

Adoptive T-cell Transfer as an Anti-tumor Approach

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Professor of Medicine

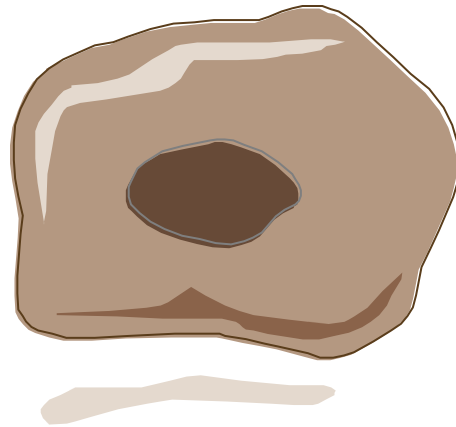
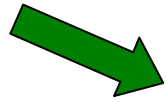
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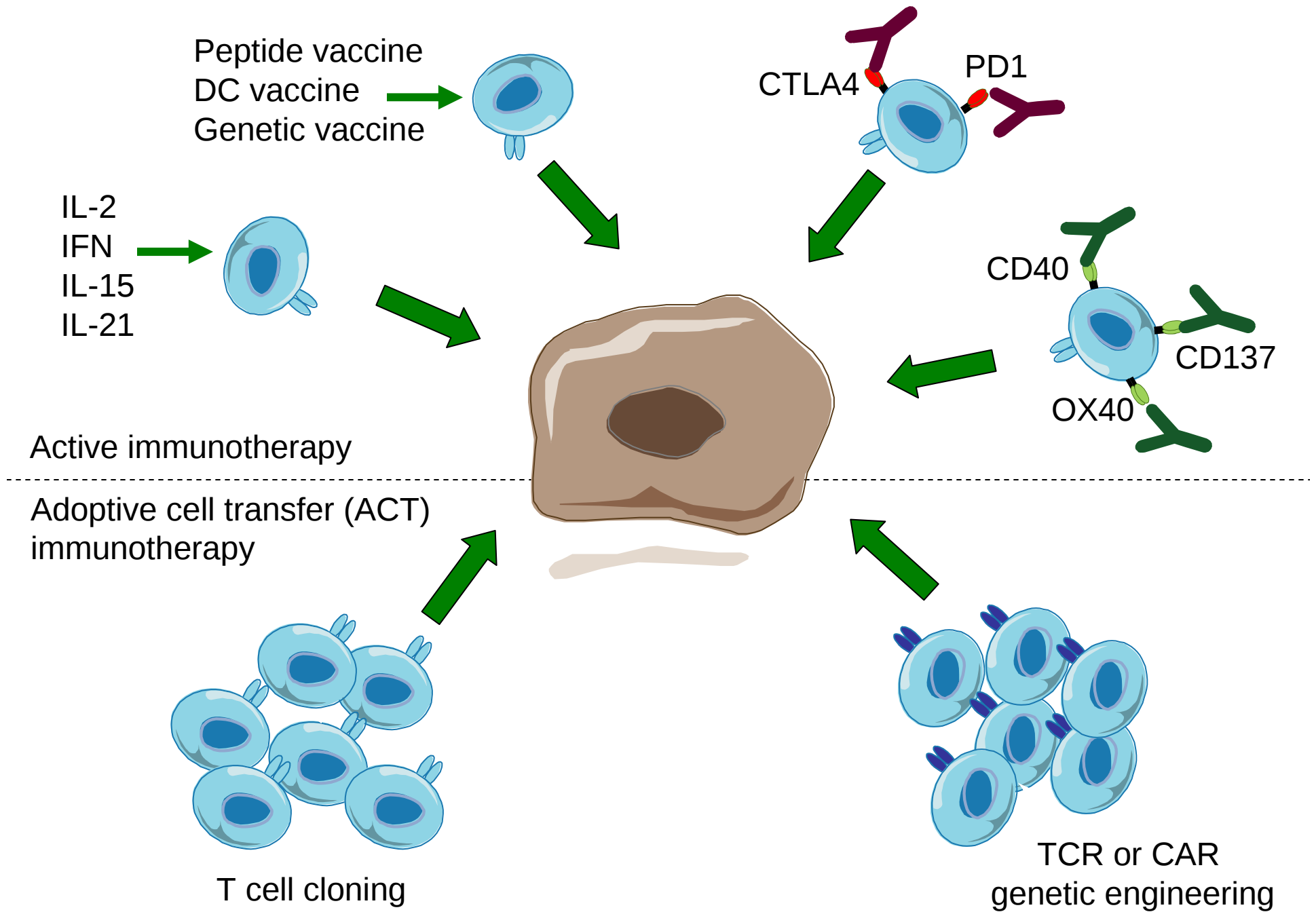
Professor of Molecular and Medical Pharmacology

Director, Tumor Immunology Program, Jonsson
Comprehensive Cancer Center (JCCC)

University of California Los Angeles (UCLA)

Chair, Melanoma Committee at SWOG





Immunotherapy for melanoma

Active immunotherapy

- Cytokines:
 - IL-2
- Antibodies:
 - anti-CTLA4
 - (anti-PD-1/L1)

General clinical effects:

- Low frequency of tumor responses
- Highly durable
- IL-2: Limited by short-term toxicities
- Anti-CTLA4: Limited by mid-term autoimmune toxicities

Adoptive cell transfer (ACT)

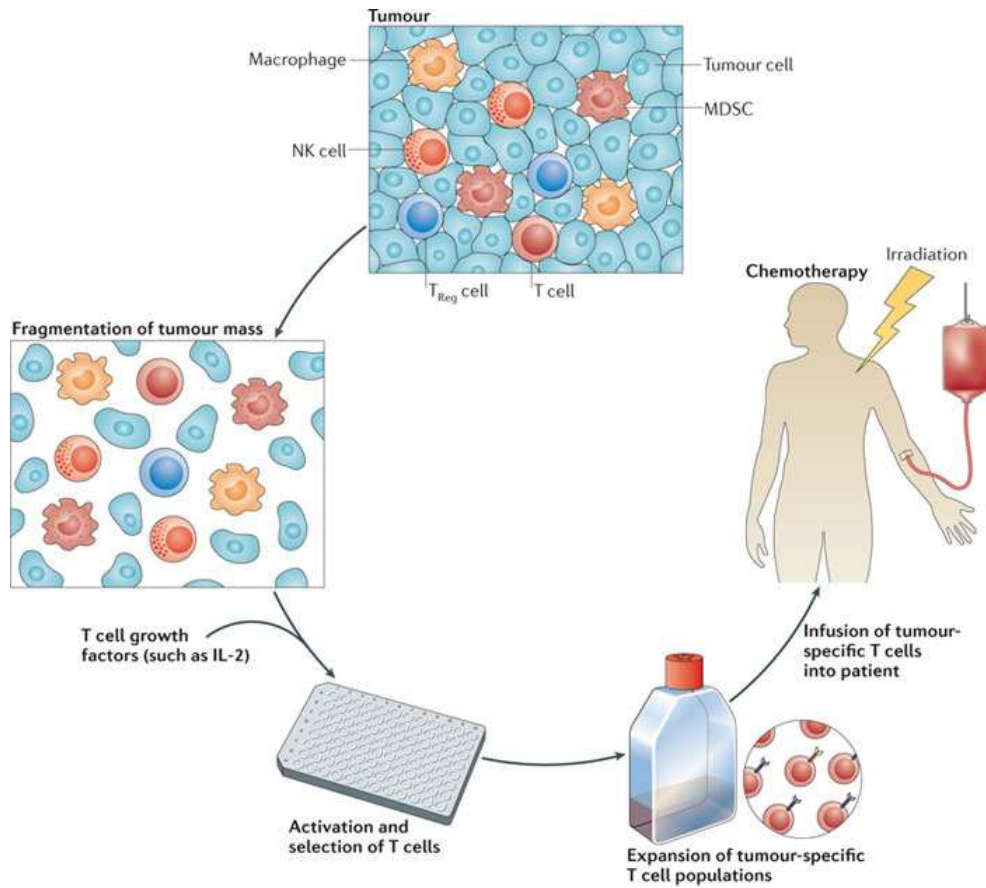
- T cell cloning:
 - From blood
 - From tumors: TIL
- T cell genetic engineering:
 - T cell receptors (TCR)
 - Chimeric antigen receptors (CAR)

- High frequency of tumor responses
- Variable durability
- Limited by requirements of preparative conditioning and IL-2

History of adoptive T-cell therapy

- 80-ties: Lymphokine activated killer cells (LAK) + IL-2 (Mule et al., Science 1984)
 - *In vitro* no cytolytic antitumor activity of LAK
 - *In vivo* not superior over HD IL-2 alone
- 90-ties: Tumor-infiltrating lymphocytes (Rosenberg et al., JNCI 1994)
 - 86 pts treated; combined with HD IL-2; 2 cycles
 - RR not different from HD-IL-2 alone
 - No persistence of transferred T cells (0.1% one week after ACT)

ACT with TIL



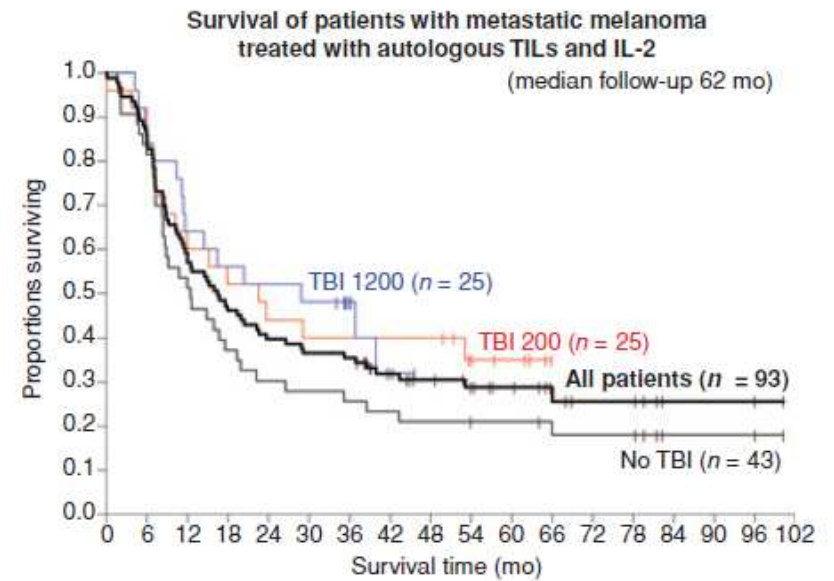
Cancer Therapy: Clinical

See commentary by Heslop, p. 4189

Clinical
Cancer
Research

Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy

Steven A. Rosenberg¹, James C. Yang¹, Richard M. Sherry¹, Udai S. Kammula¹, Marybeth S. Hughes¹, Giao Q. Phan¹, Deborah E. Citrin², Nicholas P. Restifo¹, Paul F. Robbins¹, John R. Wunderlich¹, Kathleen E. Morton¹, Carolyn M. Laurencot¹, Seth M. Steinberg³, Donald E. White¹, and Mark E. Dudley¹

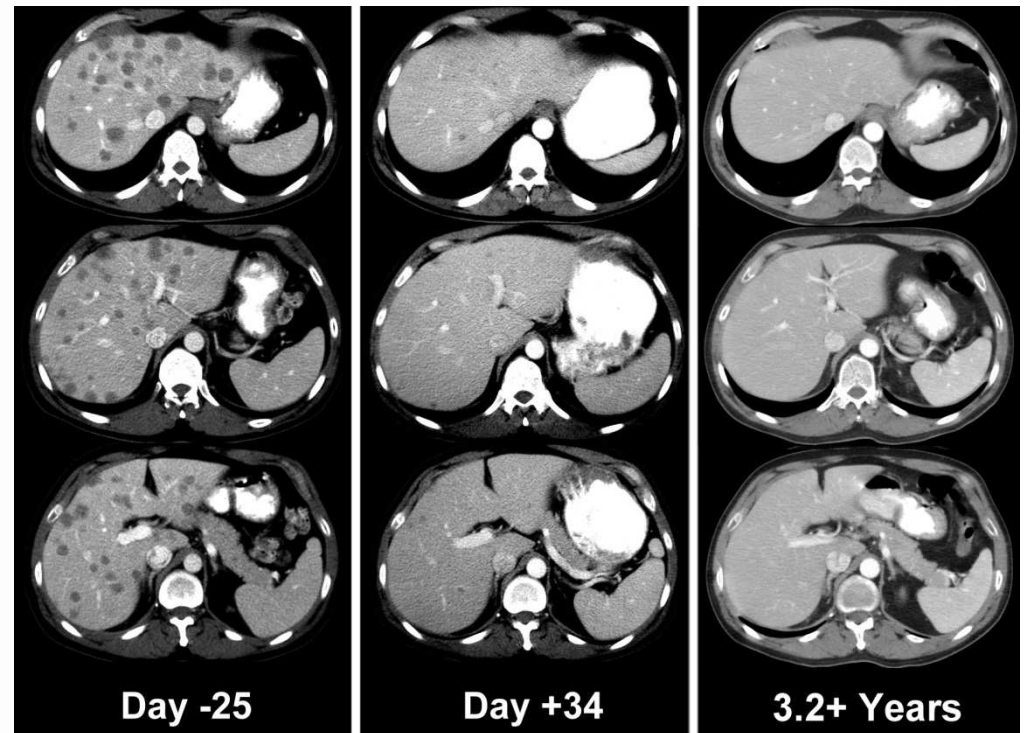


Adoptive immunotherapy for cancer: harnessing the T cell response

Nicholas P. Restifo, Mark E. Dudley and Steven A. Rosenberg

Nature Reviews | Immunology
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Clinical effectiveness of TIL therapy in melanoma

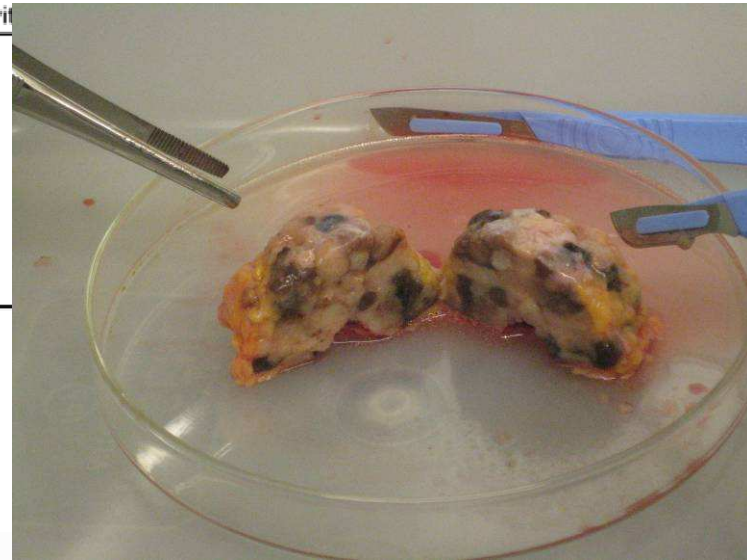
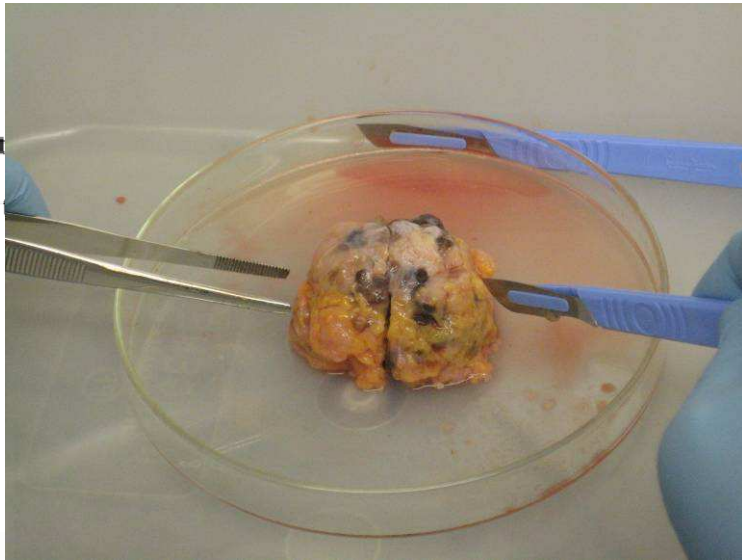


Dudley ME et al., JCO 2005

Production of TIL for melanoma patients at the NKI-AVL

Metastat

Primary

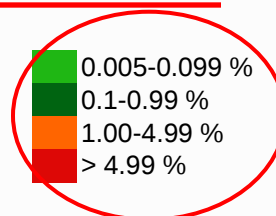


Open questions regarding TIL

1. Is high dose IL-2 required?
 - Danish TIL protocol: low dose IL-2
 - NIH: RCT TIL +/- HD IL-2
2. Which T cells confer tumor regression?
3. How does TIL compare to other treatments (ITT)

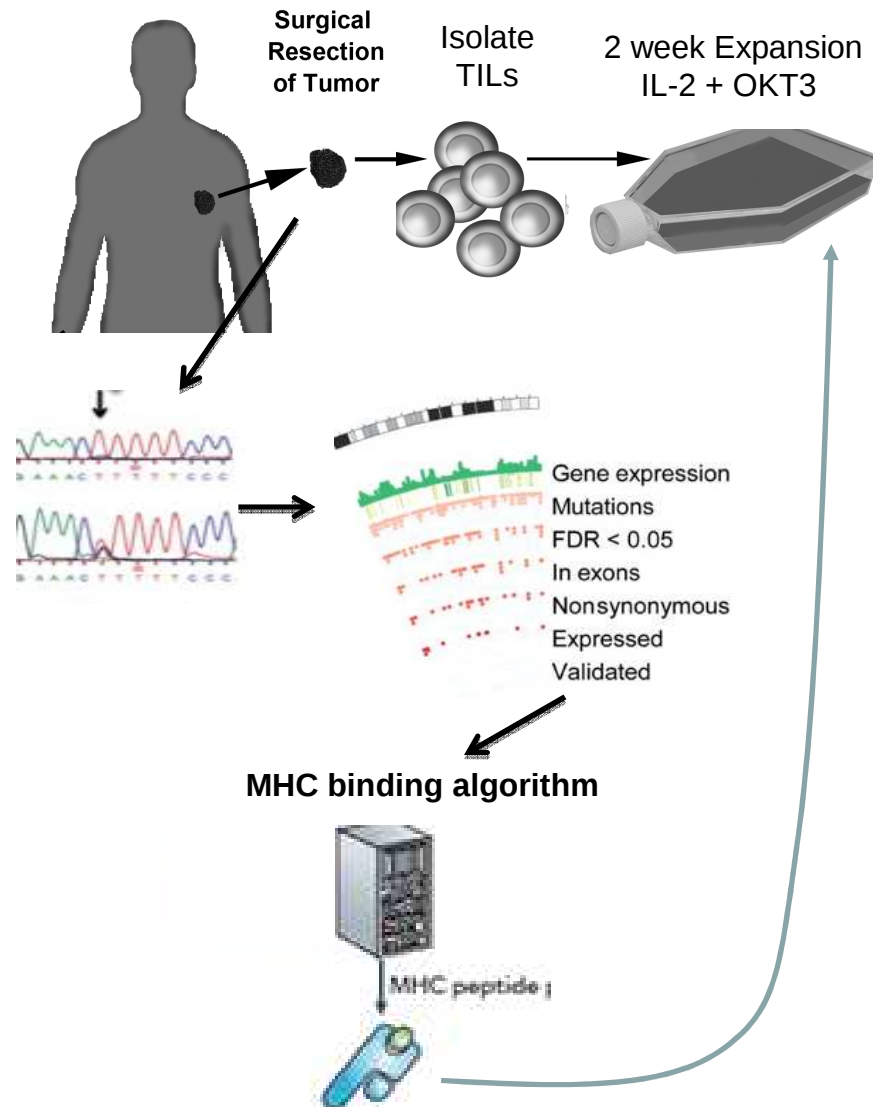
Visualizing the composition of TIL

T cell responses are very low magnitude



		Young CD8 enriched TIL (NIH)																	Young TIL (Ella)						Selected TIL													
Patient		LR	LN	KS	MV	CR	ER	MA	LD	SW	HE	AS	RE	OJ	AS	MG	NJ	BJ(f)*	SC*	57SV	63SM	51VS	60SD	41BA	52SD	14PA	09BY	31YR	PS	OM	Bj(m)	SM	ER	CR	BM	CJ	AD	
MDA	Mart-1 _{ELA}																																					
	gp100 _{IMD}																																					
	gp100 _{YLE}																																					
	gp100 _{VLY}																																					
	gp100 _{AML}																																					
	gp100 _{KTW}																																					
	TRP2 _{VYD}																																					
	TRP2 _{SVY}																																					
NY-MEL 1 _{VLH}																																						
CT	CML28 _{AVL}																																					
	Mage A4 _{GVY}																																					
	MAGE A10 _{GLY}																																					
	MageB1, B2 _{FLW}																																					
	MAGE C2 _{LLF}																																					
	MAGE C2 _{ALK}																																					
	NY-ESO 1 _{SLL}																																					
	HERV K mel _{MLA}																																					
OE	SSX-2 _{KAS}																																					
	GnTV _{VLP}																																					
	GnT-V _{VLP10mer}																																					
	Meloe-1 _{TLN}																																					
	Telomerase _{RLF}																																					
	Bing 4 _{COW}																																					
Clinical response		NR	NR	NR	PR	PR	NR	NR	PR	PR	PR	NR	NR	NR	NR	PR	NR	NR	CR	PR	NR	PR	NR	NR	PR	CR	NR	NR	PR	PR	CR	PR	PR	NR	NR	CR	NR	

Frequent TIL recognition of neoepitopes from cancer somatic mutations



nature
medicine

Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells

Paul F Robbins¹, Yong-Chen Lu¹, Mona El-Gamil¹, Yong F Li¹, Colin Gross¹, Jared Gartner², Jimmy C Lin³, Jamie K Teer^{4,5}, Paul Clifton³, Eric Tycksen³, Yardena Samuels^{2,5} & Steven A Rosenberg¹

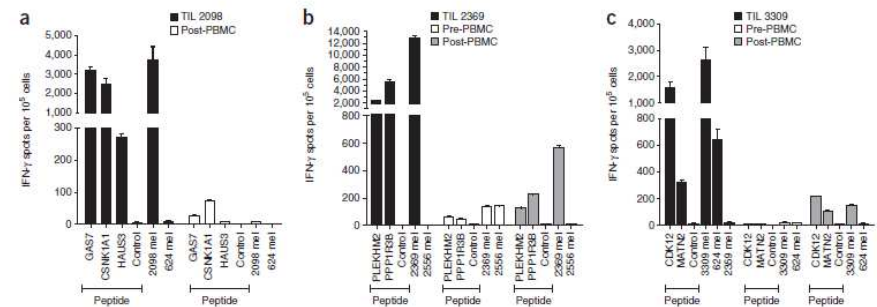
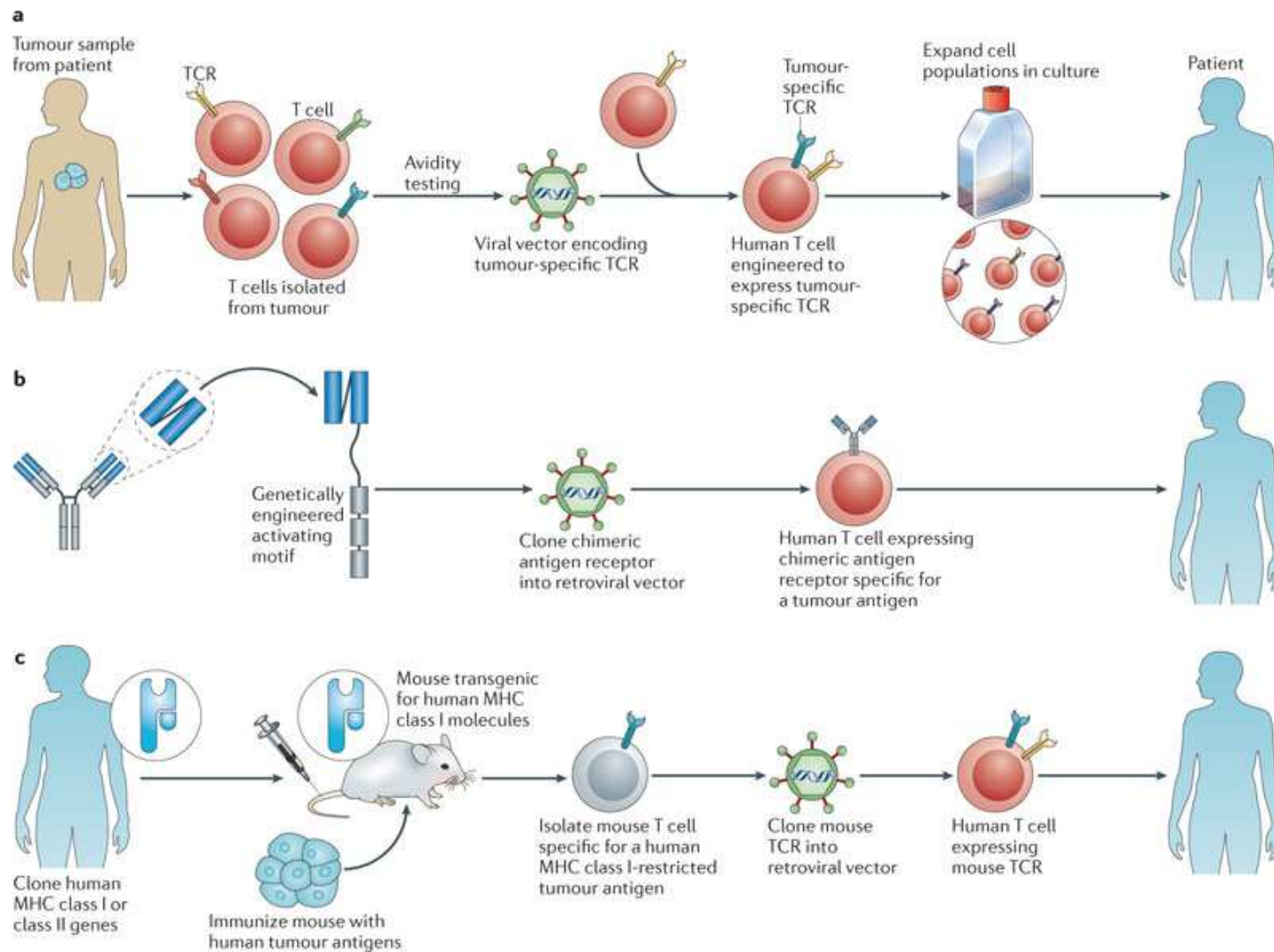


Figure 4 IFN-γ ELISPOT responses of TIL and PBMCs obtained before and after autologous TIL transfer. (a–c) IFN-γ spots per 10⁵ cells of TIL 2098 from subject 1 cultured with HLA-A*0201-positive COS-7 cells (a), TIL 2369 from subject 2 cultured with HLA-A*0101-positive COS-7 cells (b) and TIL 3309 from subject 3 cultured with HLA-A*1101-positive COS-7 cells (c). Pre-PBMC, PBMCs obtained before transfer; post-PBMC, PBMCs obtained after transfer. Data are shown as the mean ± s.e.m. of three replicate wells per group. Control groups represented cells that were not pulsed with exogenous peptides.

ACT with Genetically Modified Lymphocytes



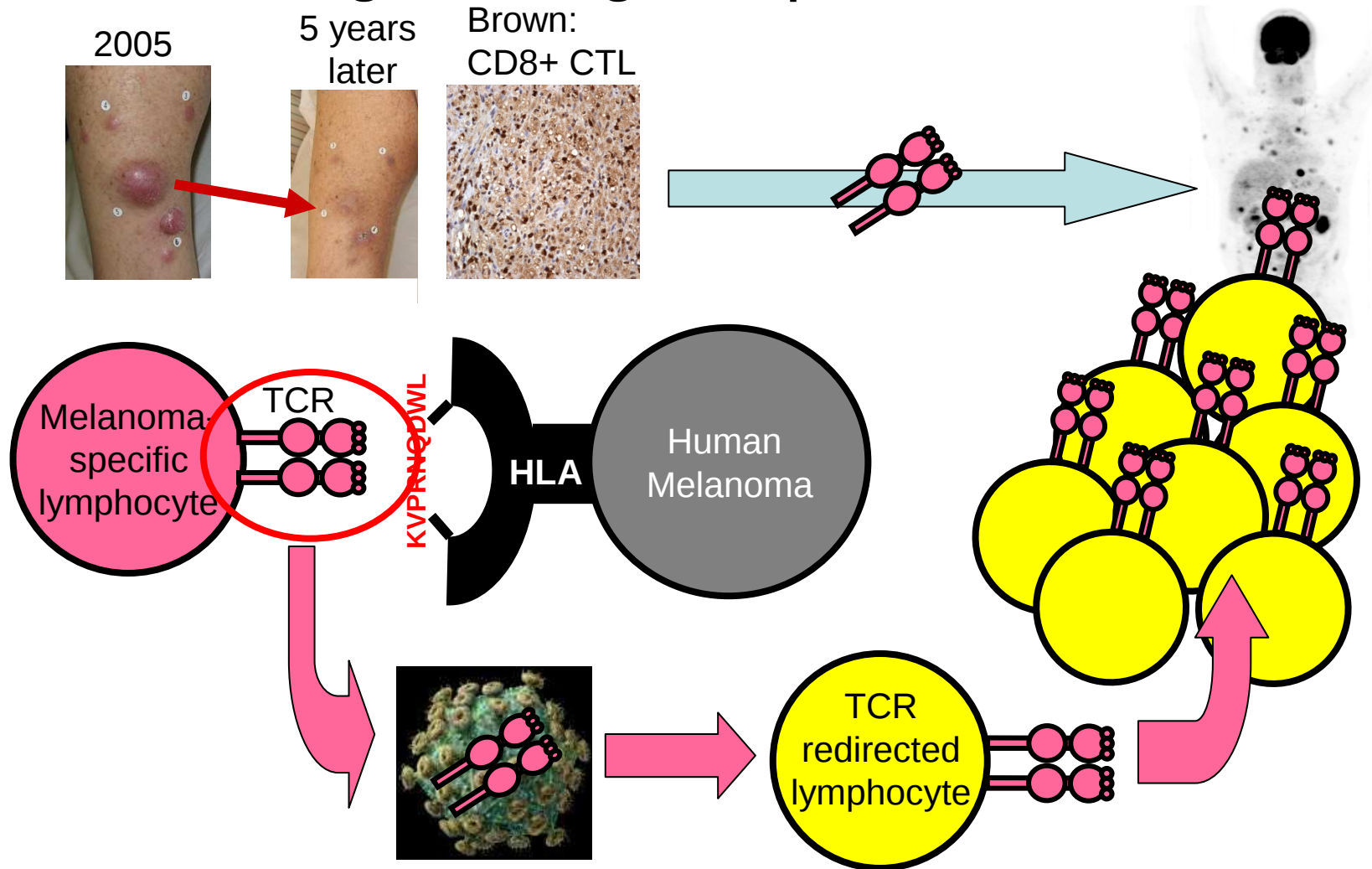
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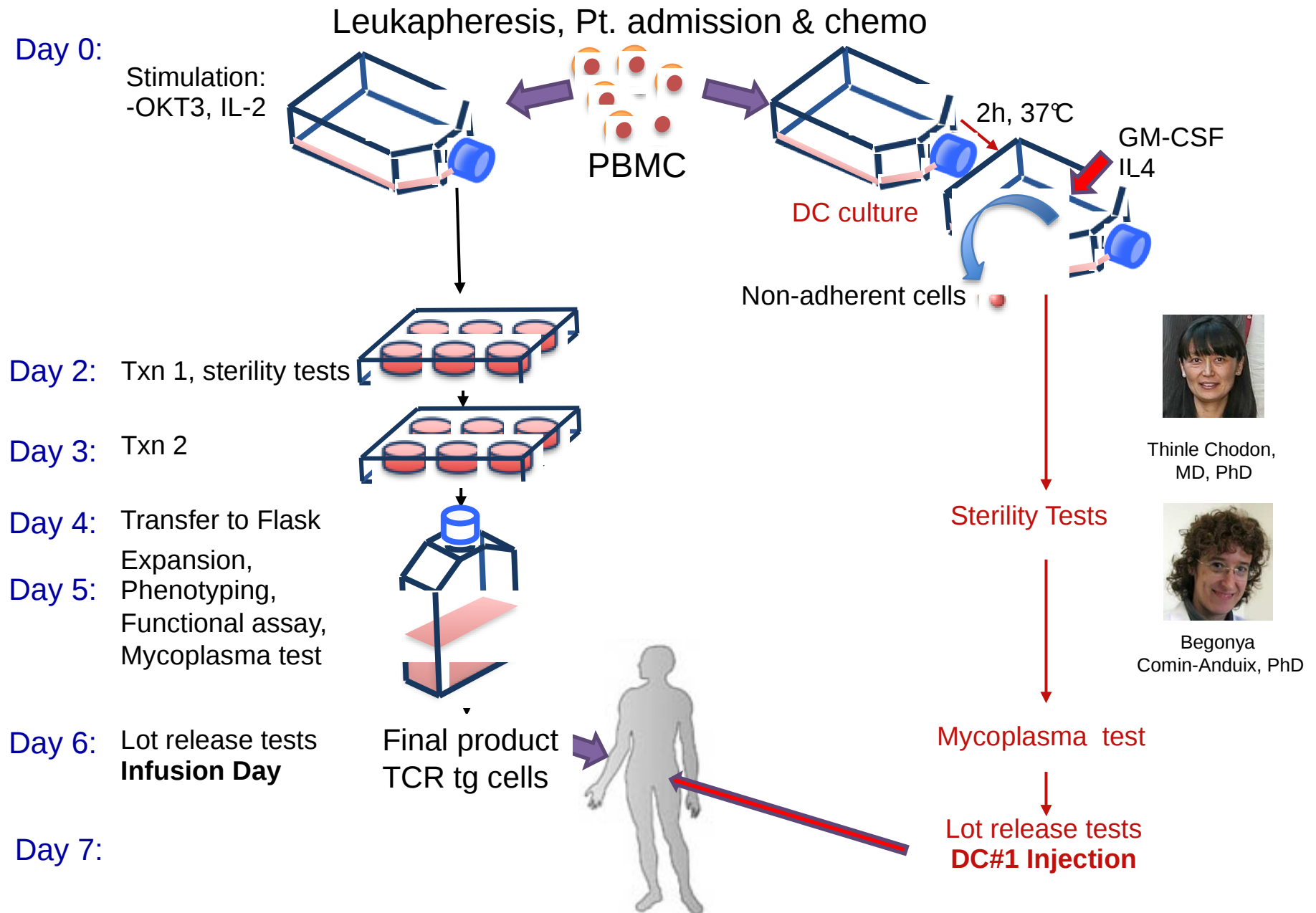
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TCR Engineering Adoptive Cell Transfer



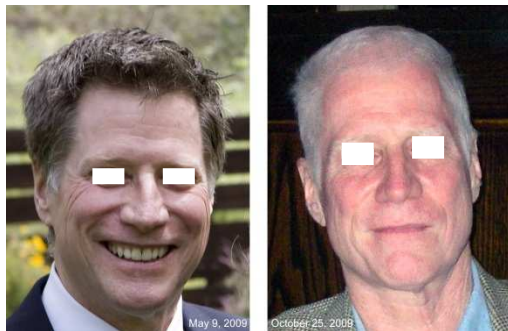
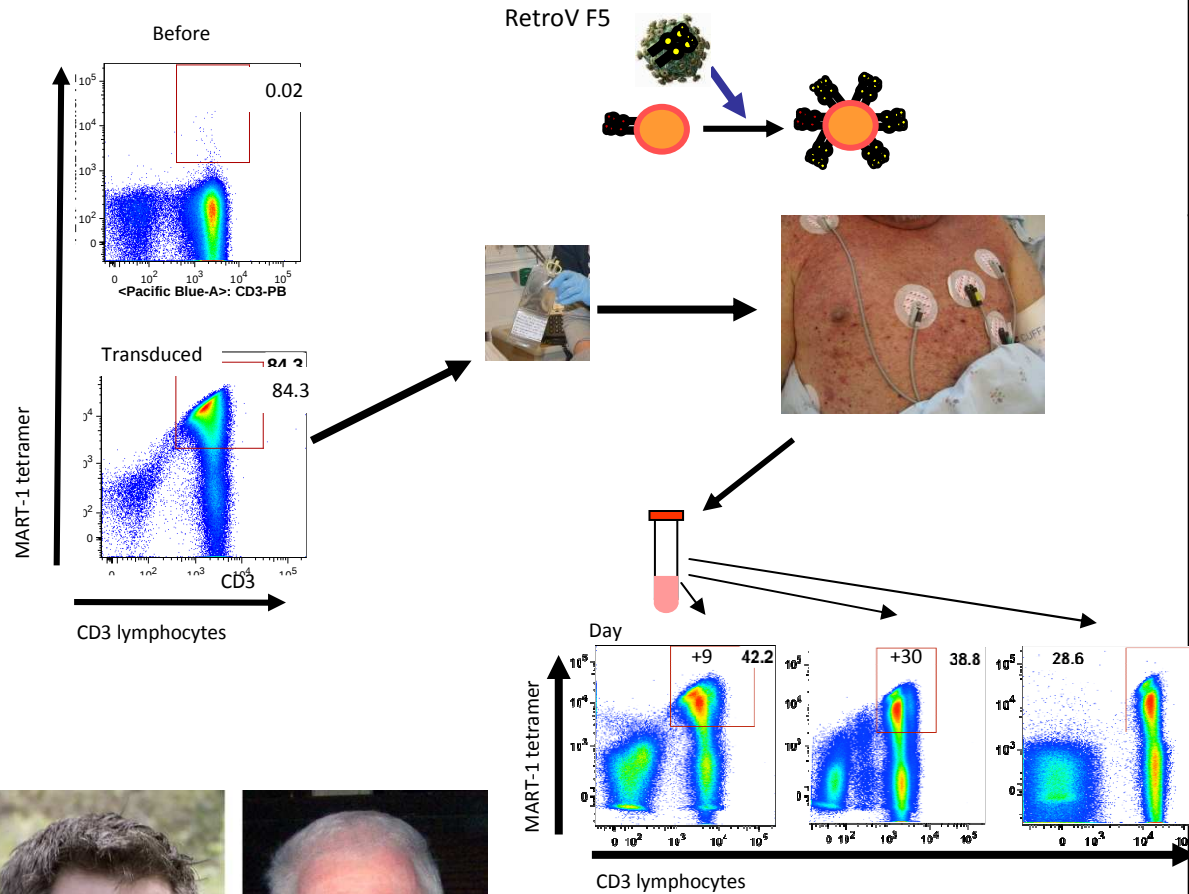
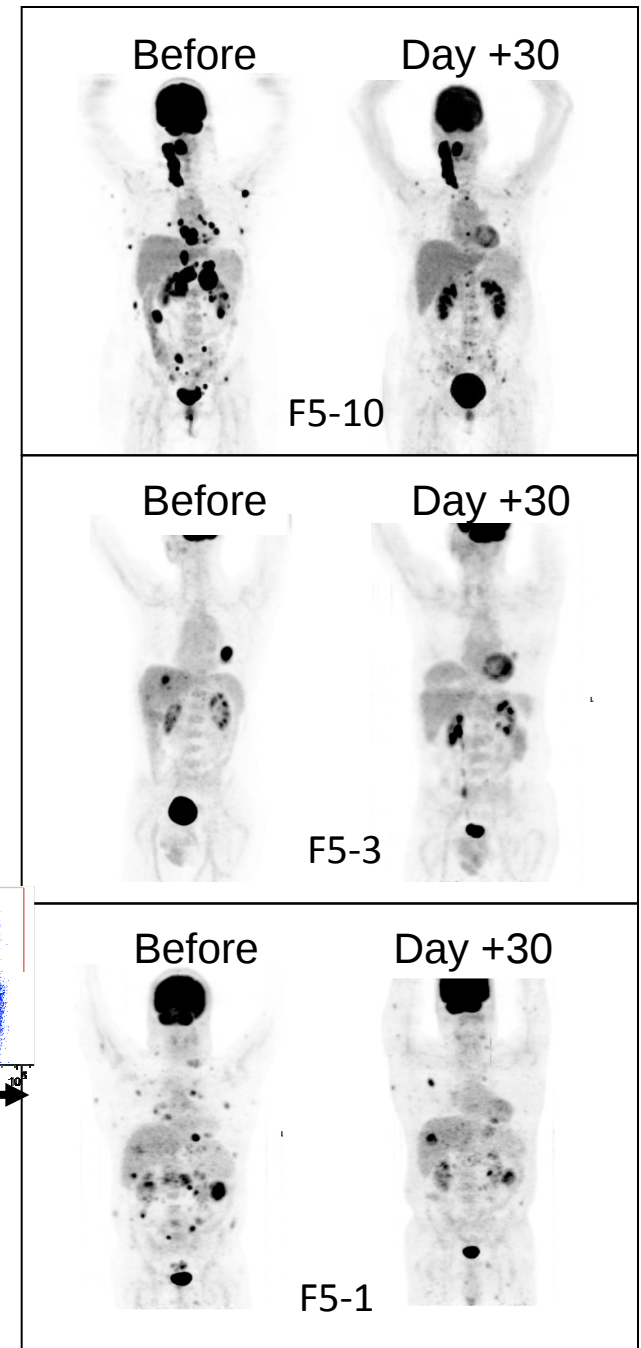
Take the TCR genes from one patient who beat melanoma and use them to engineer a melanoma-fighting immune system in other patients

Schematic of the manufacture of TCR transgenic lymphocytes and DC vaccines



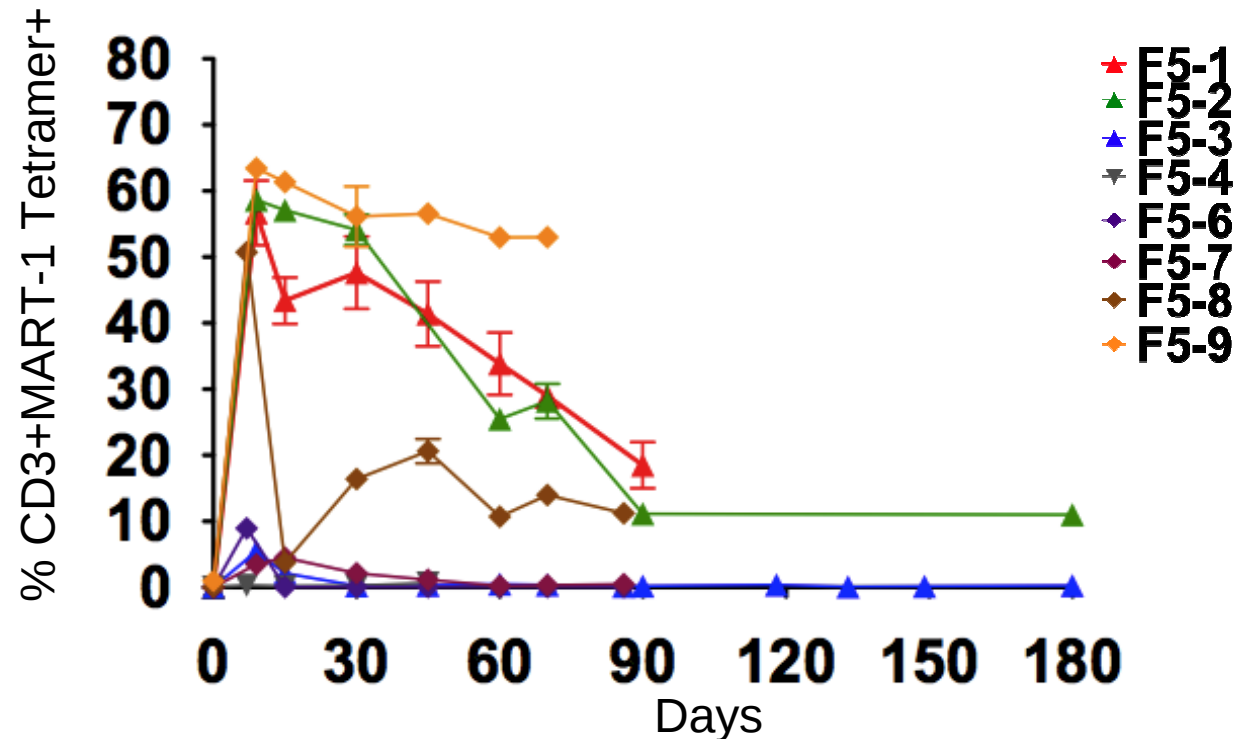
UCLA/Caltech Engineered Immunity Program

TCR engineered adoptive cell transfer therapy

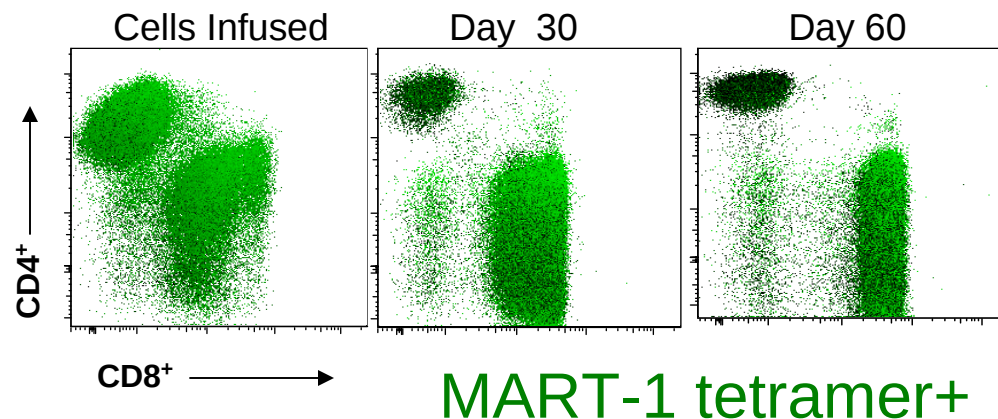


Decrease in frequency of TCR transgenic cells, in particular CD4+, after ACT

Decrease in the frequency of TCR transgenic cells among total T cells



Decrease in CD4+ T cells with the transgenic TCR compared to CD8+ T cells



Conclusions

- Adoptive cell transfer with tumor infiltrating lymphocytes results in relatively high initial antitumor activity and durable tumor responses in a subset of patients
- Fully functional clinical grade genetically modified TCR transgenic lymphocytes can be manufactured at GMP compliance and administered within one week
- TCR transgenic adoptive cell transfer results in high initial antitumor regressions
- Tumors relapse as TCR transgenic cells decrease in frequency and function in blood



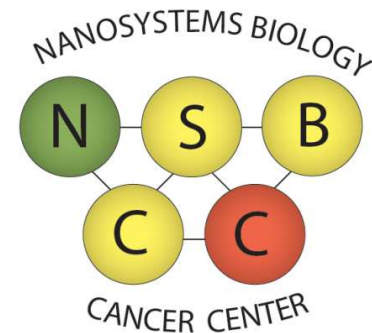
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Joint Center for
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Melanoma
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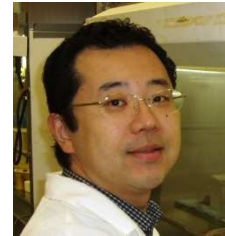
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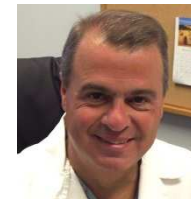


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