Adoptive T cell therapies: new tricks from old dogs?

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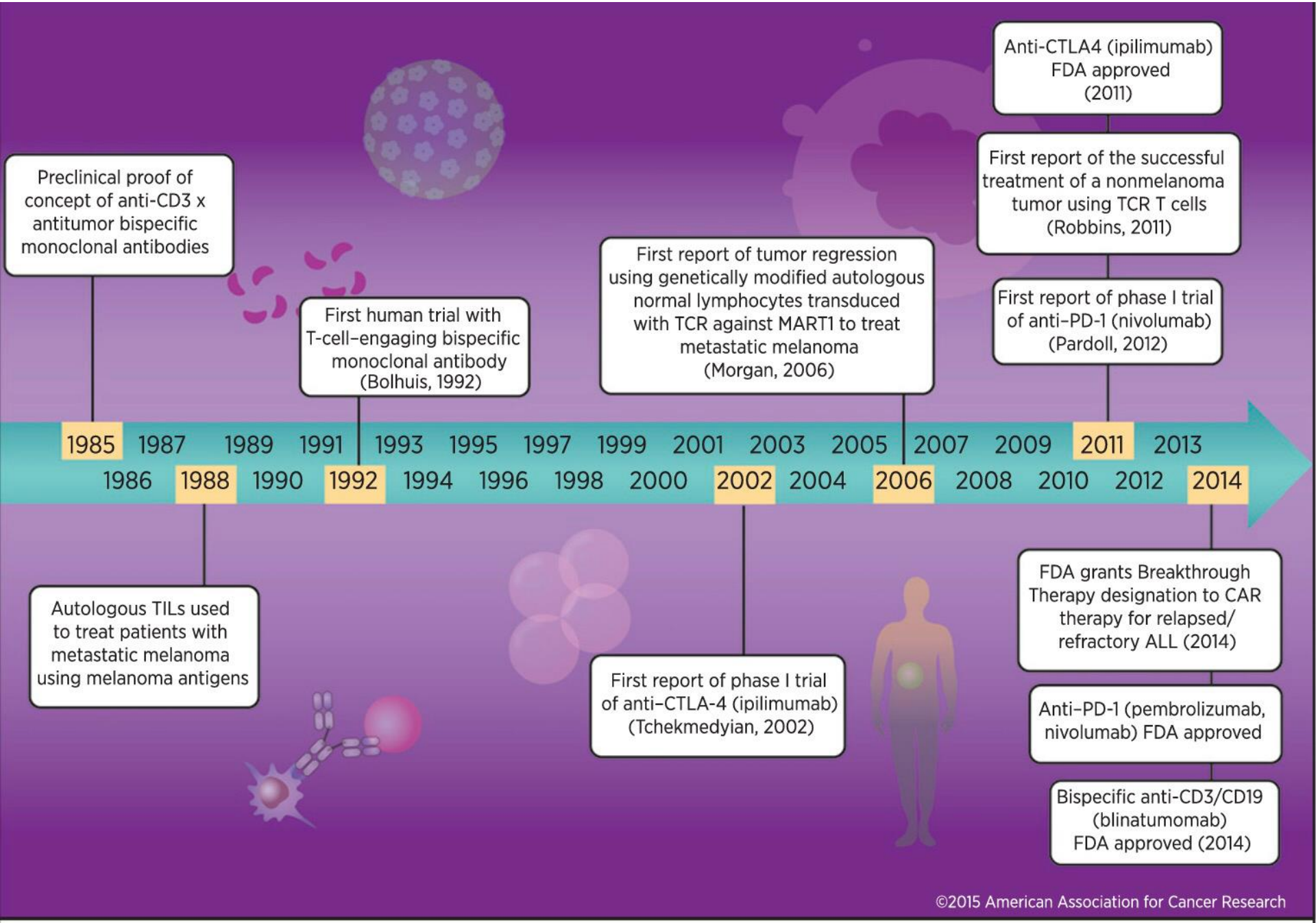
IRCCS IRST - Meldola

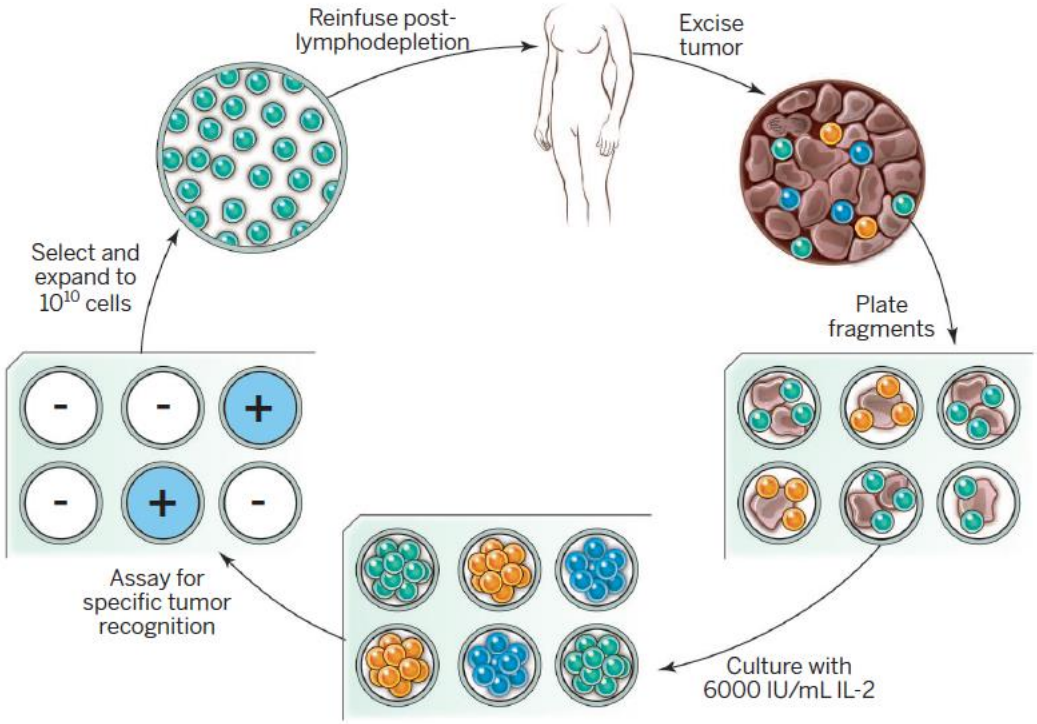
- *Adoptive cells therapies consist of the infusion of living cells into a patients for therapeutic purposes*

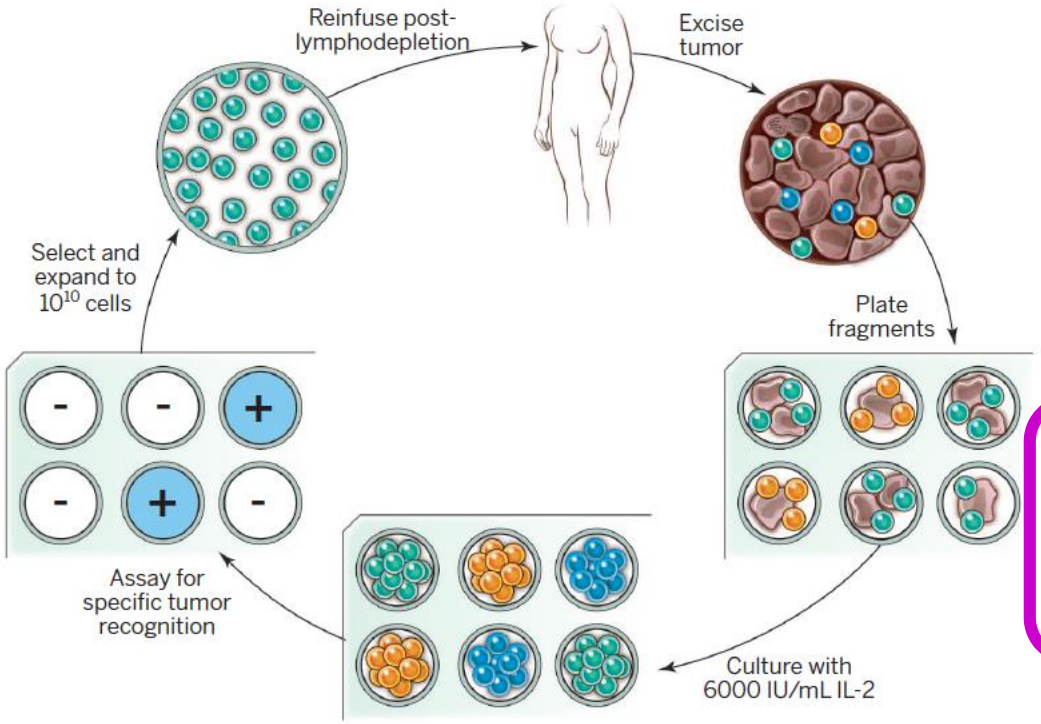
- *In oncology, they mainly involve the transfer of immune cells for inducing (e.g. dendritic cells) or "importing" an effective antitumor immune response (e.g. adoptive transfer of T cells, NK cells etc)*

- *Adoptive cell therapies are "**living drugs**"*

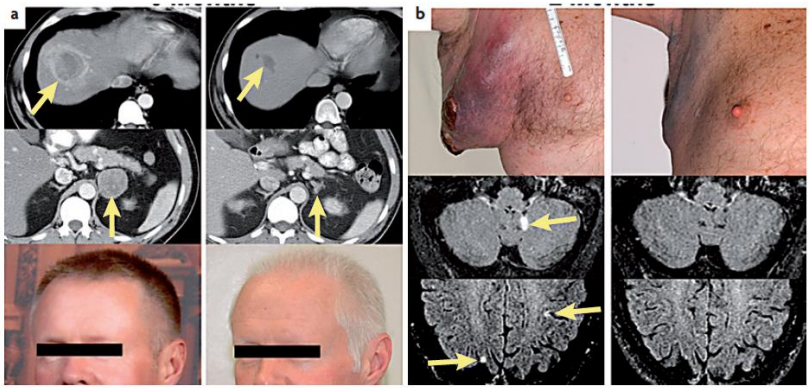
The "puppy" adoptive T cell therapy




Reinfuse post-lymphodepletion
Excise tumor
Select and expand to 10^{10} cells
Plate fragments
Assay for specific tumor recognition
Culture with 6000 IU/mL IL-2



5-y OS 93%

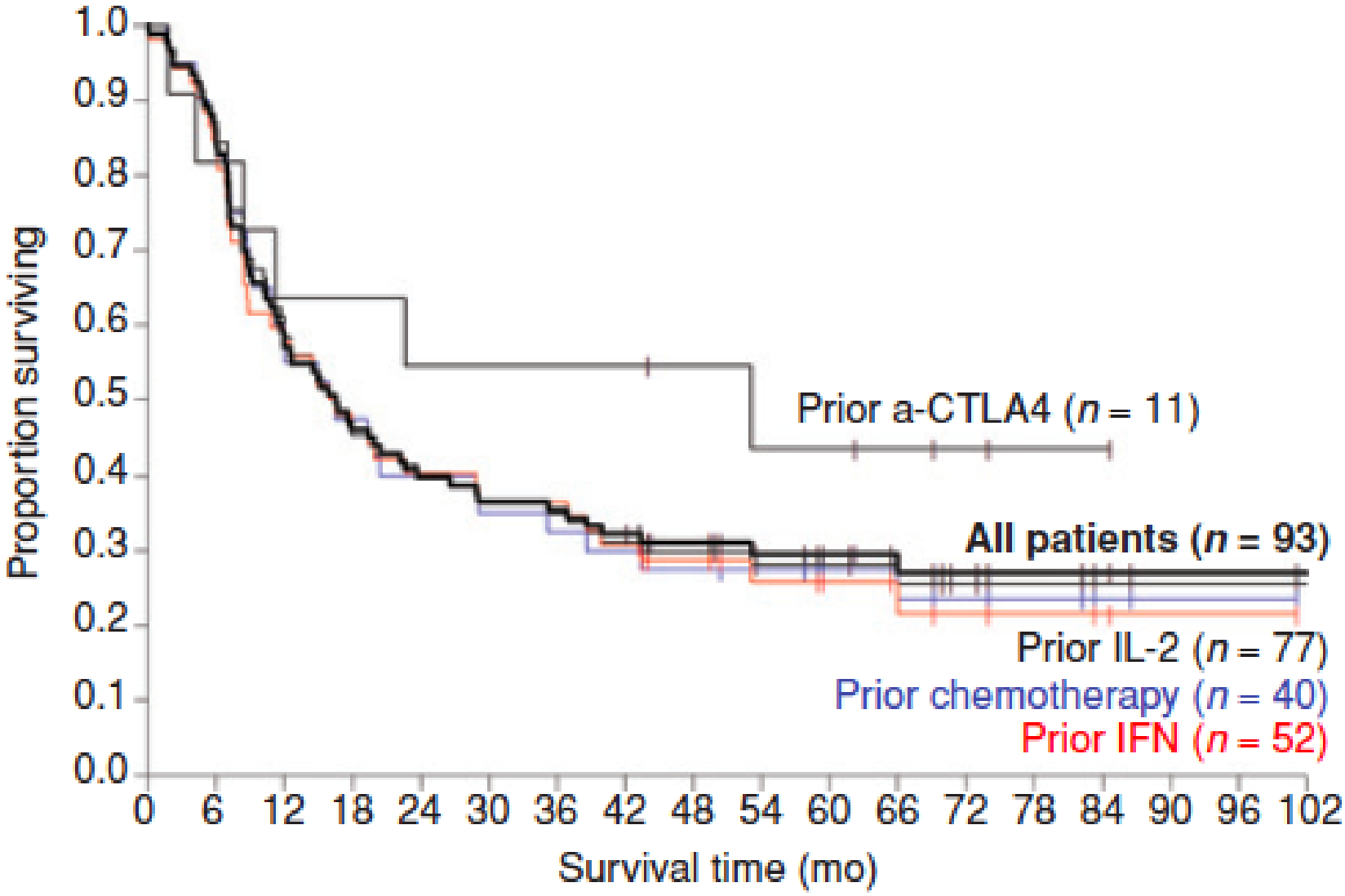


Examples of objective tumour regressions in patients receiving adoptive cell transfer of autologous anti-tumour lymphocytes following a lymphodepleting preparative regimen.

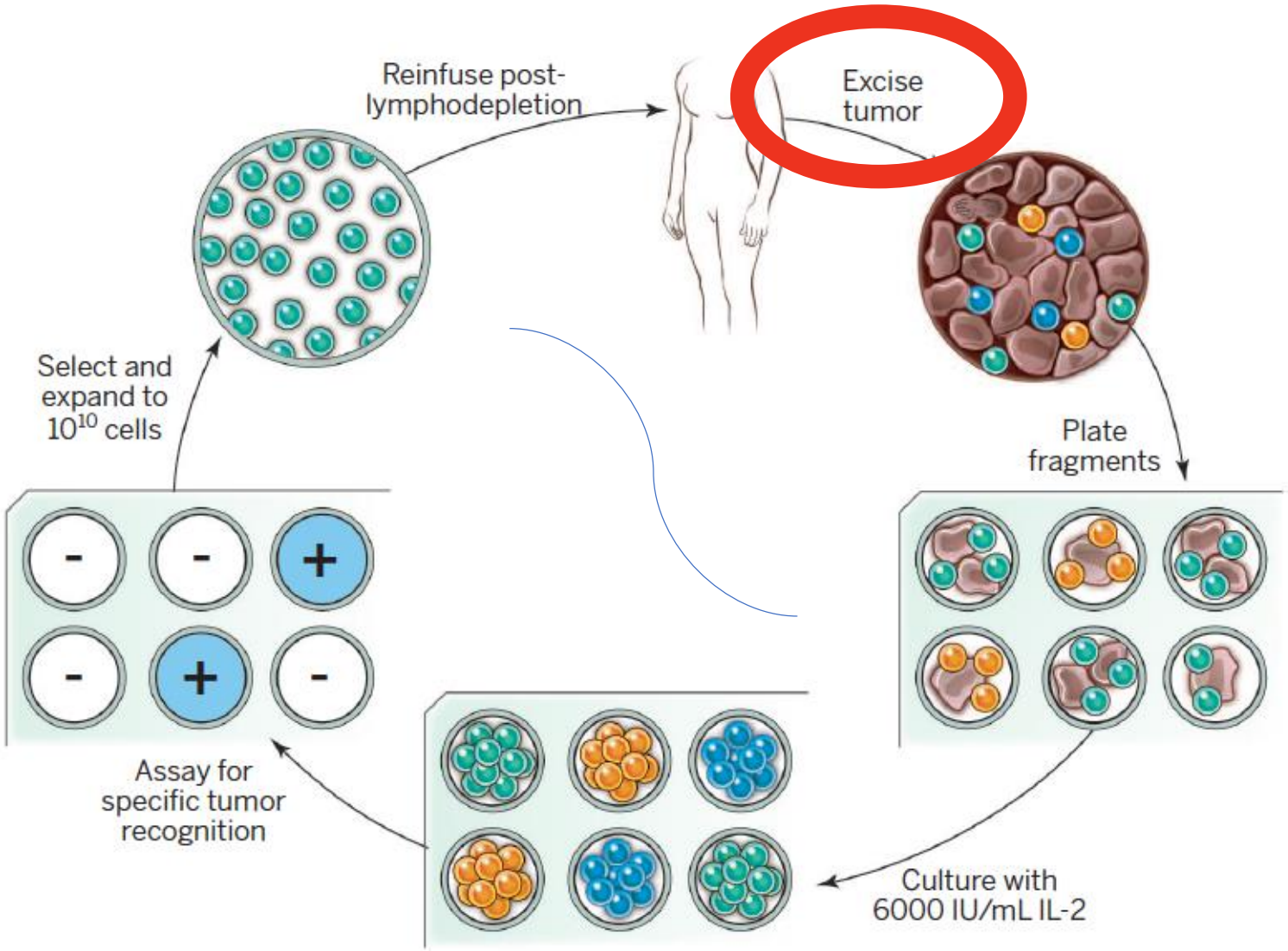
Table 1 | **Adoptive cell therapy in patients with metastatic melanoma**[79]

Treatment	Patients (*n*)	Response (*n* (%))		
		PR	CR	OR
No TBI	43	17 (39.5)	4 (9.3)	21 (48.8)
2 Gy TBI	25	11 (44.0)	2 (8.0)	13 (52.0)
12 Gy TBI	25	14 (56.0)	4 (16.0)	18 (72)

All patients received cyclophosphamide 60 mg/kg for 2 days then fludarabine 25 mg/m^2 for 5 days.



Rosenberg et al Clin Cancer Res 2011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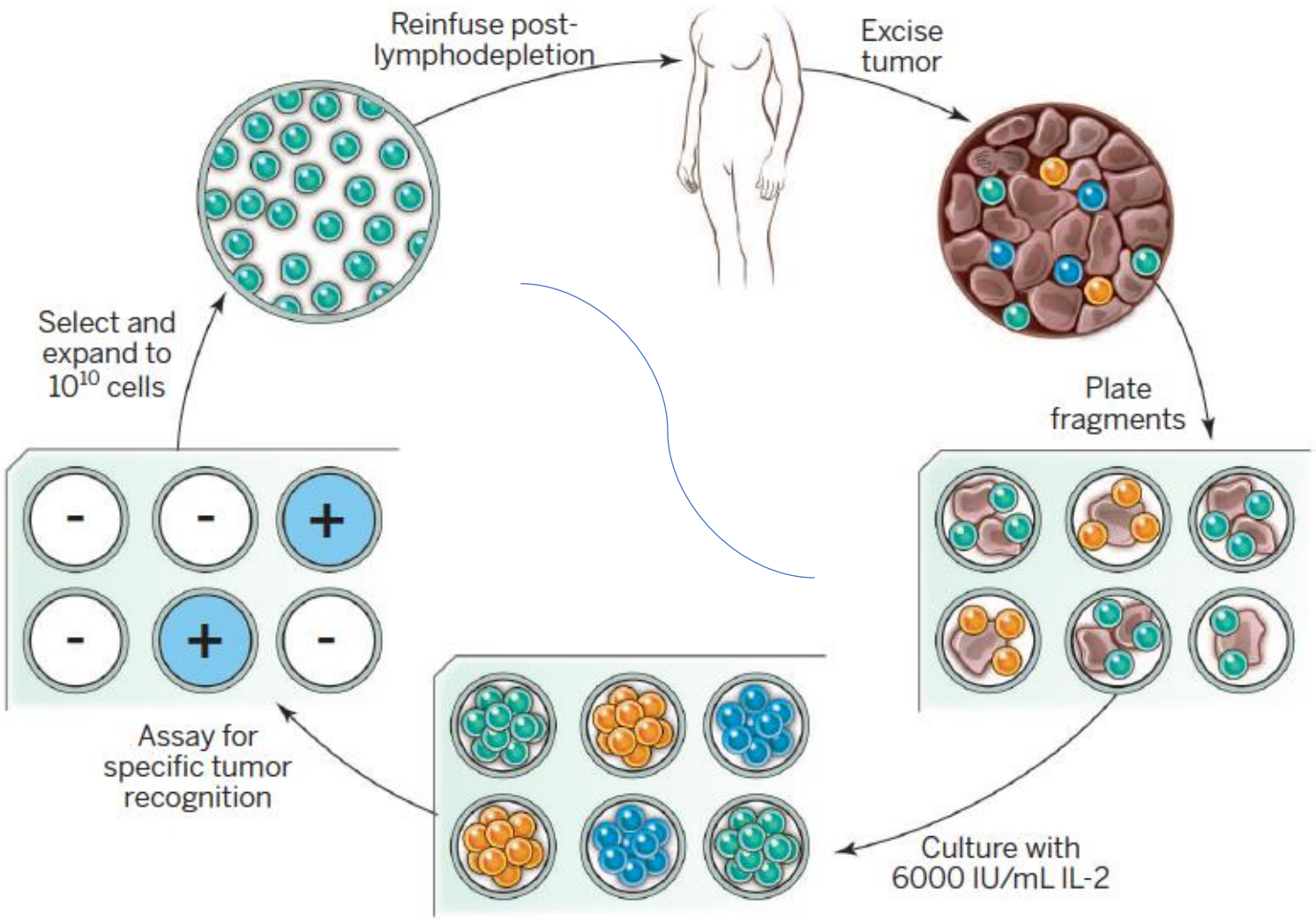
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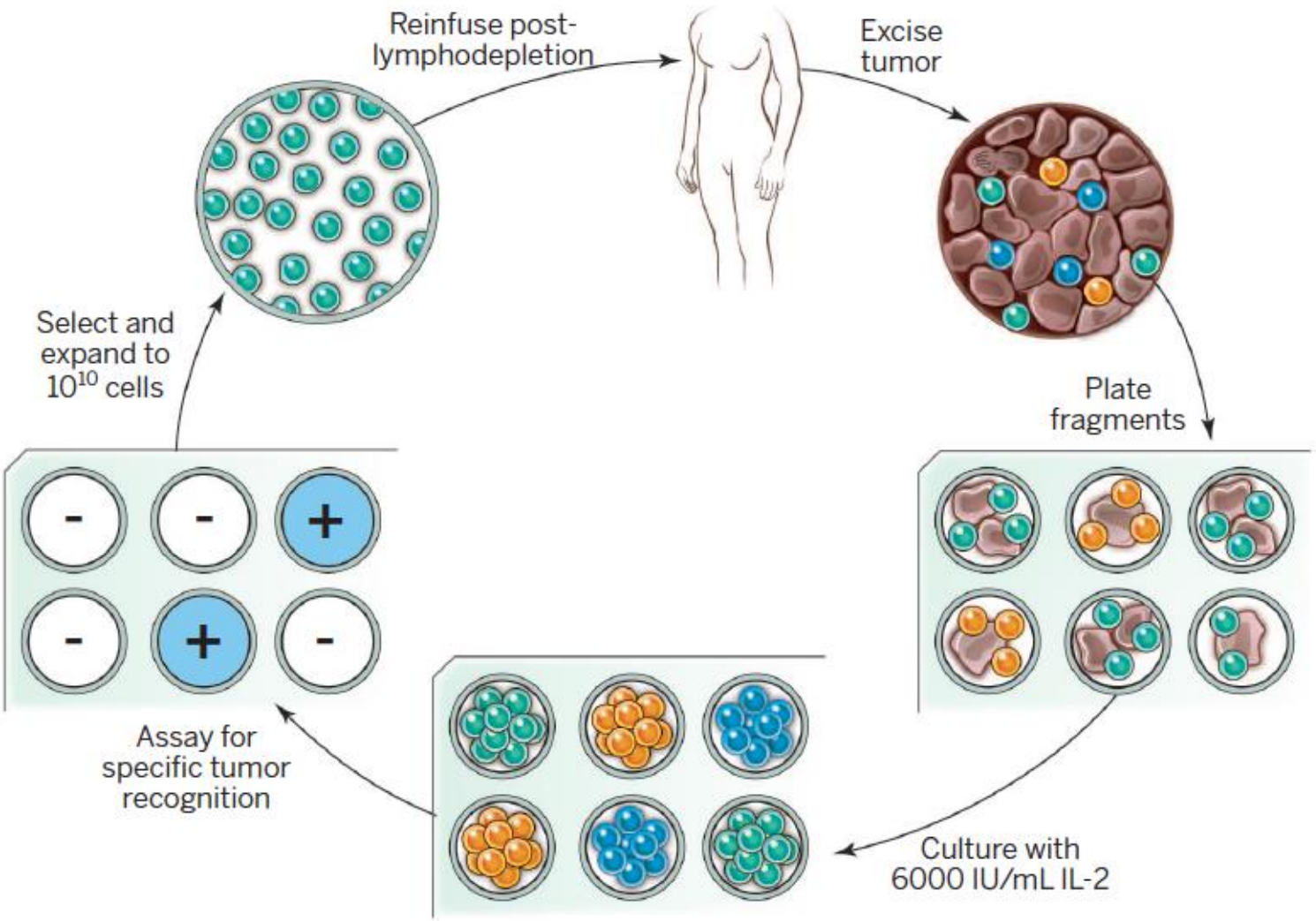
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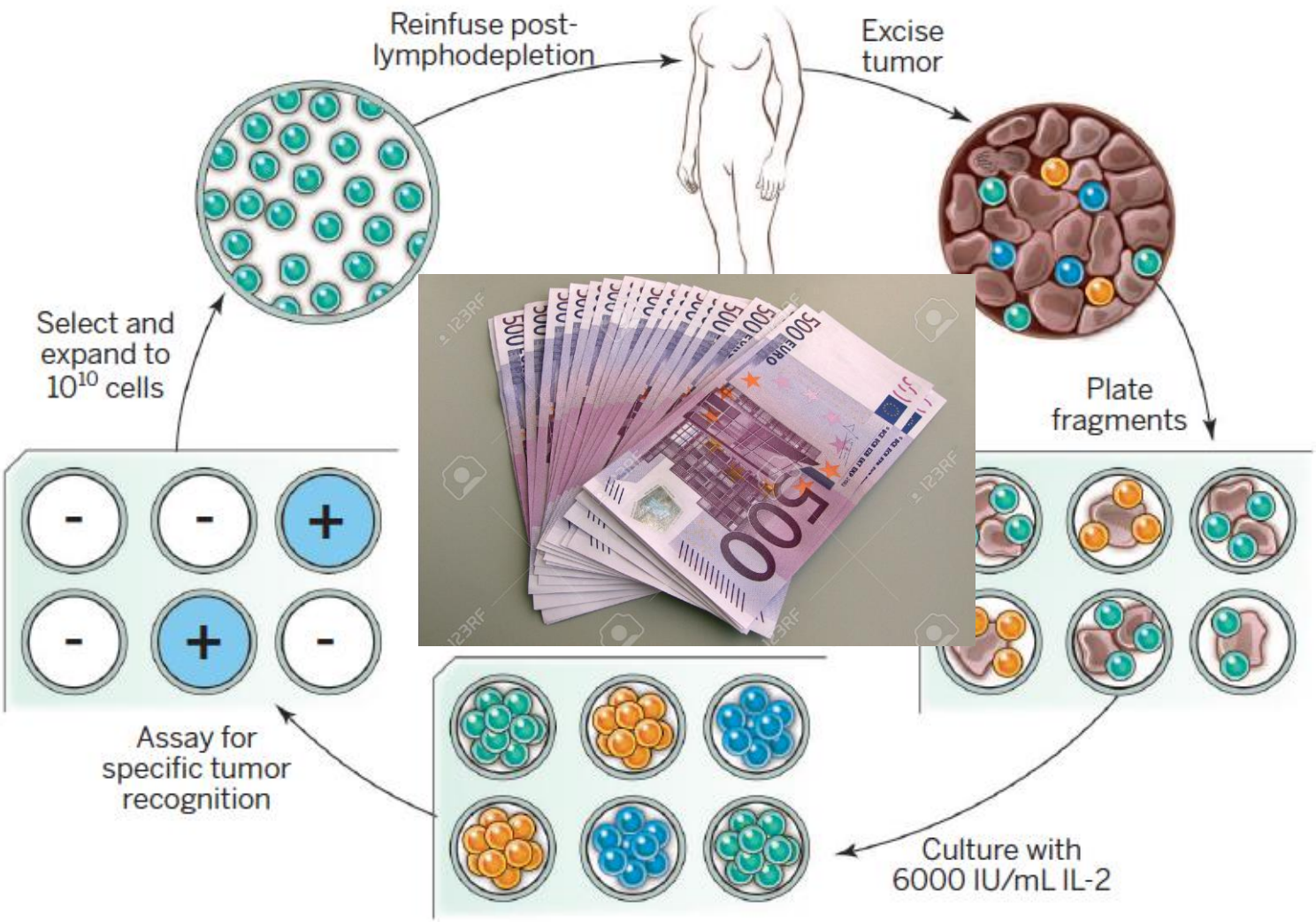
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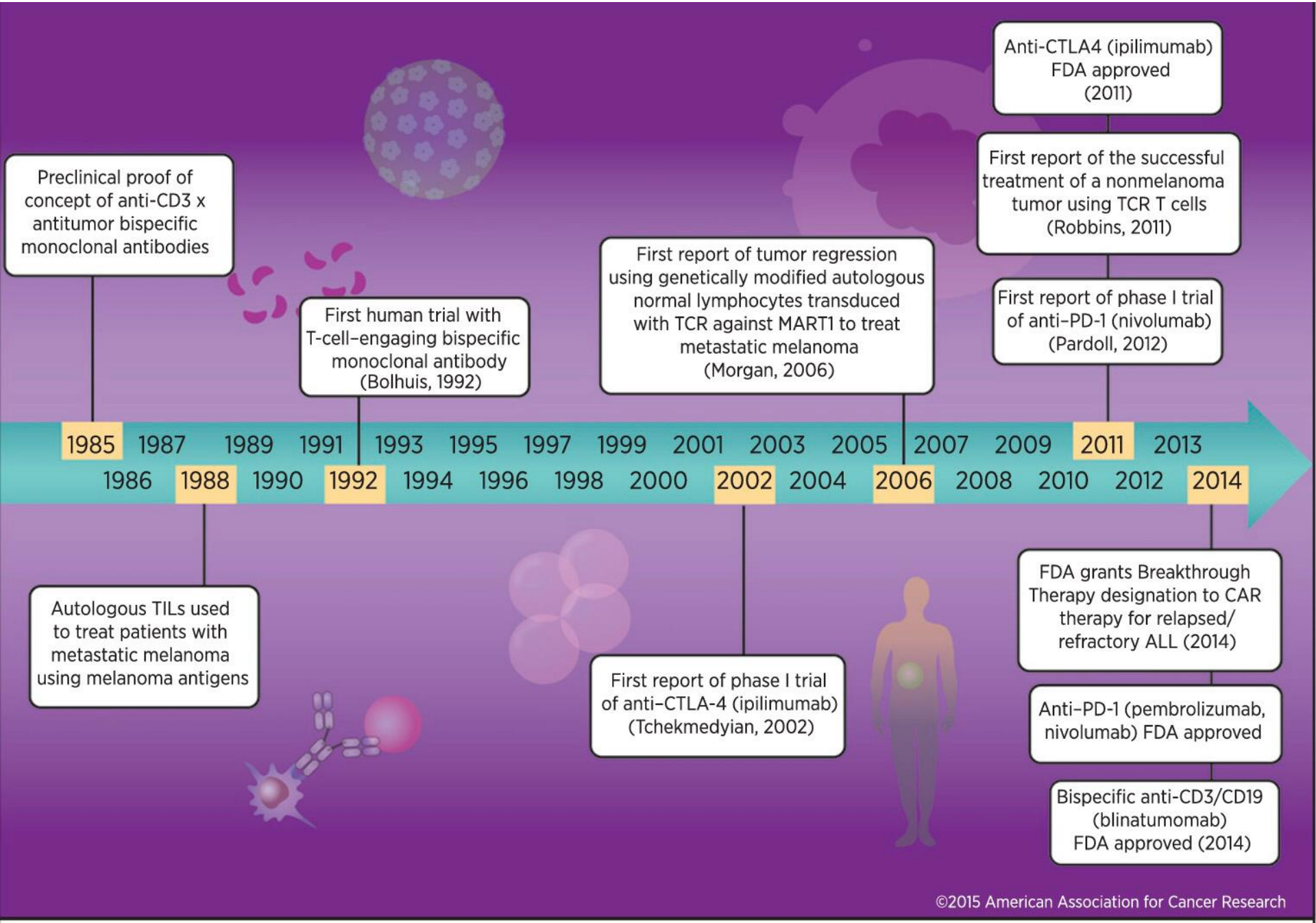
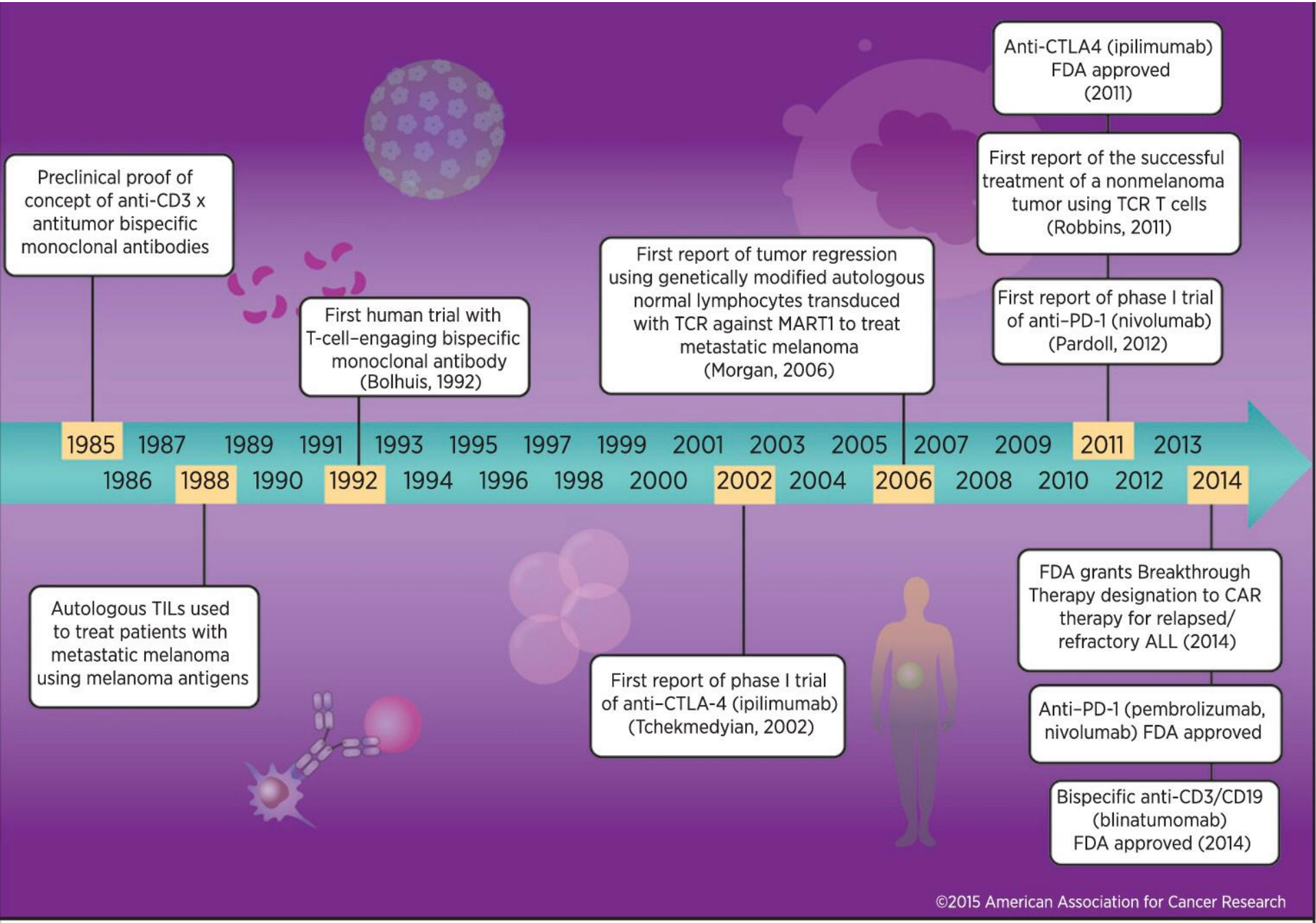
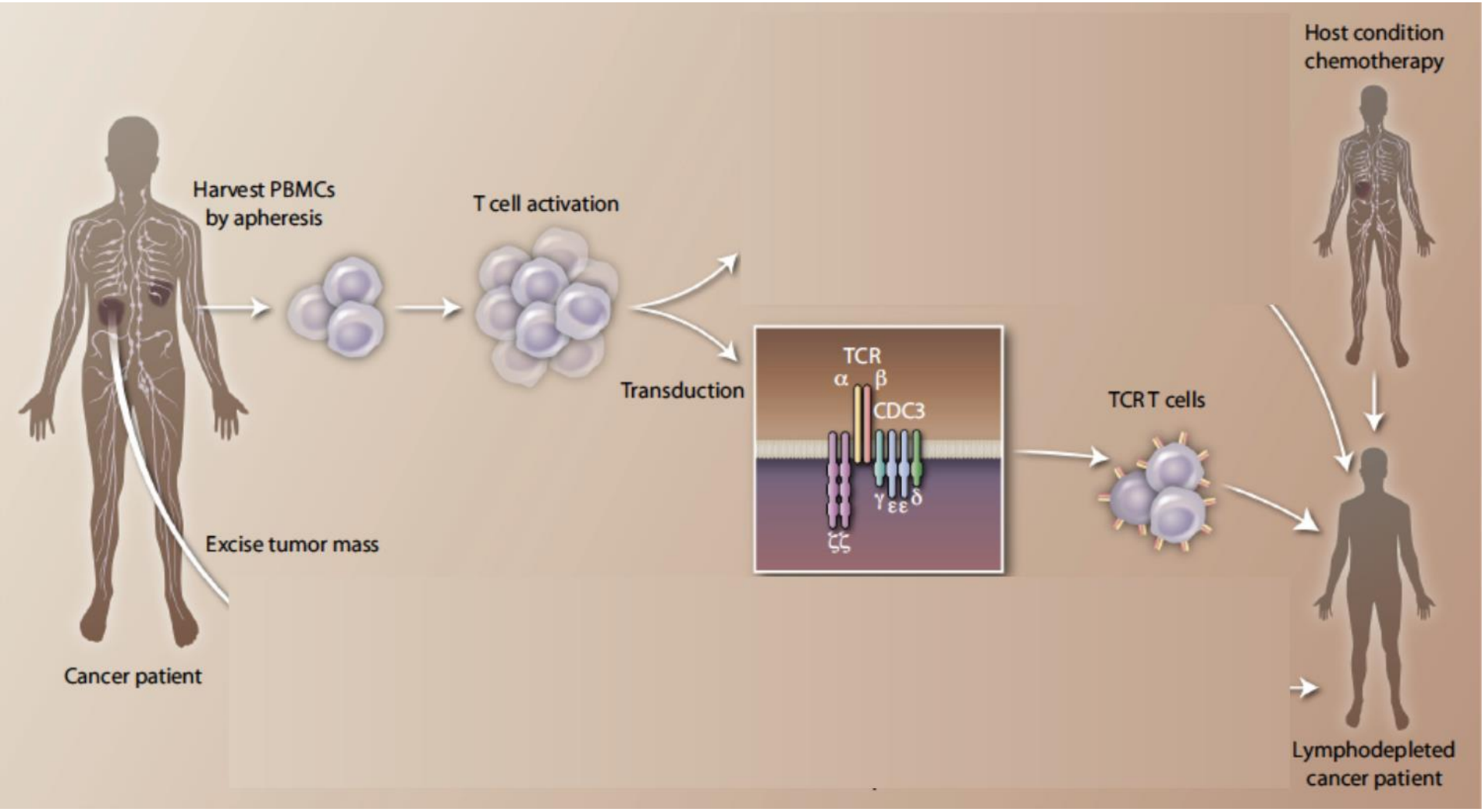
Little puppies grow up .....





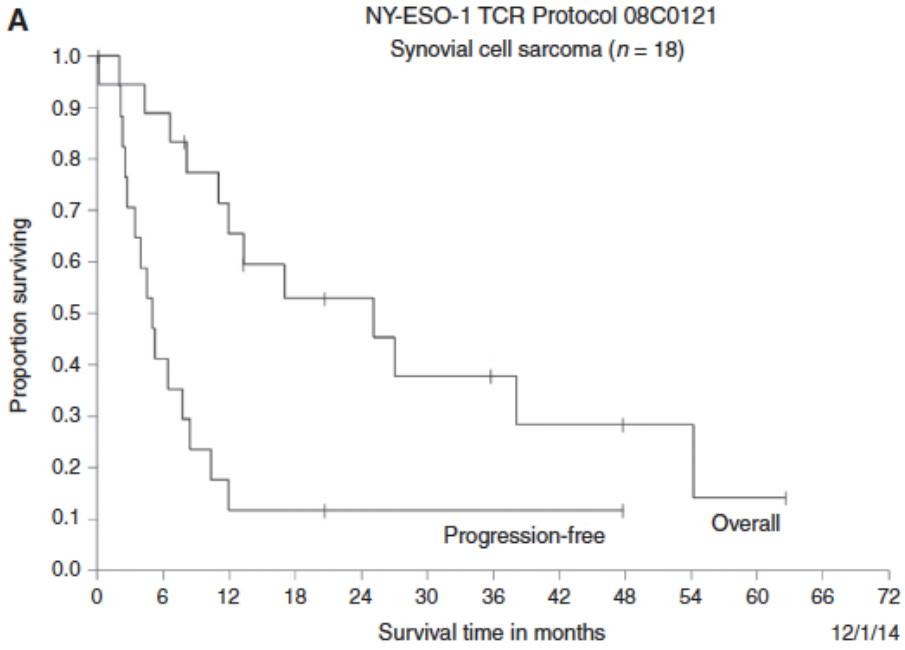

Host condition
chemotherapy
Harvest PBMCs
by apheresis
T cell activation
Transduction
TCR
α
β
CDC3
γ
εε
δ
ζζ
TCR T cells
Excise tumor mass
Cancer patient
Lymphodepleted
cancer patient

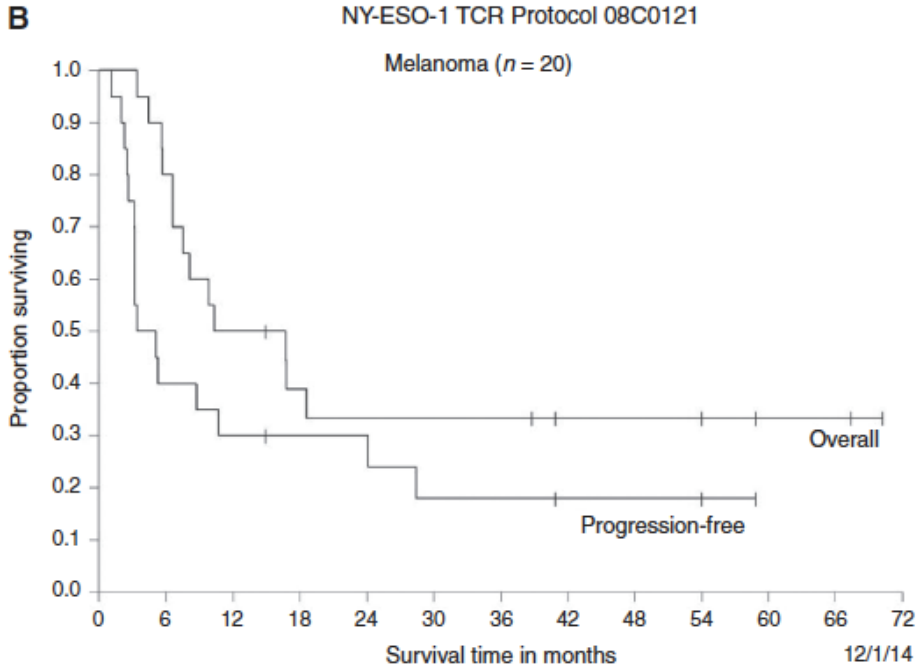
Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes

Richard A. Morgan, Mark E. Dudley, John R. Wunderlich, Marybeth S. Hughes, James C. Yang, Richard M. Sherry, Richard E. Royal, Suzanne L. Topalian, Udai S. Kammula, Nicholas P. Restifo, Zhili Zheng, Azam Nahvi, Christiaan R. de Vries, Linda J. Rogers-Freezer, Sharon A. Mavroukakis, Steven A. Rosenberg*

A Pilot Trial Using Lymphocytes Genetically Engineered with an NY-ESO-1–Reactive T-cell Receptor: Long-term Follow-up and Correlates with Response

Clin Cancer Res; 21(5) March 1, 2015





PROs

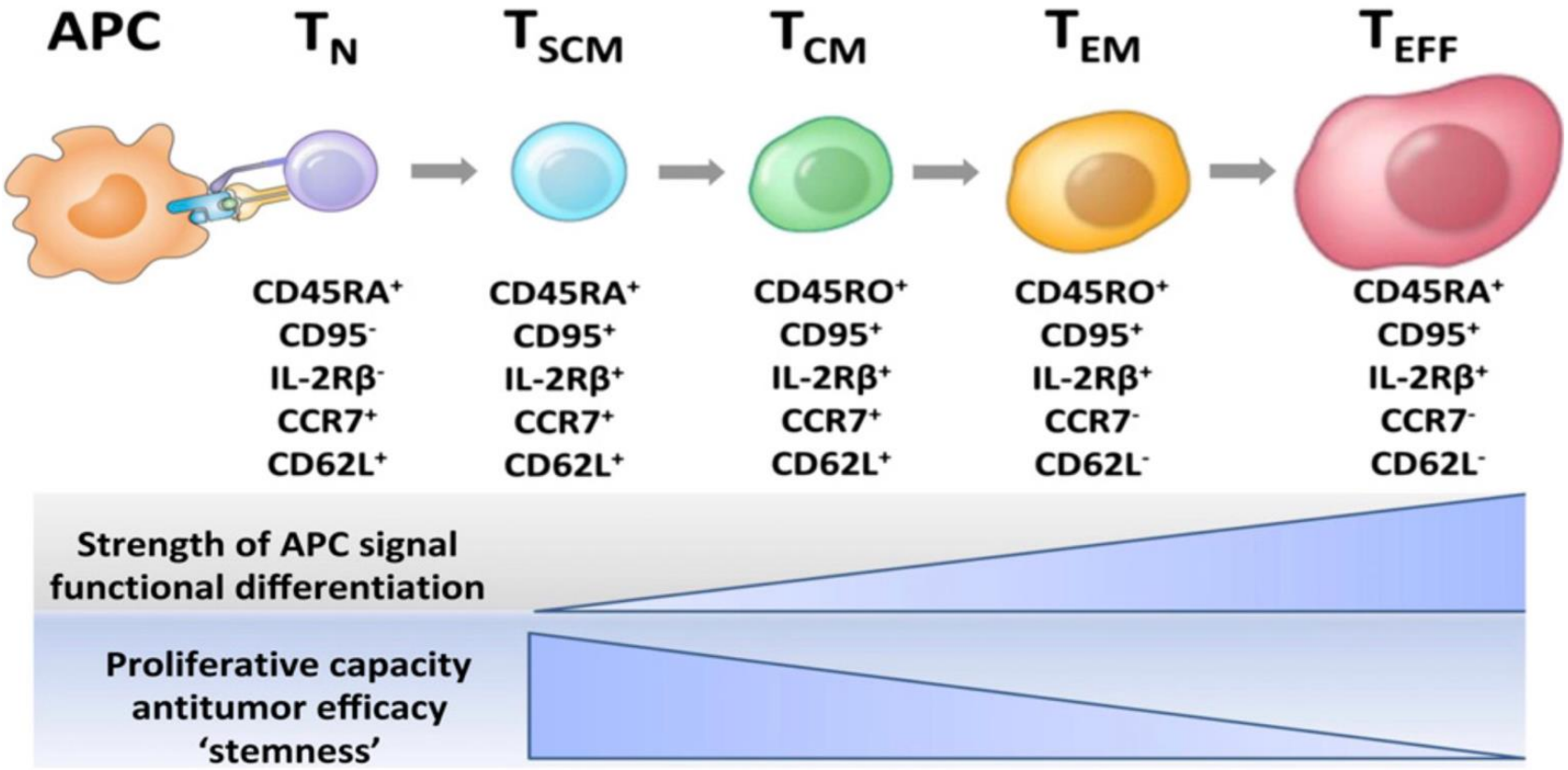
- Different types of antigens can be targeted by redirected T cells: tissue-specific differentiation Ags (e.g. Melanoma Differentiation Ags, CD19), Cancer Testis Antigens, mutated antigens, overexpressed self-proteins (e.g. HER2), viral antigens => more tumor types targetable
- Shorter manufacturing times => more patients treatable

CONTRA

- NEW TOXICITIES
  - On target/off tumor
    - gp100-TCR and MART1-TCR can give skin rash, uveitis, hearing loss (these Ag are expressed by normal melanocytes in the skin, retina and inner ear)
    - CEA-TCR can lead to severe colitis (CEA is expressed on normal GI epithelial cells)
    - MAGEA3-TCR can give neurological toxicity
  - Off target
    - MAGEA3-TCR can cross-recognize titin, a protein expressed by myocardiocytes
  - “Cytokine storm”
- Costs even higher than TILs

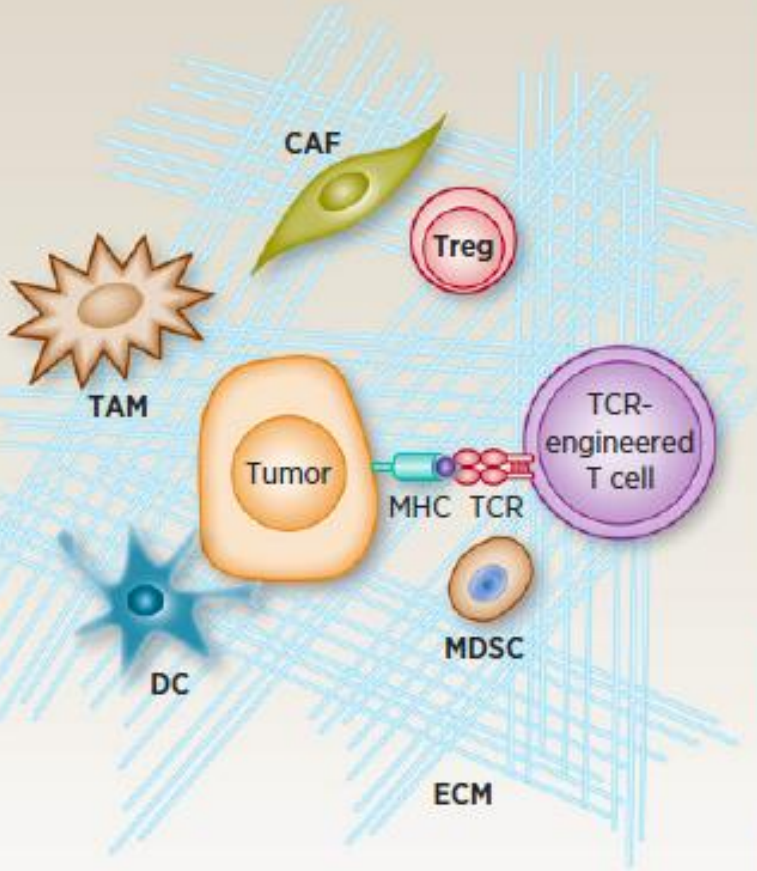
New tricks from an old dog …

Clinical response is strictly related with persistence of adoptive T cells in the host..... Must utilize "young TILs" or induce in vitro tumor-specific stem cell memory T cells (CD62L positive).



A

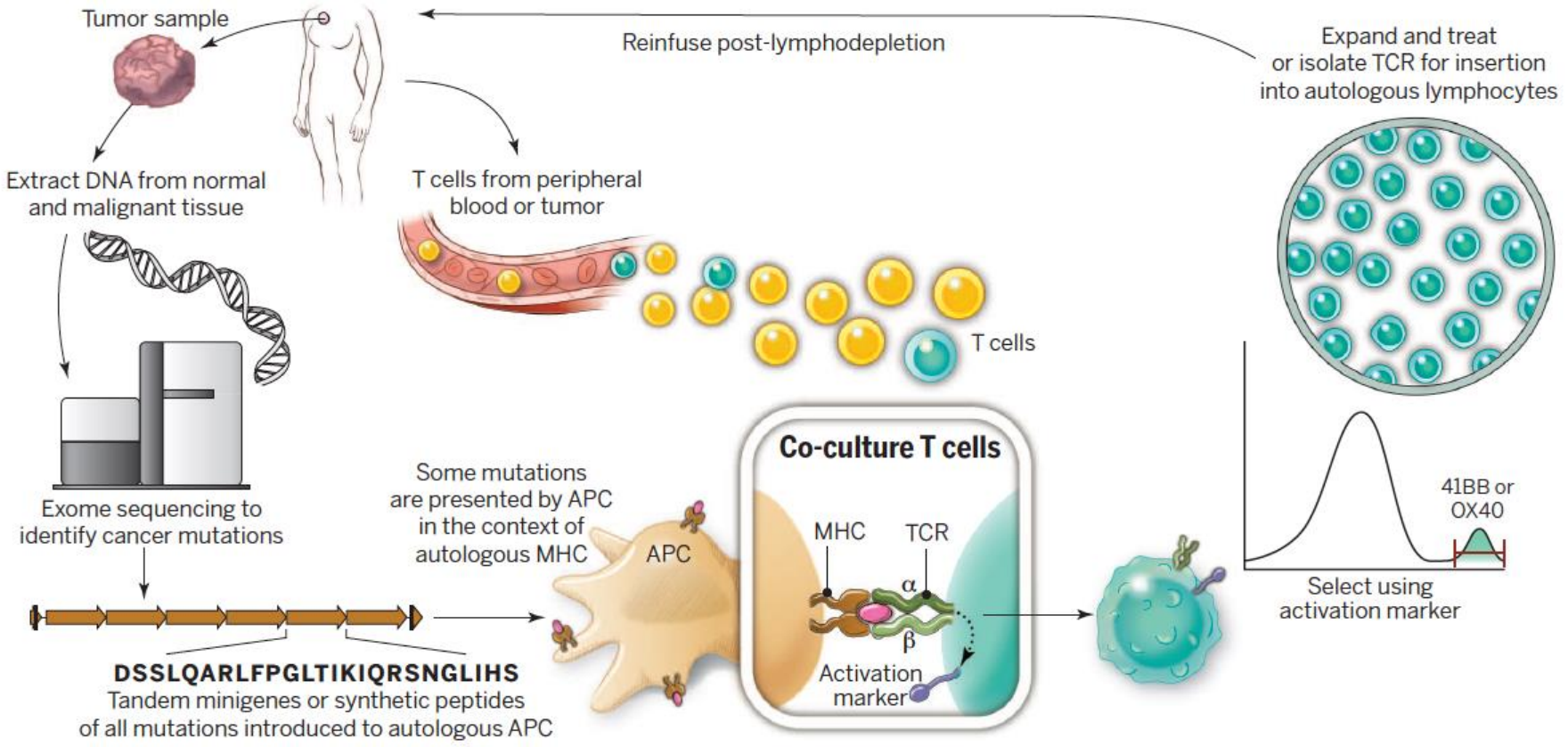
Tumor environment in which TCR-engineered T cells must function

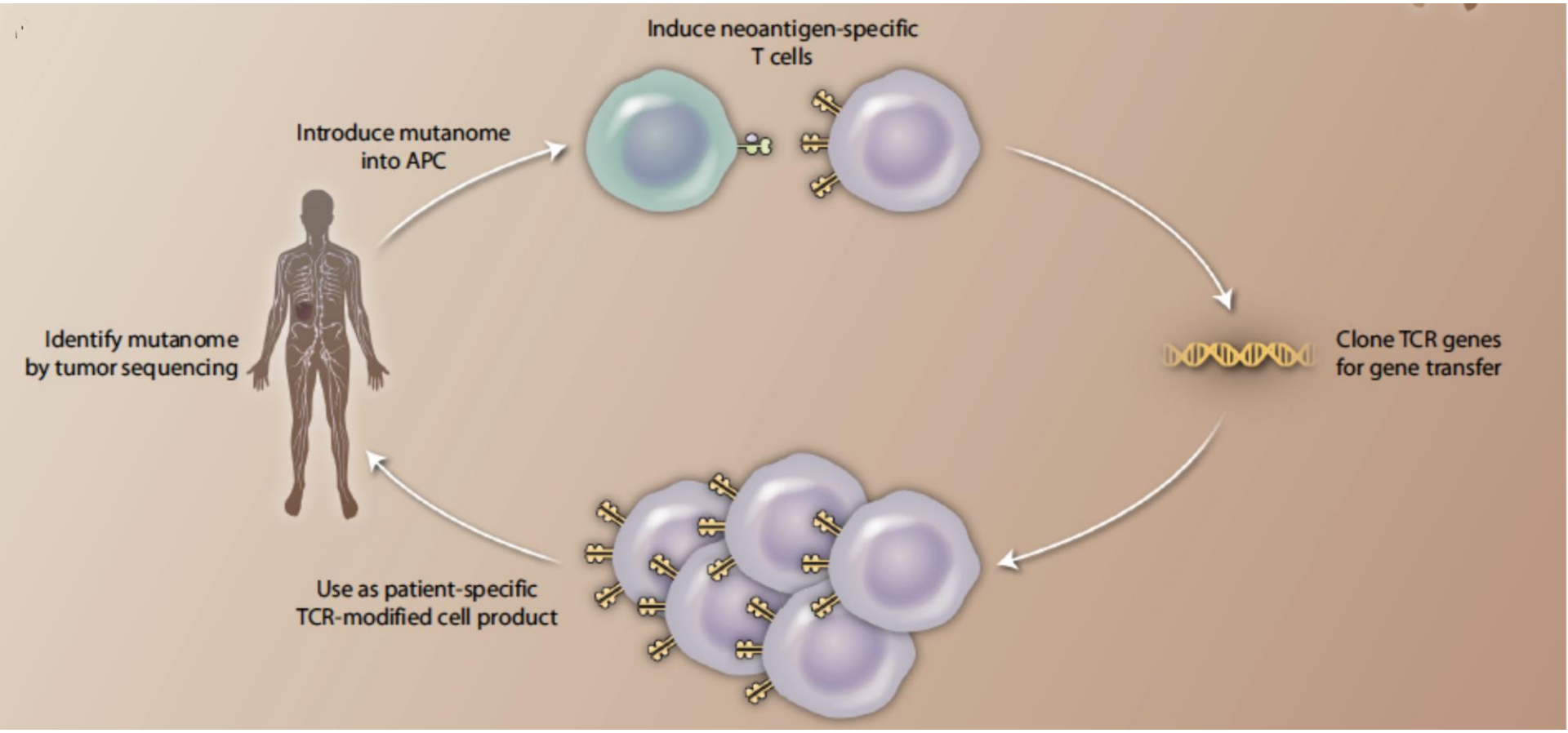


B: Obstacles for curative responses	C: Further T-cell engineering
Suboptimal TCR affinity for self-/tumor antigens	Select higher affinity TCRs; modify CDR3 to increase TCR affinity
Immunosuppressive factors (TGFβ, IL10)	Engineer T cells to be refractory to inhibition; engineer T cells to produce proinflammatory factors (IL12, TLR agonists)
Chronic TCR signaling; upregulation of inhibitory receptors (PD-1, Tim3, Lag3)	Design chimeric costimulatory constructs (PD1-CD28); knock down/ablate receptors in donor T cells; combine cell therapy and blockade with mAbs
Failure of T cells to persist at sufficiently high numbers	Engineer costimulation by expressing receptors (41BB, CD28) and/or ligands (CD80, 41BBL); utilize alternative T-cell subsets (T_{CM}, CD4)
Therapy-induced selection of tumor antigen-low/loss variants	Modify CDR3 to increase TCR affinity; develop a catalog of clinical TCR vectors to allow simultaneous targeting of multiple tumor antigens

1) Strong evidence that higher load of mutations is associated to better outcome on immunotherapy (e.g. melanoma, squamous NSCLC, bladder cancer, MSI+ CRC etc)

2) TILs from 21 ACT-responder melanoma patients specifically recognized 45 mutations (non shared among patients!!)




Induce neoantigen-specific
T cells
Introduce mutanome
into APC
Identify mutanome
by tumor sequencing
Clone TCR genes
for gene transfer
Use as patient-specific
TCR-modified cell product

A

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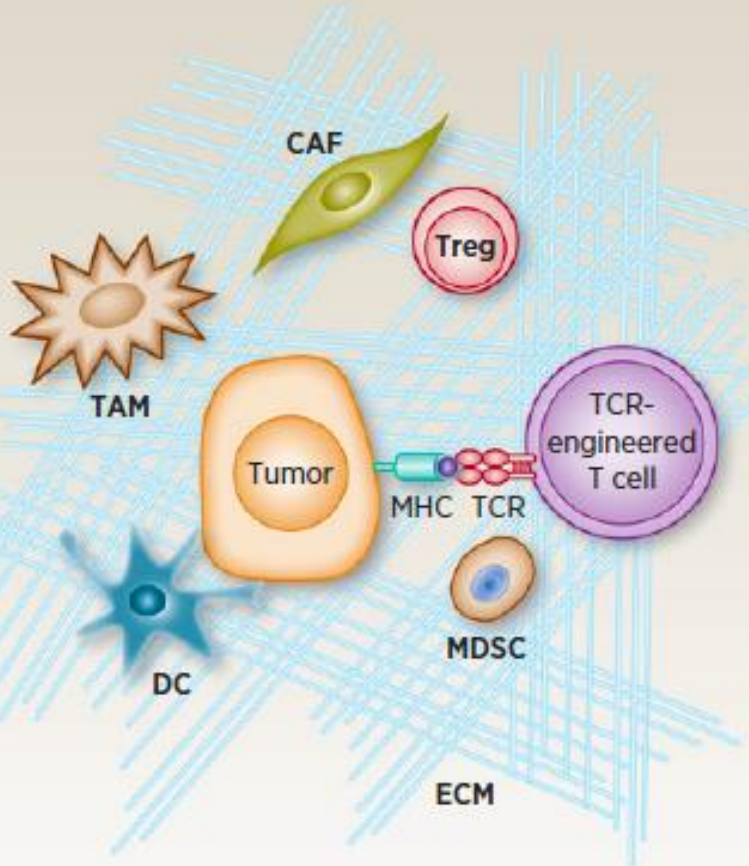

B

Obstacles for curative responses

C

Further T-cell engineering

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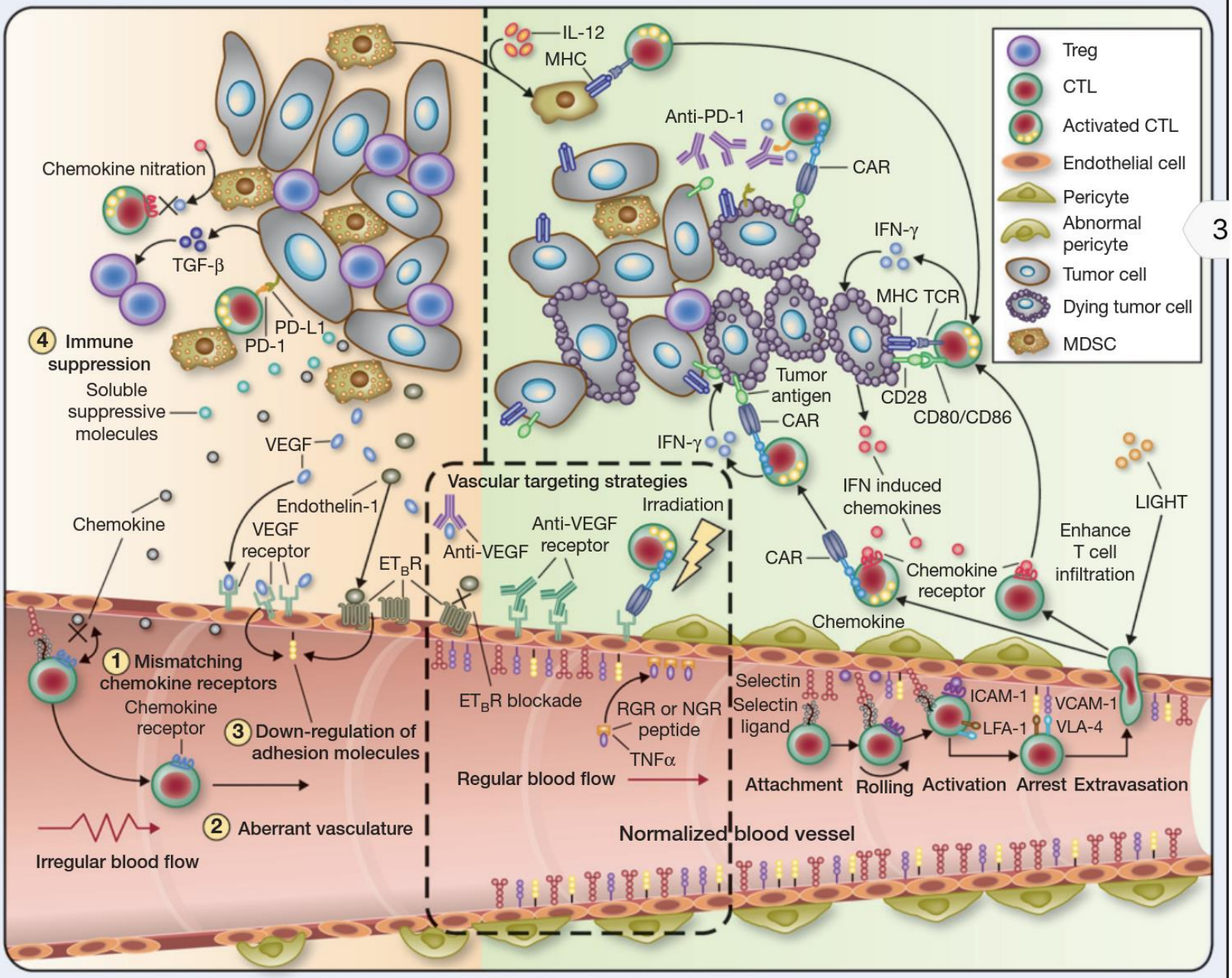
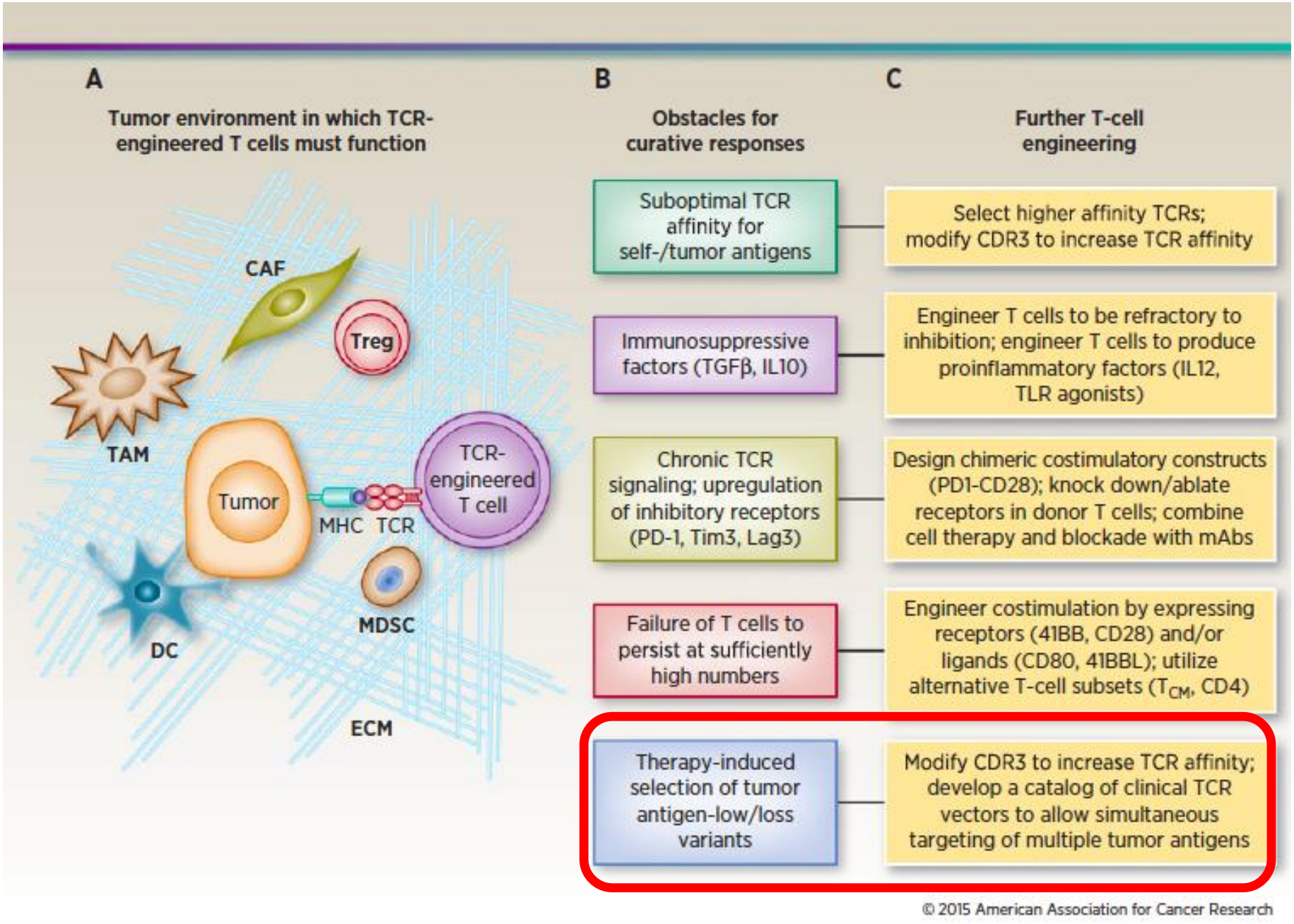
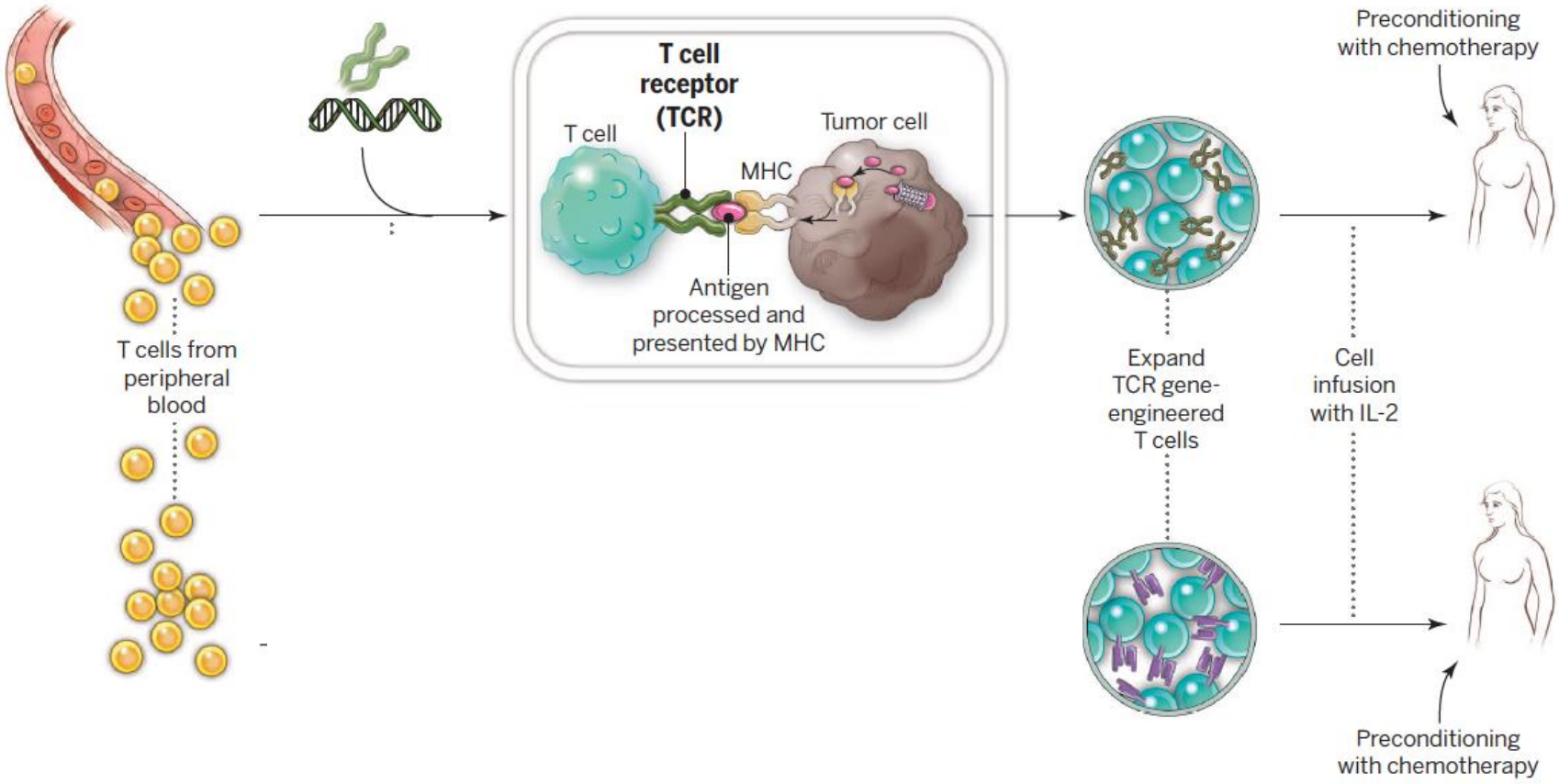
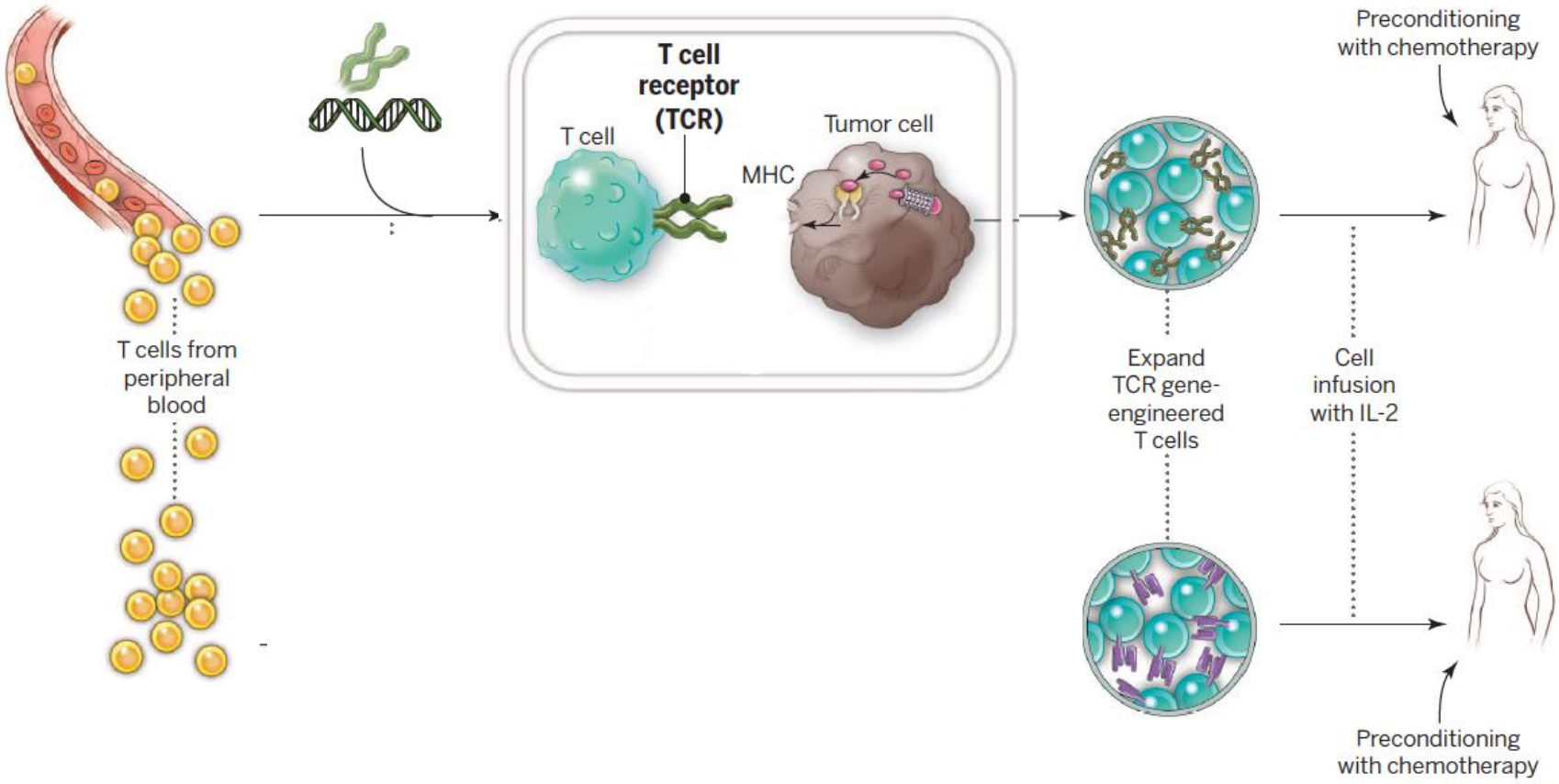





T cell receptor (TCR)
T cell
Tumor cell
MHC
Antigen processed and presented by MHC
T cells from peripheral blood
Expand TCR gene-engineered T cells
Preconditioning with chemotherapy
Cell infusion with IL-2
Preconditioning with chemotherapy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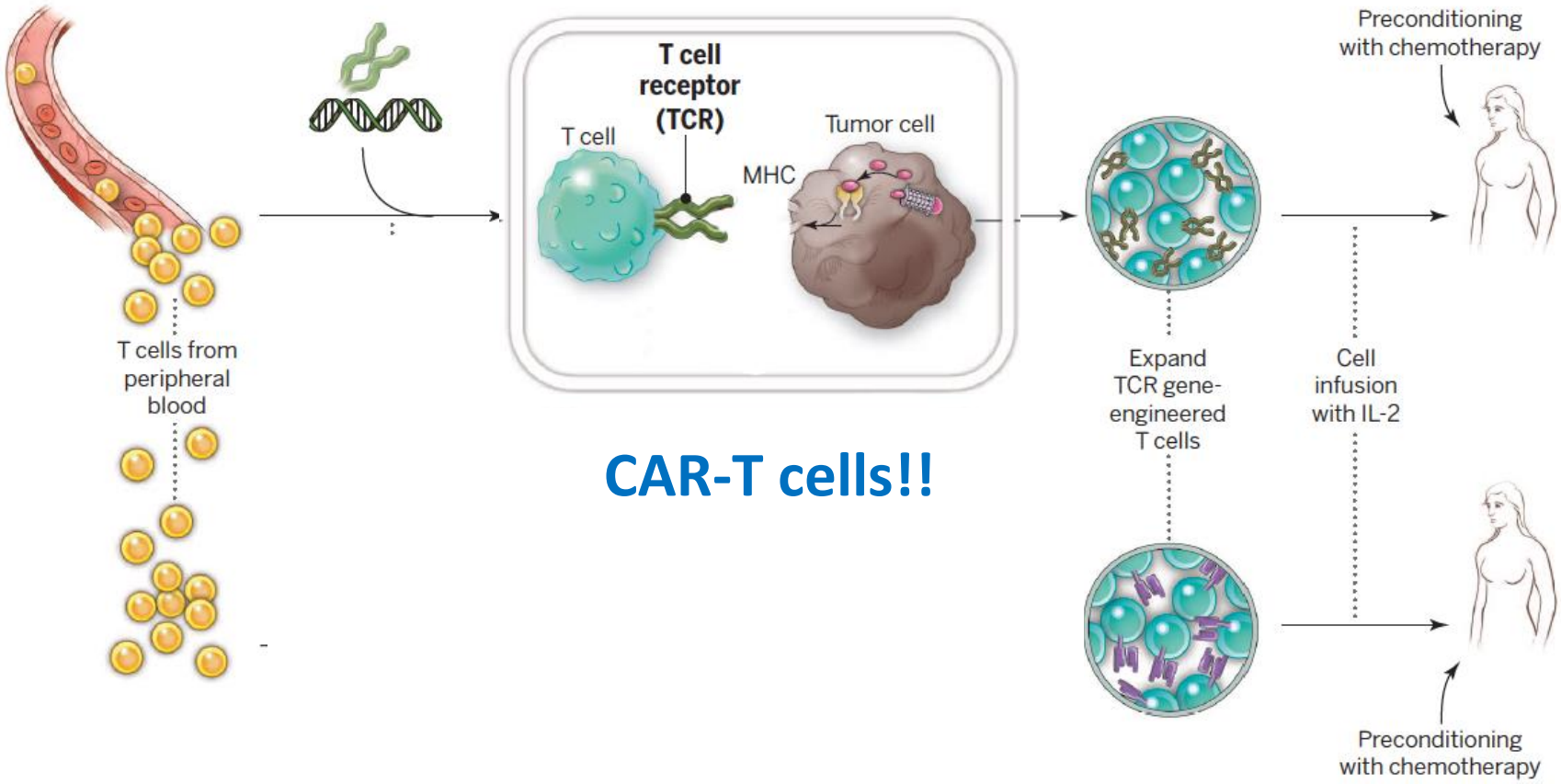
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T cells from peripheral blood
Expand TCR gene-engineered T cells
Cell infusion with IL-2
Preconditioning with chemotherapy

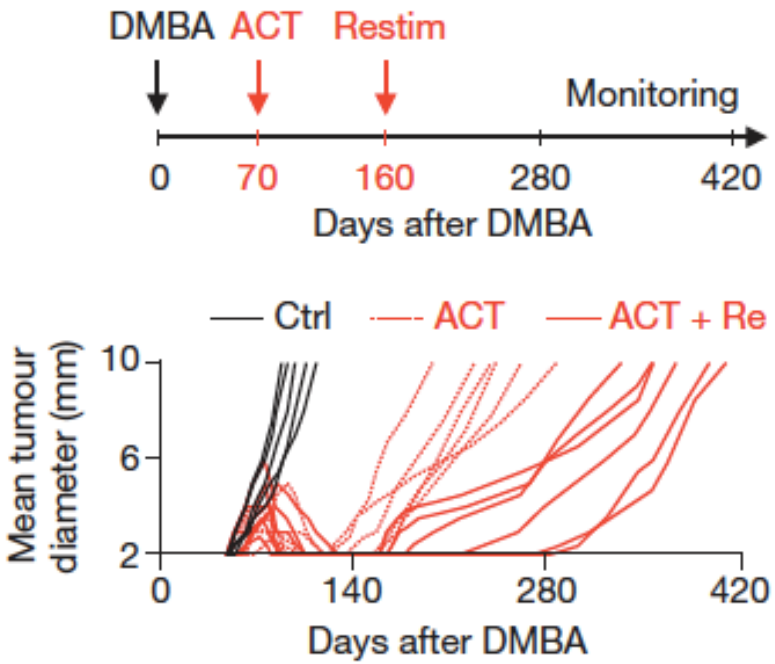
CAR-T cells!!

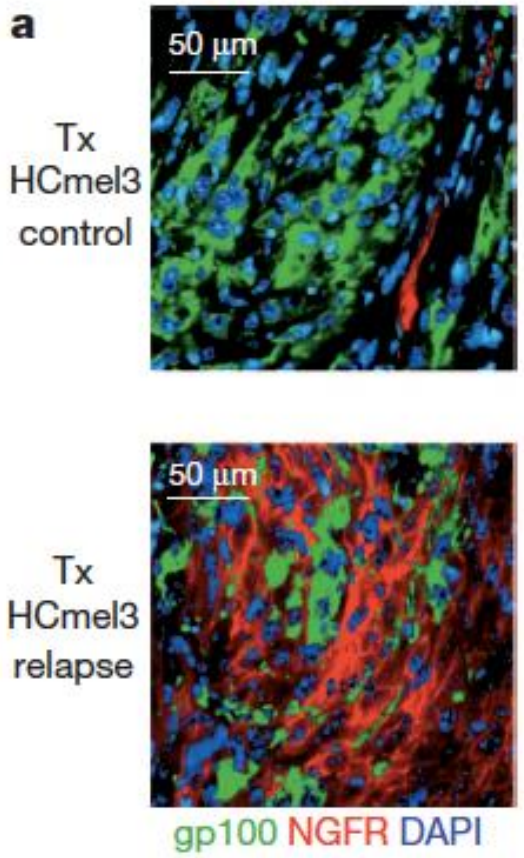
LETTER

doi:10.1038/nature11538

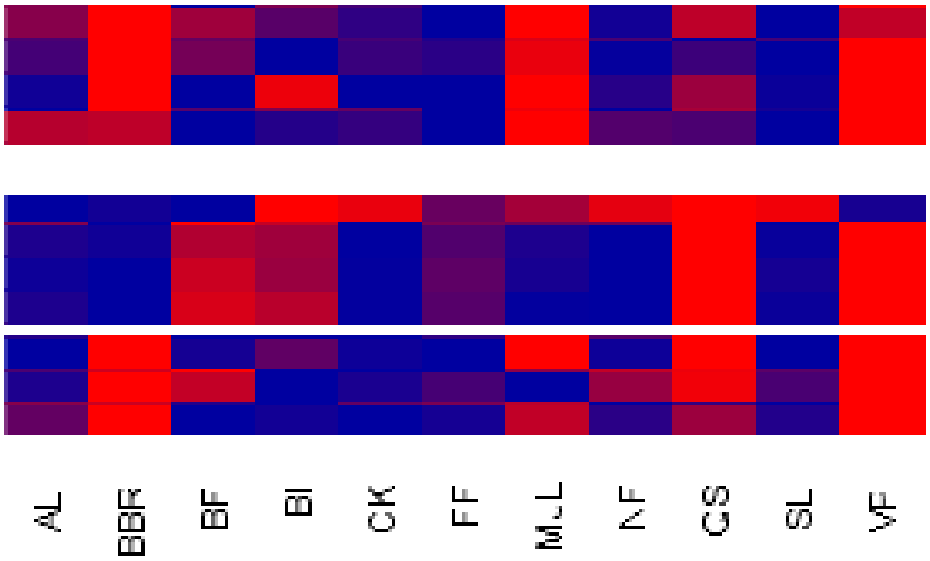
Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation

Jennifer Landsberg[1]*, Judith Kohlmeyer[1]*, Marcel Renn[1]*, Tobias Bald[1], Meri Rogava[1], Mira Cron[1], Martina Fatho[2], Volker Lennerz[2], Thomas Wölfel[2], Michael Hölzel[3] & Thomas Tüting[1]





Th1 response after DC vaccination induces upregulation of melanoma stem cells-associated genes

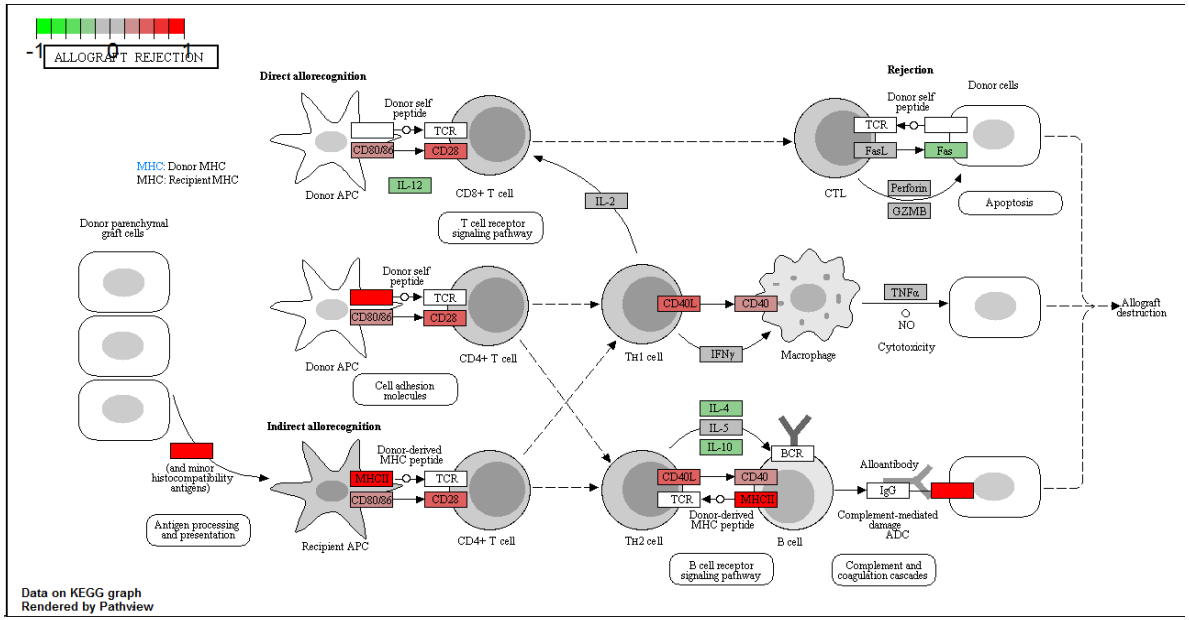


Immune activation related genes

Cancer Testis Antigens

Melanoma stem cells markers

Th1 response after DC vaccination led to upregulation of stemness genes

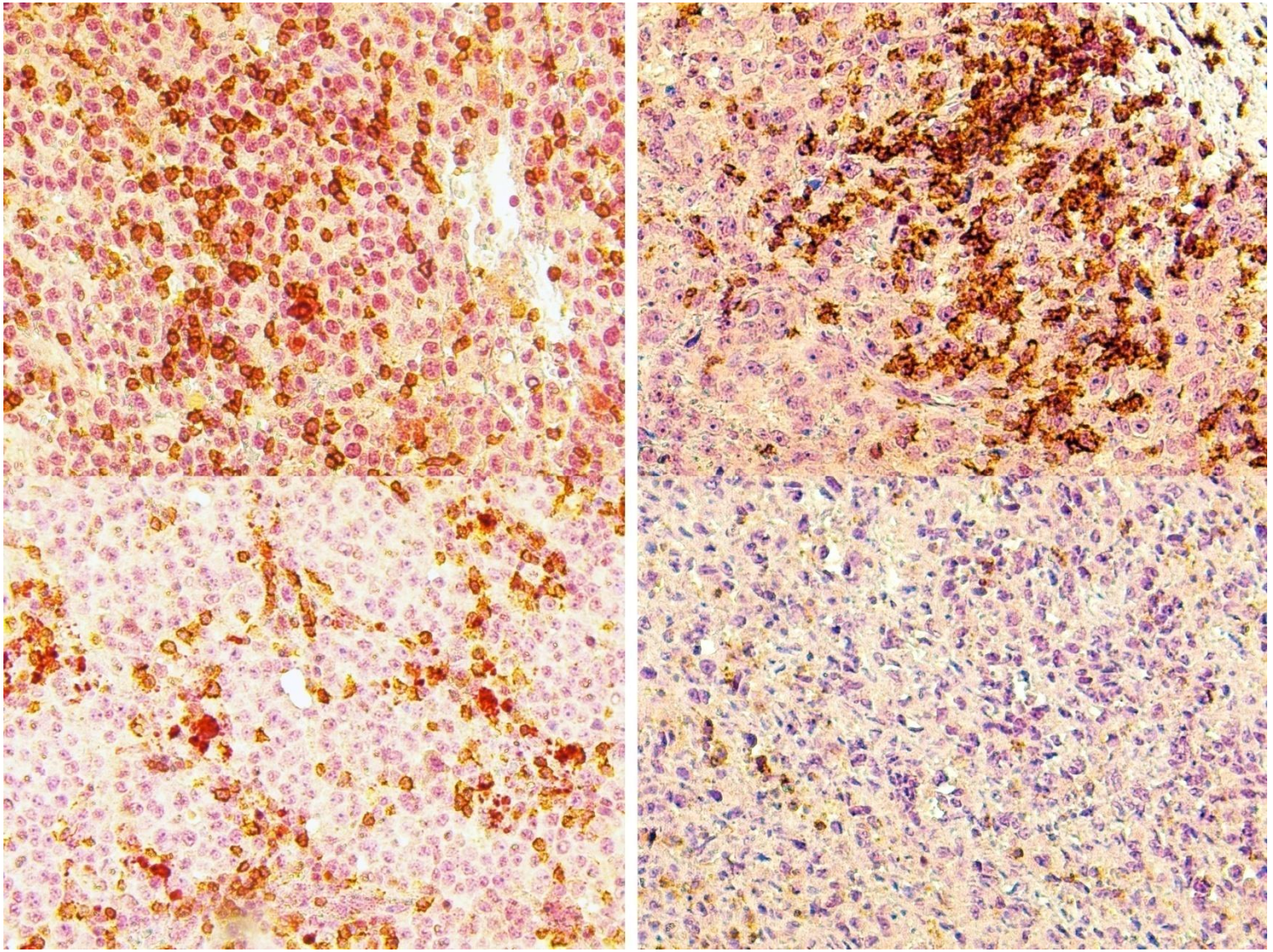


Cell Type	*Set Size*	*Overlapping Genes*	*Pvalue*	*Adjusted Pvalue*
Embryonic Stem cells	3029	54	8.209E-10	7.388E-9
Neural Stem cells	168	1	0.732	1
Hematopoietic Stem cells	969	9	0.342	1
Mammary Stem cells	306	2	0.691	1
Induced pluripotent Stem cells	80	1	0.465	1
Mesenchymal Stem cells	114	1	0.591	1
Embryonal carcinoma	653	7	0.247	0.812

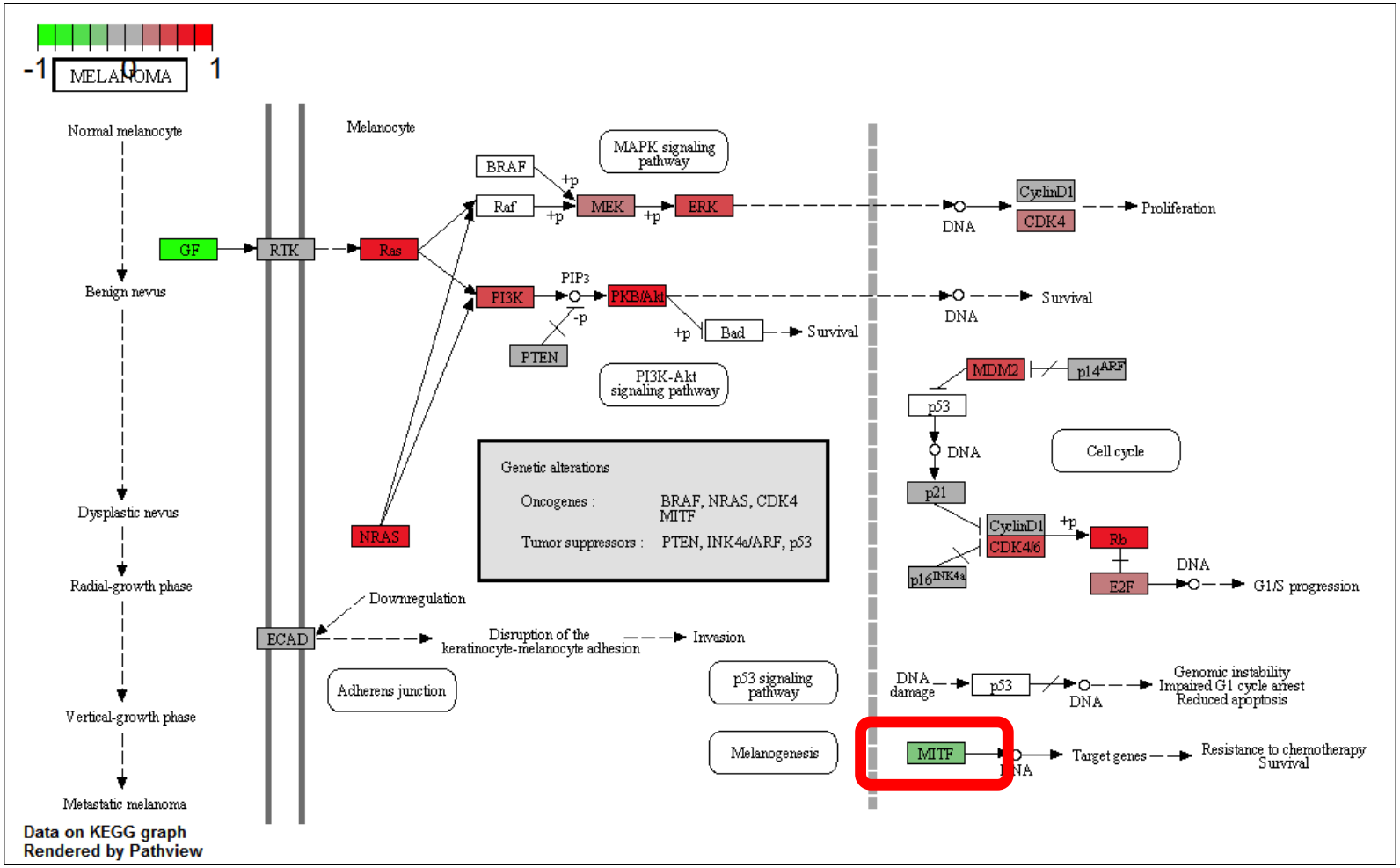
Double stainings CD8 /BMI-1

Prevaccine

Postvaccine



Strong induction of CD8 intratumor immune response shifts tumors from MITF-high/AXL-low to a MITF-low/AXL-high




Thanks for your attention...


Thanks for your patience ...