

UMBILICAL CORD BLOOD AND BONE MARROW AS A SOURCE OF NATURAL KILLERS FOR KIR- ALLOREACTIVE ADOPTIVE IMMUNOTHERAPY

Zh. Sharoyan, K. Melkova, G. Frolov



Definitions

Adoptive immunotherapy (AI)

type of treatment that uses the immune cells to modulates and improve the immune response

- auto-AI
 - with manipulated cells
- allo-AI
 - Manipulated cells
 - Unmanipulated

Alloreactivity

the ability of immune cells to recognize and interact with dangerous cells with allo-antigens (cancer, virus etc)



AlloBMT a type of alloAI

Similarities

- Same steps:
 - «preparatory» step (conditioning);
 - cells transfusion
 - immune reconstitution
- Strong correlation between outcome and donor's cells alloreactivity
- Different sources of cells
 - BM
 - UCB
 - PBSC

Differences

- Cells engraftment in case of BMT



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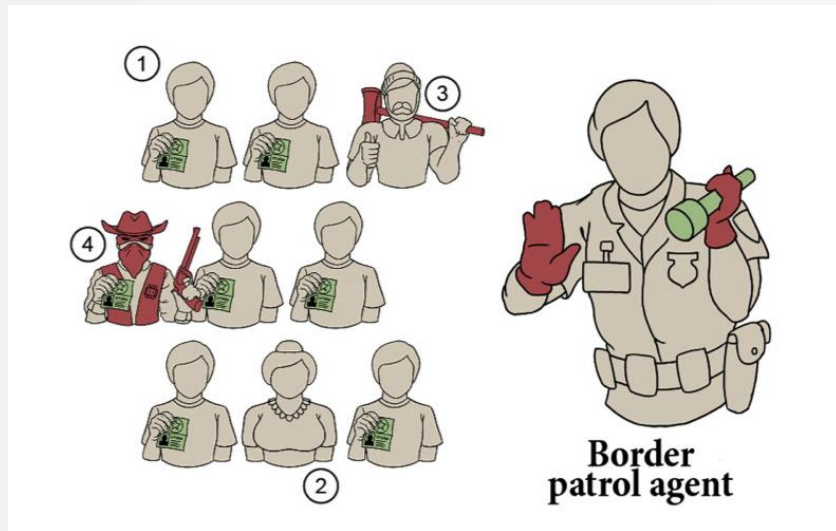
- Cells engraftment in case of BMT



Variations in search of «criminal» cells

Unmanipulated (naive) cells

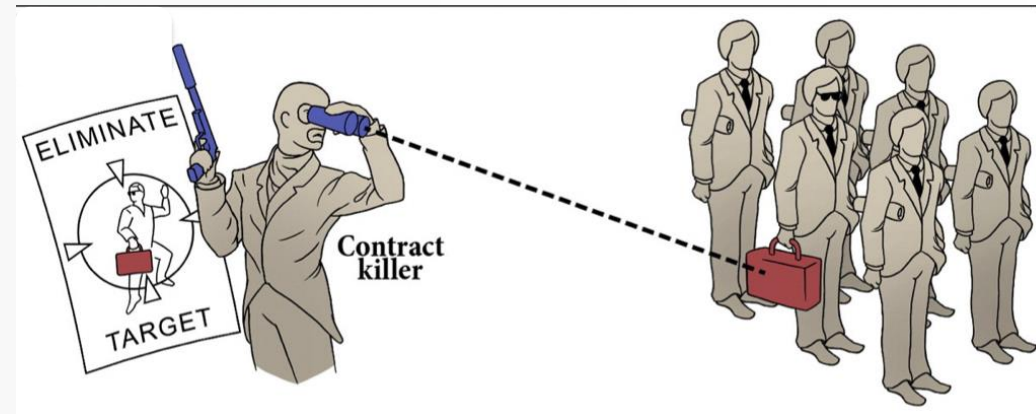
- eliminate all danger cells



Allo-BMT, allo-AI

Manipulated cells

need targets/ markers of cancer cells



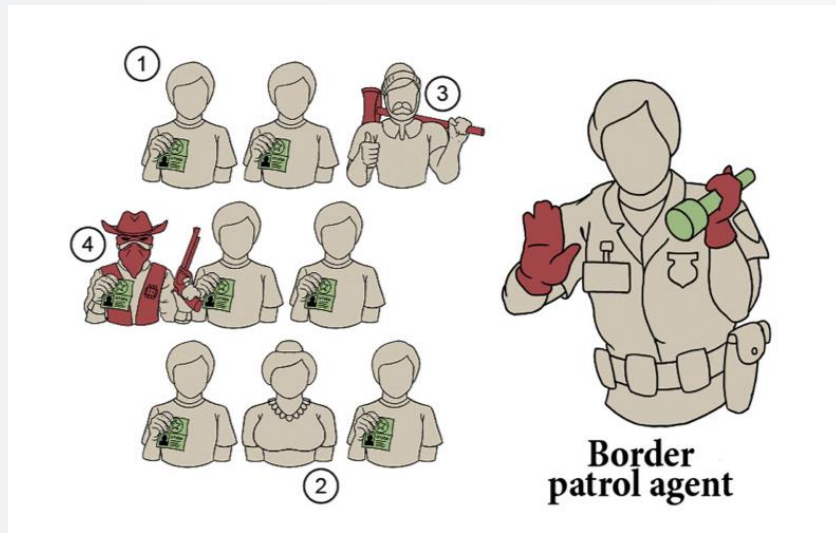
CAR-T, CAR-NK, LAK, TILs



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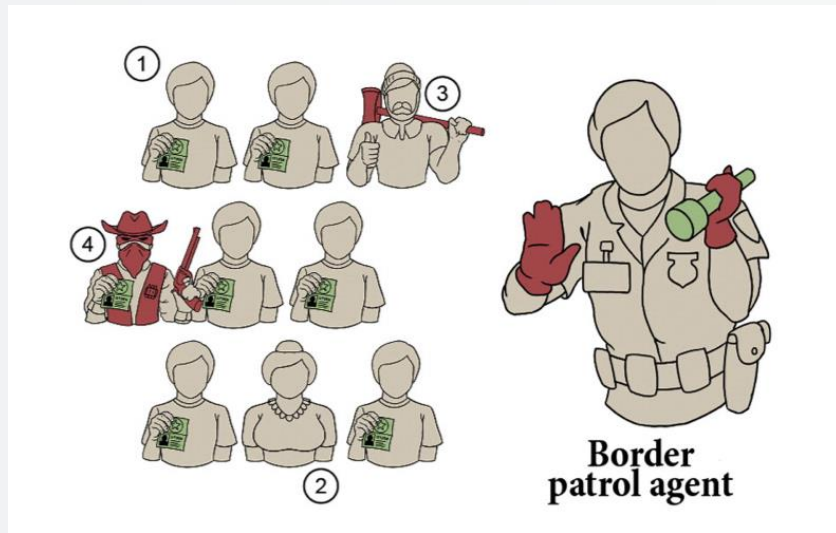
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Alloreactivity of donor's cells plays a crucial role in the outcome of BMT and AI



Indications for AI

- Oncology and hematology
- Autoimmune diseases
- Neurodegenerative diseases



Basis of KIR-AI



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Immune system is an essential part of cancer treatment

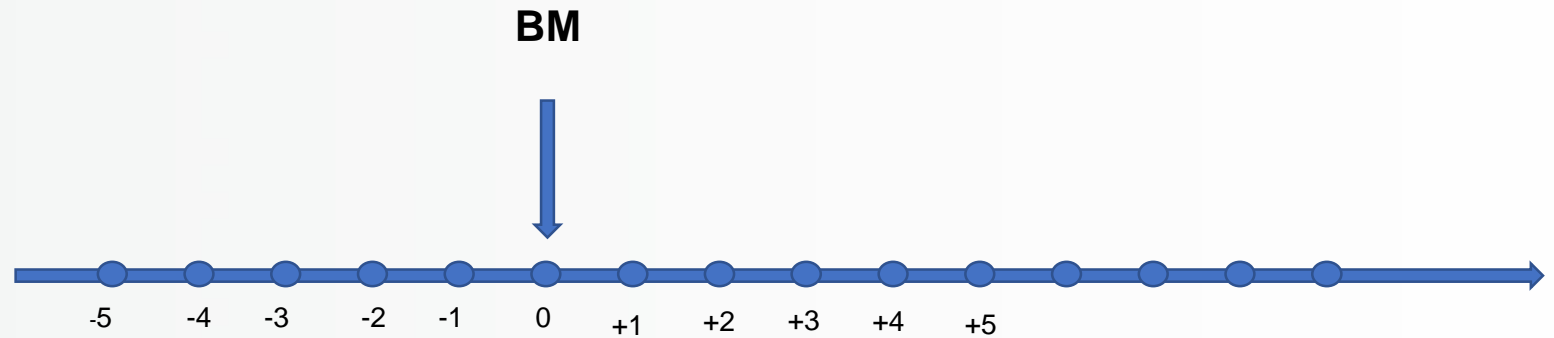
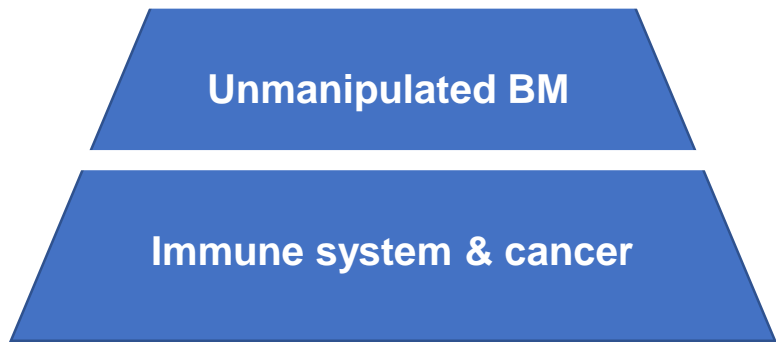


Immune system & cancer

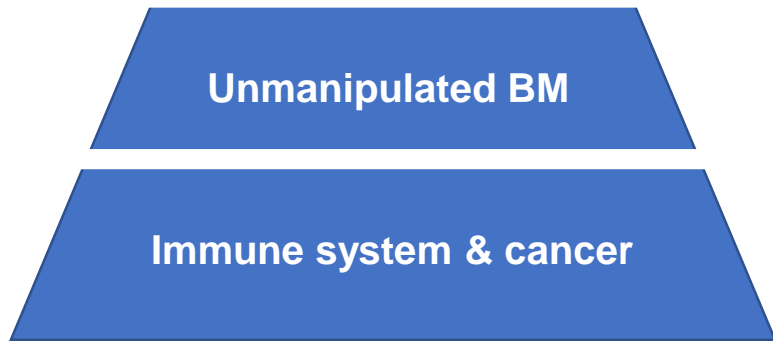


Basis of KIR-AI

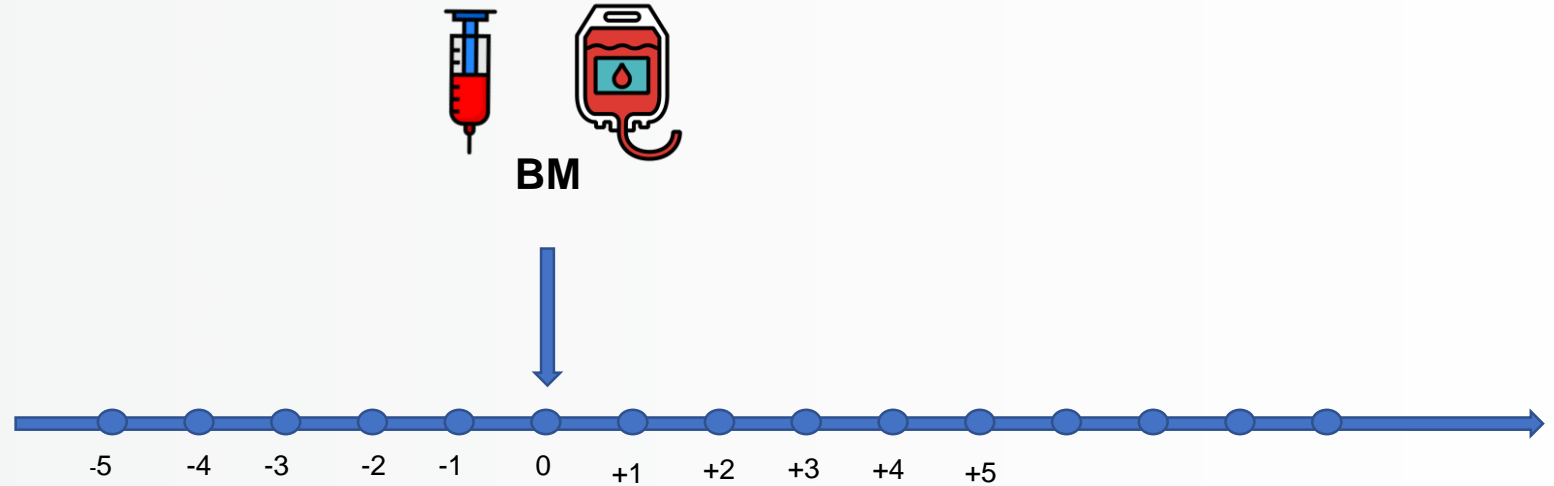
Bone marrow is a source of unmanipulated cells



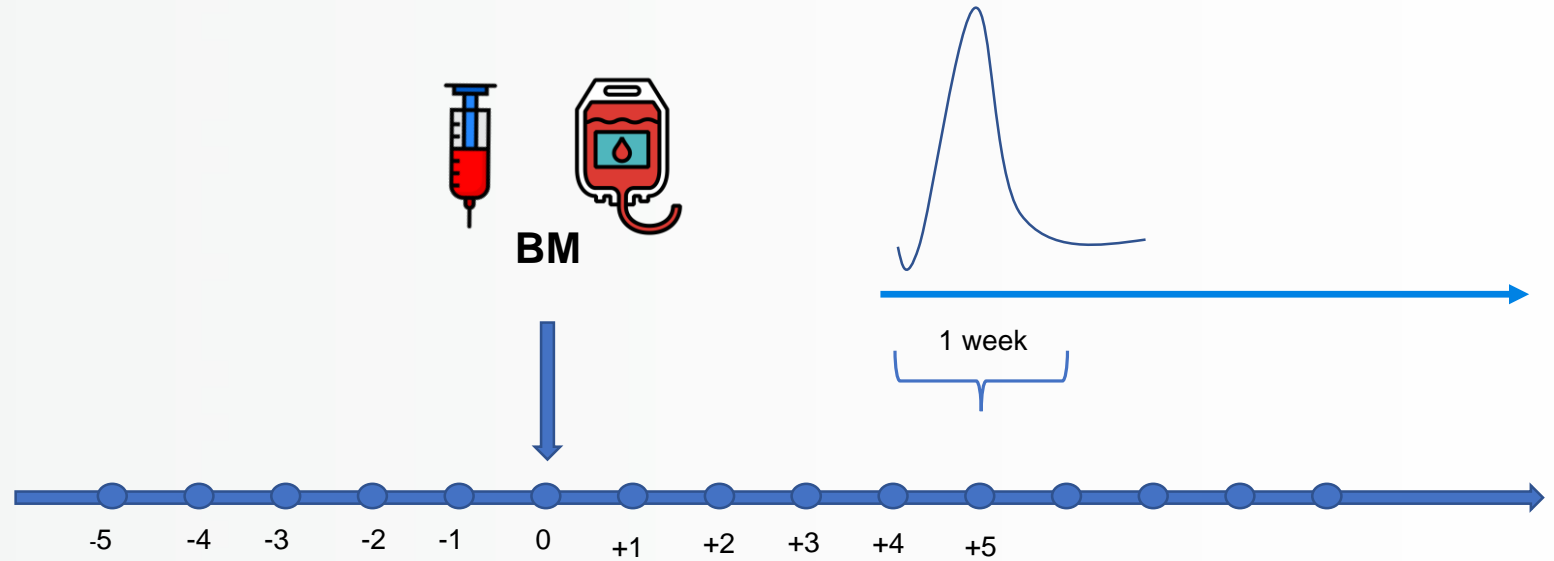
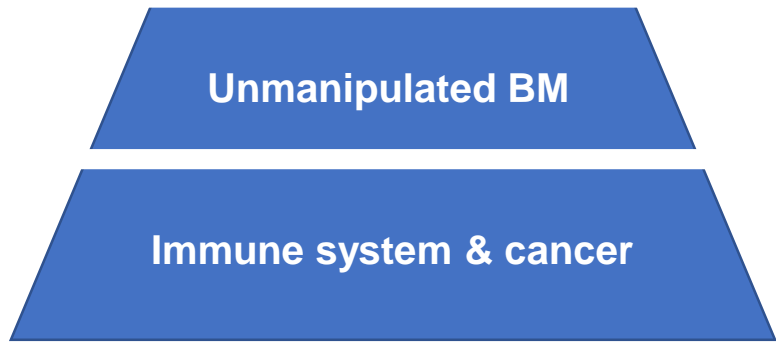
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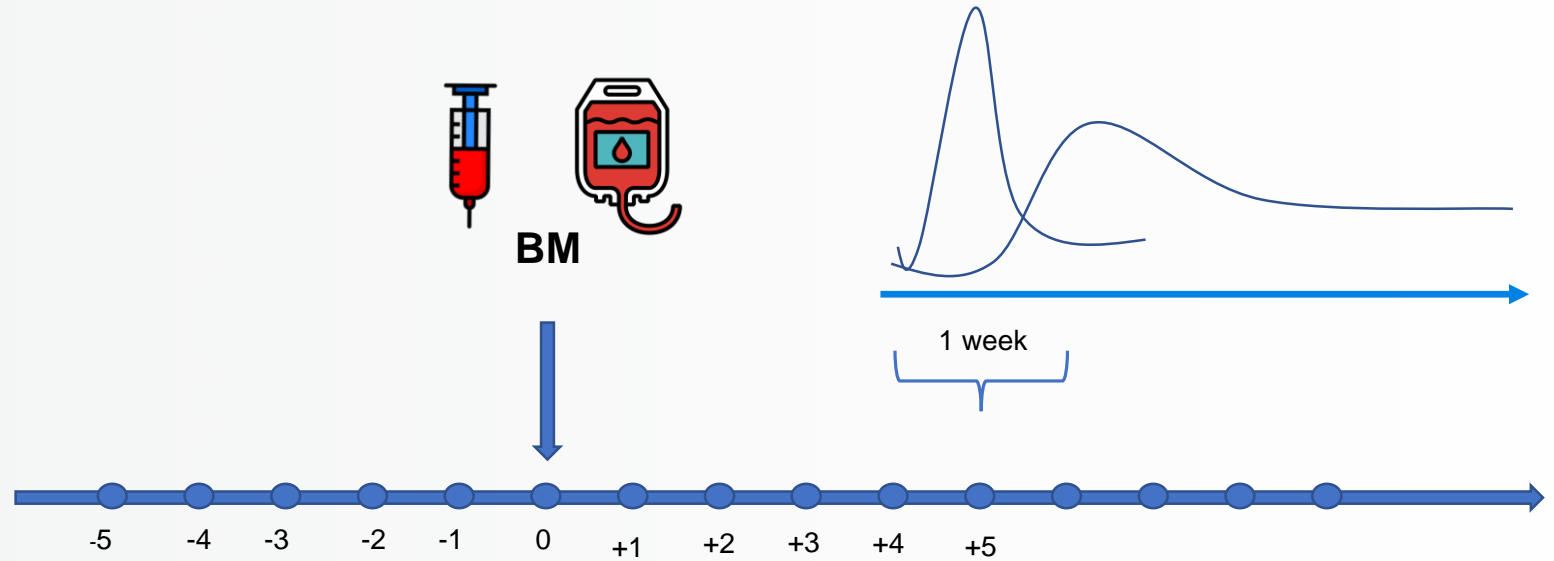
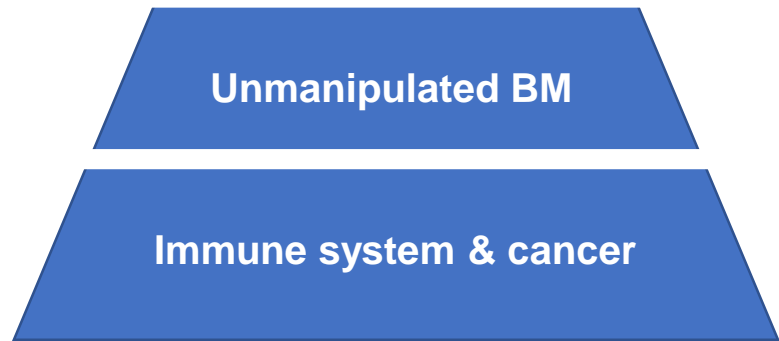
Immediate effect depends on cells amount



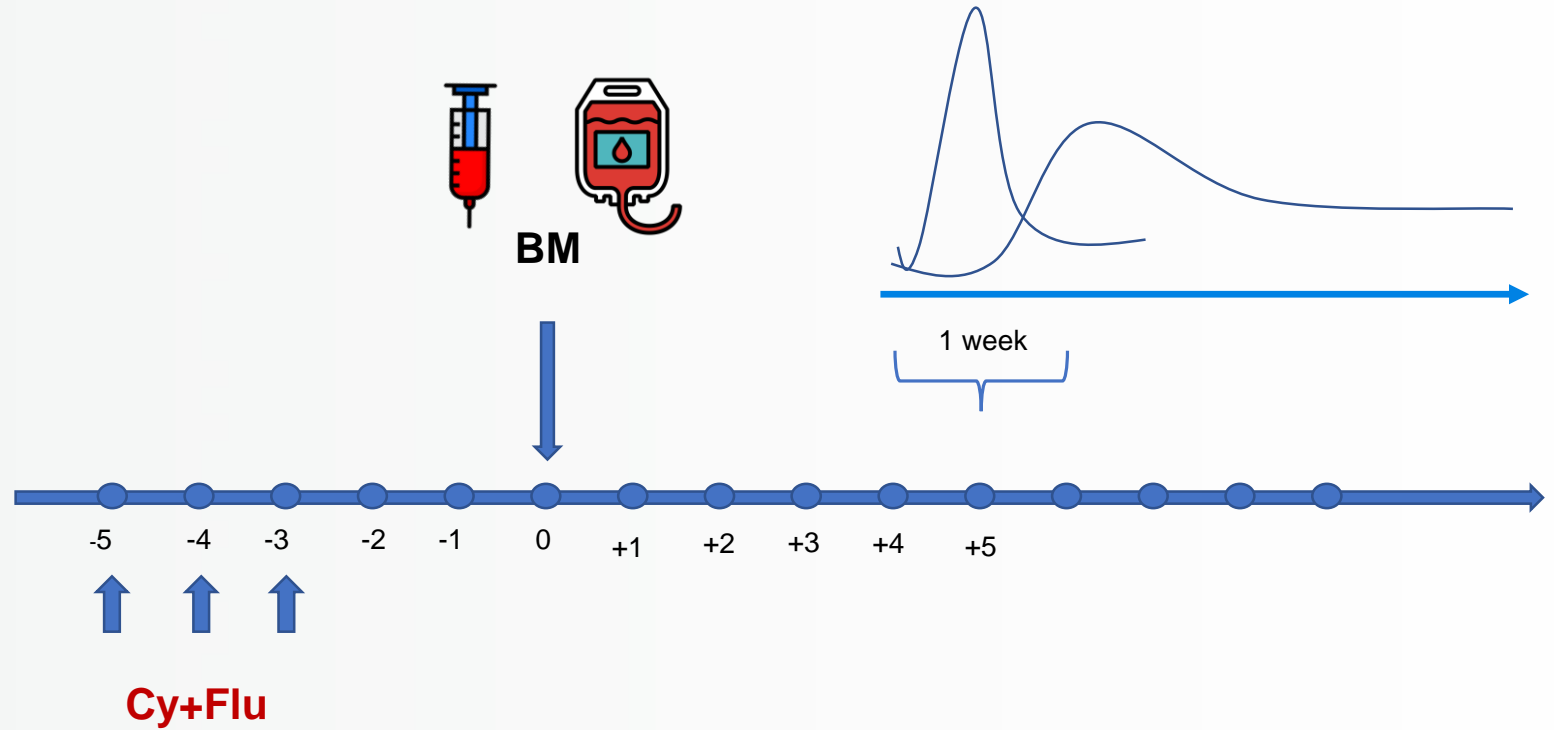
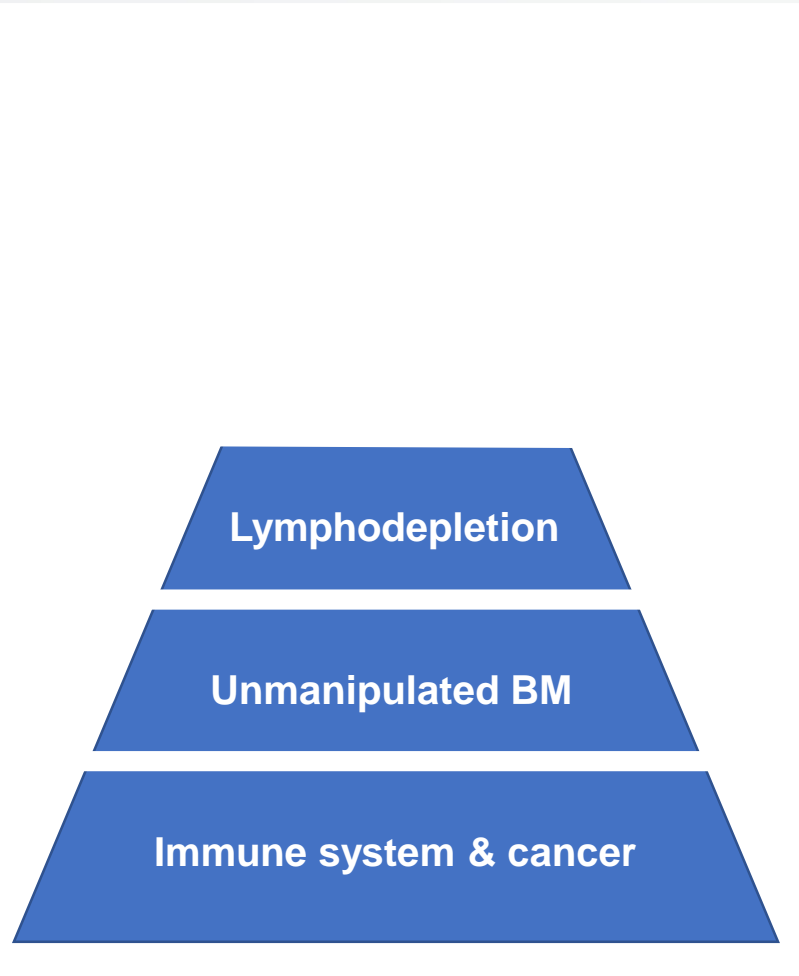
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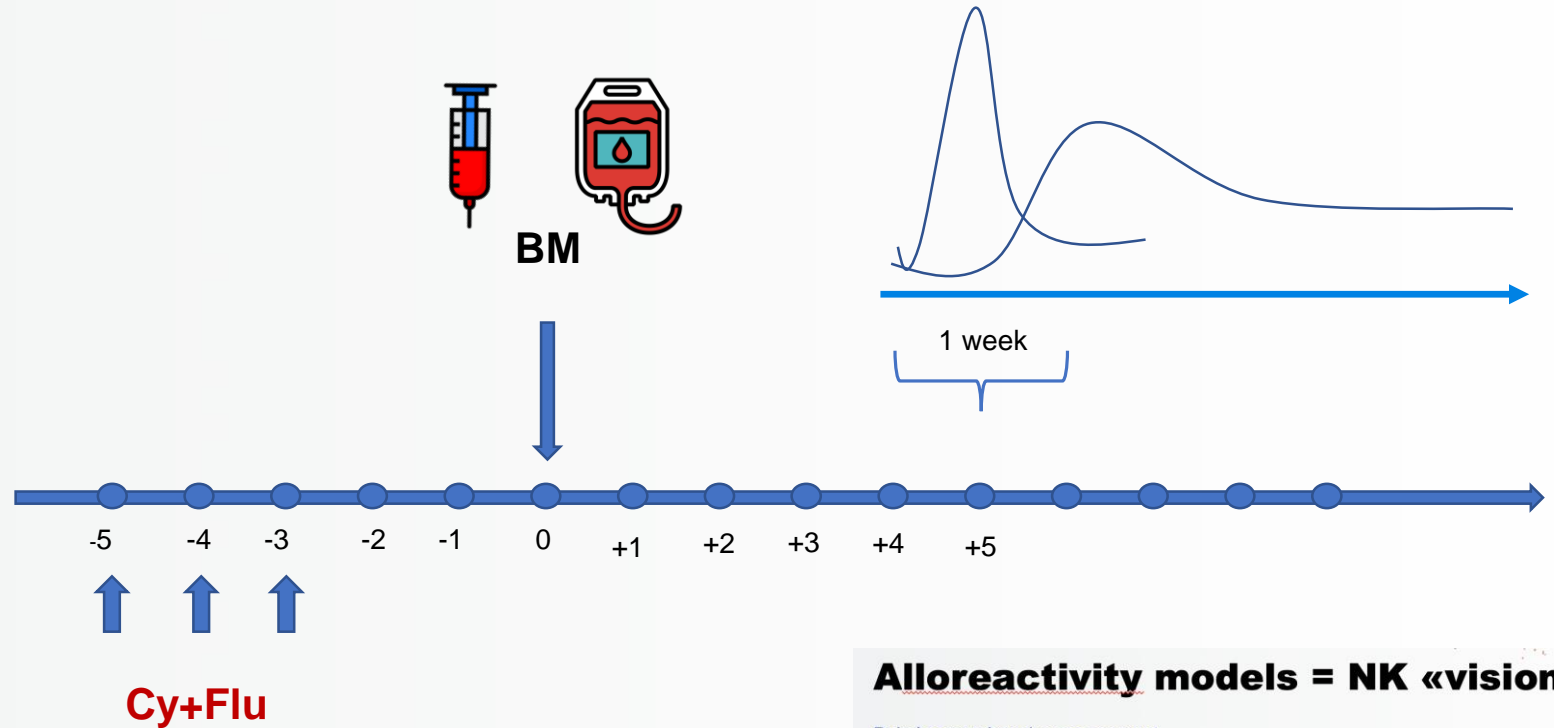
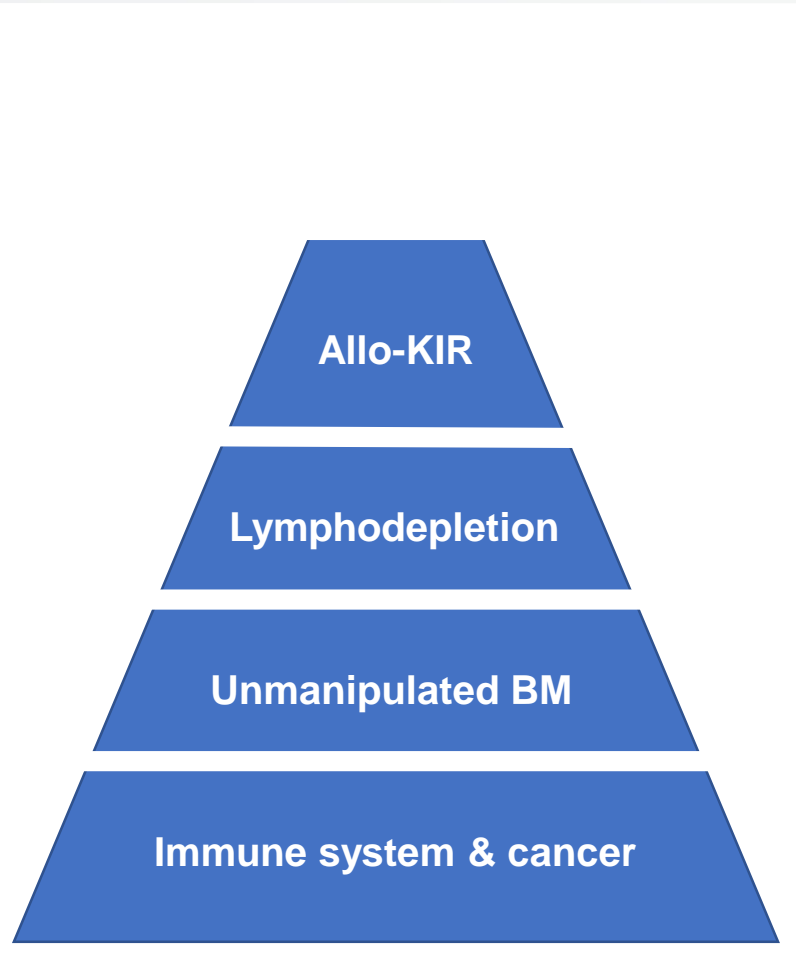
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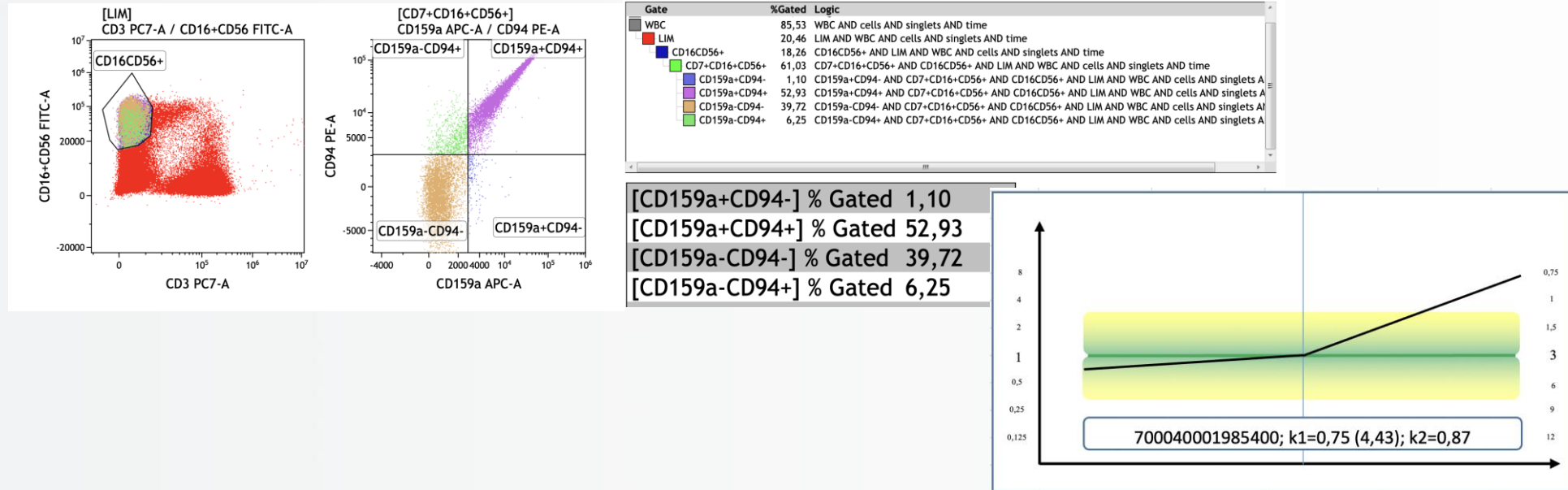
Alloreactivity models = NK «vision»

Pairs' comprehensive assessment

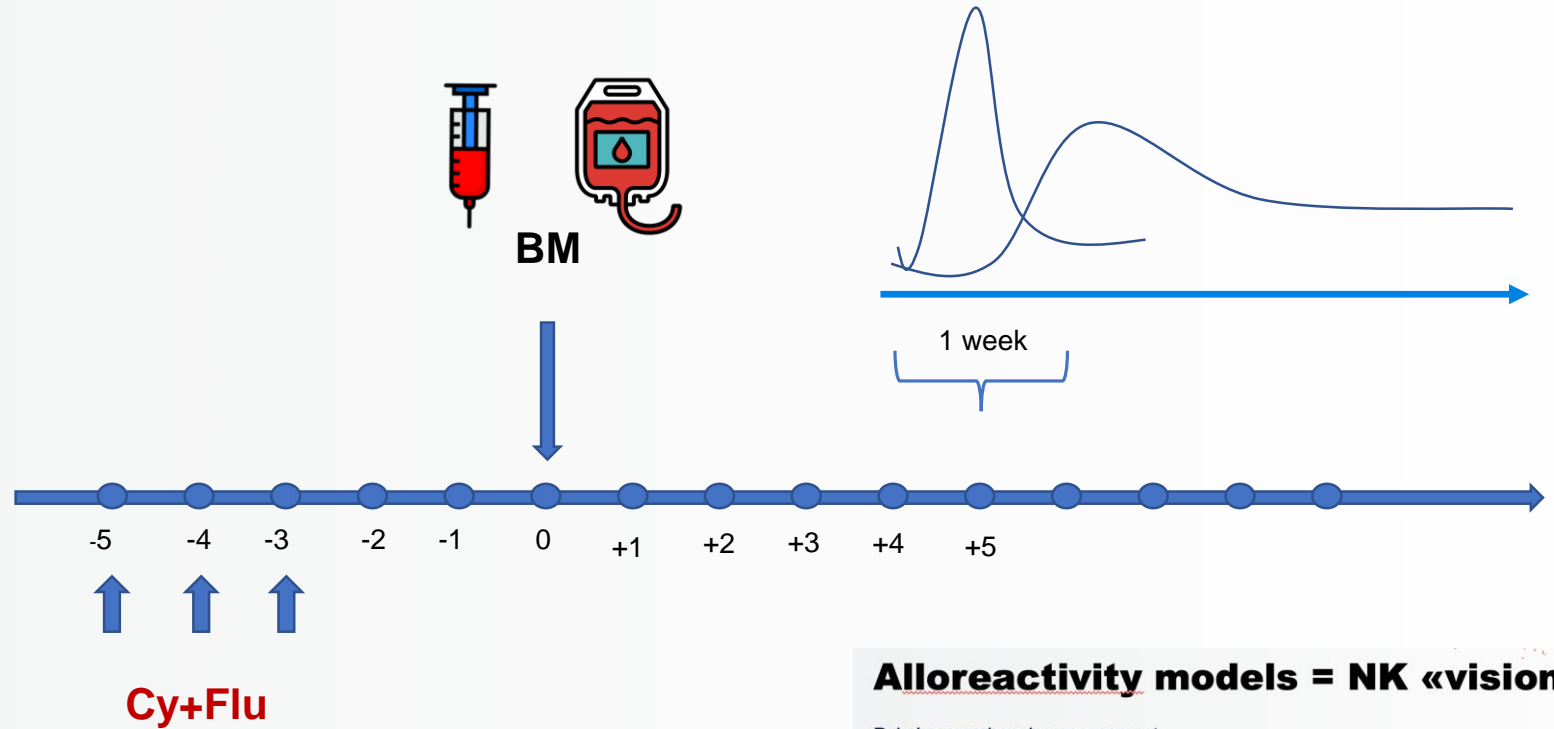
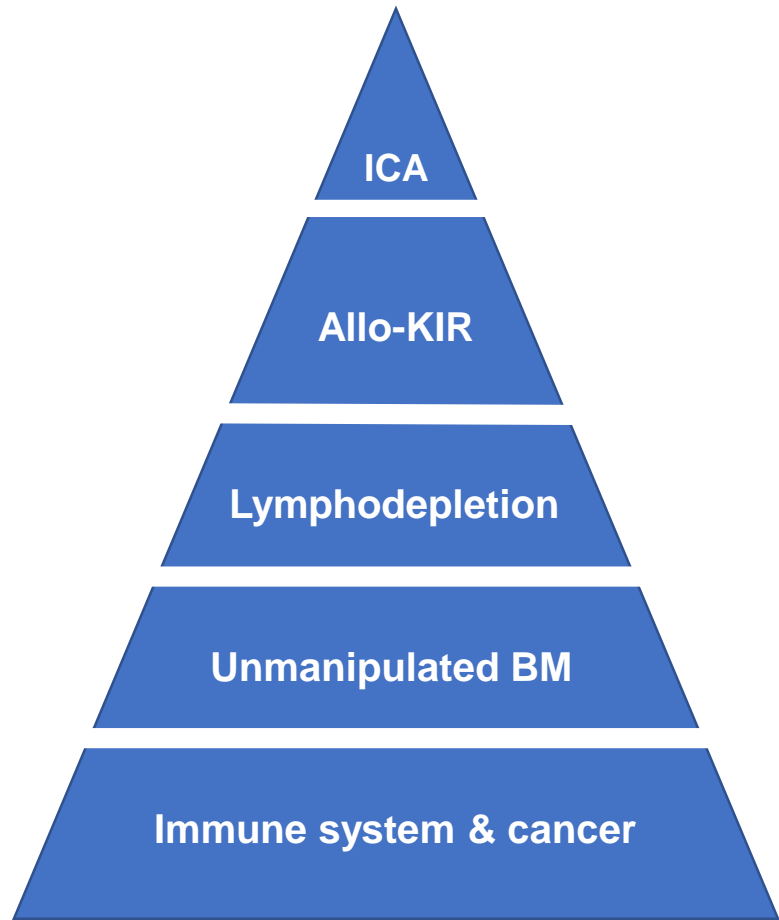
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- HLA-HLA **T-deplete BM AML /sAML / MDS**
- KIR-KIR mismatch **postTBM-Cy**
- KIRgrA-KIRgrB hematological malignant
- CD94/NKG2A **in vitro**
- CD94/NKG2C **family of lectin receptors**

ICA = «power» of NK

The index of cytotoxic activity - math model of the balance of activating and inhibitory Rp of NK



Basis of KIR-AI

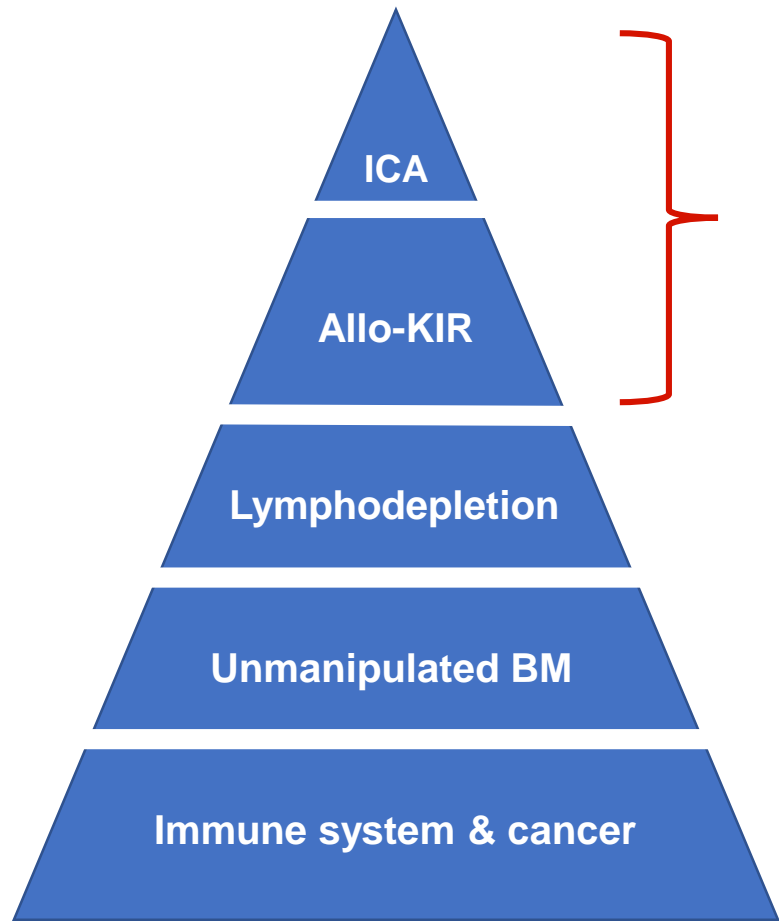


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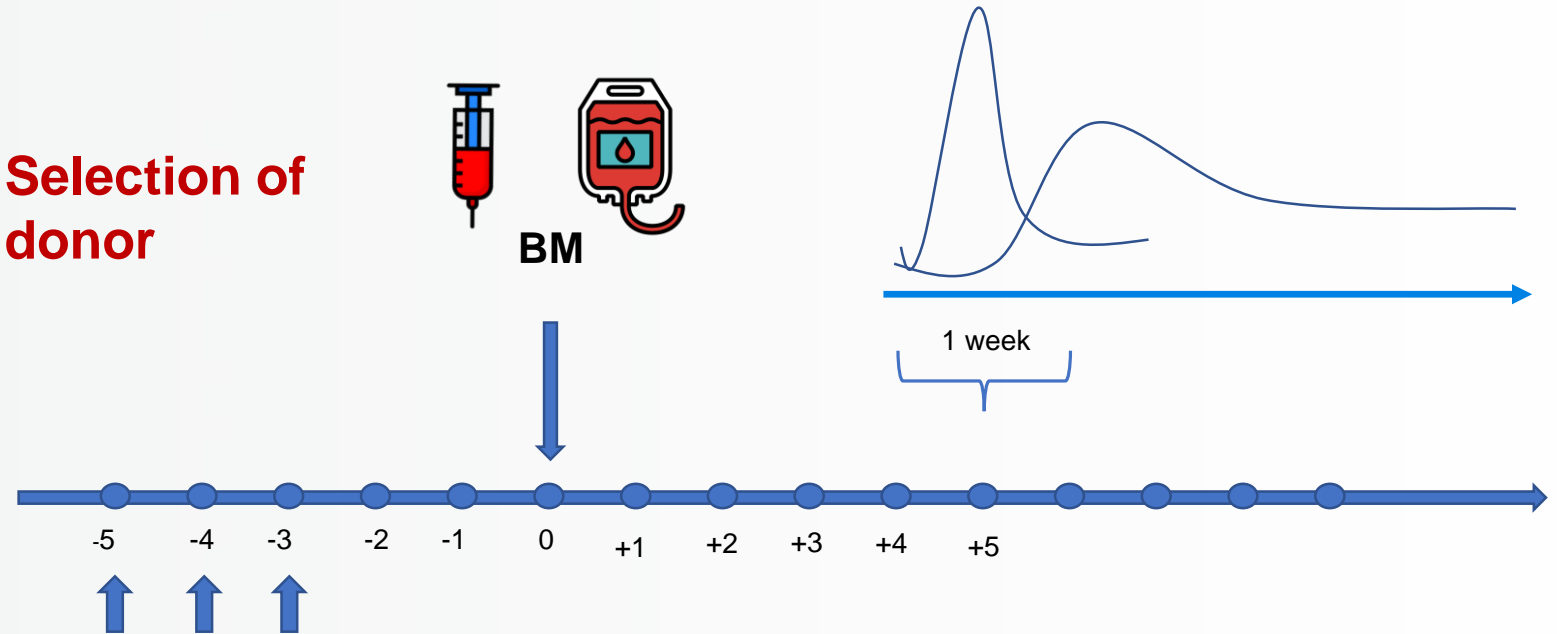
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Basis of KIR-AI



Selection of donor

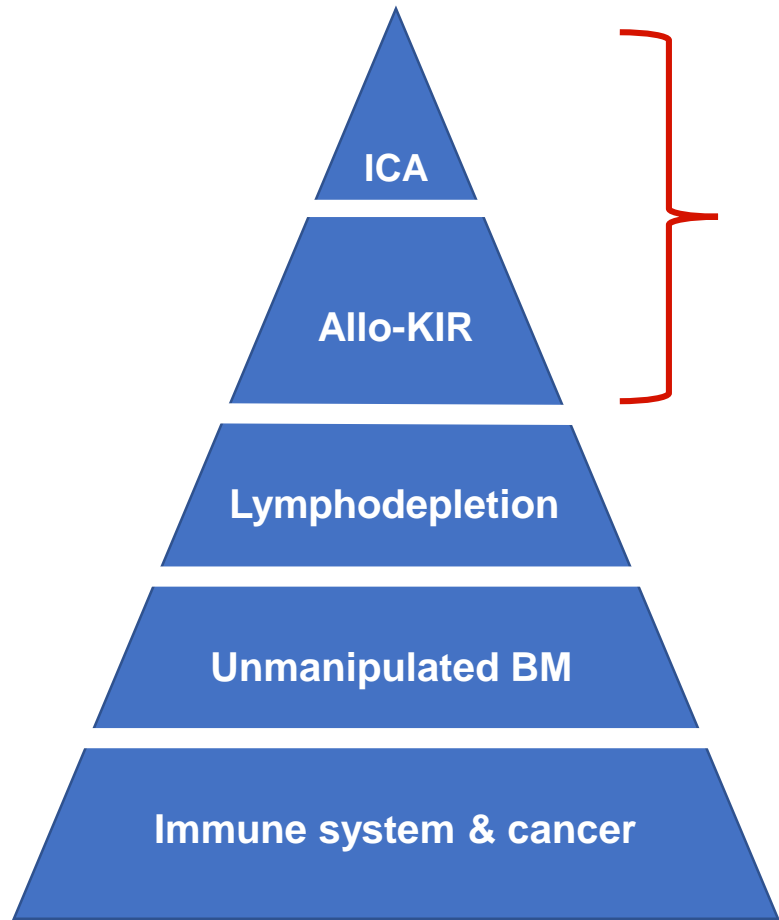


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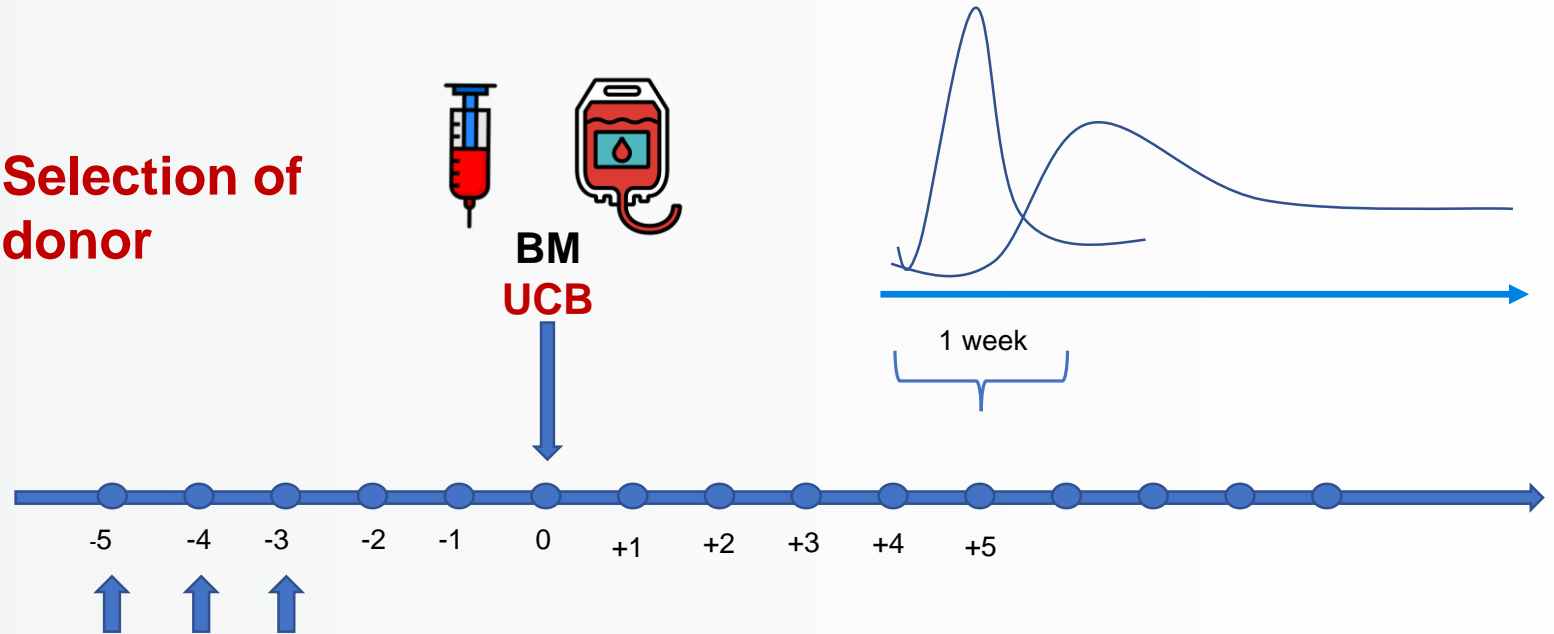
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Umbilical cord blood & unstimulated BM as sources of naive unmanipulated cells



KIR-AI

	BM+UCB	BM	UCB	p
Total, pts PD/ Rf at the time of AI	23	12	11	ns
ECOG	2-4 (med 3)	2-4 (med 3)	2-4 (med 3)	ns
Gender M/ F	8/ 15	3/ 9	5/ 6	ns
Age	22-78 (med 48)	22-54 (med 44,5)	26-78 (med 52)	ns
CT lines courses	1-8 (med 3) 0-61 (med 9)	1-8 (med 3) 3-29 (med 9)	0-7 (med 4) 0-61 (med 12)	ns ns
Time from ds to AI, mo	1-316 (med 26)	3-234 (med 29)	1-316 (med 14)	ns
RT, pts	10	9	1	p=0.02
DS hematology multiple tumours GB IV + breast c-r + other	9 4 4 + 3 + 3	6 2 3 + 1 + 0	3 2 1 + 2 + 3	ns
FU, mo	6-114 (med 27)	25-114 (med 41)	6-56 (med 11)	p=0.01
Total, transfusions	27	13	14	ns



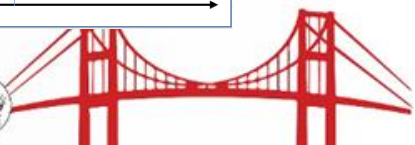
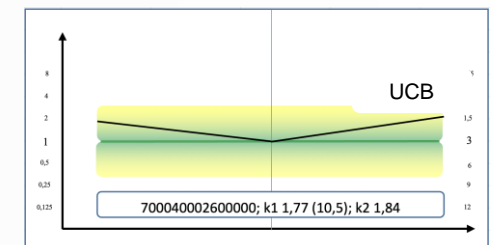
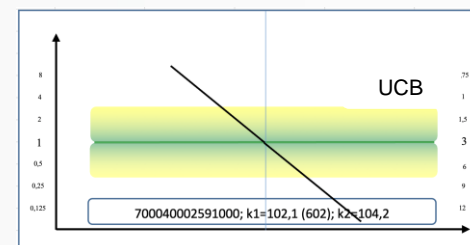
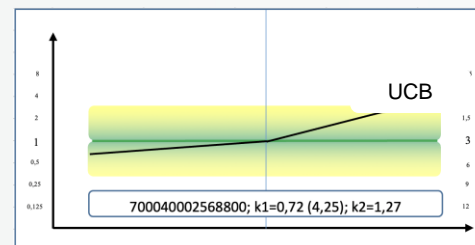
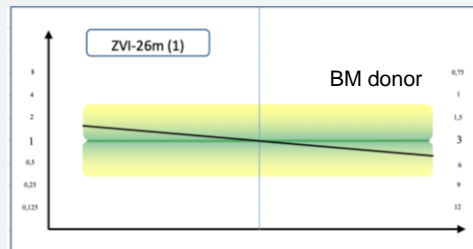
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	BM+UCB	BM	UCB	p
Lymphodepletion, pts	16	10	6	p=0.01
ICA recipients	0,3-14 (med 2,42)	0,3-3 (med 1,92)	0,98-14 (med 4,26)	p=0.03
ICA dn	0,3-100+(med 4,4)	0,3 -47,1 (med 5,3)	0,76-100+(med 4,3)	ns
CR	26%	33%	18%	ns
Long-term CR	22%	25%	18%	ns
OS, mo	1-54 (med 7)	1-54+ (med 9)	1-13+ (med 6)	p=0.03
OS, mo only pts with lymphodepletion	1-49,9(med 8,7)	1-49,9 (med 9)	3-13 + (med 6)	Ns



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Indications for AI in oncology

- Modulation of chemosensitivity for refractory cancer
- Salvage therapy, including relapse after alloBMT, CAR-T
- MRD-persistent
- Inability to complete the treatment
 - ECOG-status
 - Age
 - Cumulative dose of CT/ RT
- High risk of relapse after treatment
 - >50% in 1 year
 - >80% in 3 years



Thanks to our teachers & partners



Baranov AE



Typichin NN

