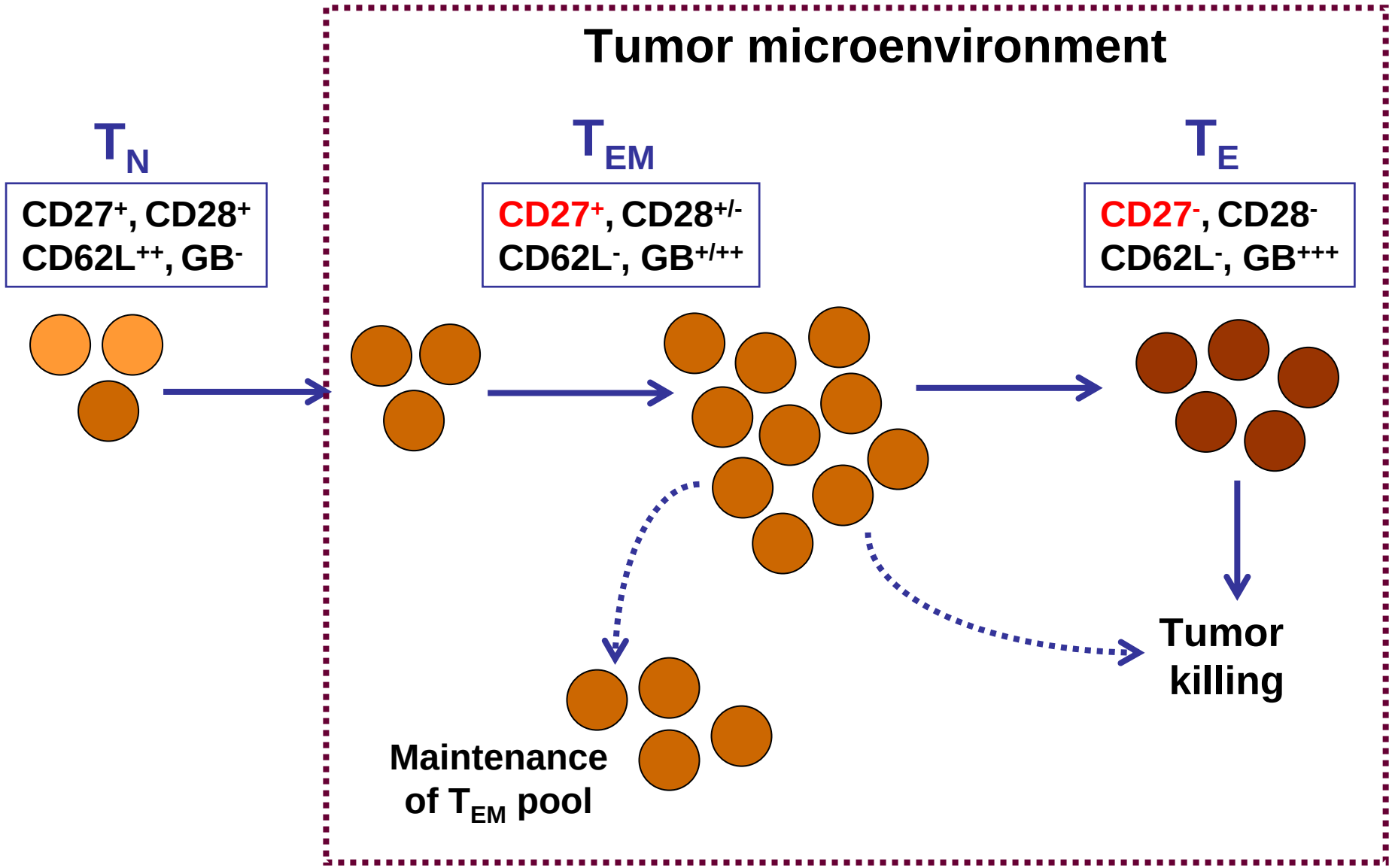
Maintenance of CD27^{+} Effector Memory T Cells During *ex vivo* Expansion of Melanoma TIL for Adoptive T-cell Therapy

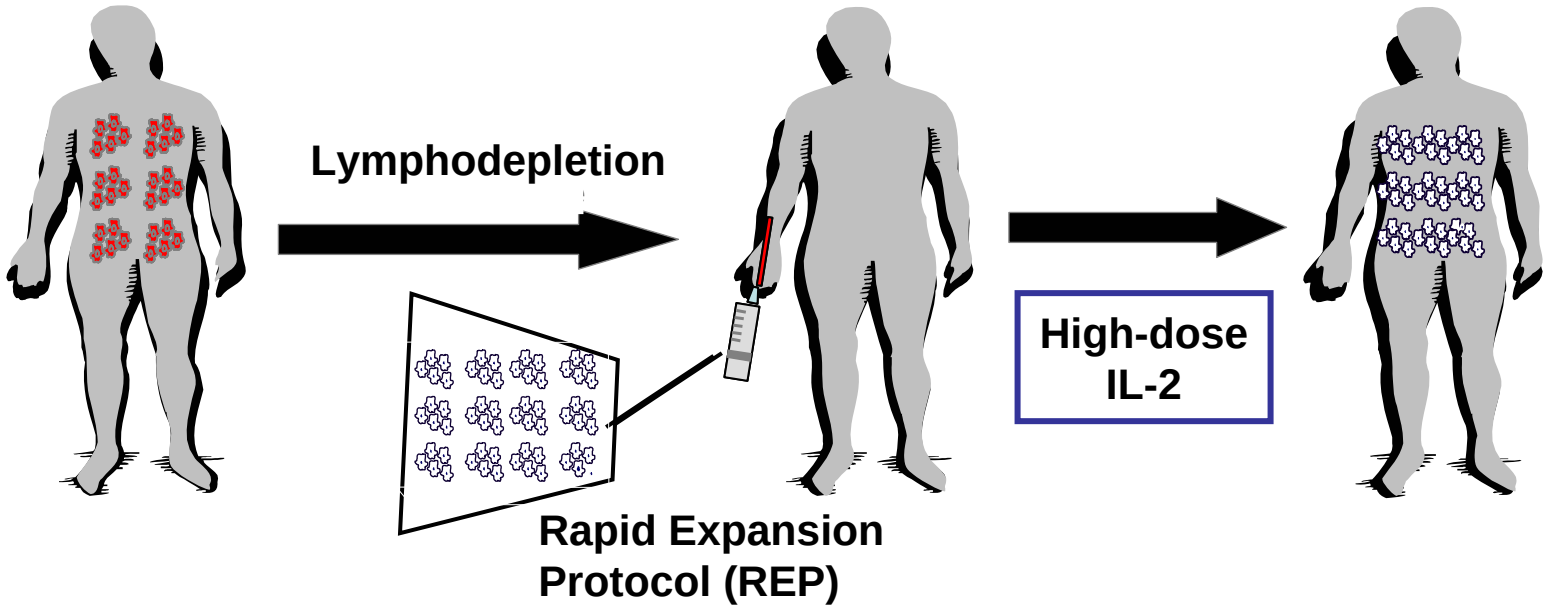
Yufeng Li

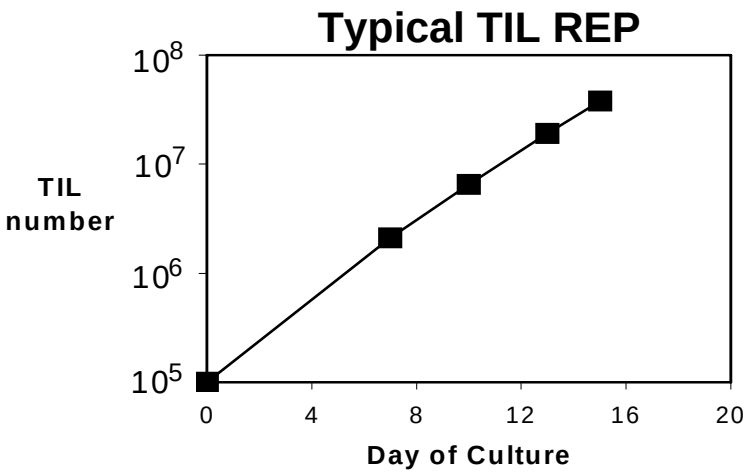
The University of Texas
M. D. Anderson Cancer Center
Dept of Melanoma Medical Oncology

$CD8^+$ T-cell differentiation: T-effector memory → T-effector transition



Adoptive Cell Therapy (ACT): Current State-of-the-Art





- anti-CD3 Ab + IL-2 + allogeneic feeders
- 500X to 1000X expansion
- 5 to 100 billion cells infused
- The more cells infused the better the CR

Clinical efficacy of metastatic melanoma treatment with adoptive cell therapy

# Patients enrolled	CR	PR	Total
35	4	14	18 (51%)

11%

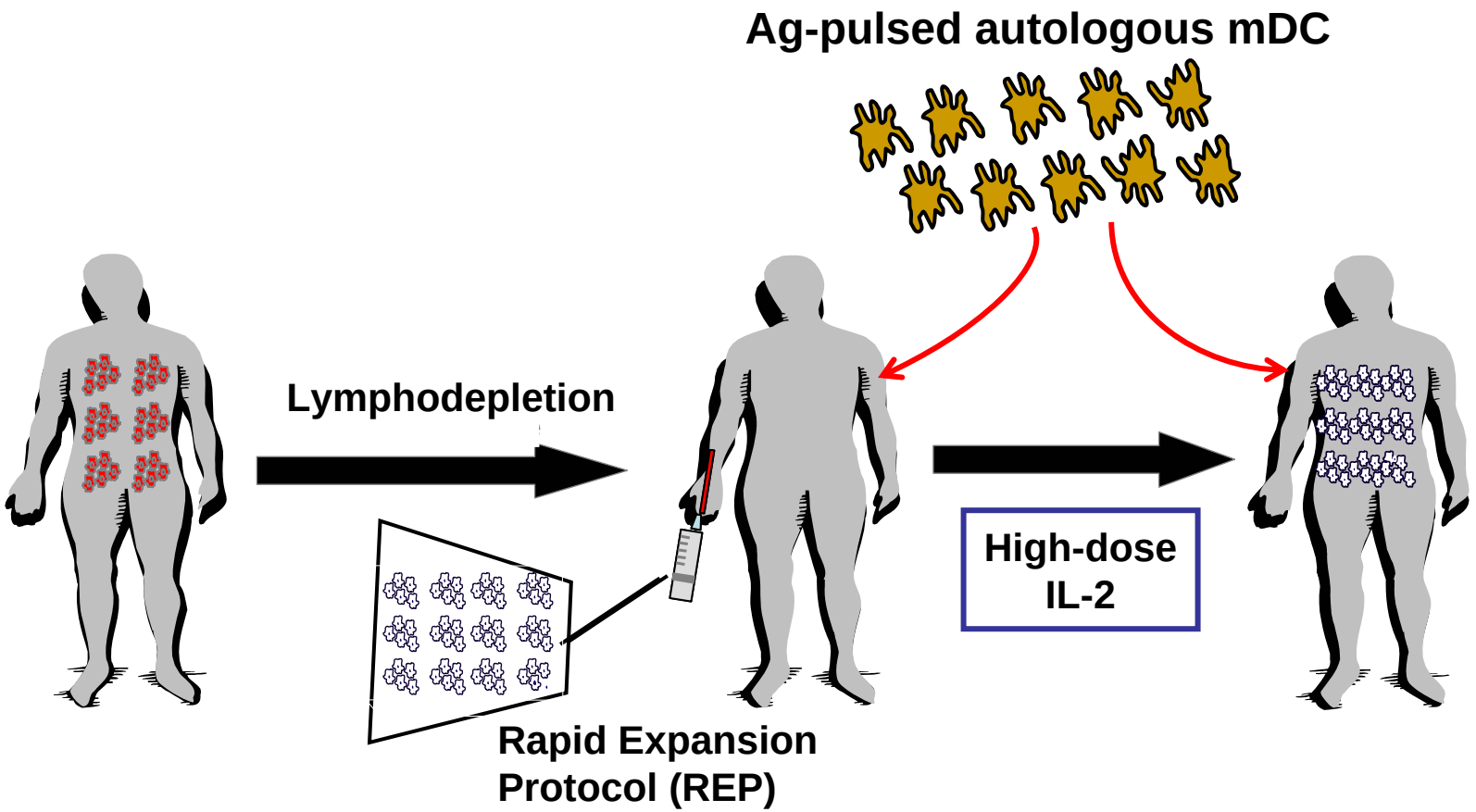
Dudley et al, J Clin Oncol 2005 April; 23(10):2346-57

Current Issues with ACT in Melanoma

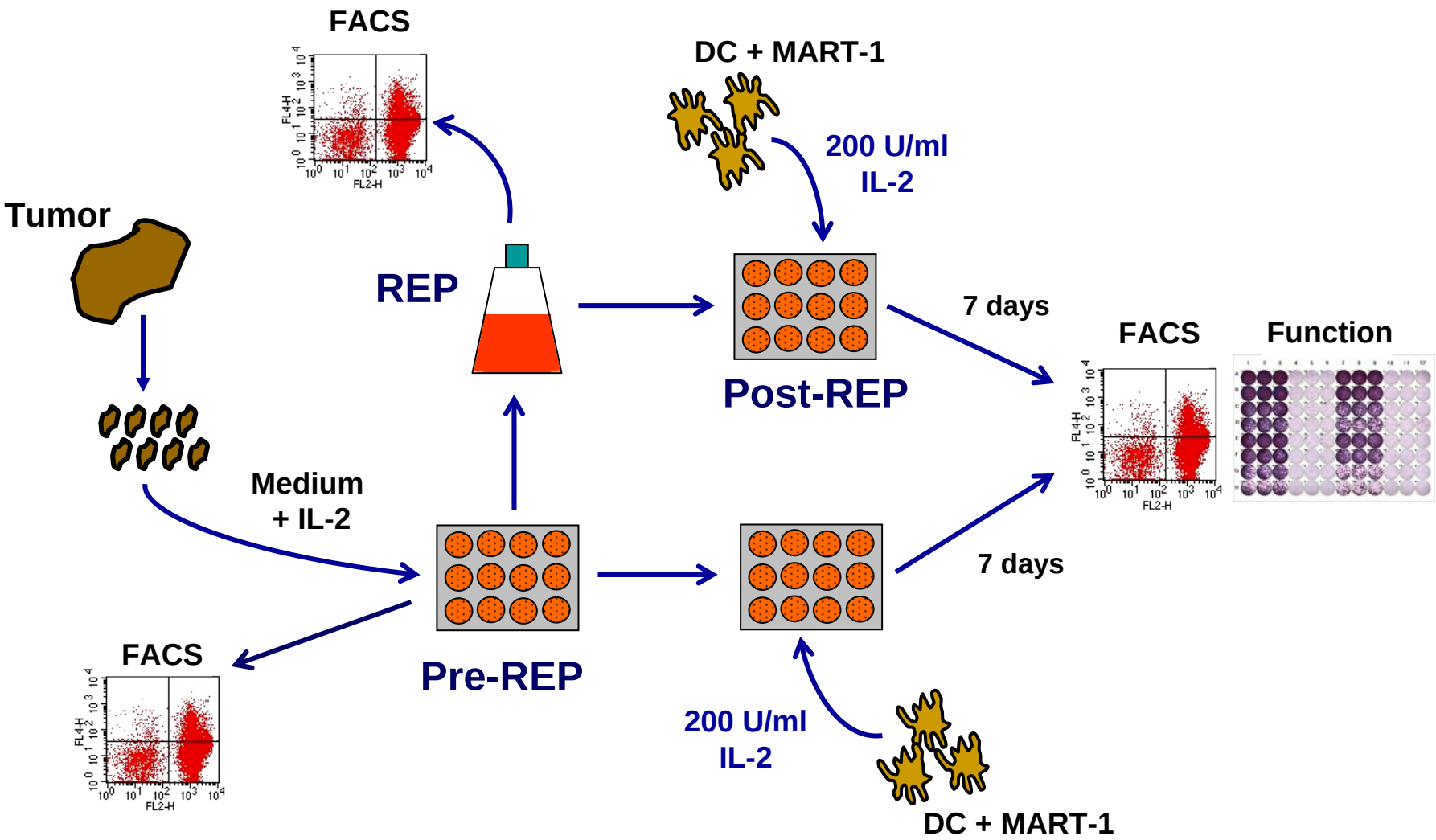
1. Rapid Expansion Protocol (REP)
2. Choice of cytokine co-therapy

- **Need for large cell numbers: (>10 billion for CR) → WHY?**
- **Cell expansion during REP may negatively affect ability of cells to respond to Ag re-stimulation *in vivo*.**
- **Little is known on TIL phenotypes and how they further differentiate and persist following melanoma Ag contact.**
- **Is IL-2 the best cytokine to work with?**

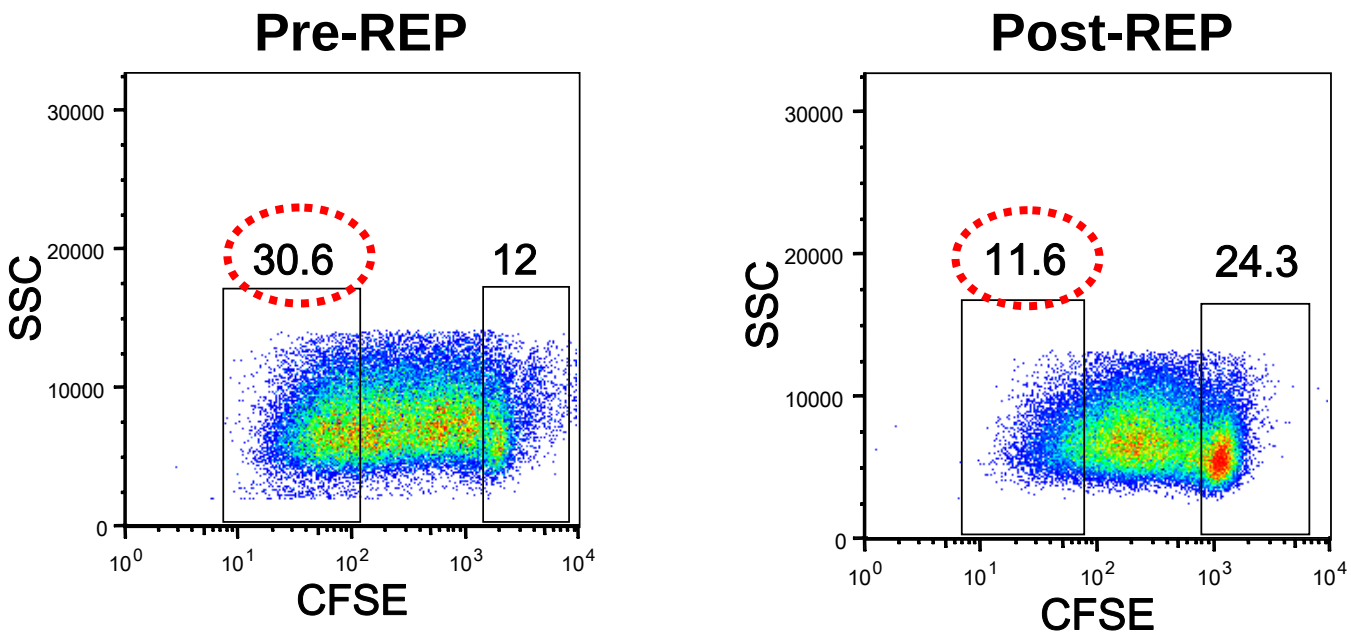
Adoptive Cell Therapy (ACT): DC co-vaccination



Stimulation of Pre-REP and Post-REP TIL with Peptide-pulsed Mature DC

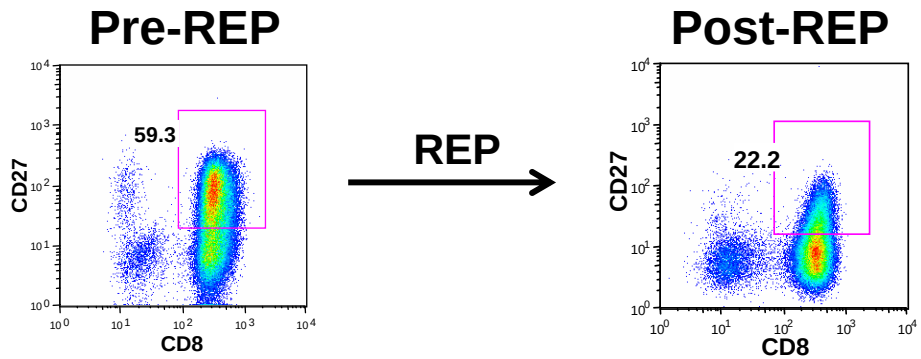


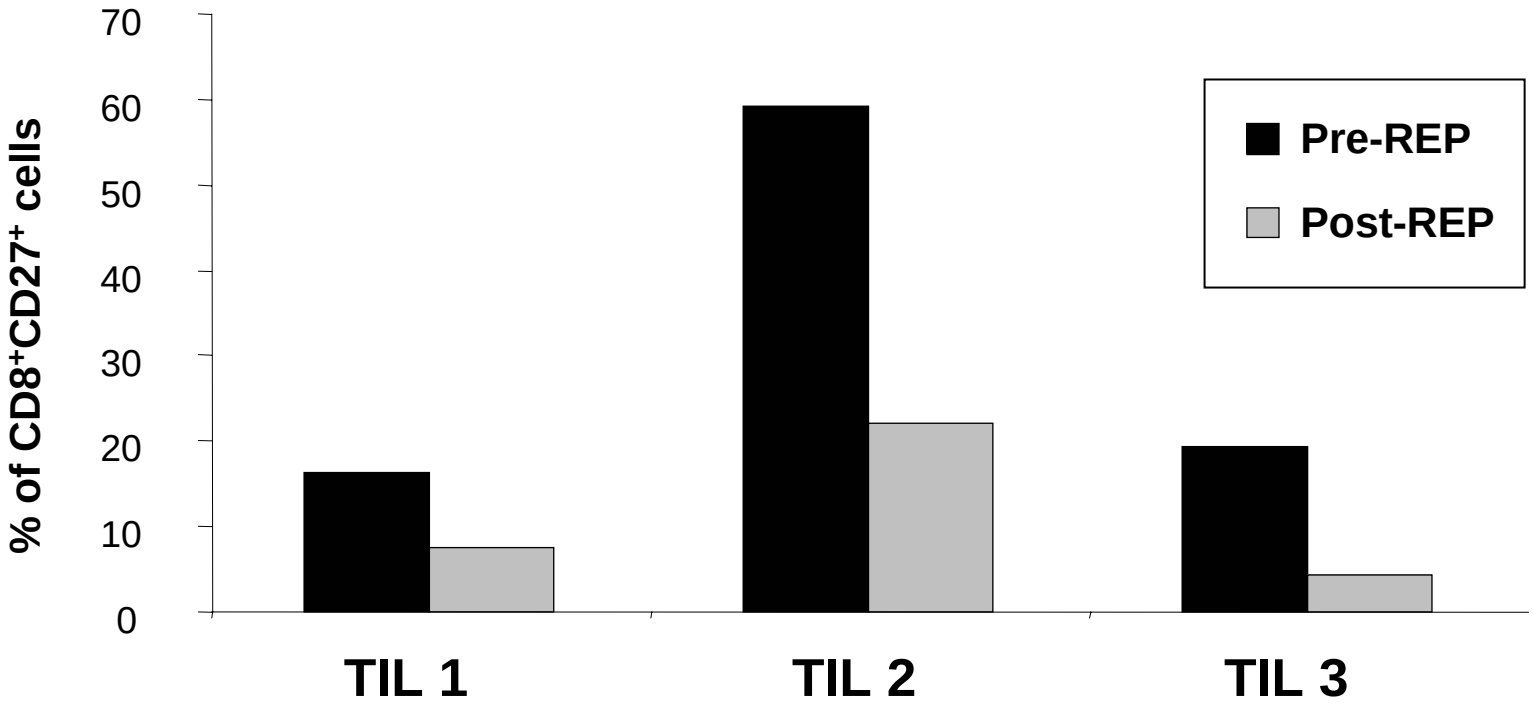
Post-REP TIL proliferate less after Ag re-stimulation



CFSE labeling → DC + MART-1 stimulation → FACS analysis

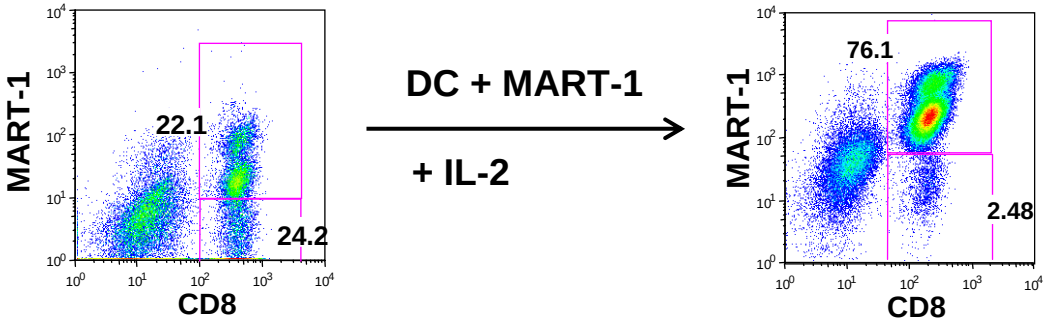
T_{EM} ($CD8^+CD27^+$) lost upon REP



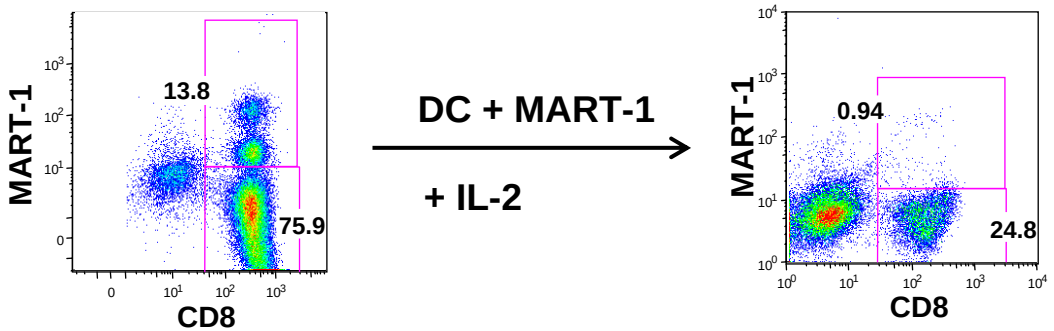


Post-REP MART-1-specific TIL: Loss of expansion after DC re-stimulation

Pre-REP

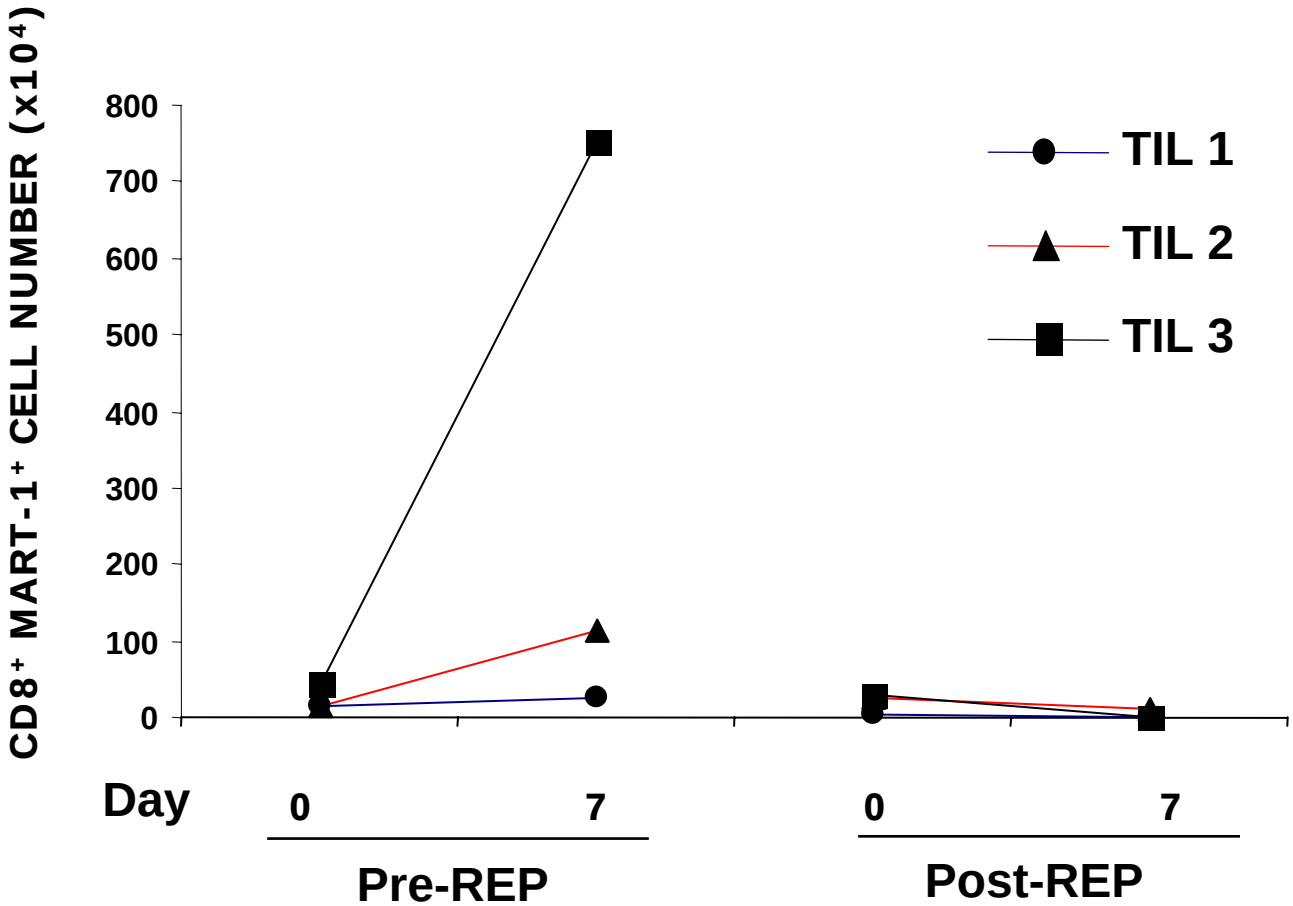


Post-REP



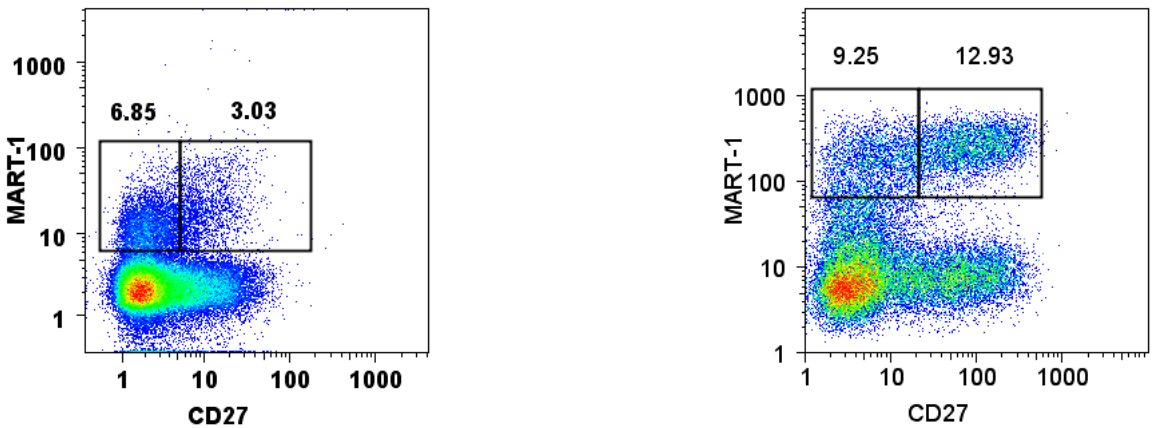
Representative results of 3 independent TIL lines

Post-REP MART-1-specific TIL: Loss of expansion after DC re-stimulation



MART-1-specific CD27^{+} cells expand following Ag-specific re-stimulation

Before DC stimulation → **After DC stimulation**



Cell number (x10^5)	Cell number (x10^5)
CD27+ cells= 0.6	CD27+ cells= 2.7 → 4.5X
CD27- cells= 1.4	CD27- cells= 1.9 → 1.3X

TIL after REP:

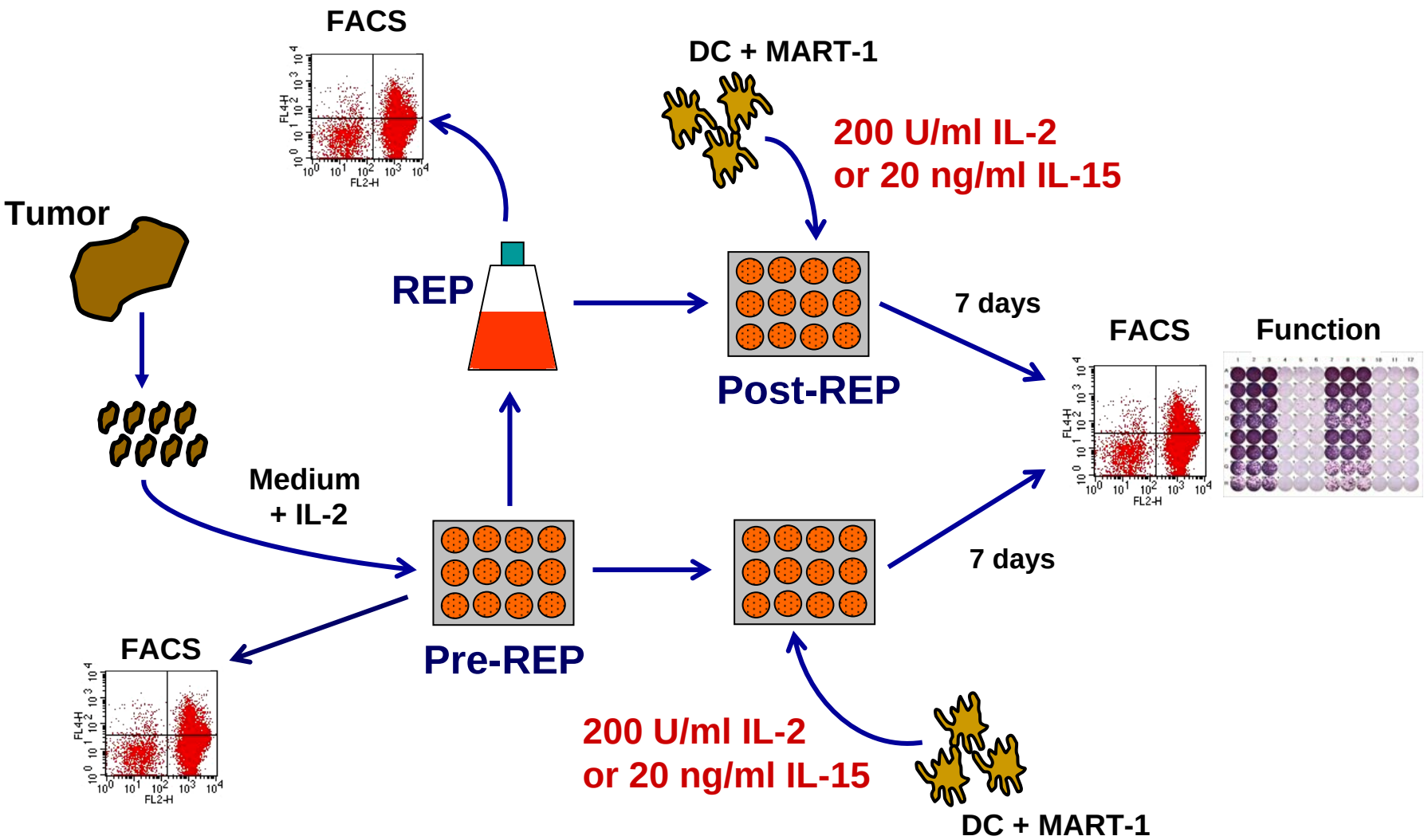
- **Loss of T_{EM} ($CD27^+$, $CD28^+$, $CD57^-$) phenotype.**
- **Loss of proliferative capacity after Ag stimulation.**

IL-15 instead of IL-2 ?

- **Common γc cytokine: Signaling through unique IL-15Rα.**
- **Supports survival of T_{EM} and homeostatic expansion of memory $CD8^+$ T cells.**
- **Can induce Granzyme B and perforin expression.**
- **Inefficient at T-reg cell expansion versus IL-2.**
- **Not used clinically so far.**

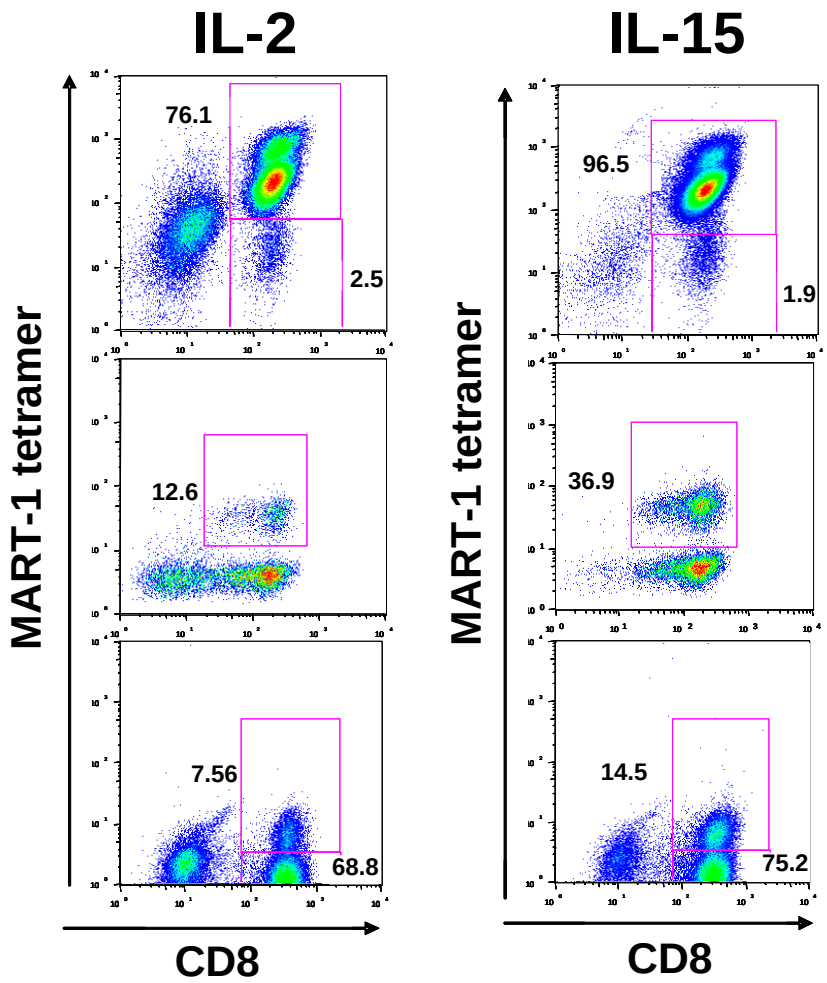
Liu etc. PNAS, 2002, 99: 6192-7; Yajima etc. JI, 2005, 174: 3590-7.

DC stimulation of melanoma TIL with IL-15 versus IL-2 as cytokine support

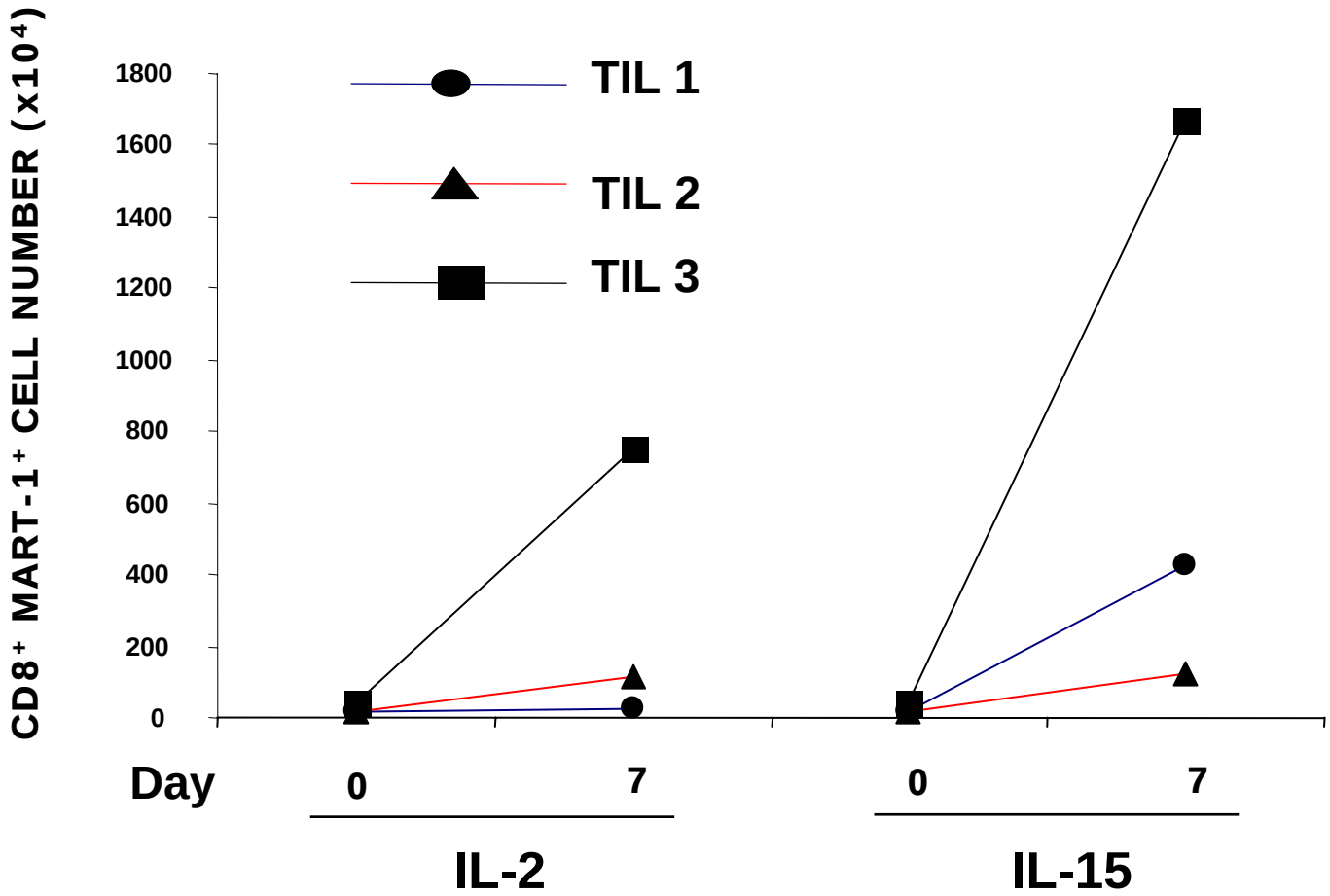


IL-15 is superior to IL-2 in expanding MART-1-specific TIL

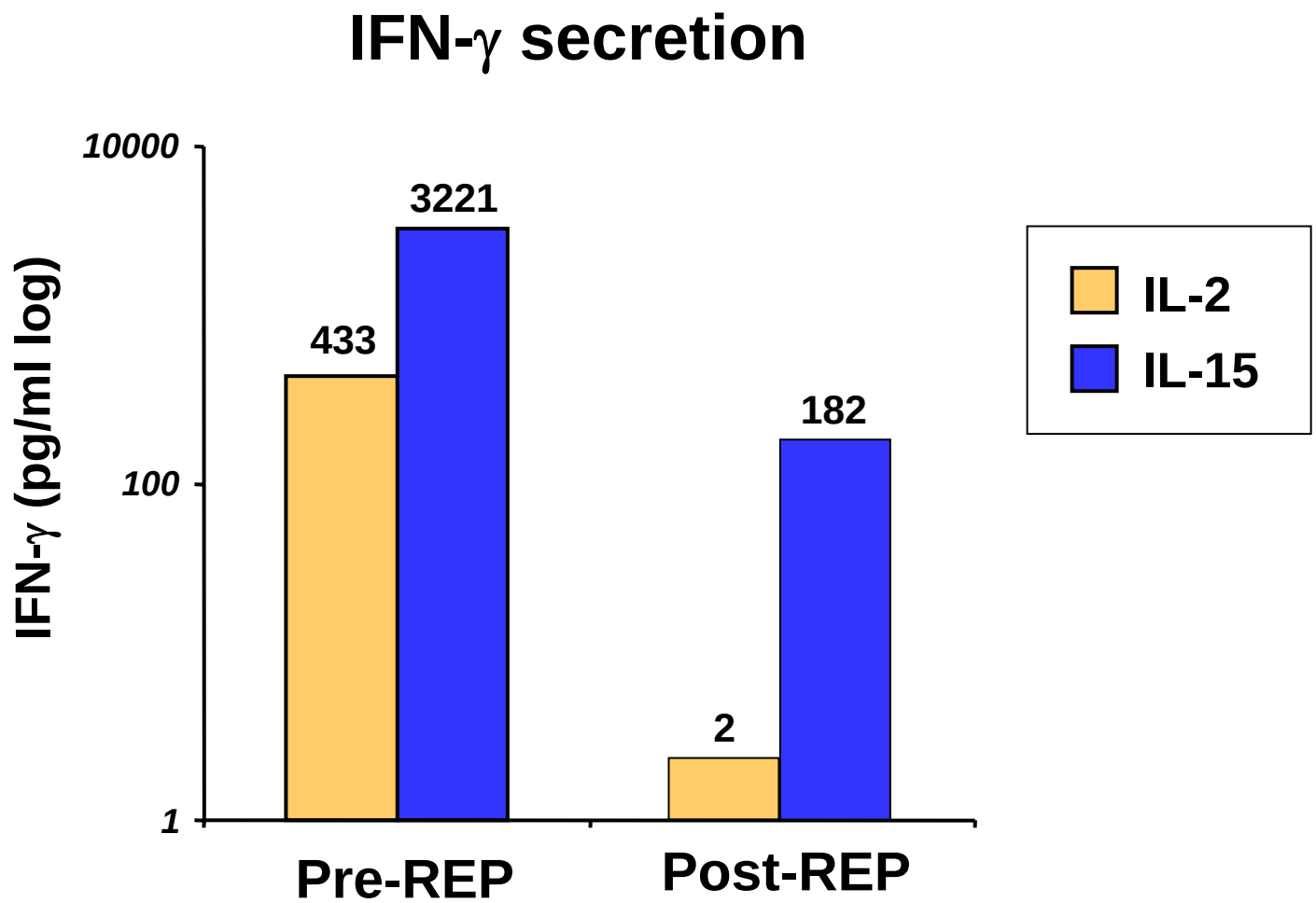
- **Pre-REP TIL.**
- **Stimulation with MART-1 peptide-pulsed mDC.**
- **7-day incubation**



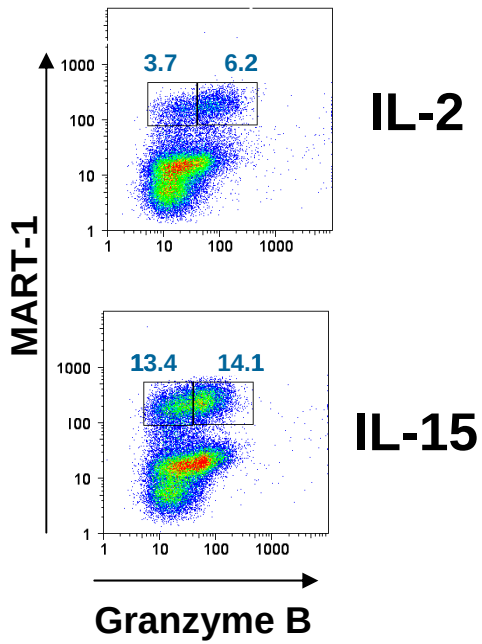
IL-15 is superior to IL-2 in expanding MART-1-specific TIL

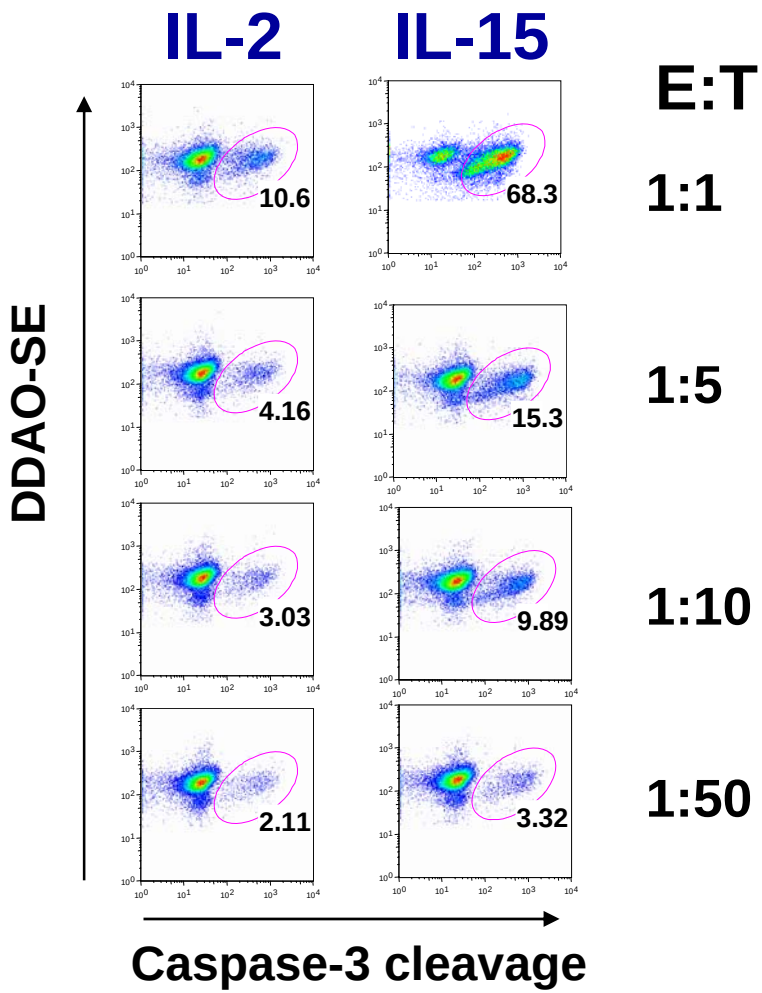


IL-15 induces superior effector cells following melanoma Ag re-stimulation



IL-15 induces superior effector cells following melanoma Ag re-stimulation

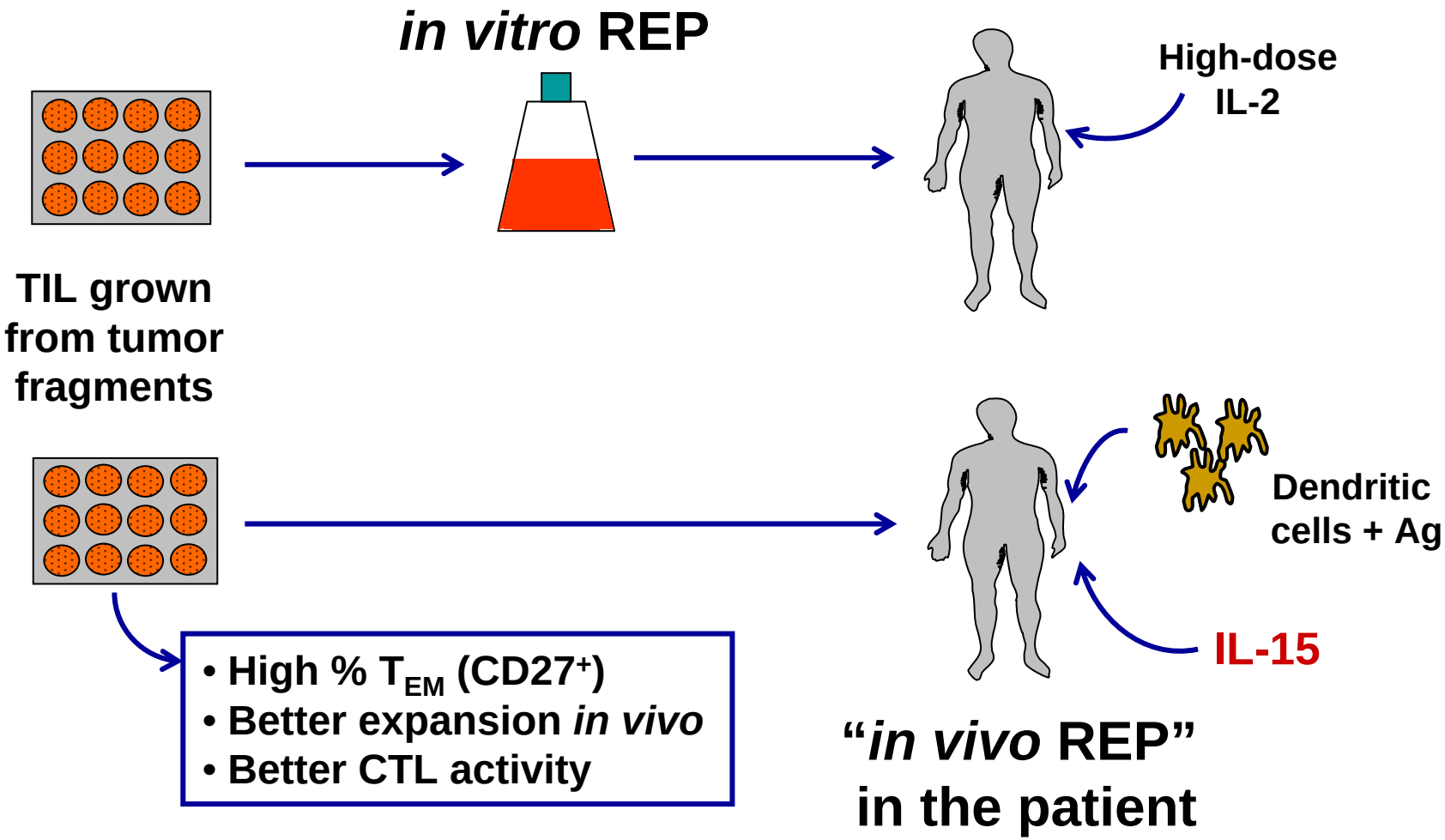




IL-15 is superior:

- **Expands and maintains T_{EM} better than IL-2.**
- **Enhances CTL activity (more GB+ T cells).**
- **Capable of long-term expansion following DC re-stimulation (>3 week continued expansion).**
- **Effects are Ag-specific.**

Proposed adoptive cell therapy approach with pre-REP TIL and DC co-vaccination



Acknowledgements

Laszlo G. Radvanyi

Shujuan Liu
Yijun Wang
Ryan Campbell
Greg Lizee
Willem Overwijk
Patrick Hwu

Kathryn Bushnell

Karena Fernandez

Rahmatu Bassie