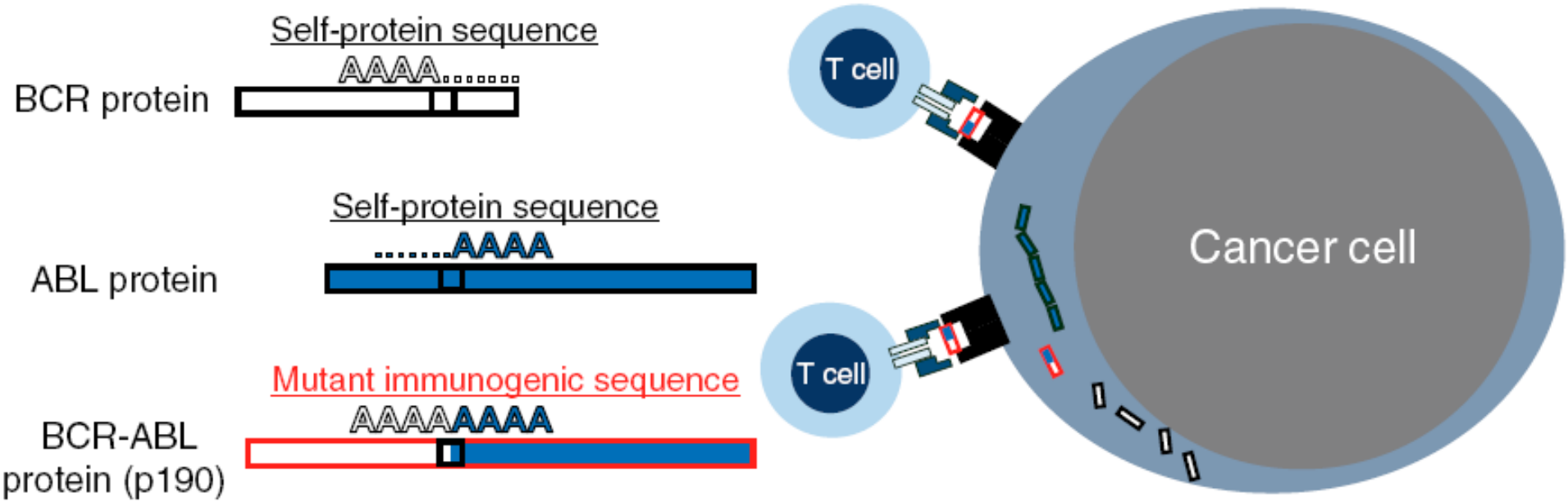
Table 1. Characteristics of the HA-1-specific CD8⁺ T-cell lines generated for *in vivo* administration.

CTL Line	Culture period (days)	Cells (x 10^6)	$CD8^+HA\text{-}1^+$ T cells (x 10^6)	Composition T-cell line (% positive cells)			Phenotype $HA\text{-}1^+$ T cells (% positive cells)					Cytotoxicity (% lysis)[1]			
				CD4	CD8	$CD8^+HA\text{-}1^+$	CD45RO	CD45RA	CCR7	CD27	CD28	PHA[2] donor - peptide	PHA donor + peptide[3]	PHA patient	Leukemia
Administered															
NMJ - 1	30	869	243	12	84	27	84	51	1	93	30	8	72	56	n.a.
KHP	38	56	11	3	89	19	n.a.	n.a.	n.a.	n.a.	n.a.	5	57	30	61[4]
AHP - 2	35	325	20	1	61	6	n.a.	n.a.	n.a.	n.a.	n.a.	6[4]	63[4]	68[4]	13[4]
Not-administered															
NMJ - 2	34	30	11	20	80	36	98	2	5	85	11	1	58	43	n.a.
UBW	29	600	60	1	70	10	99	29	0	74	85	1	59	64	35
FPW - 3	28	6200	372	9	91	6	97	21	2	71	75	2	39	64[4]	60[4]
VWX	35	239	14	11	70	6	99	7	0	30	73	3	83	34	n.a.
AHP - 3	37	660	224	1	82	34	99	0	8	4	46	0	61	37	32
AHP - 4	36	3600	252	2	90	7	99	0	8	12	18	0	38	35	36[4]

[1]Percentage lysis after 4 h in a ^{51}Cr release assay, E:T ratio of 30:1; [2]PHA blasts; [3]Pulsed with HA-1 peptide; [4]lysis after 24 h and E:T ratio 10:1; n.a.: not available.

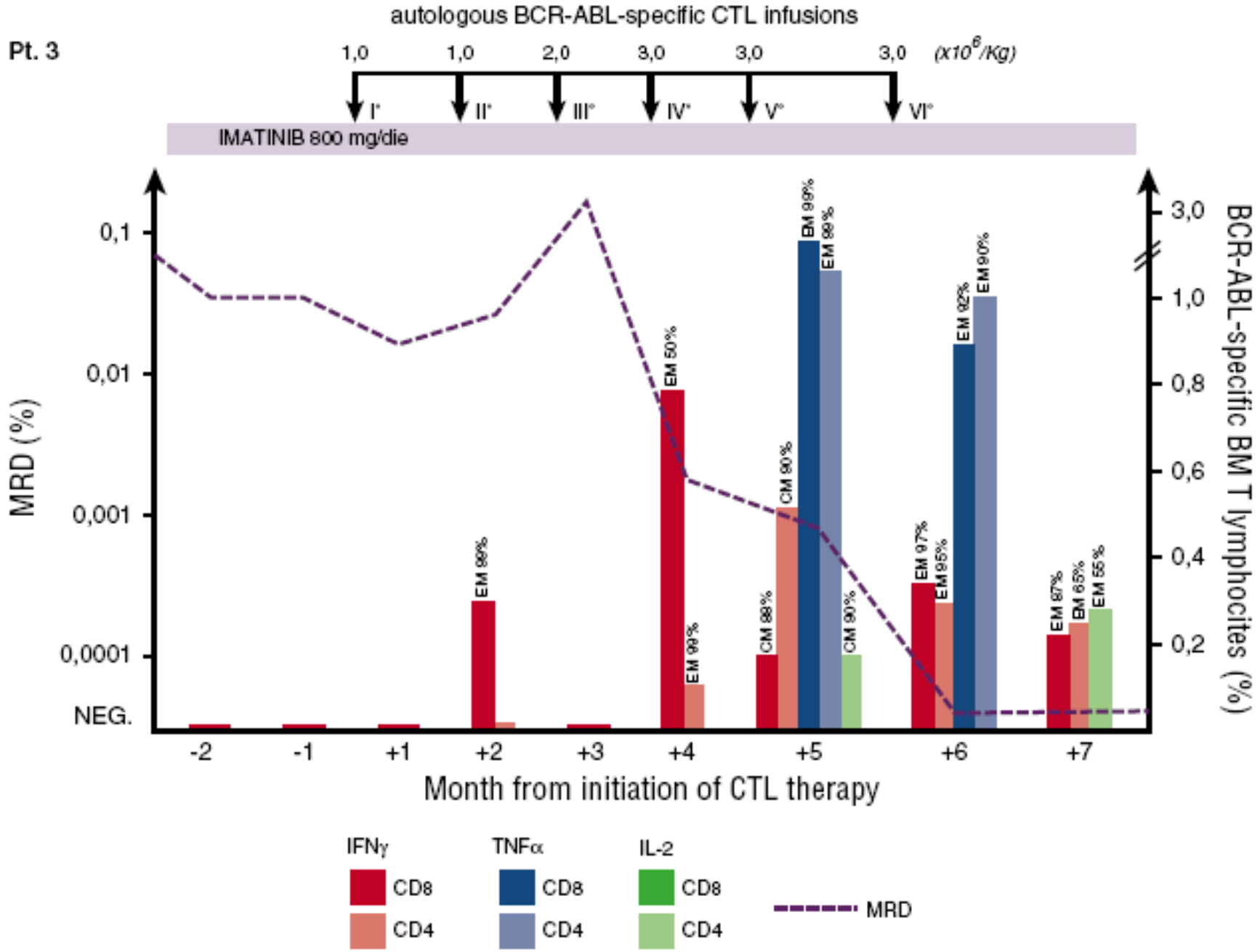
Three patients were treated with HA-1-specific T-cell lines. After infusion, no toxicity was observed, showing that administration of these T-cell lines was safe. Although in one patient, during a period of stable disease, HA-1-specific T cells could be detected in the peripheral blood and bone marrow, no clear clinical response occurred in these patients.

Meij P. et al, Haematologica, 2012



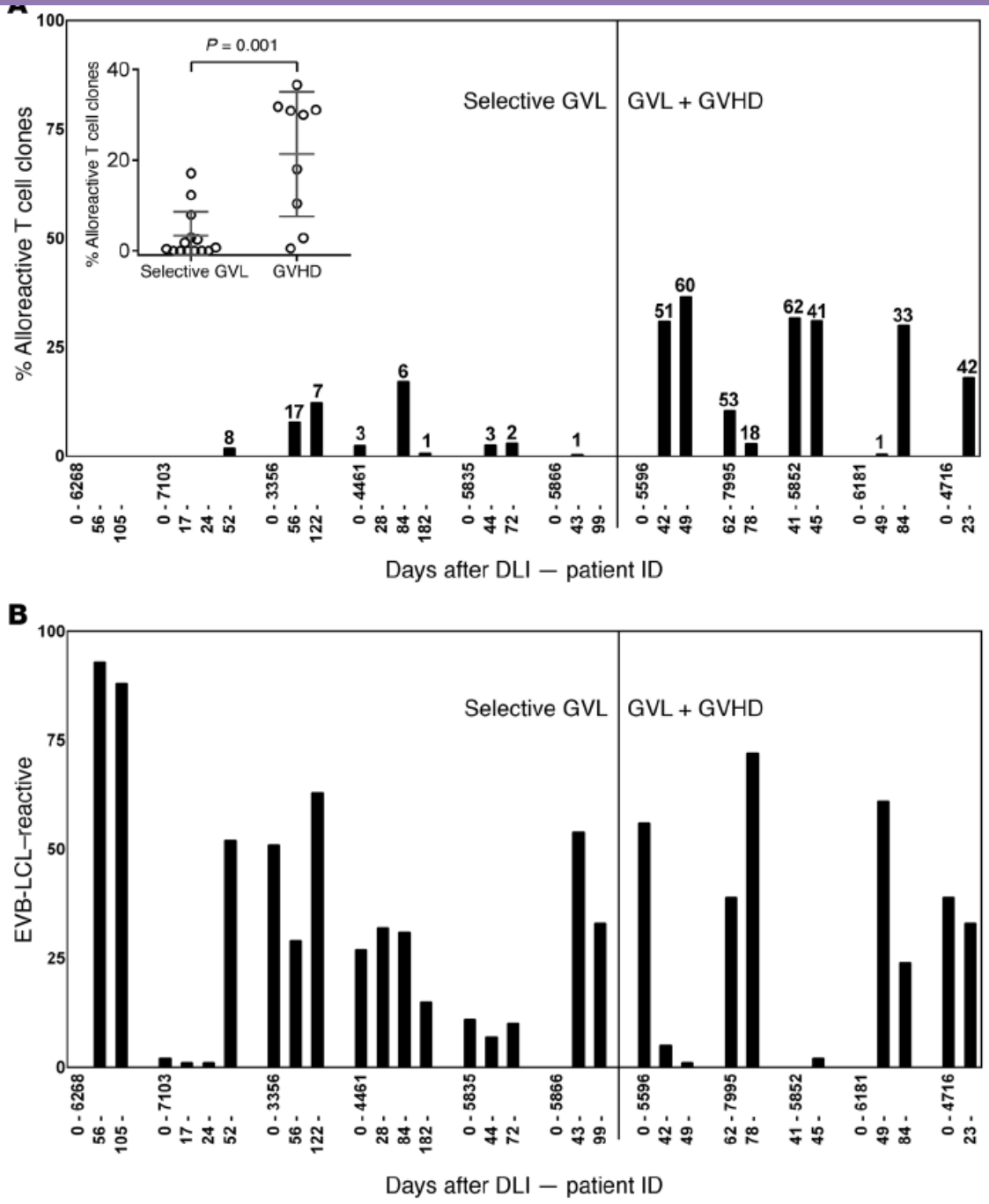
Lulla P. et al, Blood, 2017

BCR-ABL–specific T-cell therapy in Ph1 ALL patients on tyrosine-kinase inhibitors



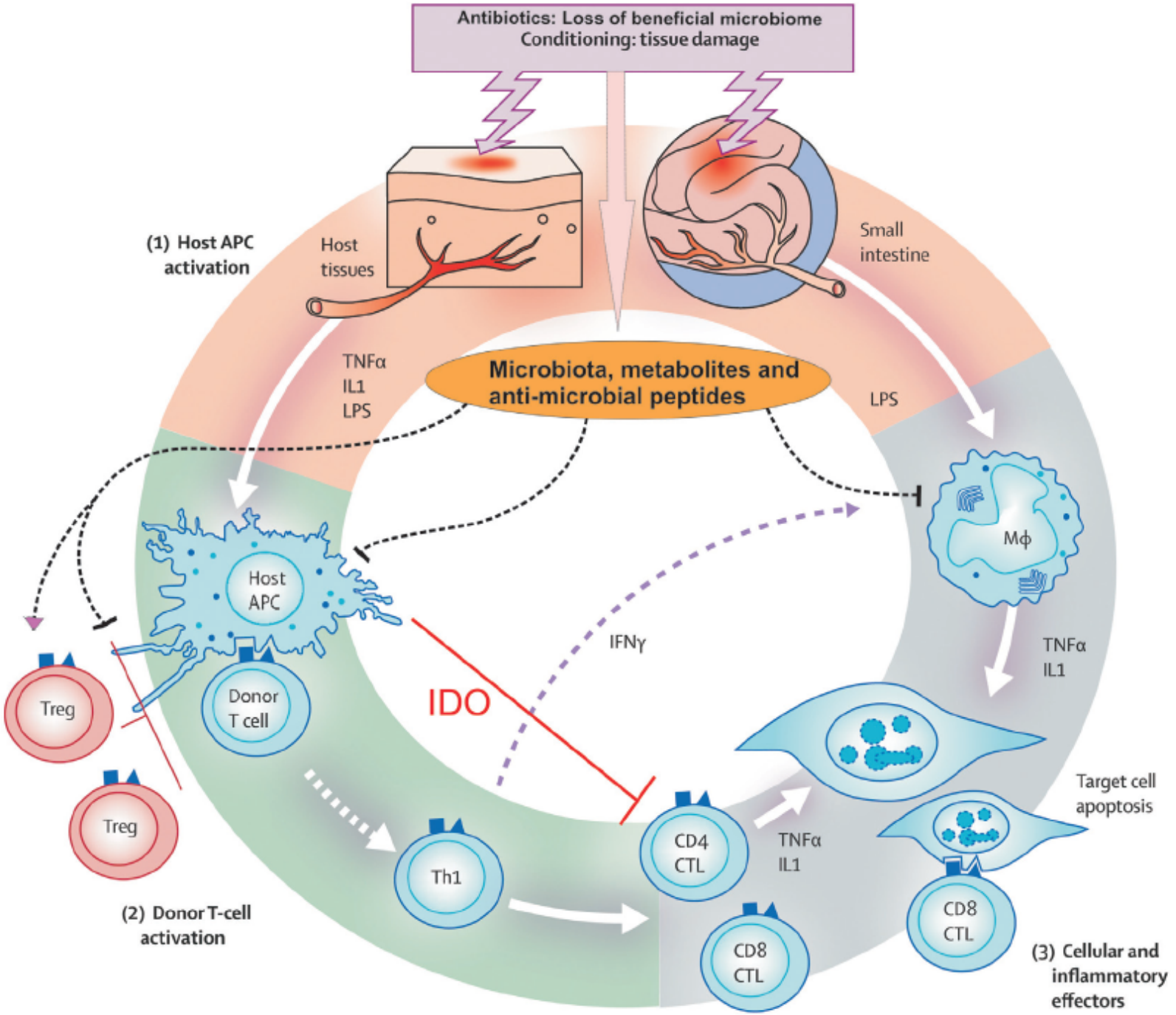
Comoli P. et al, Blood, 2017

Selective GVL depends on magnitude and diversity of the alloreactive T cell response: frequencies of alloreactive T cells



Absolute numbers of identified alloreactive T cells clones are depicted on top of the bars.

Cornelis A.M. et al, JCI, 2017



Ghimire S. et al, Frontiers in Immunology, 2017

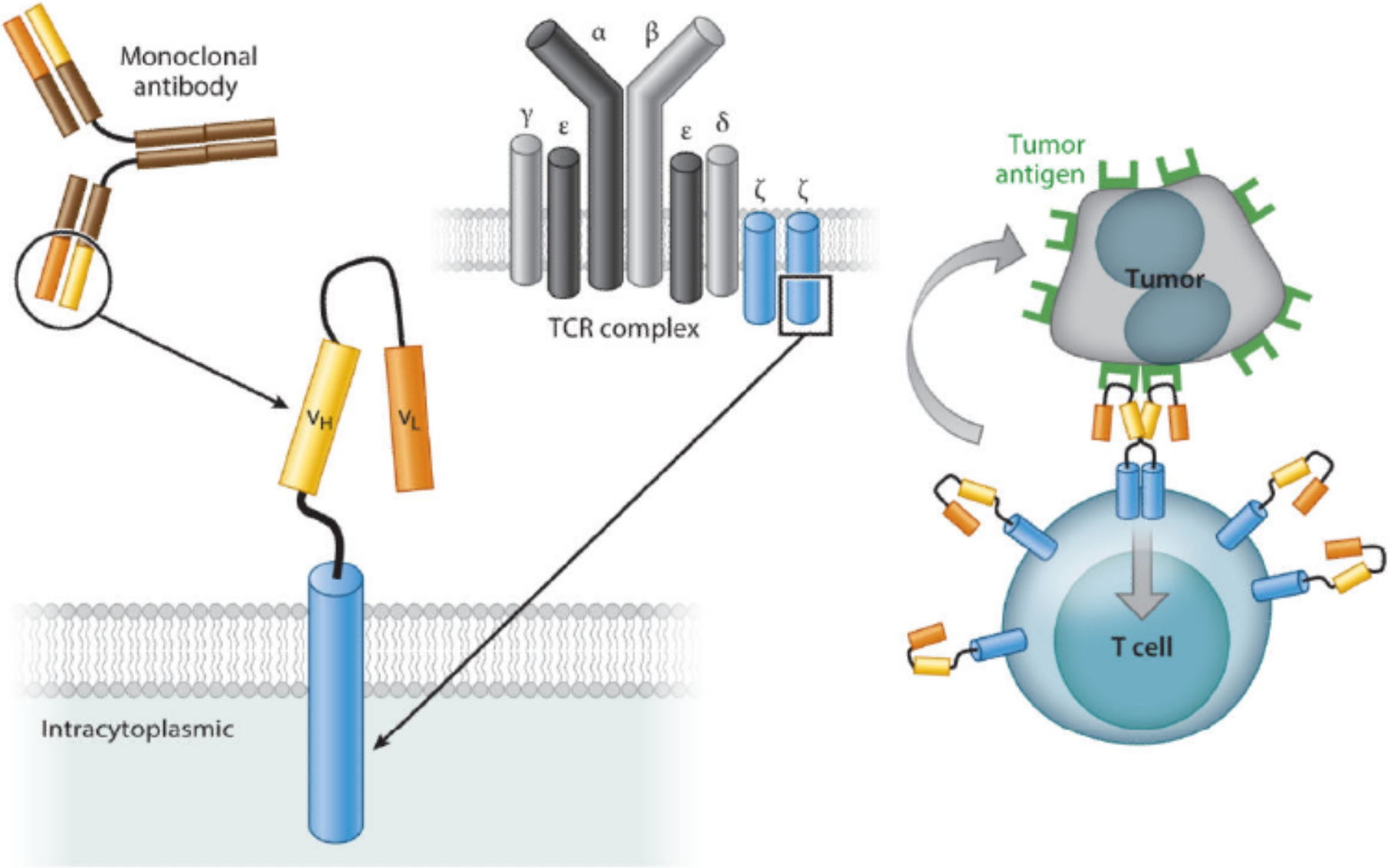
Adoptive immunotherapy in canine chimeras

DLT (time after marrow transplant)	No. of dogs			Survival time
	Studied	With GVHD	Alive	
—	9	0	9	>2 yr, >2 yr, >2 yr, >2 yr, >2 yr, >2 yr, >2 yr, >2 yr, >2 yr
Day 1+2	2	2	0	51 days, 83 days
Day 21+22	2	2	0	56 days, 72 days
Day 61+62	7	0	7	>2 yr, >2 yr, >2 yr, >2 yr, >2 yr, >2 yr, >2 yr
2 years[a]	1	0	1	>2 yr.
4.5 years[a]	1	0	1	>2 yr.

[a] These dogs had served as controls for 2 years. DLT, donor lymphocyte transfusion.

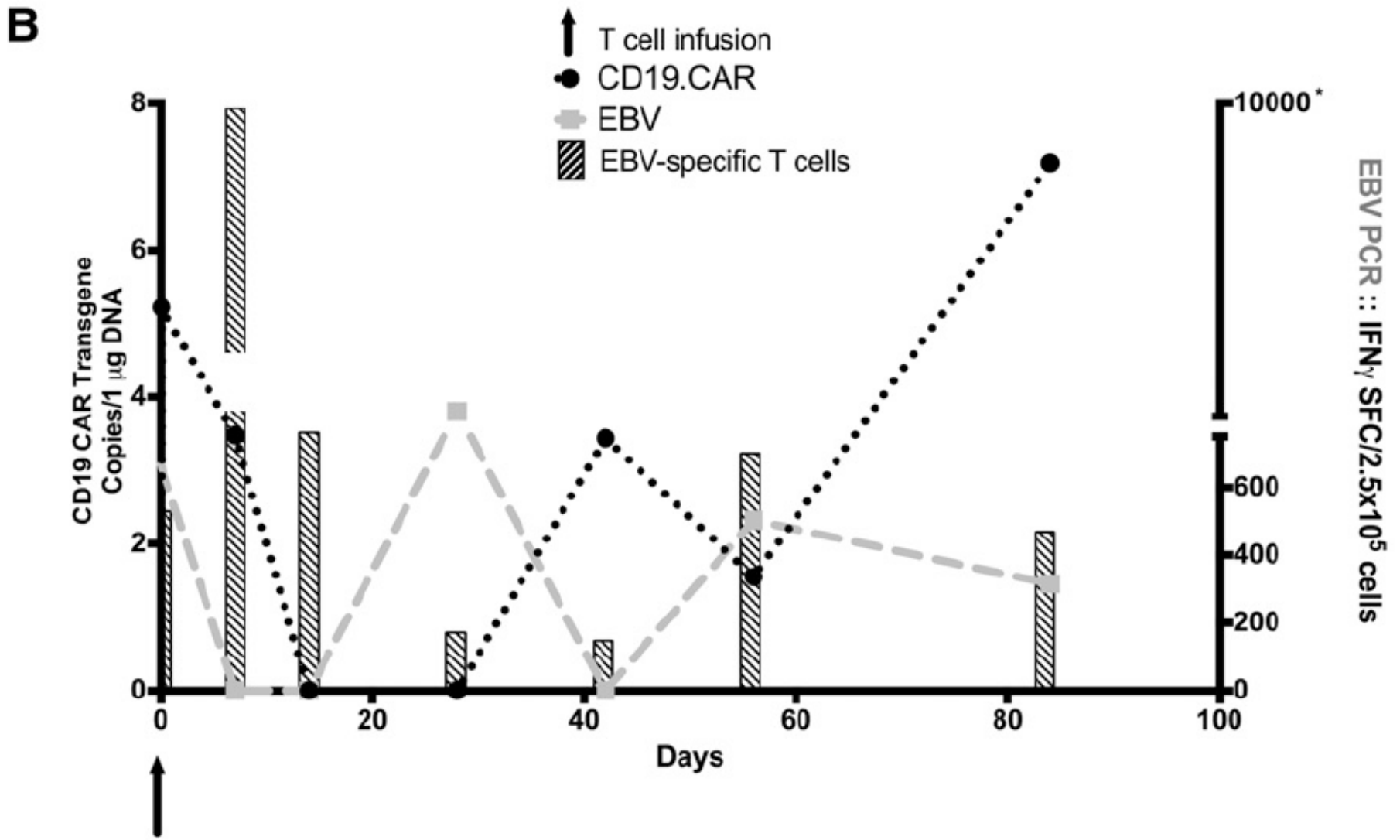
Kolb H. et al, Transplantation, 1997

Basic structure of first generation chimeric antigen receptors (CAR)s



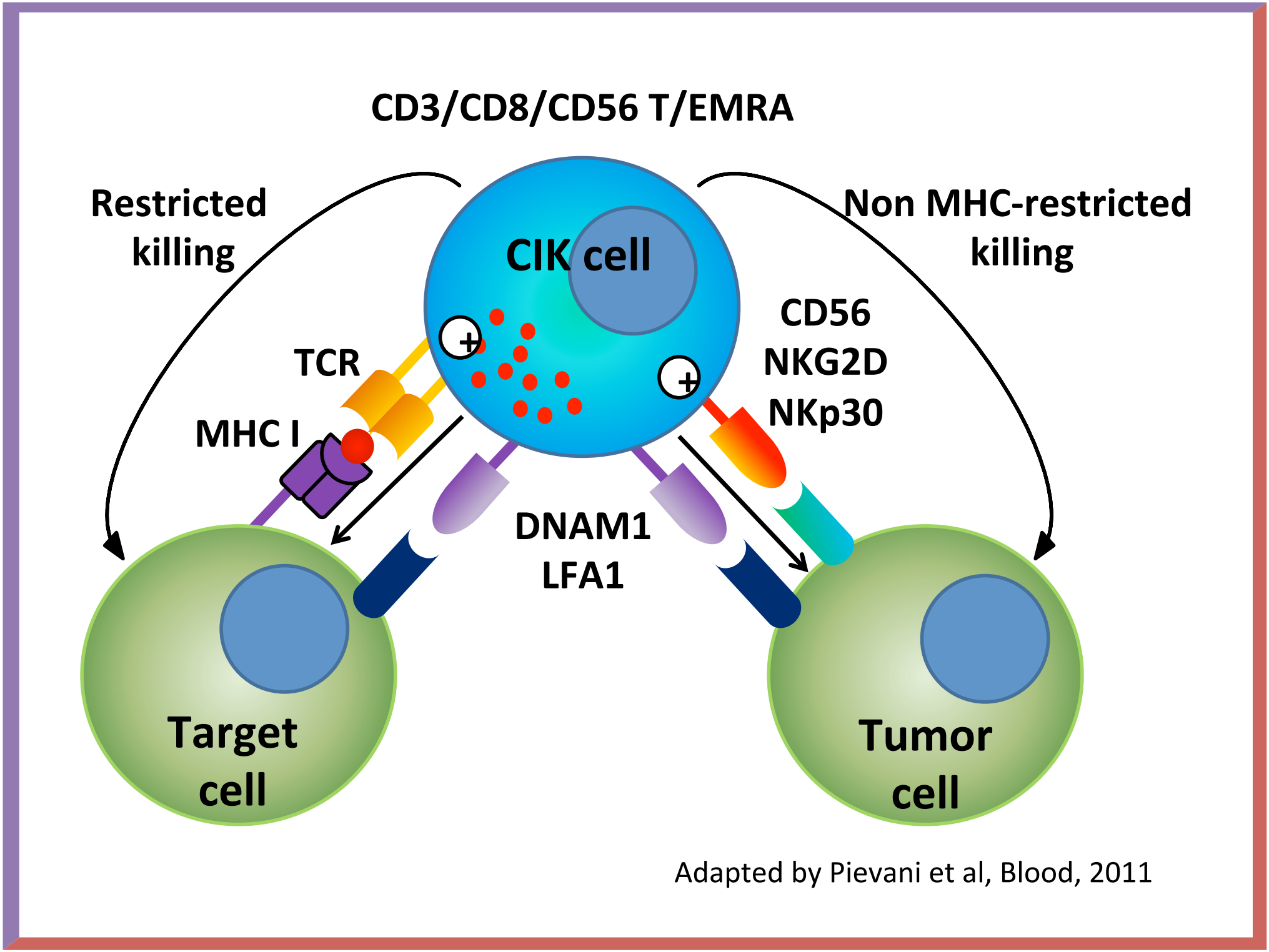
Ramos C. et al, Annual Review of Medicine, 2017

Donor derived CD19 (CAR) redirected VST for B-cell malignancies relapsed after allo BMT



EBV reactivation and immune responses in patient 7. Detection of EBV-DNA viral load by Q-PCR (light gray squares), CD19.CAR transgene by Q-PCR (black circles), and EBV-specific T-cell responses (striped bars) by IFNg ELISpot in the PB are illustrated. Arrows denote time of CD19.CAR-VSTs infusions.
This patient is described in complete response after 8 months follow up.

Cruz C. et al, Blood, 2013



Adapted by Pievani et al, Blood, 2011

Phase II study: Clinical Response

	N	%
Total evaluable patients	73	
Complete remission	19	26
Partial remission	3	4
Stable disease	8	11
Progression of disease	41	56
Early death	2	3

22 (30%) response

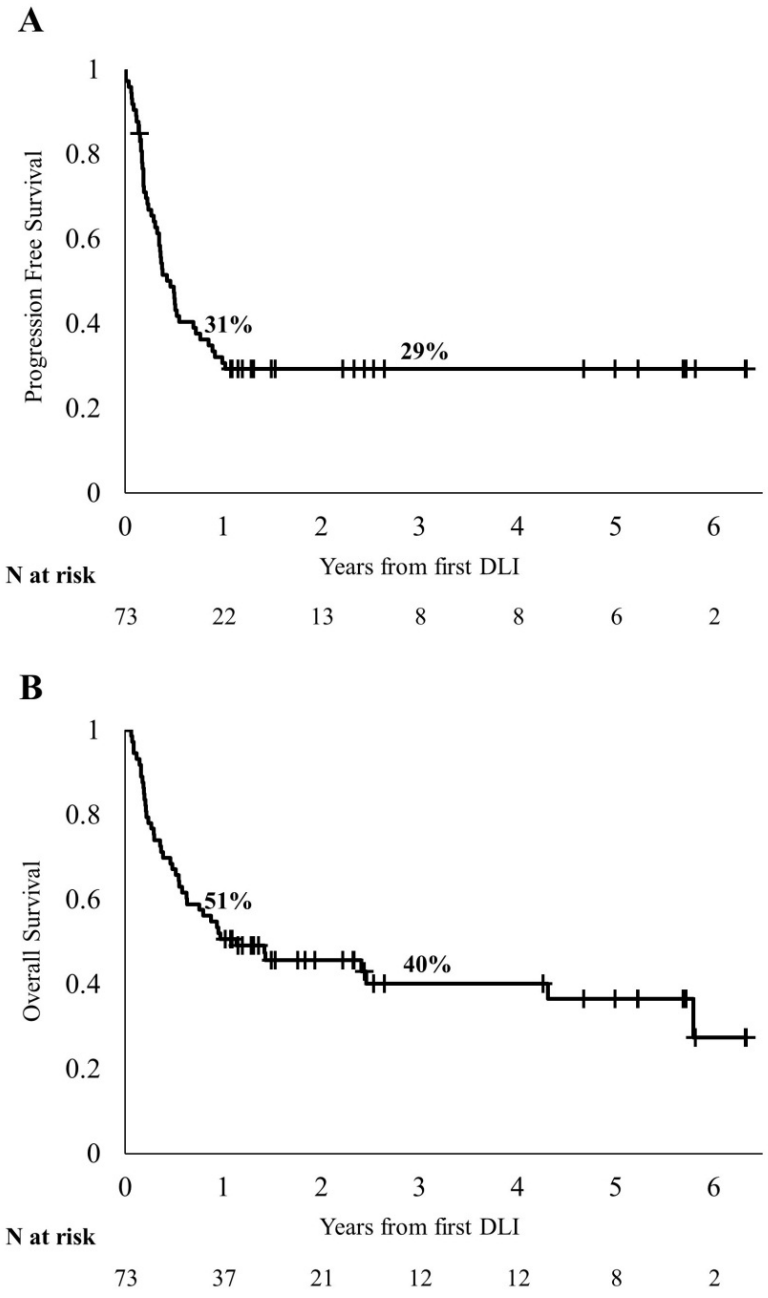
Introna M. et al, submitted

Phase II study: Toxicity

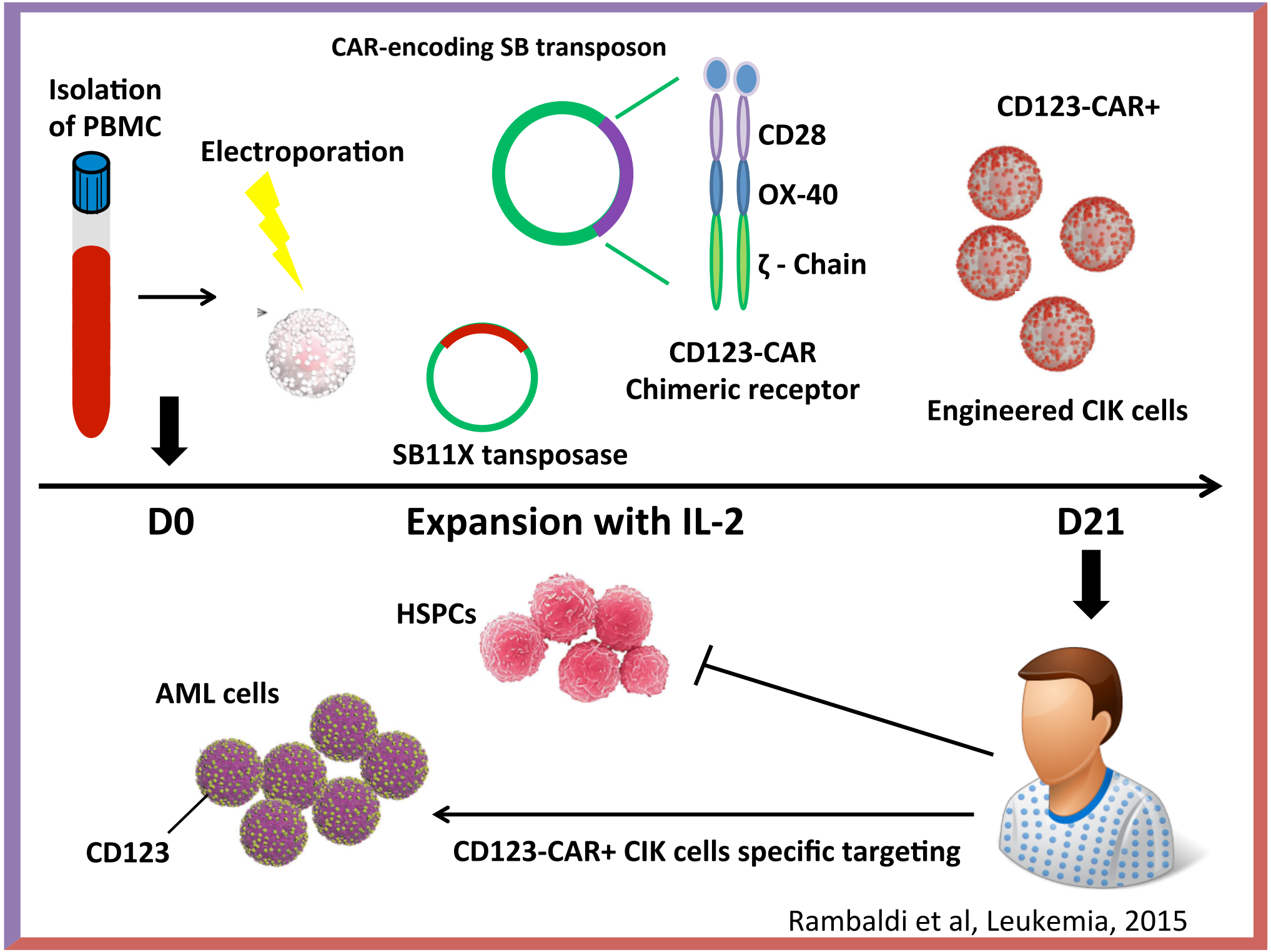
	Grade	N patients (%)	N insurgence during or after DLI treatment	N insurgence during or after CIK treatment
aGvHD	1-2	7 (9)	5	2
	3-4	5 (7)	3	2
cGvHD*	Mild	4 (5)	0	4
	Moderate	5 (7)	0	5
	Severe	2 (3)	1	1
Hemolitic Anemia	N.A.	1 (2)	0	1

Introna M. et al, submitted

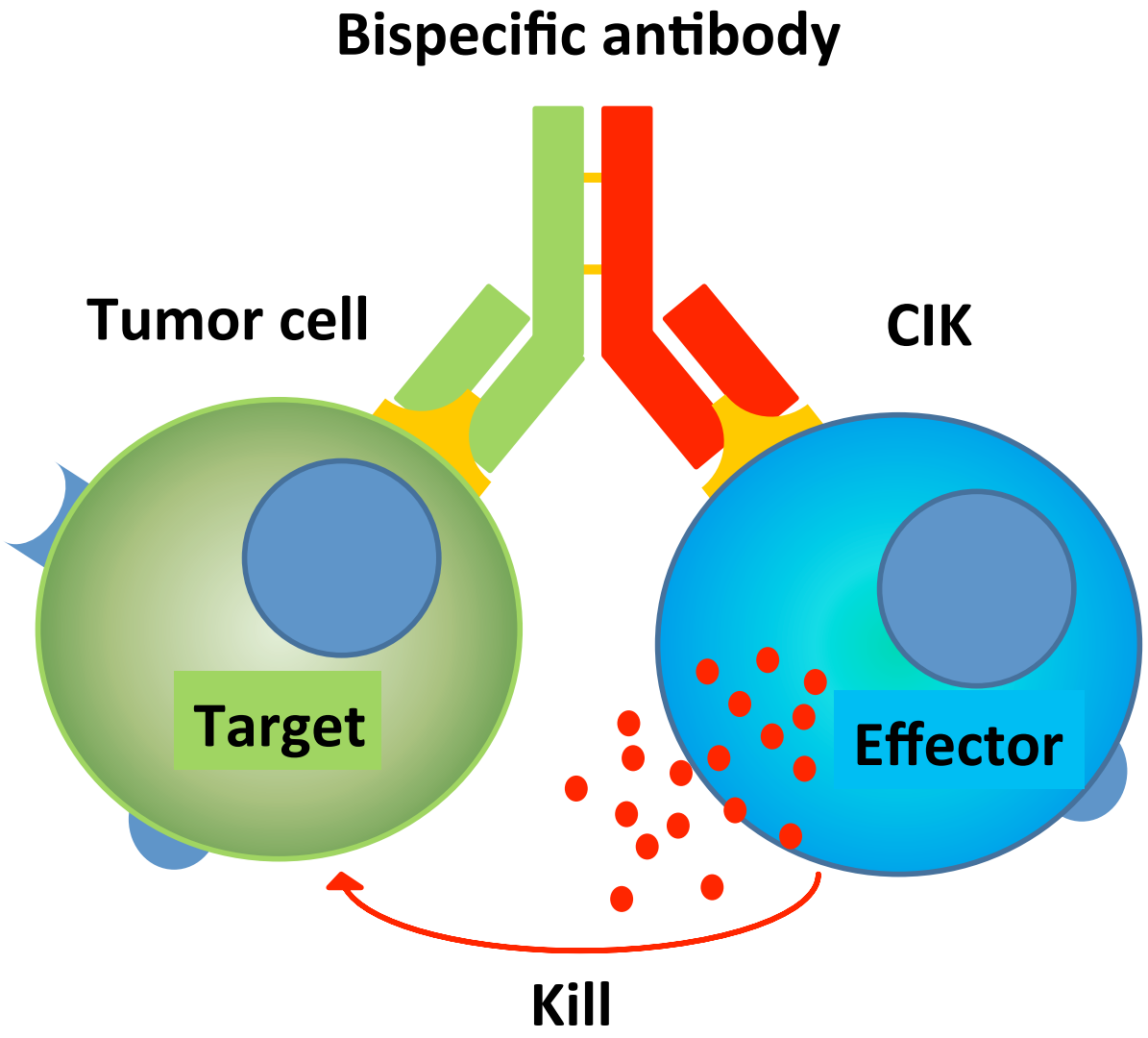
Phase II study: PFS and OS

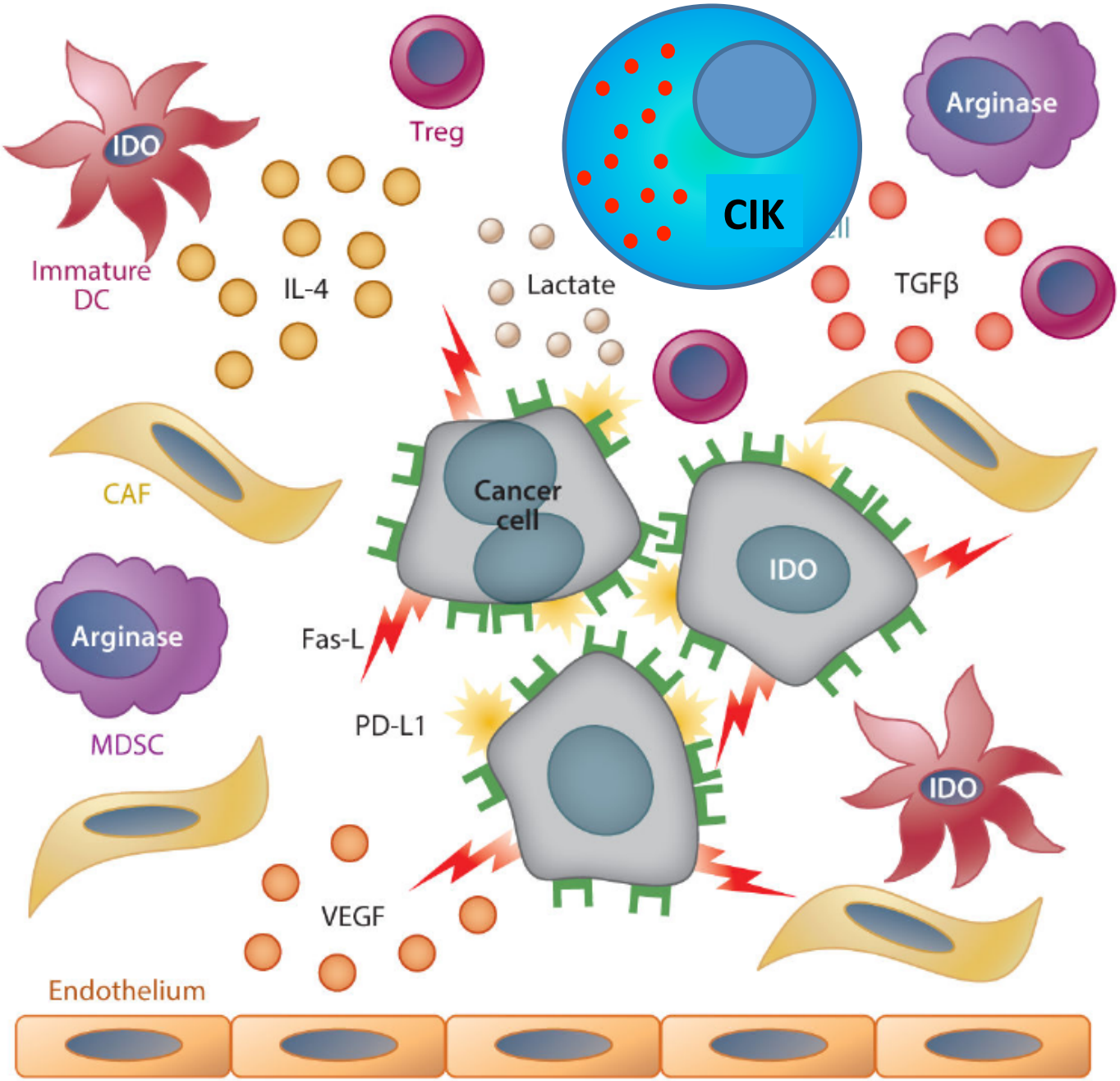


Introna M. et al, submitted

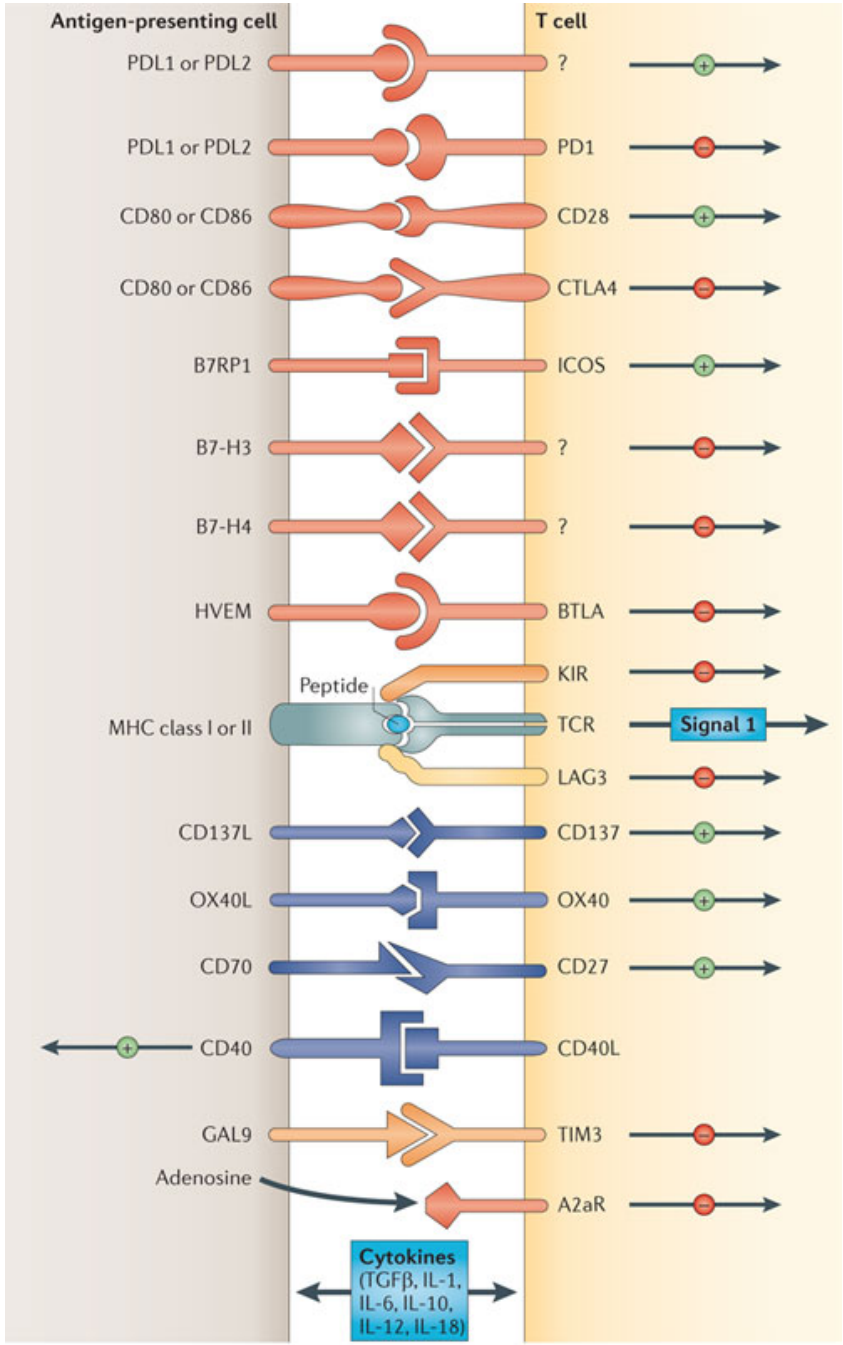


Rambaldi et al, Leukemia, 2015


Bispecific antibody
Tumor cell
CIK
Target
Effector
Kill



Adapted from Ramos C. et al, Annual Review of Medicine, 2017



Pardoll D. et al, Nature Reviews Cancer, 2012

- L’immunità è perfettamente capace di combattere le infezioni e costituisce un esempio di risposta adattativa a una fortissima pressione selettiva (morte precoce).
- L’immunità non è perfettamente capace di combattere i tumori perché questi non sono una forza selettiva, insorgendo, per lo più, dopo la generazione dei figli.
- Forse si possono immaginare strategie terapeutiche cellulari di combinazione (massimizzando gli effetti (GVL+GVI) e riducendo la tossicità (GVH).

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