

Sviluppo di programmi di immunoterapia con CAR Tcells all'Ospedale Pediatrico Bambino Gesù

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Why Immunotherapy for Pediatric Tumors?

Dose-intense multimodality
Multiagent approaches



Improved outcome for
childhood cancers

Unsolved
Issues



How to treat children with refractory
and relapsed malignancies?

How to manage toxicities
related to intense chemo/radiation therapy?



Target Therapies

20 December 2013 | \$18

Science

Breakthrough of the Year

Cancer Immunotherapy

T cells on the attack



AAAS

Adoptive T cell therapy projects at OPBG

- Evaluation of potential tumor-specific antigens;
- Cloning of specific T Cell Receptors (TCR, HLA-restricted);
- Cloning of specific Chimeric Antigen Receptors (CAR, HLA-unrestricted);
- Production of clinical grade products;
- Conduction of Clinical Trials.

mAbs

vs

CARs

Transient effect

Limited tissue bio-distribution

Requirement for high expression of the target molecule

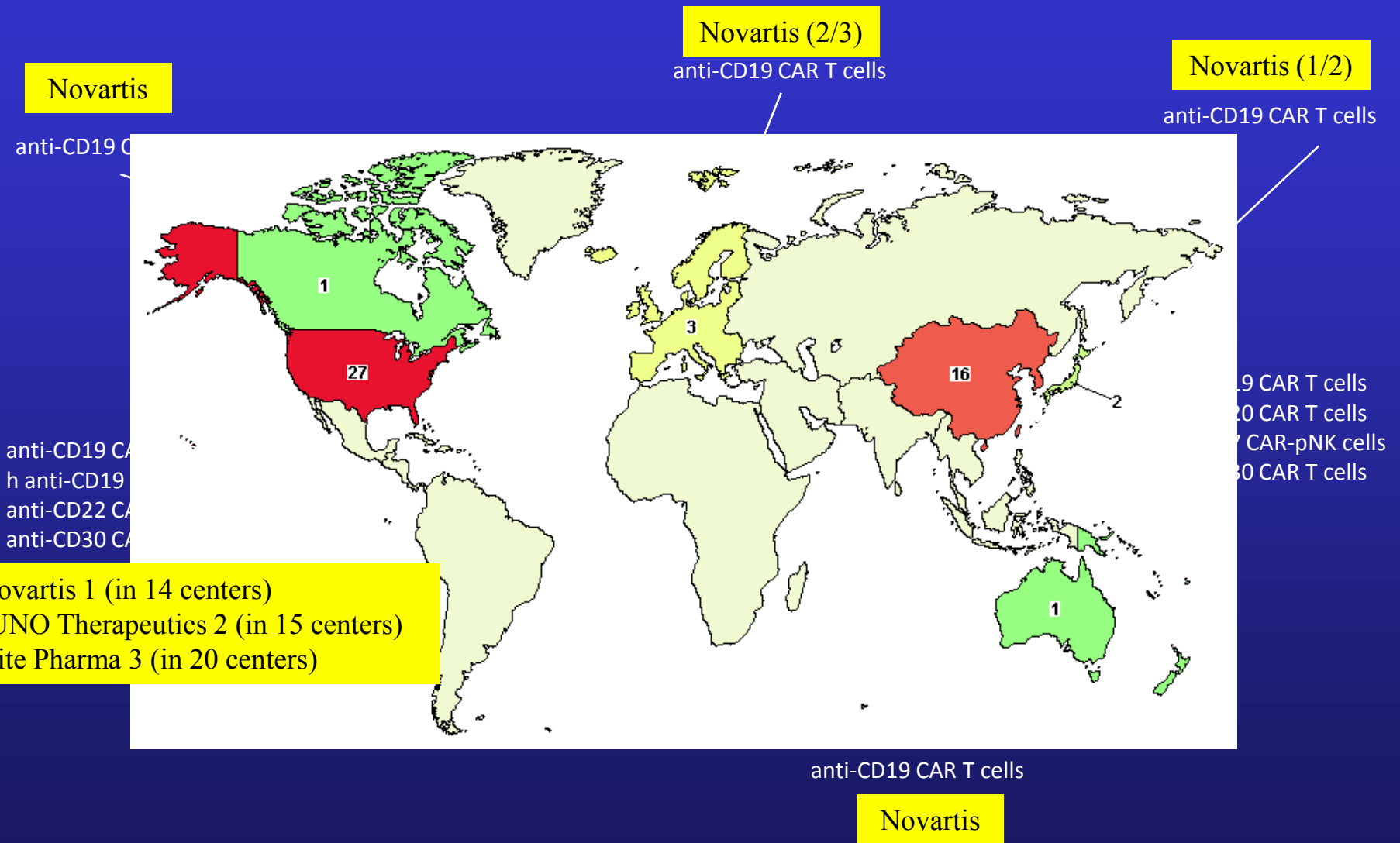
Persistence for the prolonged lifetime of the cell

Active penetration of solid tissues

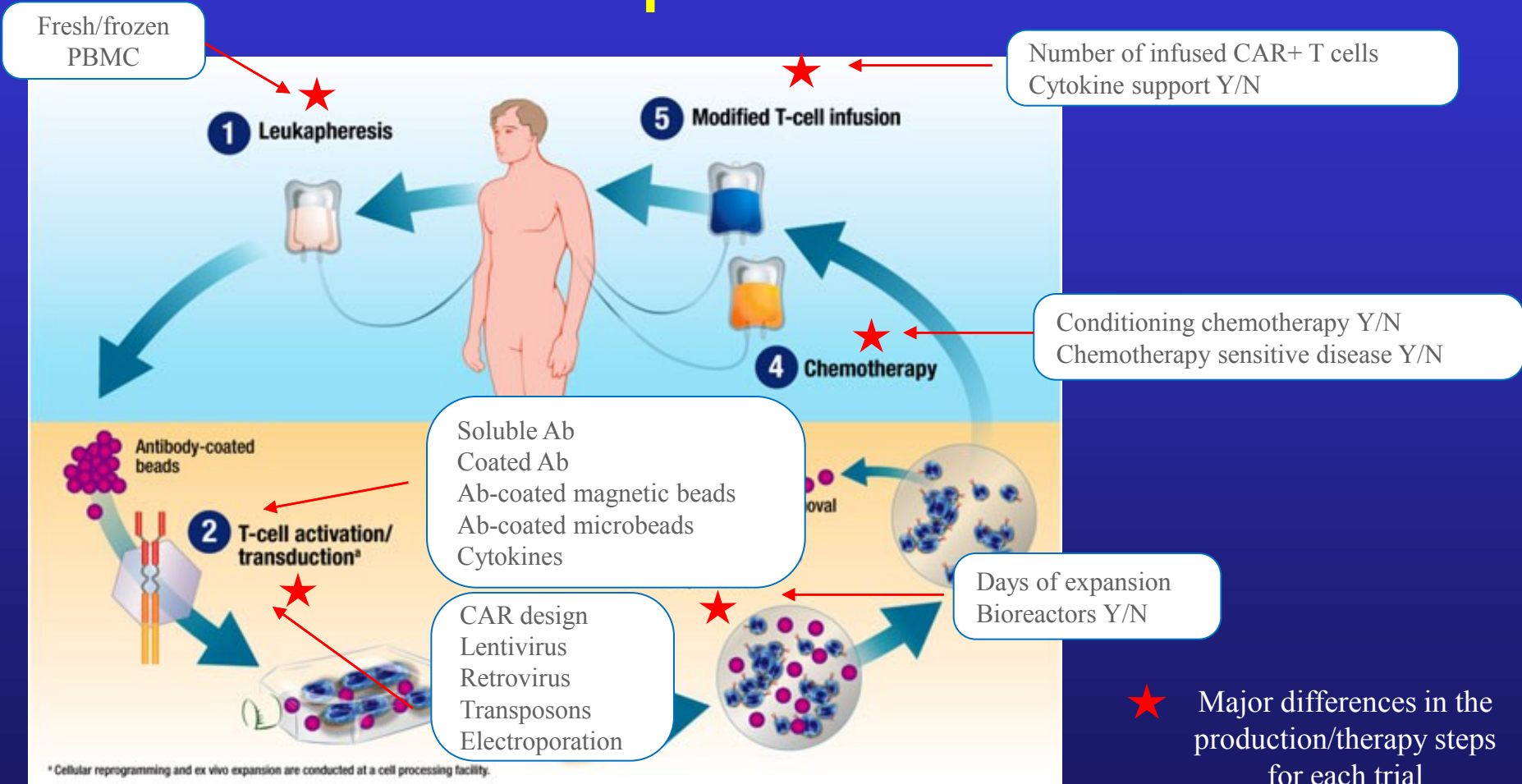
Ability to recognize tumor cell subsets with low antigen density

Multiple lytic activities following target recognition

CAR T CELL THERAPY TRIALS FOR LEUKEMIA AND/OR LYMPHOMA: WORLD DISTRIBUTION



Example of approach to CAR T cell production

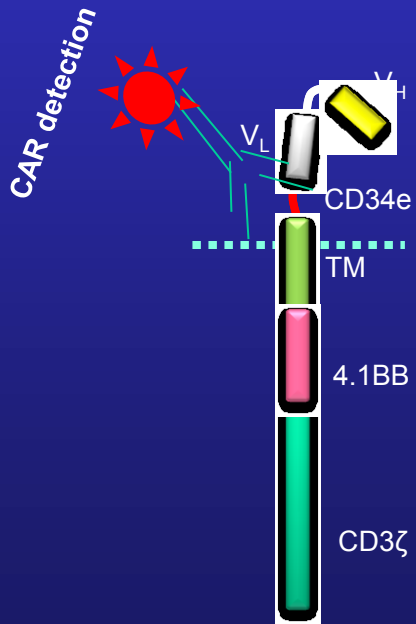


Ab, antibody; PBMC, peripheral blood mononuclear cells

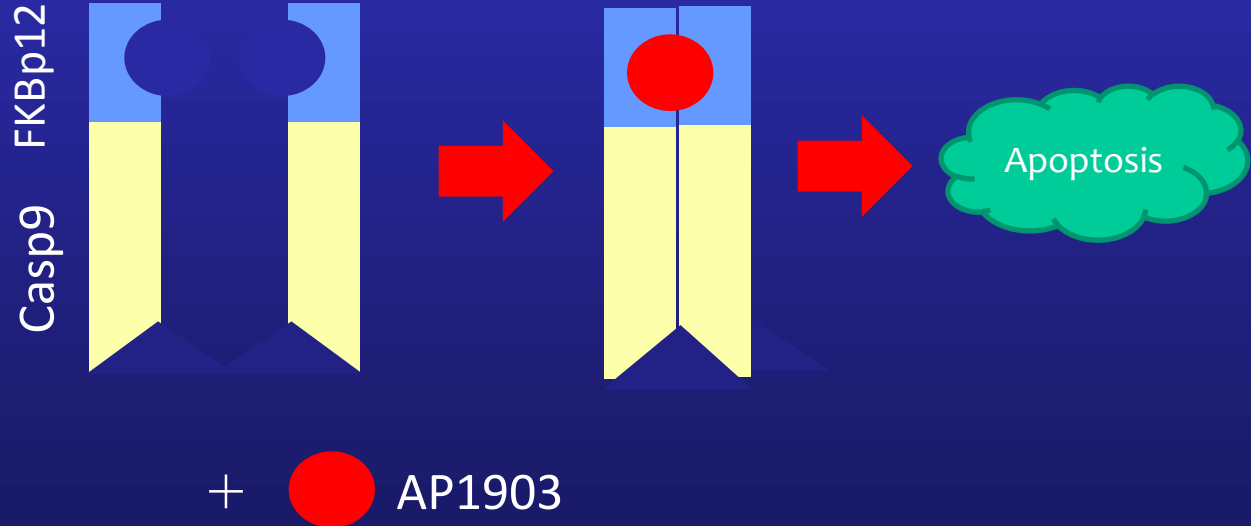
Second Generation CAR Targeting CD19



CAR.CD19-4.1BB-ζ



Suicide gene



In vivo CAR.CD19 Anti-leukemia mouse model

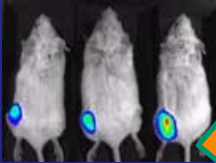
NSG model



- Control
 - CAR-CD19.41bb
- T cells (iv)

Tumour CD19+ cells FF Luc (iv)

Xenogen IVIS



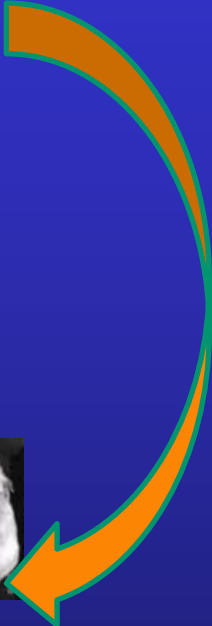
SFG.eGFP-FFluc

eGFP-Firefly luciferase

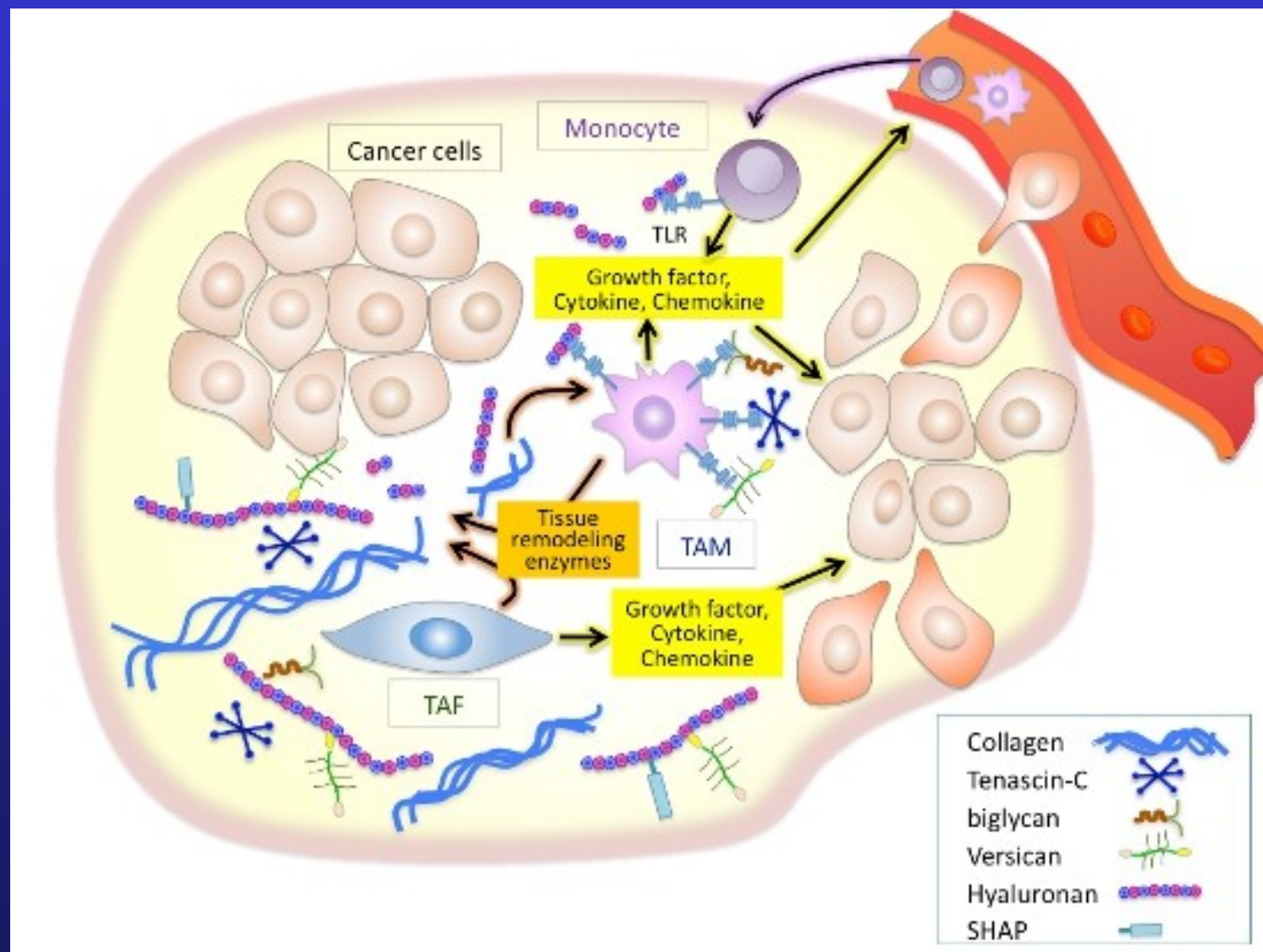
LTR

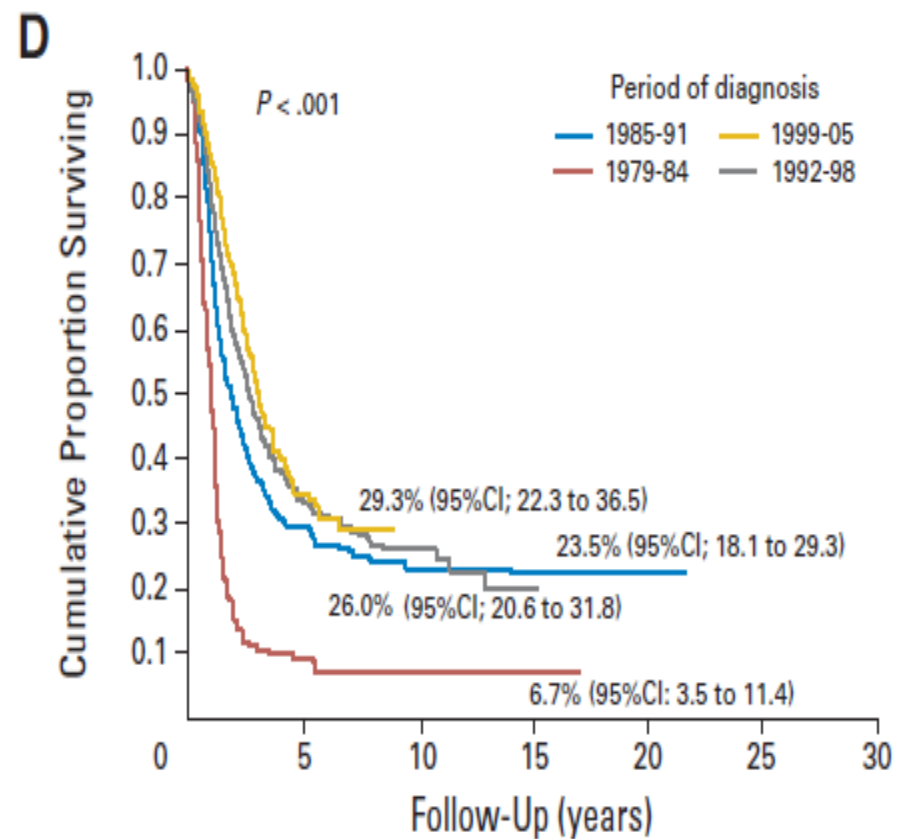
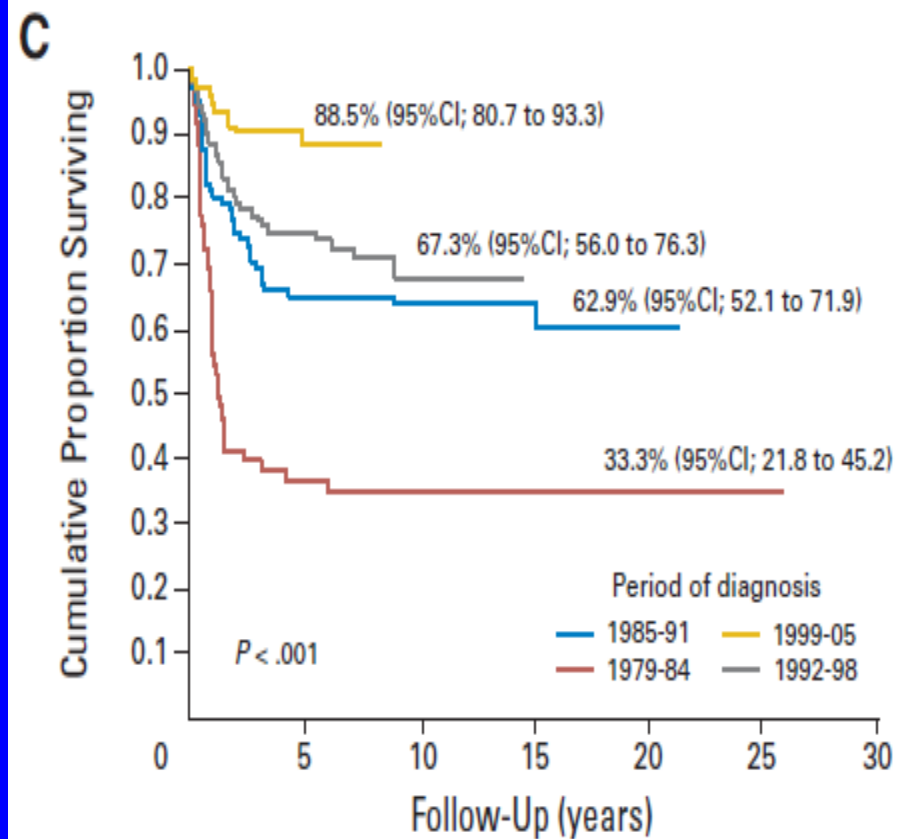
Ψ

LTR



NEXT CHALLENGES: CAR T cell in solid tumors





Baylor College of Medicine (BCM) Phase I trial (NCT00085930) – Study design

- 19 pts with High-Risk Neuroblastoma, relapsed/refractory or after initial therapy
- Partial in vivo lymphodepletion (unconjugated rat anti-hCD45)
- First generation CAR-ATCs + CAR-CTLs administered at 3 dose levels:
 - $1,2 \times 10^7$ cells/m² ($0,4 \times 10^6$ cells/Kg)
 - 5×10^7 cells/m² (1.7×10^6 cells/Kg)
 - 1×10^8 cells/m² (3.3×10^6 cells/Kg)

Safety data

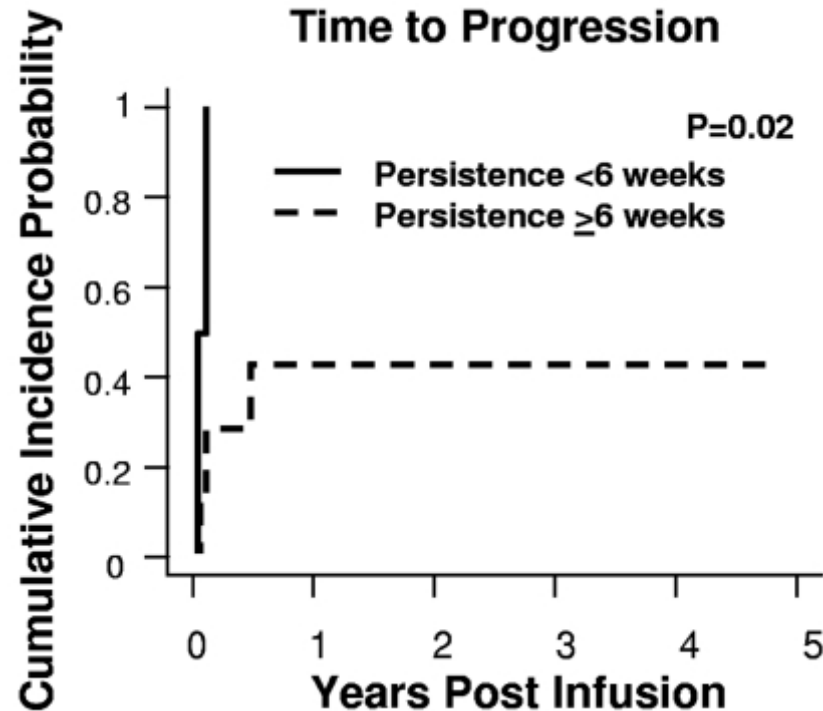
No severe or dose-limiting toxicities have been identified.

Three patients had grade 1 to 3 localized pain (2 at a site of biopsy-proven tumor necrosis and 1 in her lower leg at a site with no evidence of active disease).

BCM Phase I trial (NCT00085930) – Results (1)

CAGT no.	Age, y	Sex	Stage at diagnosis	Dose level	Disease burden at CTL infusion	Response at 6 weeks	Best response	GD2 T cells last detected, weeks after infusion	Clinical outcome
1662	9	Male	IV	1	NED	NED	NED	24	NED 11 mo after infusion
1738	5	Male	IV	1	NED	NED	NED	1	NED 10 mo after infusion
1705	4	Male	IV	1	NED	NED	NED	4	NED 10 mo after infusion
1632	20	Female	Ila	1	Relapsed, NED	NED	NED	2	AWD 13 mo after infusion
1629	7	Male	IV	1	Relapsed, NED	NED	NED	12	AWD 7 mo after infusion
1571	4	Female	IV	1	Relapsed, bone lesion	PD	PD	4	DOD 4 mo after infusion
1290	9	Female	IV	1	Relapsed, bone lesion	CR	CR	72	CR 1 yr 9 mo after infusion
1144	4	Female	IV	1	Refractory, bone lesion	PR	CR	192	CR 4 y 10 mo after infusion
1040	10	Male	IV	1	Relapsed, bulky	PD	PD	6	DOD 10 mo after infusion
717	11	Male	IV	1	Relapsed, bulky	PD	PD	1	DOD 2 mo after infusion
1151	10	Female	IV	2	Relapsed, NED	NED	NED	2	DOD 3 y after infusion
1089	4	Female	IV	2	Relapsed, NED	NED	NED	96	NED 3 y 3 mo after infusion
1035	15	Female	IV	2	Relapsed, bone marrow	CR	CR	6	DOD 6 mo after infusion
1117	9	Female	IV	2	Relapsed, bulky	PD	PD	28	DOD 10 mo after infusion
1208	3	Male	IV	2	Relapsed, bulky	SD	SD	12	DOD 6 mo after infusion
1253	9	Female	III	2	Relapsed, bulky	Tumor necrosis	Tumor necrosis	4	DOD 14 mo after infusion
1353	7	Male	IV	3	Relapsed, NED	NED	NED	12	DOD 2 y 7 mo after infusion
1237	4	Female	IV	3	Relapsed, bulky	Tumor necrosis	Tumor necrosis	2	DOD 2 mo after infusion
1361	7	Male	IV	3	Relapsed, bulky	SD	PR	72	AWD 2 y 8 mo after infusion

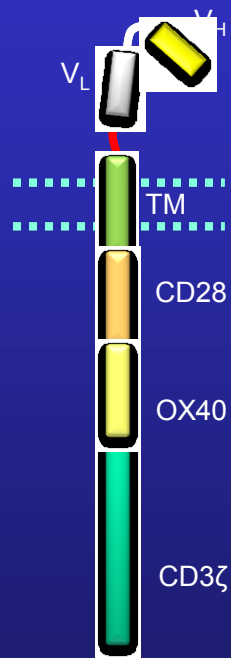
BCM Phase I trial (NCT00085930) – Results (2)



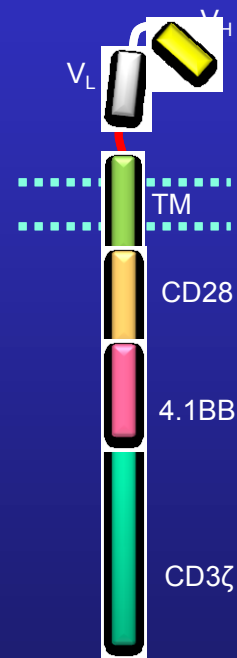
- Improving CAR T cells persistence is mandatory:
- Lymphodepletion
 - 2nd and 3rd generation CAR constructs

Third Generation CARs Targeting GD2 (14.G2a)

scFv.CD28-OX40- ζ



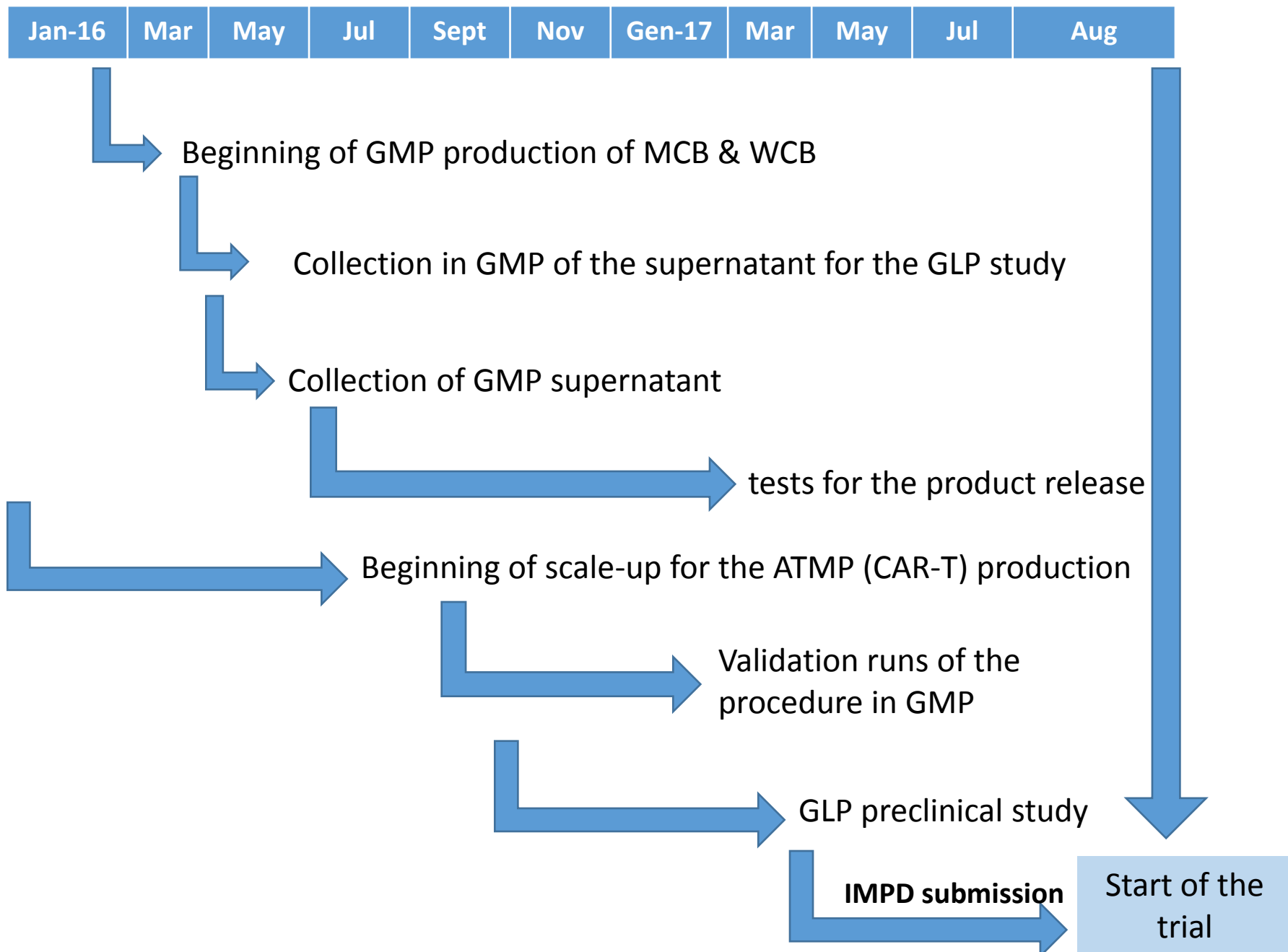
scFv.CD28-4.1BB- ζ



Which is the optimal co-stimulation for adoptive T cell therapy in neuroblastoma?

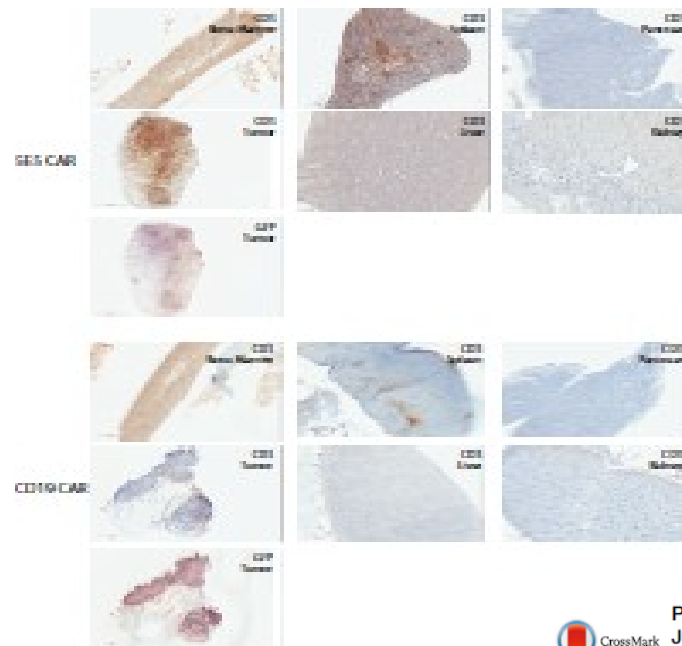
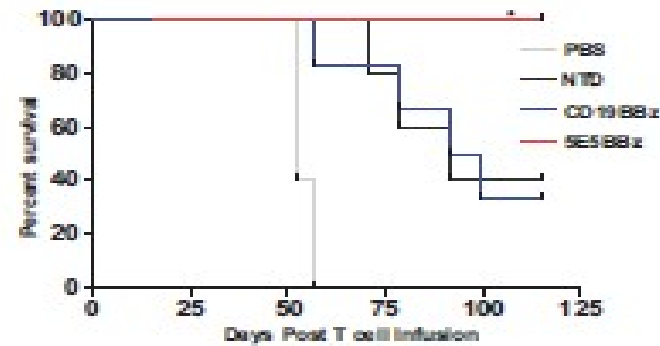
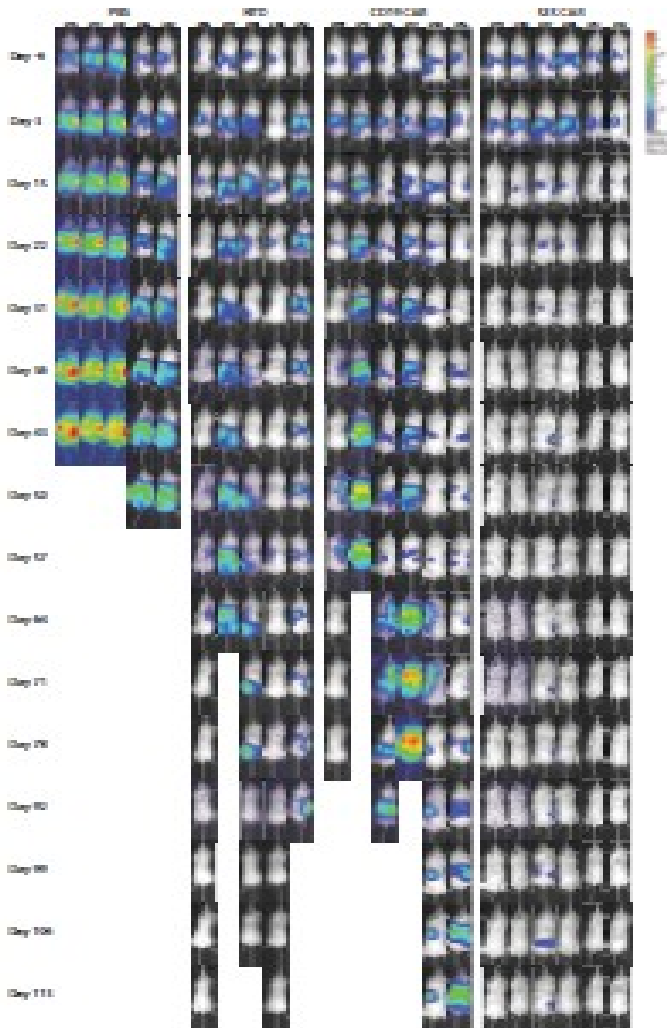


Timeline for starting treatment of patients



Immunity

Engineered CAR T Cells Targeting the Cancer-Associated Tn-Glycoform of the Membrane Mucin MUC1 Control Adenocarcinoma



ACKNOWLEDGEMENTS

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