Adoptive T-cell Therapy for Melanoma: Trials and Tribulations in the Quest for FDA Approval

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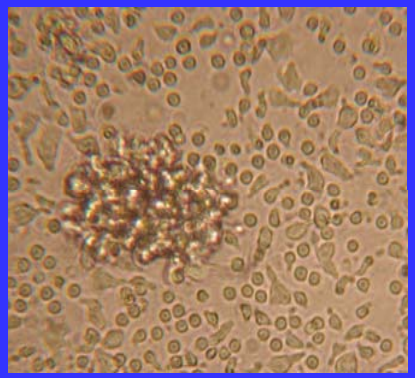
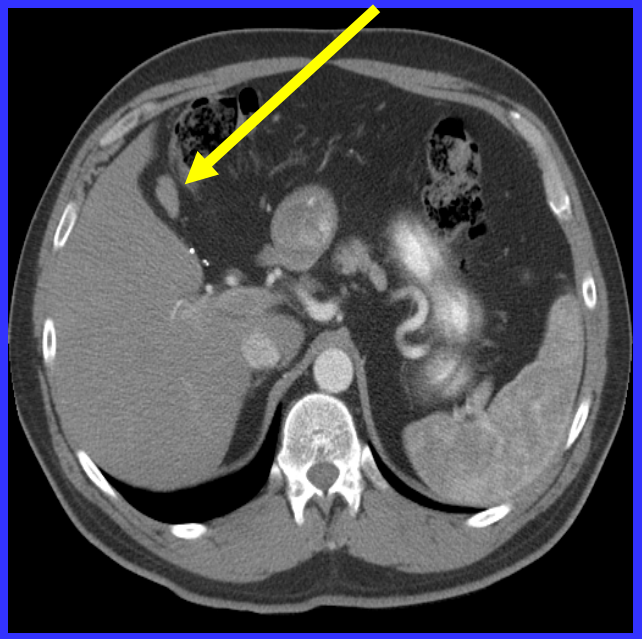


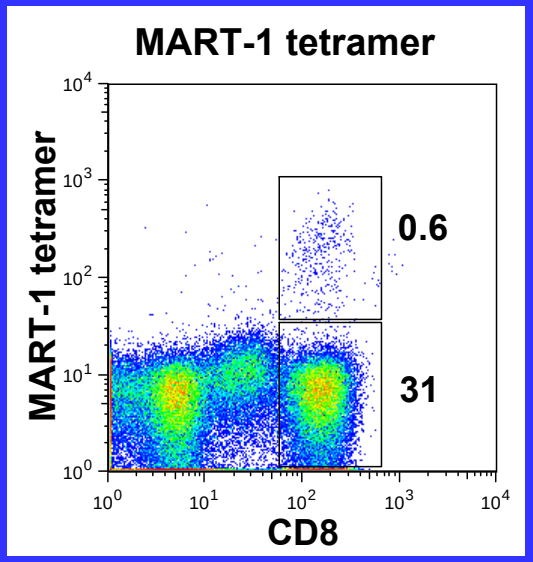
Disclosures

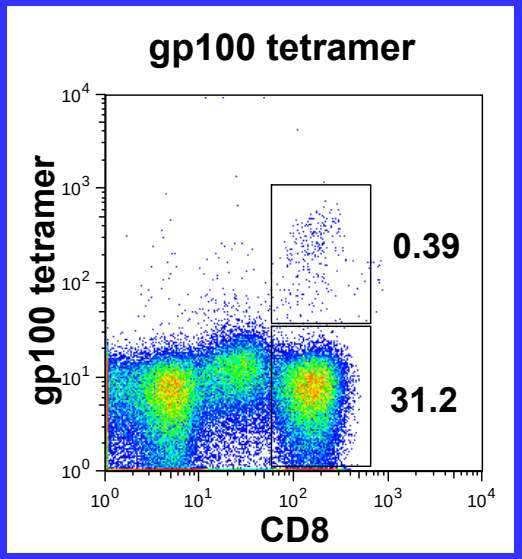
- Genesis BioPharma - SAB

Presence of tumor-reactive T-cells in metastatic melanomas (TIL)



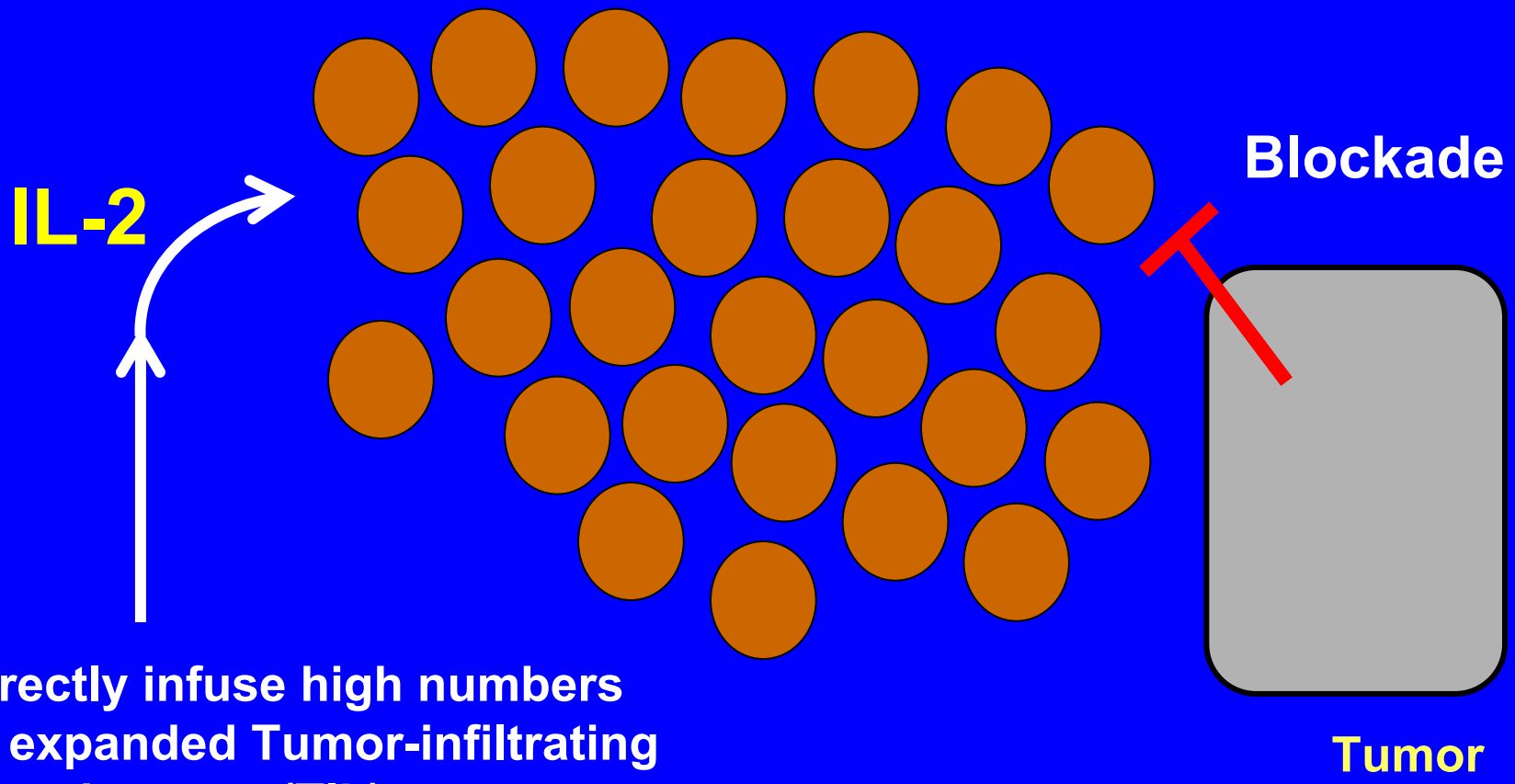
Gall bladder-associated metastasis





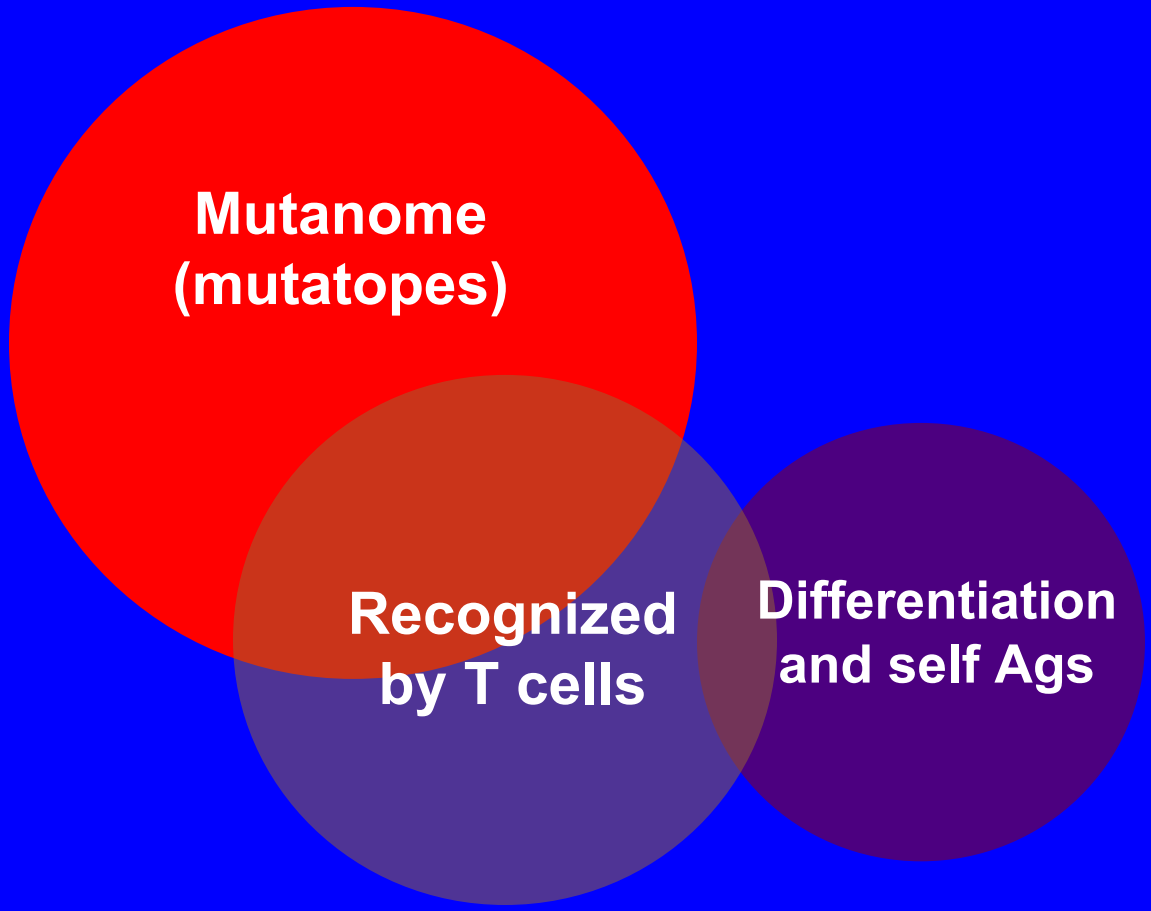
M. Ross, L. Radvanyi

Adoptive T-cell therapy (ACT): Increasing the tumor-specific T-cell army

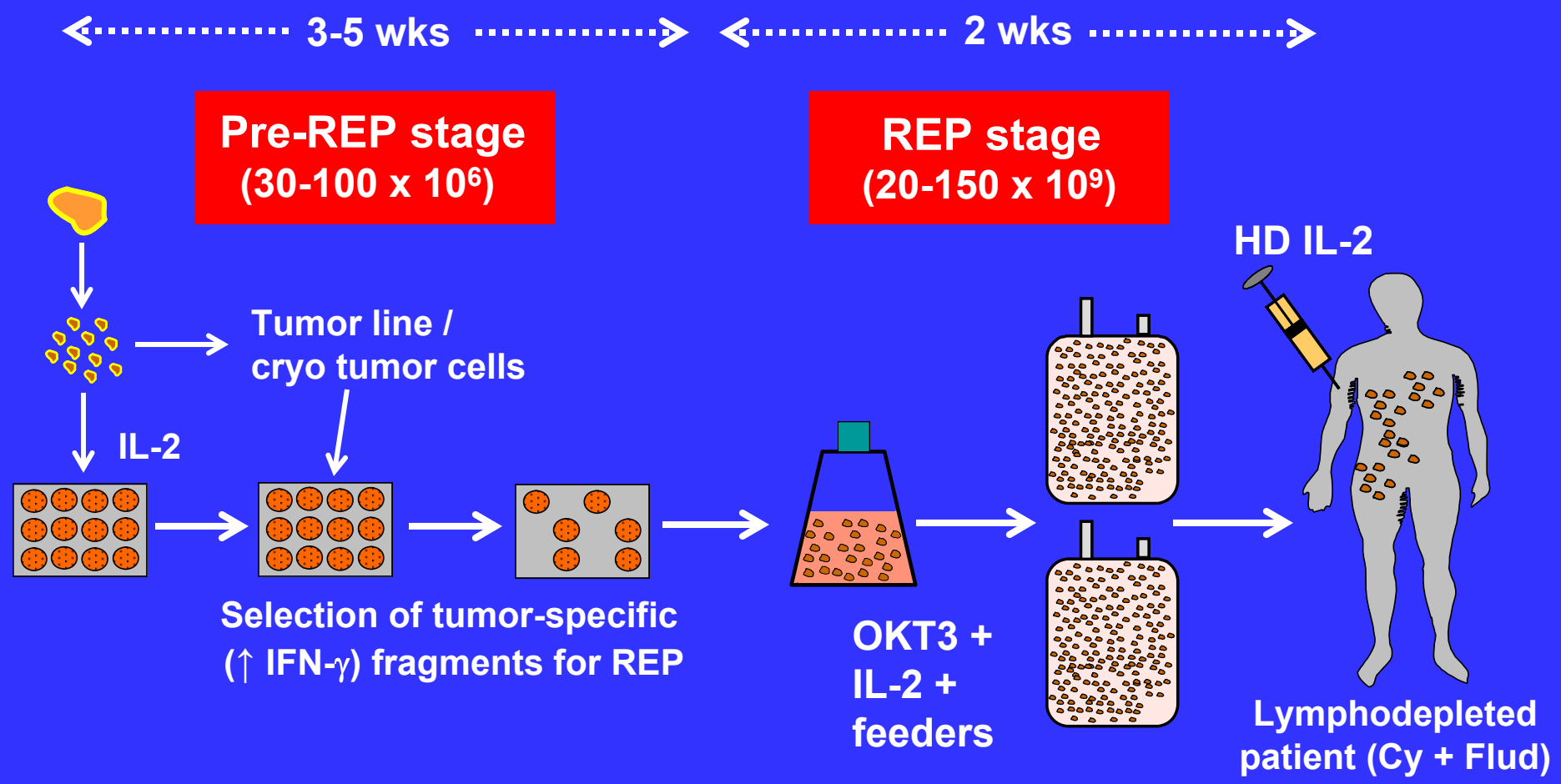


Directly infuse high numbers of expanded Tumor-infiltrating Lymphocytes (TIL)

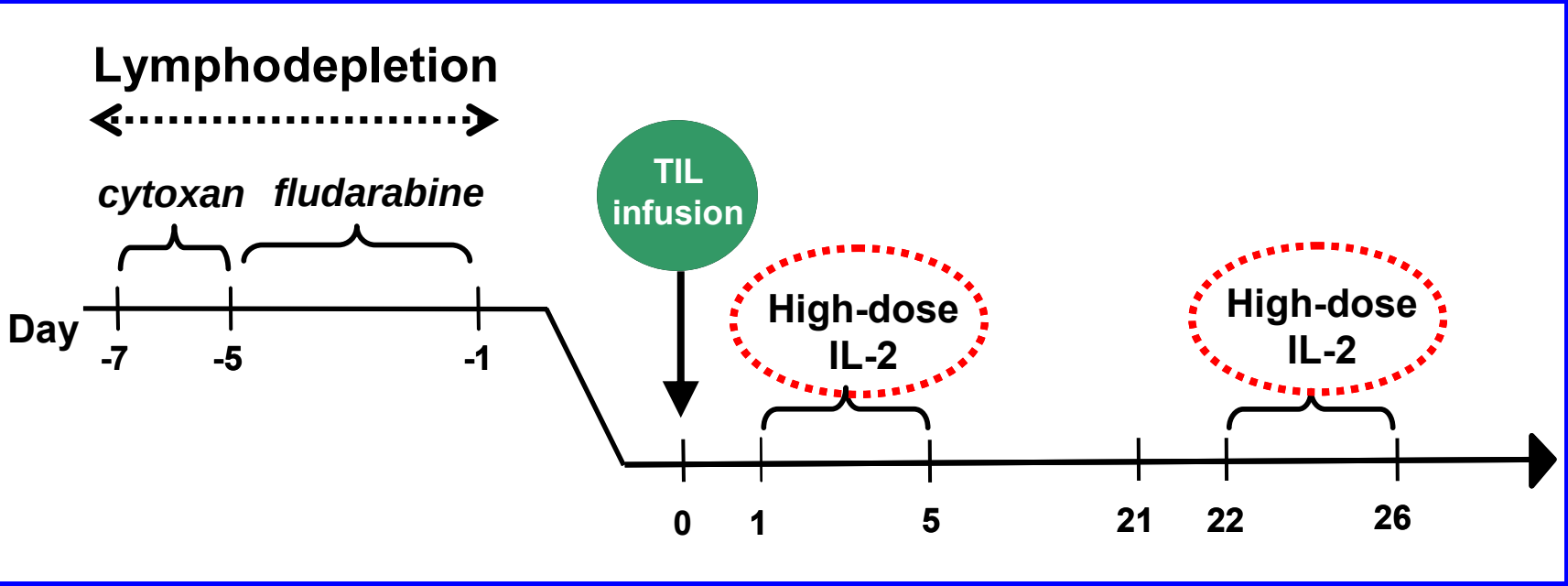
TIL versus single target Ag approaches (TCR/CAR transduction)



Current state-of-the-art "selected" TIL ACT protocol for melanoma



Timing of preconditioning and TIL+IL-2 therapy: MDACC

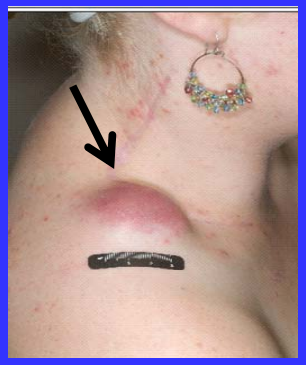


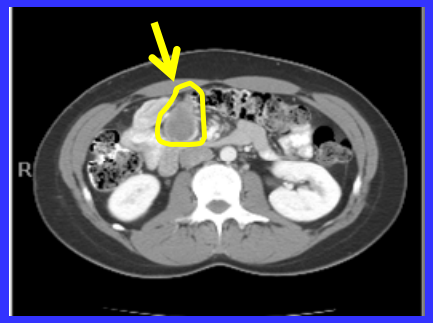
Responses to TIL therapy

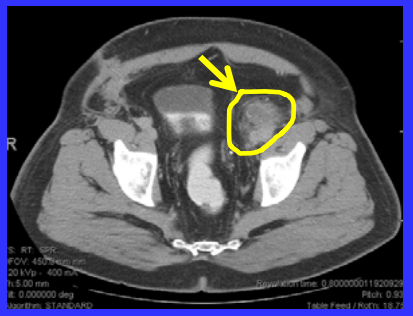
Patient #2150/2153

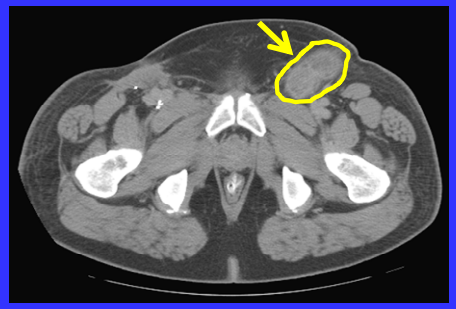
Patient #2054/2256

Before therapy

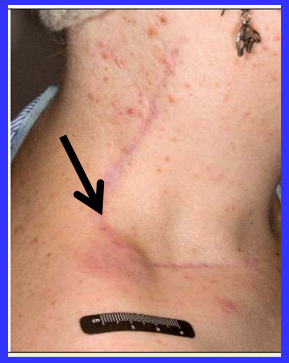


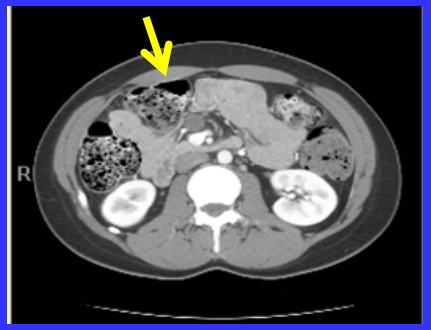


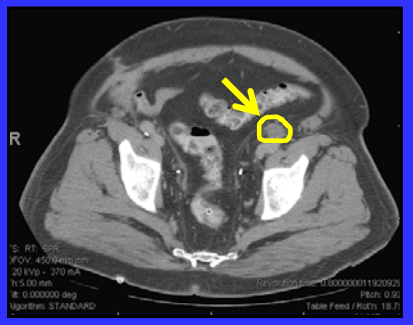


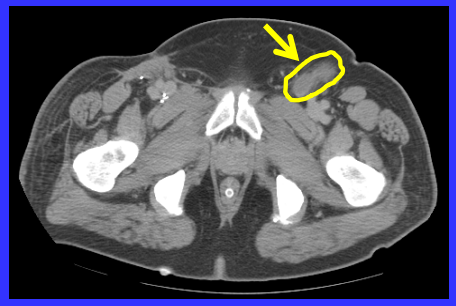


1 month

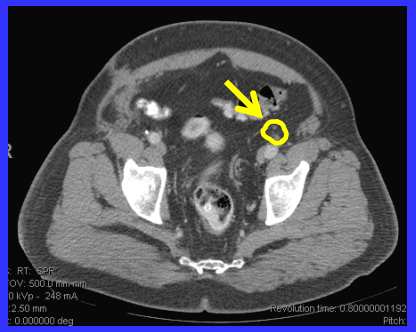


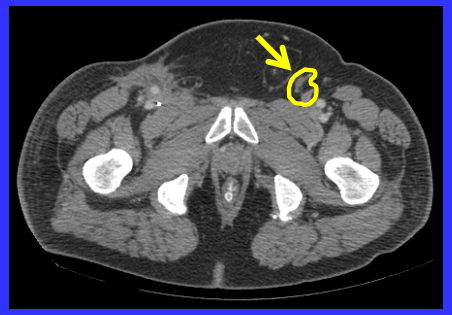






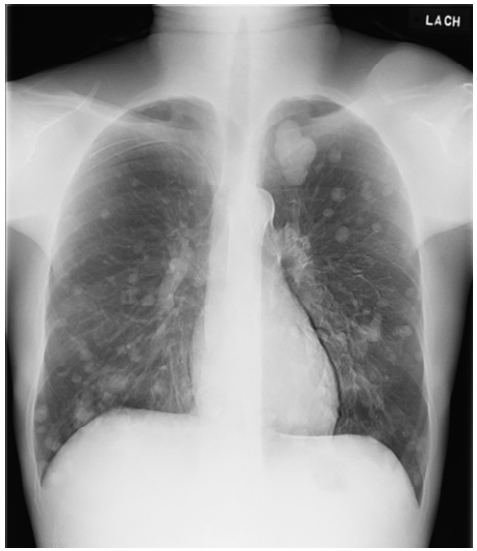
18 months

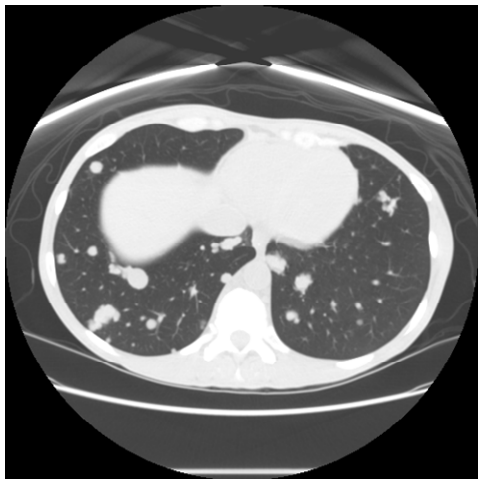




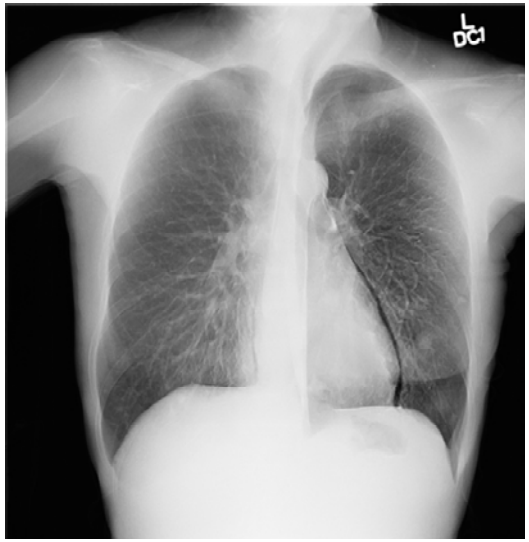
Response to TIL therapy

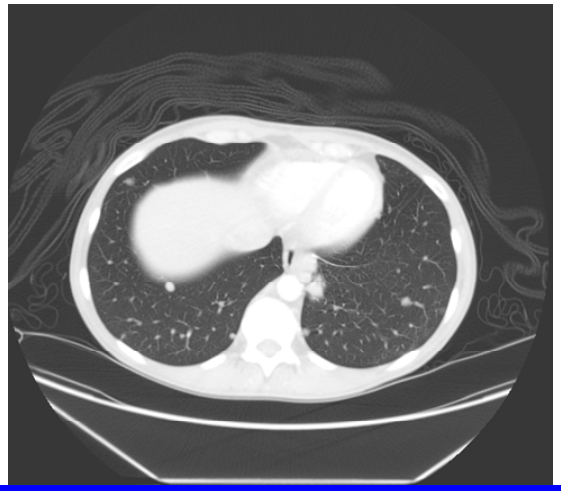
Pre-treatment



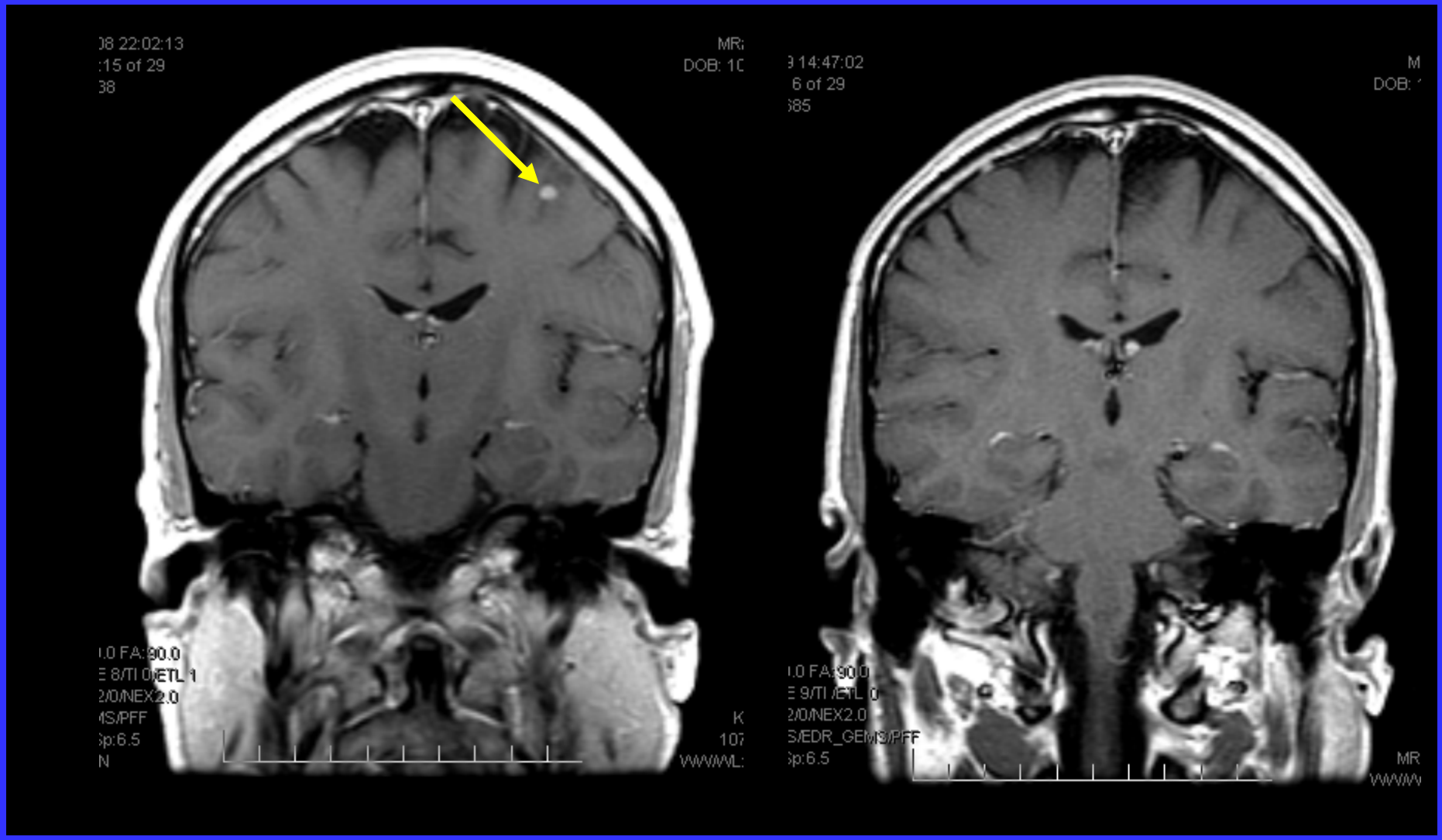


1-2 months
Post-treatment

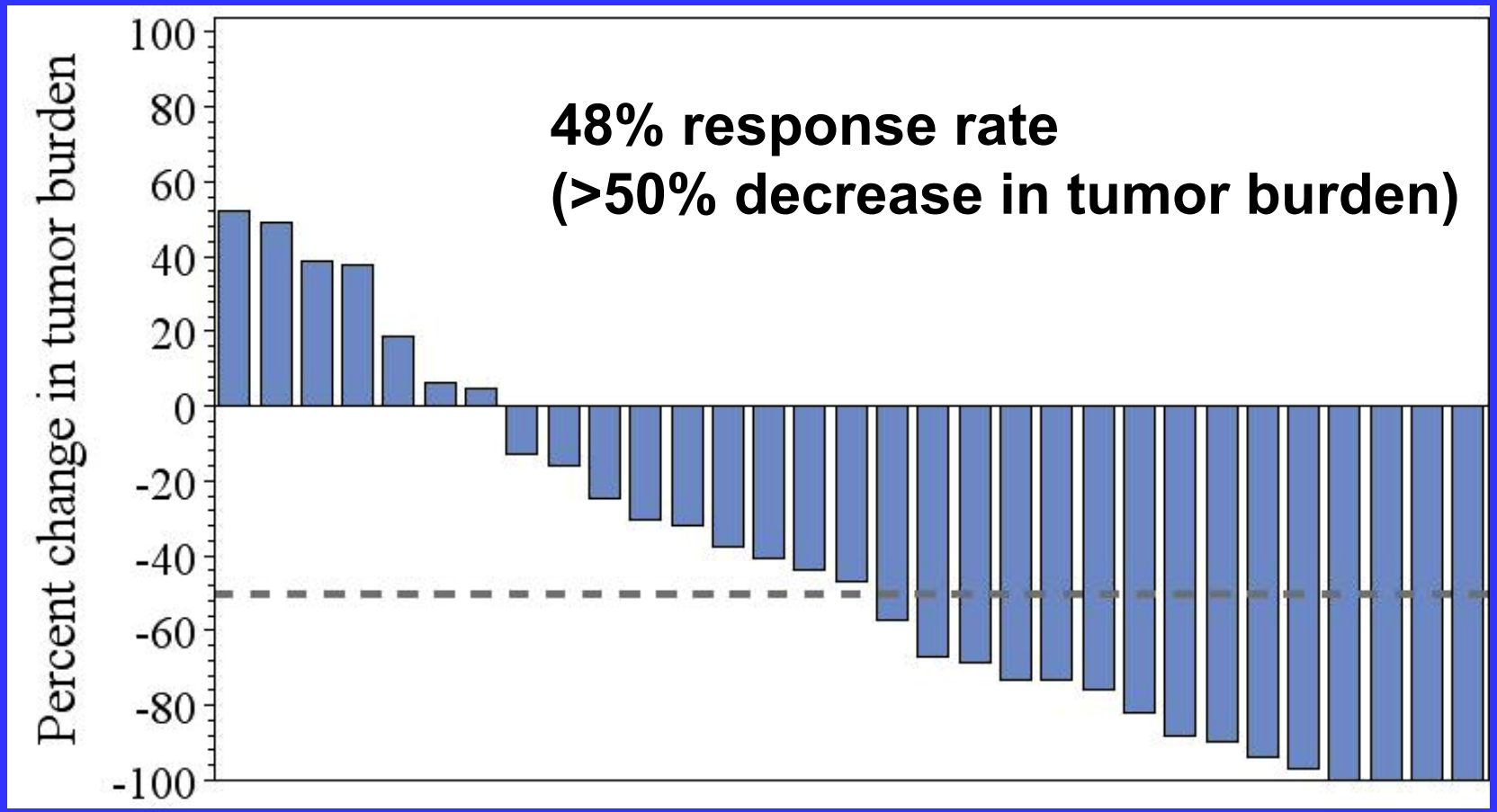




Response of brain metastasis to TIL



Waterfall plot of tumor regression in first 31 treated patients: MDACC



Clinical Response data from MDACC (as of July 10, 2012)

Best overall response:

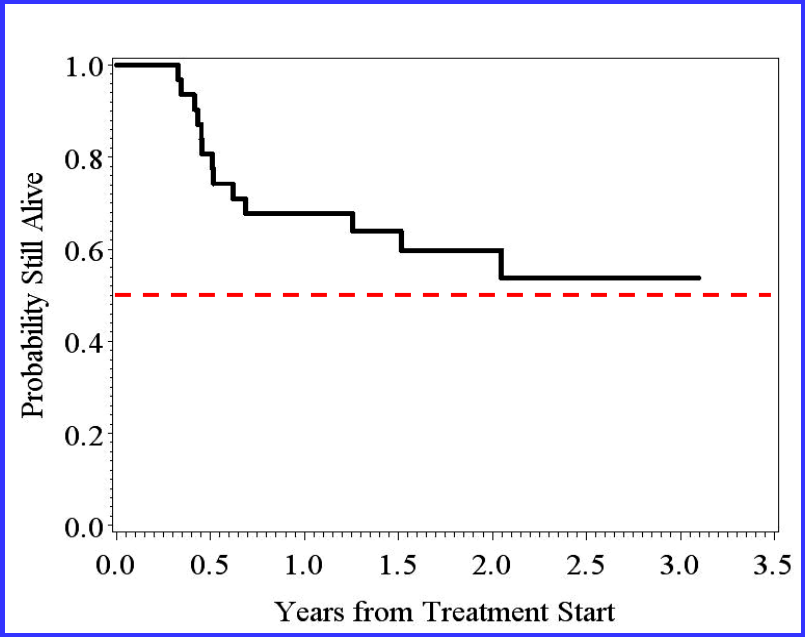
Number of patients	CR*	PR*	Total
51	2 (4%)	21(41%)	23 (45%)

*Some patients are still undergoing clinical response

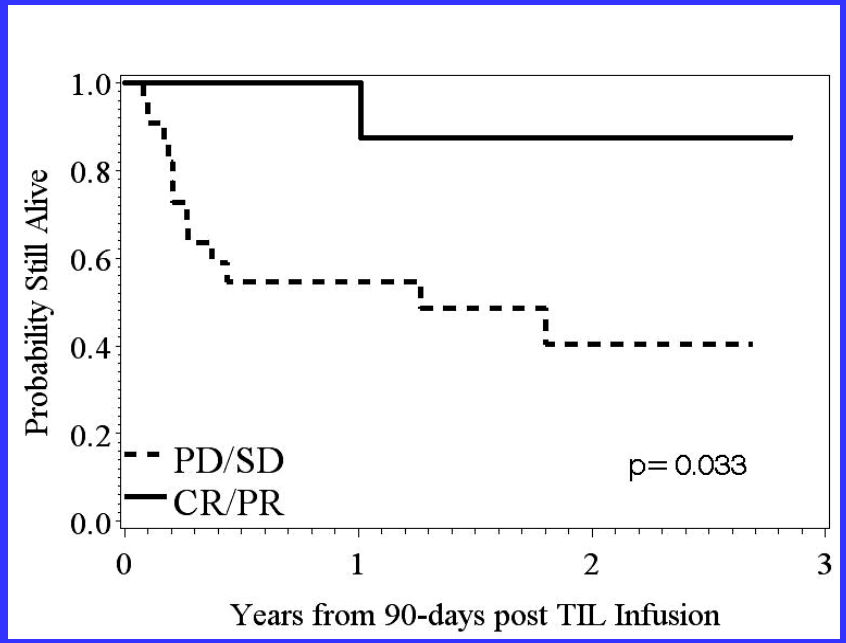
Poster #1: Bernatchez et al.
Adoptive cell therapy using expanded autologous tumor-infiltrating lymphocytes in metastatic melanoma patients: Role of specific lymphocyte subsets

Kaplan-Meier curves of overall survival at MDACC (N=31)

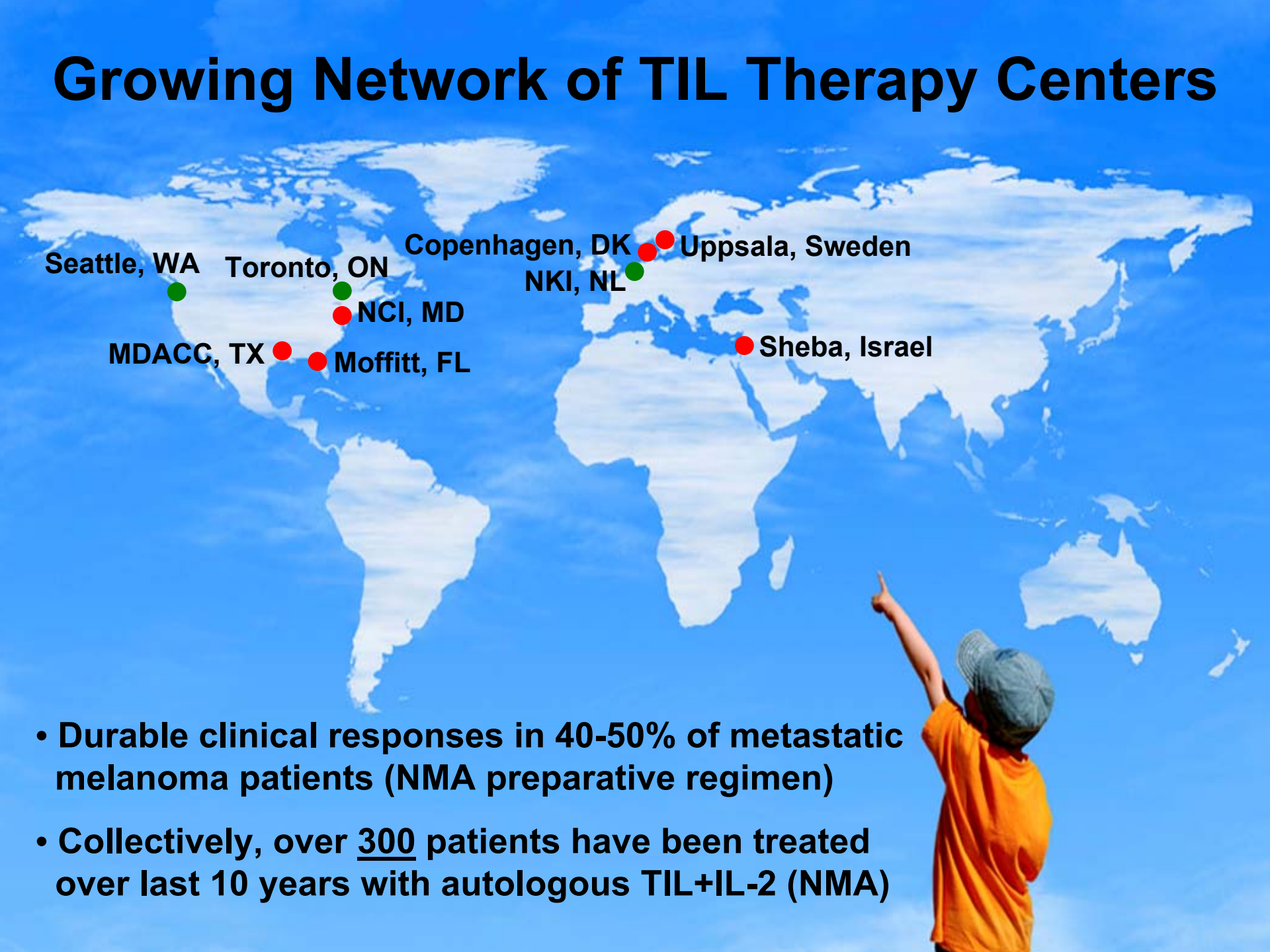
Overall survival (from time of TIL infusion)



Landmark analysis (from 3 month post-TIL)

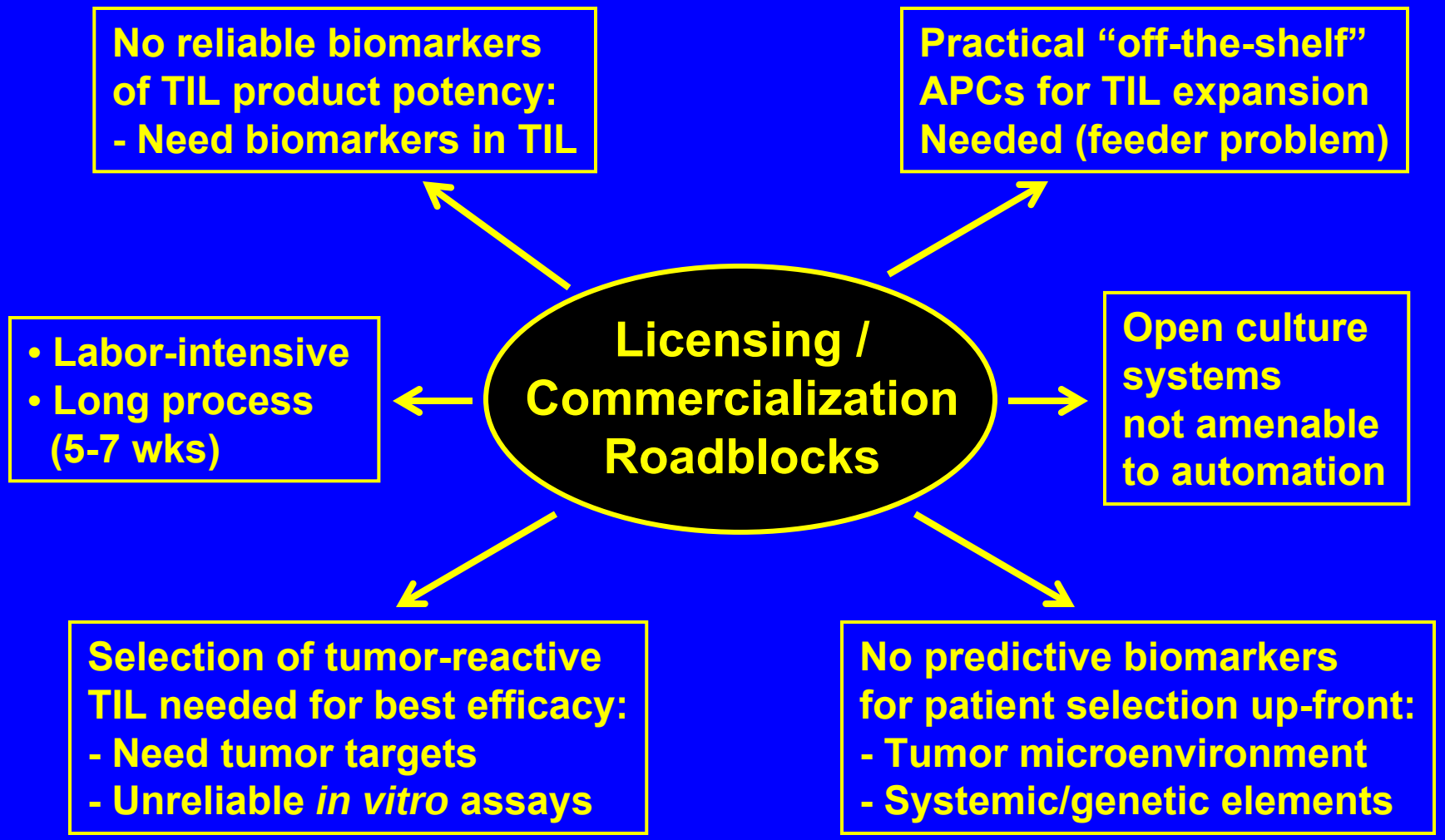


Growing Network of TIL Therapy Centers



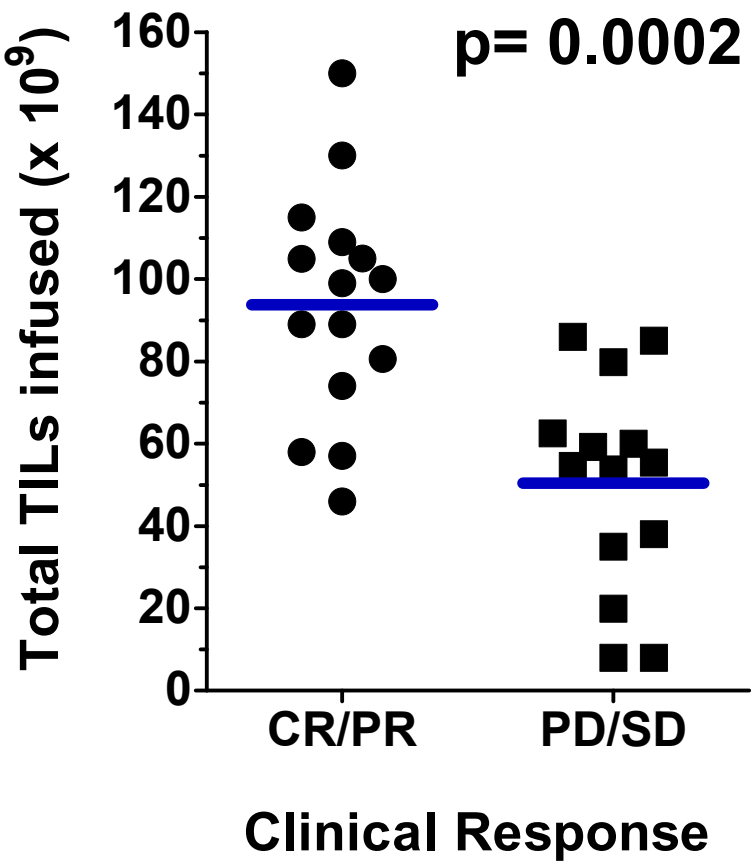
- Durable clinical responses in 40-50% of metastatic melanoma patients (NMA preparative regimen)
- Collectively, over 300 patients have been treated over last 10 years with autologous TIL+IL-2 (NMA)

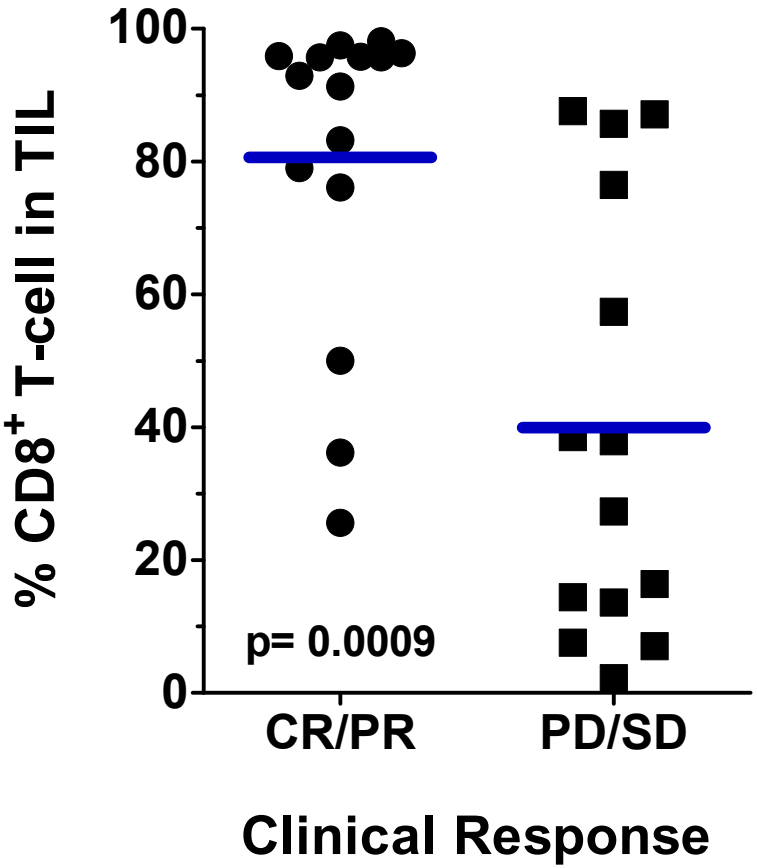
Roadblocks to TIL Commercialization



Problem	Solution
• No reliable biomarkers of infused TIL potency predictive of response	• Phenotypic biomarker analysis: - T-cell EM subsets (CD8) - Novel markers - Function (Ag-specific / polyclonal)
• No predictive biomarkers for patient selection for therapy: - clinical response - initial TIL outgrowth - expanded TIL phenotypes	• Predictive tests before tumor resection for TIL outgrowth: - IHC biomarkers in tumors - gene expression in tumors - systemic/genetic markers (blood)
• No method to isolate tumor-specific TIL up-front for expansion (save time)	• Selection from fresh TIL isolates using activation markers?
• PBMC feeder problem and availability (costs)	• Off-the-shelf APCs with defined stimulatory molecules
• Open systems → too much manual handling (labor/cost)	• Automated closed systems for selection and expansion

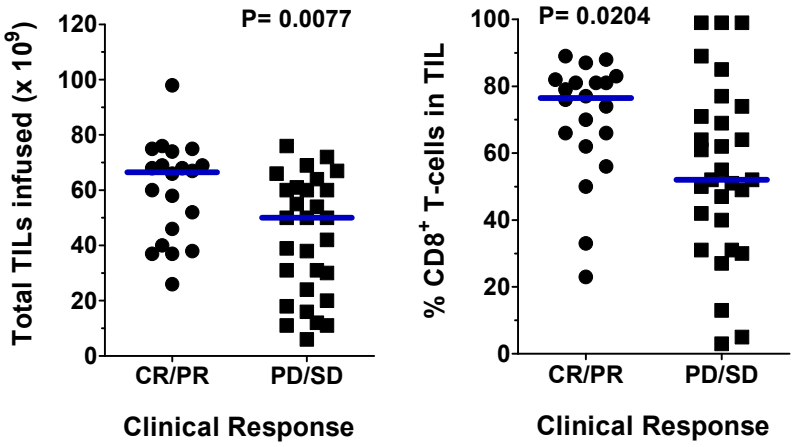
Total TIL infused and CD8+ T cells are critical parameters



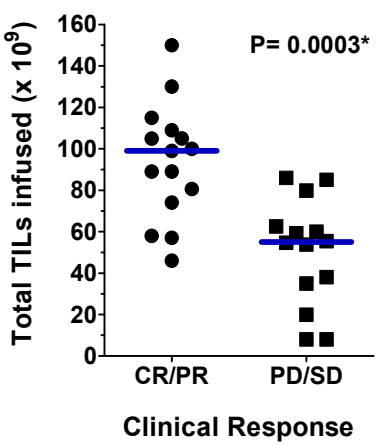


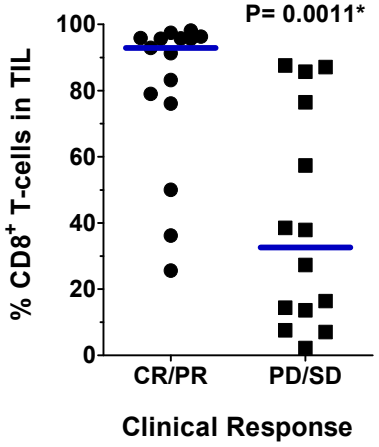
Total TIL and % CD8 TIL Infused and Clinical Response: Sheba and MDACC Data

Sheba (N= 49)

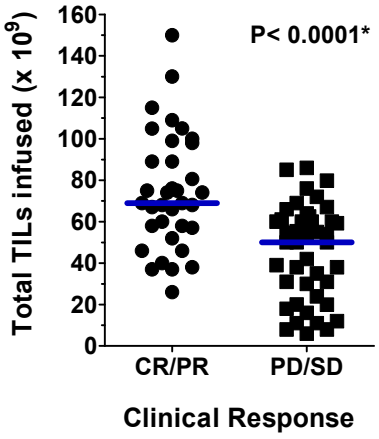


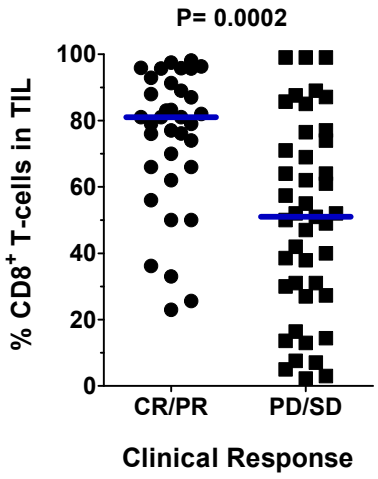
MDACC (N= 29)

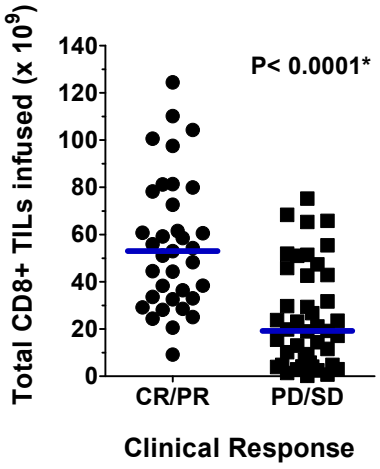




Sheba + MDACC combined (N= 78)

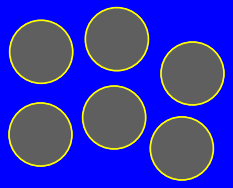






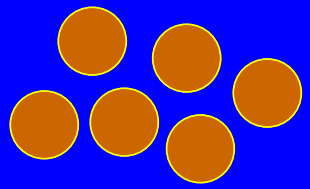
Analysis of CD8+ T-cell differentiation status in infused TIL

$T_{CM/MSC}$



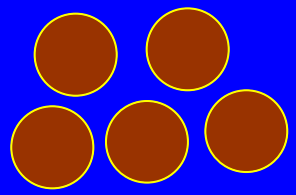
CD45RA-
CD62L+
CD27+
CD28+

T_{EM}



CD45RA-
CD62L-
CD27+
CD28+
GB+
Perf-

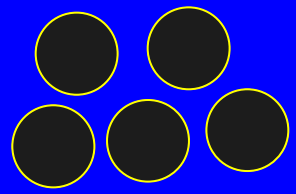
T_{EFF}



CD45RA-
CD62L-
CD27-
CD28+
GB++
Perf+

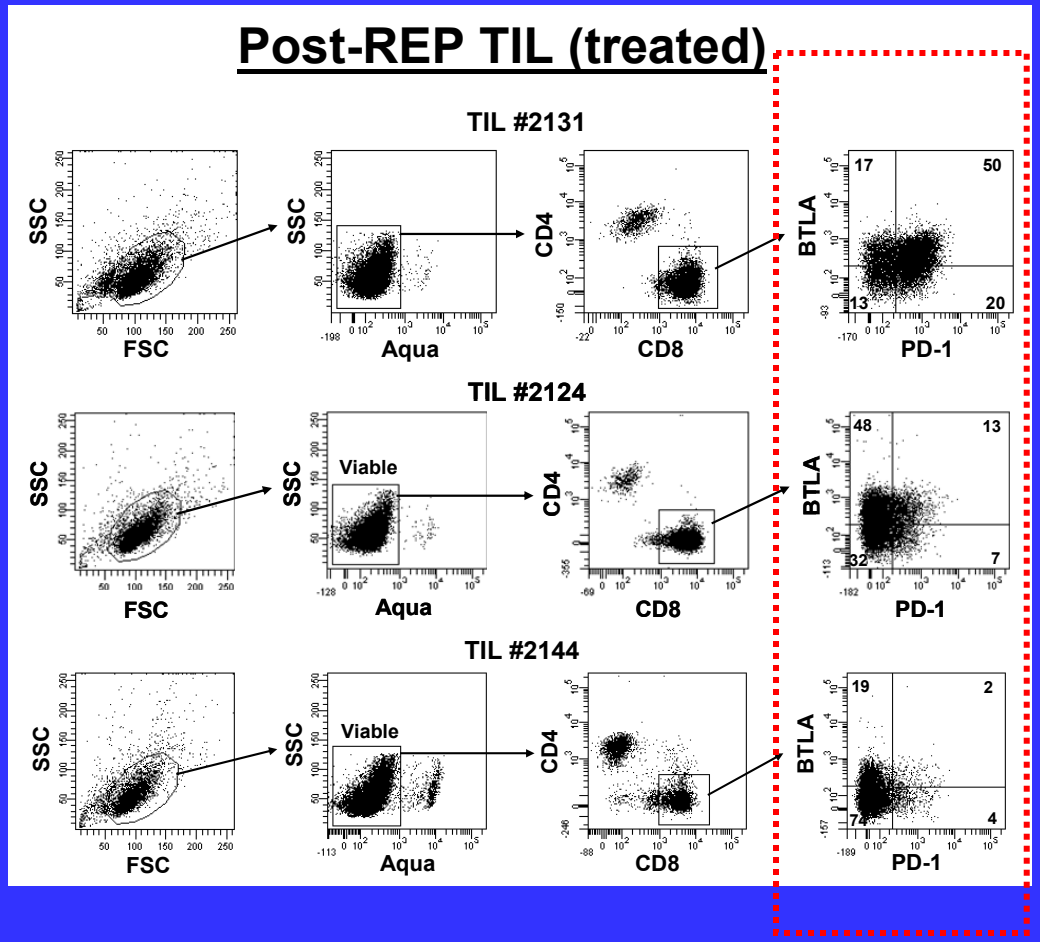
PD-1
BTLA
TIM-3

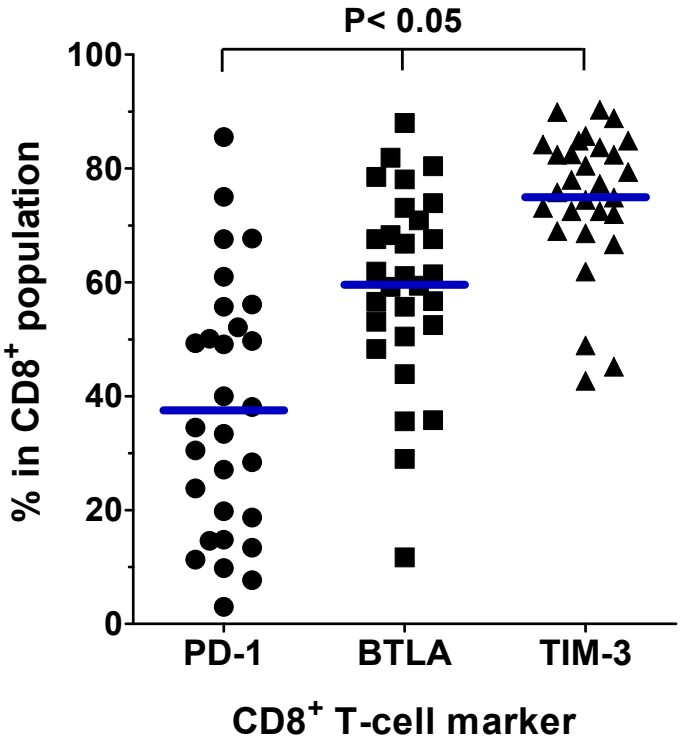
T_{TDE}



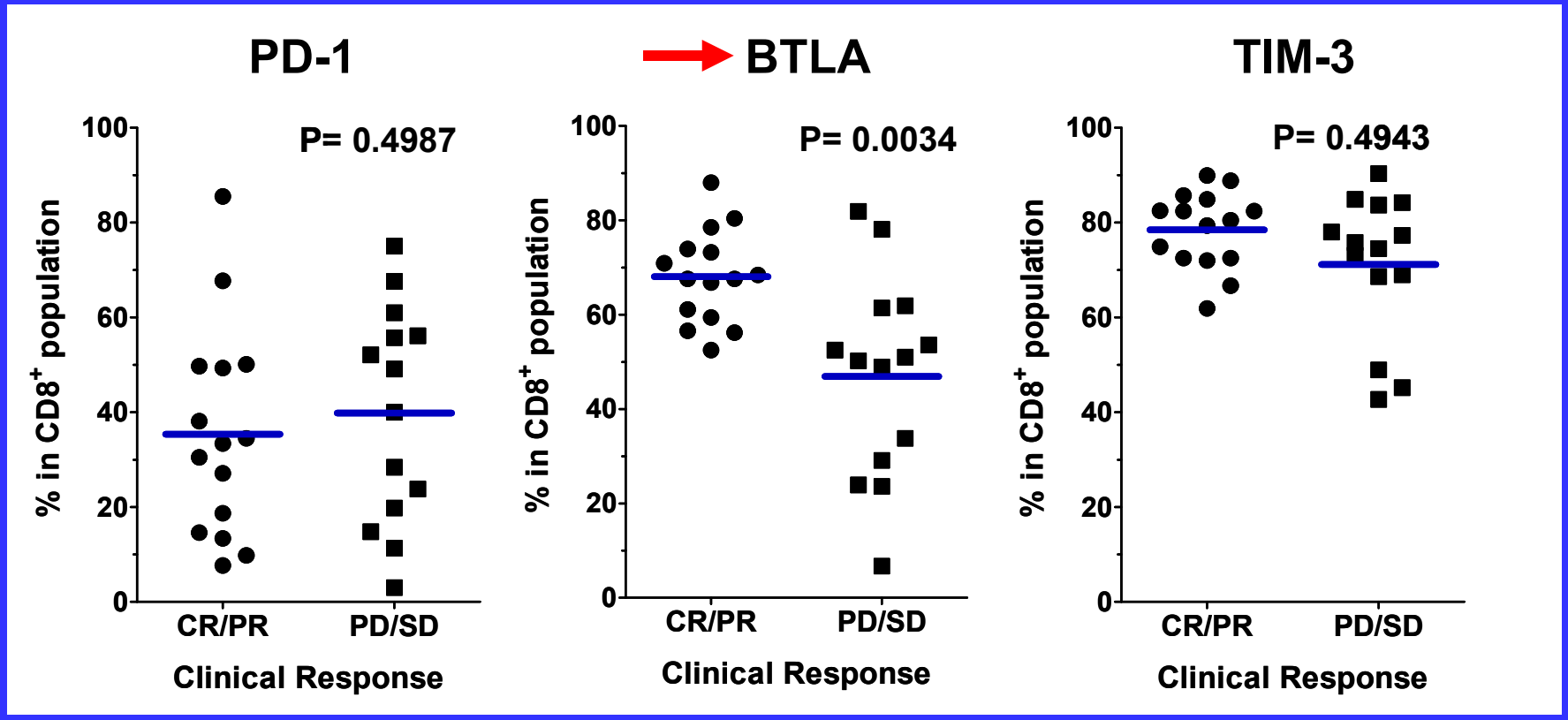
CD45RA-/+
CD62L-
CD27-
CD28-
CD57+
GB++
Perf++

PD-1 and BTLA expression on CD8+ TIL





BTLA+ TIL correlated with positive clinical response and not PD-1+ or TIM3+



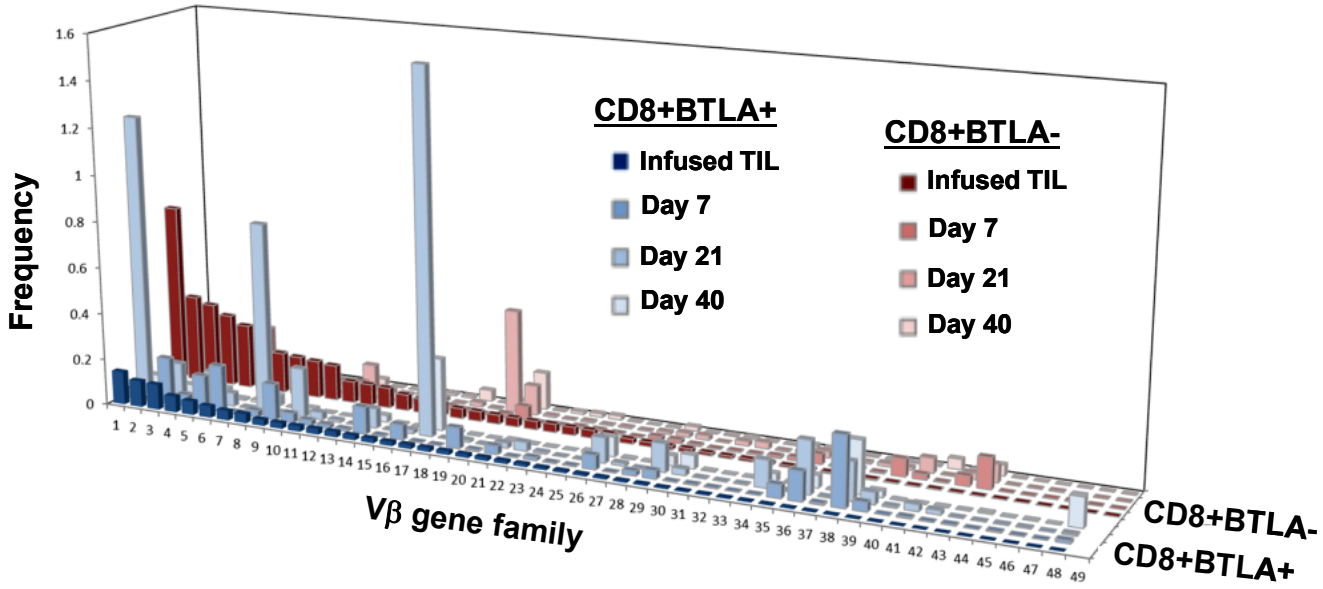
BTLA:
"B- and T- Lymphocyte Attenuator"

- Ig family member (monomer like PD-1).
- Negative costimulatory molecule binding HVEM.

- May be a novel CD8+ T-cell differentiation marker.

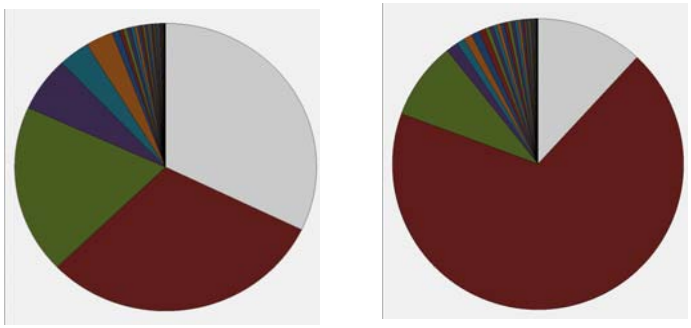
Poster #8: Haymaker et al.
BTLA: New marker for a highly proliferative CD8+ TIL subset associated with melanoma regression during adoptive cell therapy

Persistence of CD8+BTLA+ TIL clones



Infused TIL Vβ genes

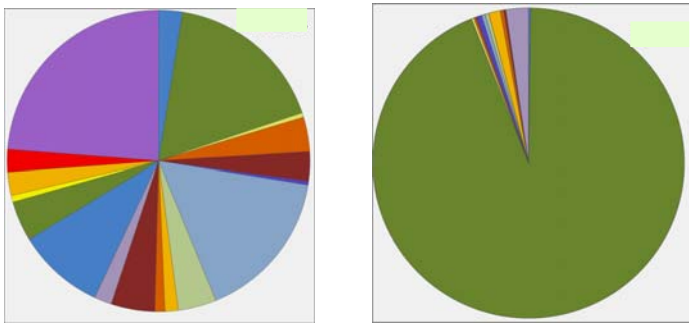
BTLA+ BTLA-



Day 0

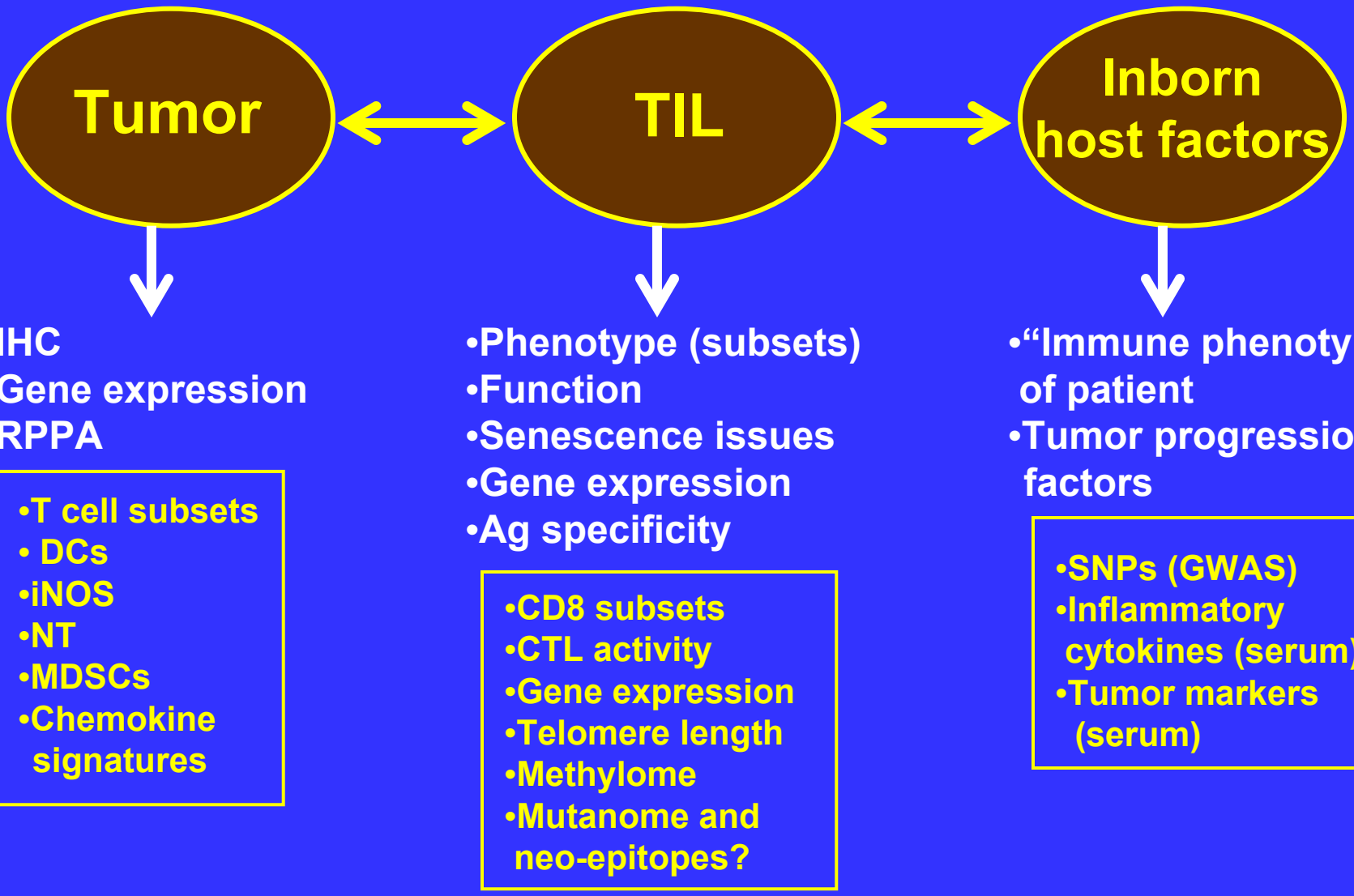
Persisting Vβ genes in blood

BTLA+ BTLA-

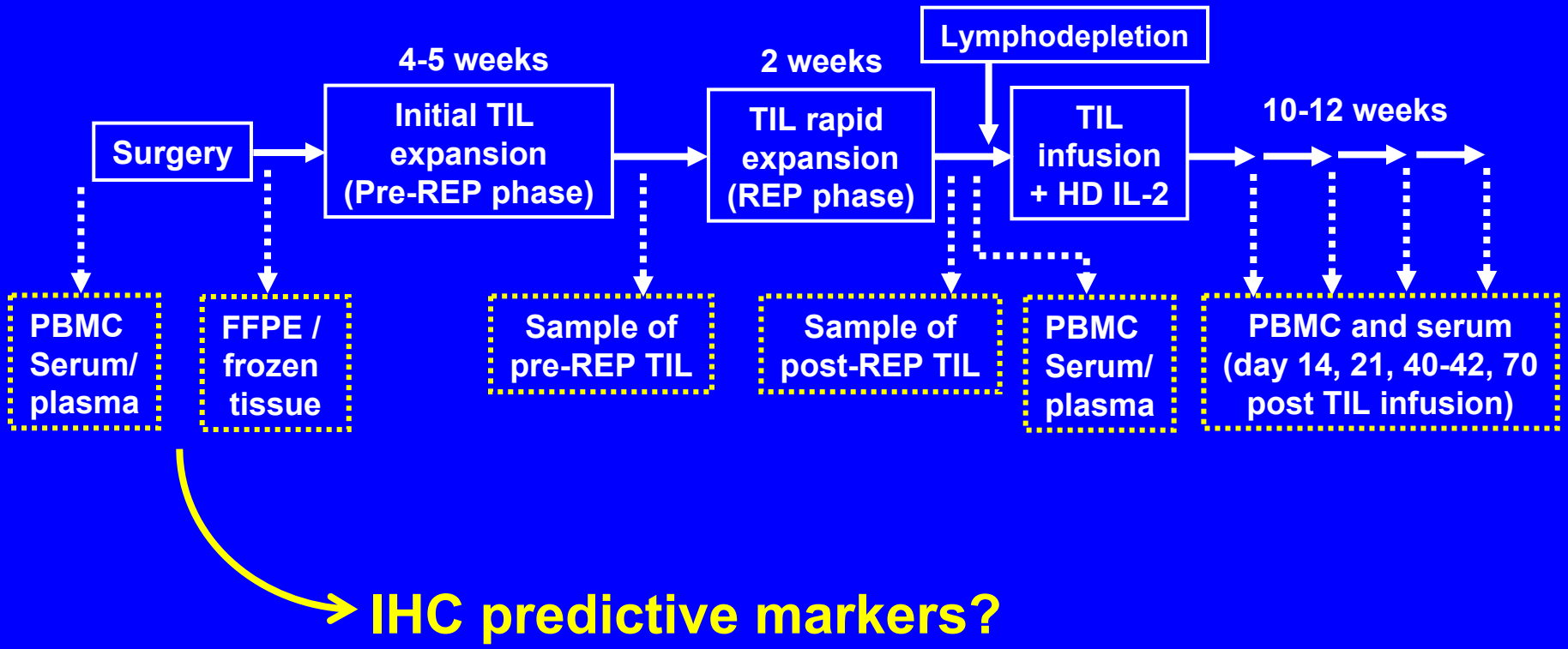


Day 56

Can biomarkers or signatures be identified as predictors of TIL efficacy?



Predictive biomarkers in TIL therapy



Predictive biomarkers by IHC in original tumors used to grow TIL

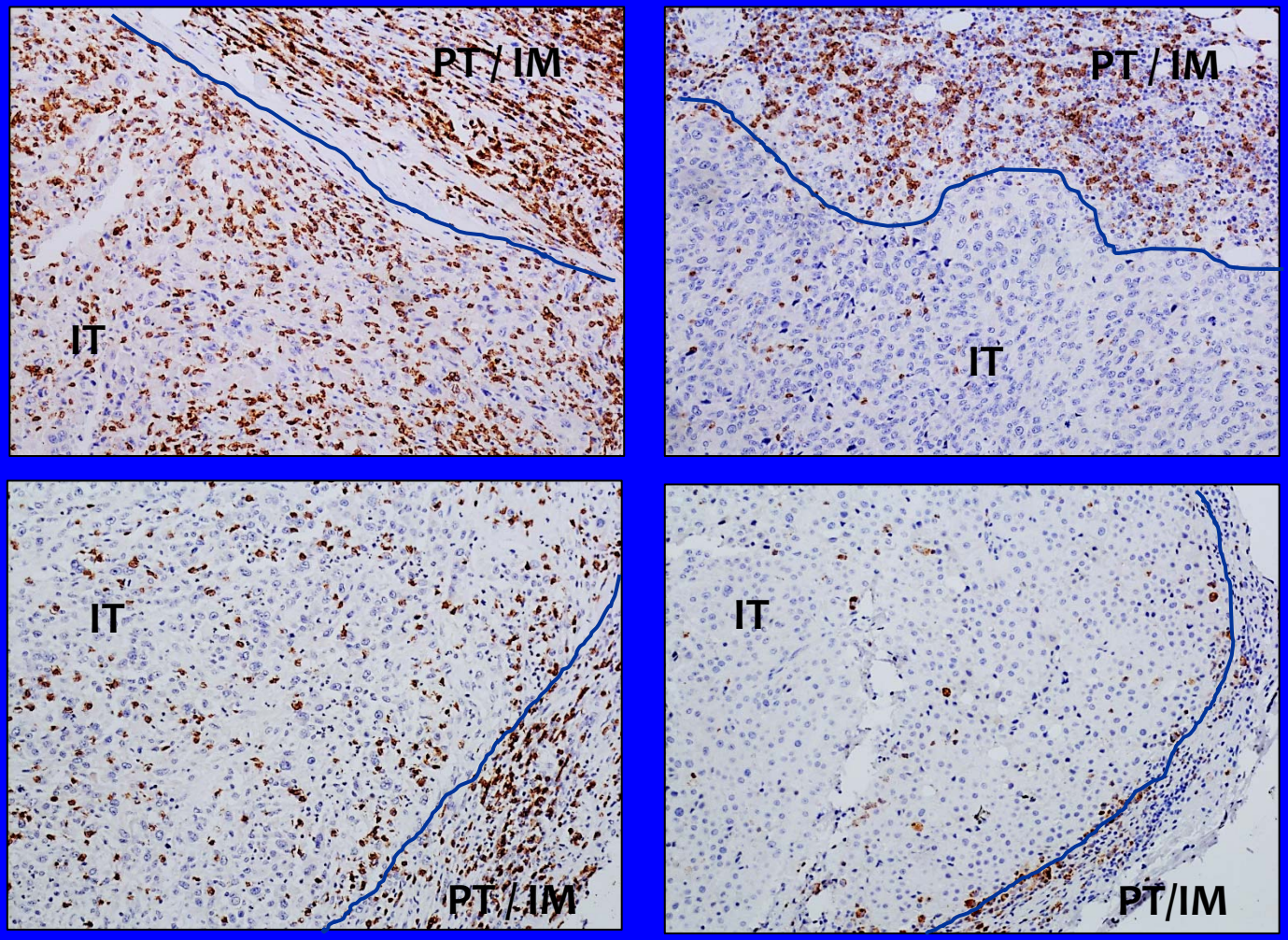
1. T cells:
   - CD3, CD8, CD4 (peri-tumoral / intra-tumoral)
   - Foxp3
   - PD-1 / BTLA - TNF-R family (4-1BB / OX40)

2. Negative and positive markers of inflammation:
   - protein nitrotyrosination (NT) → peroxynitrite
   - iNOS
   - CXCL10/IP-10

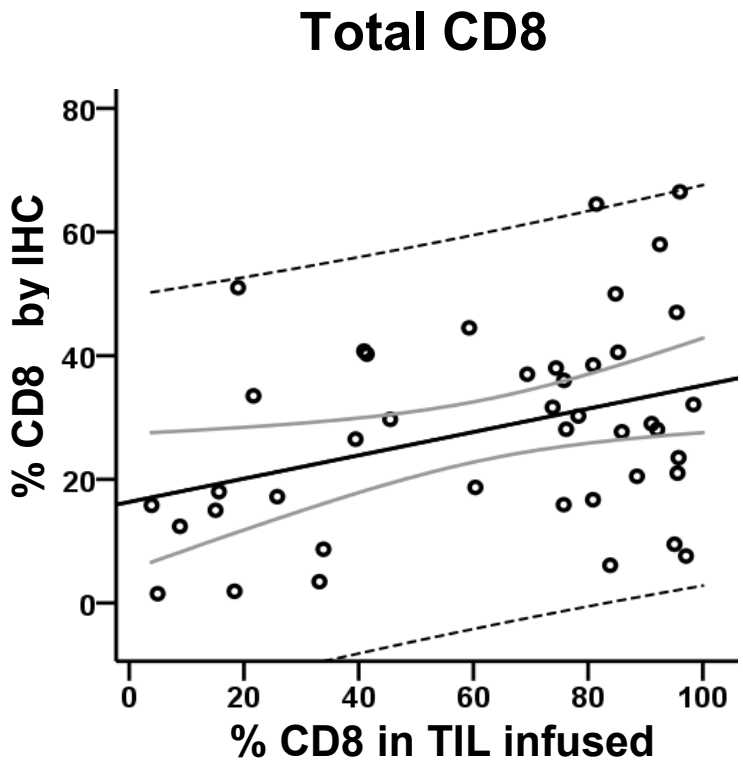
3. Macrophages/myeloid cells/DCs:
   - CD163 - S100A9
   - CD66b
   - DC-LAMP

4. Other immunosuppressive factors:
   - pSTAT3
   - IDO

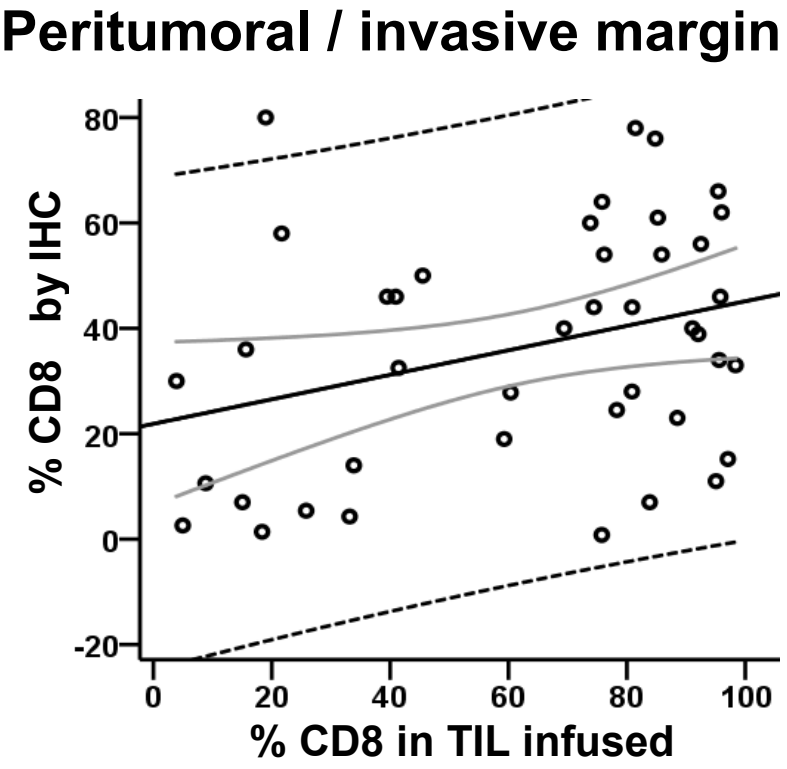
CD8 in original tumor used to grow TIL (peritumoral near invasive margin versus intratumoral



Association between CD8 by IHC and CD8 % in expanded TIL (N= 42 pts)

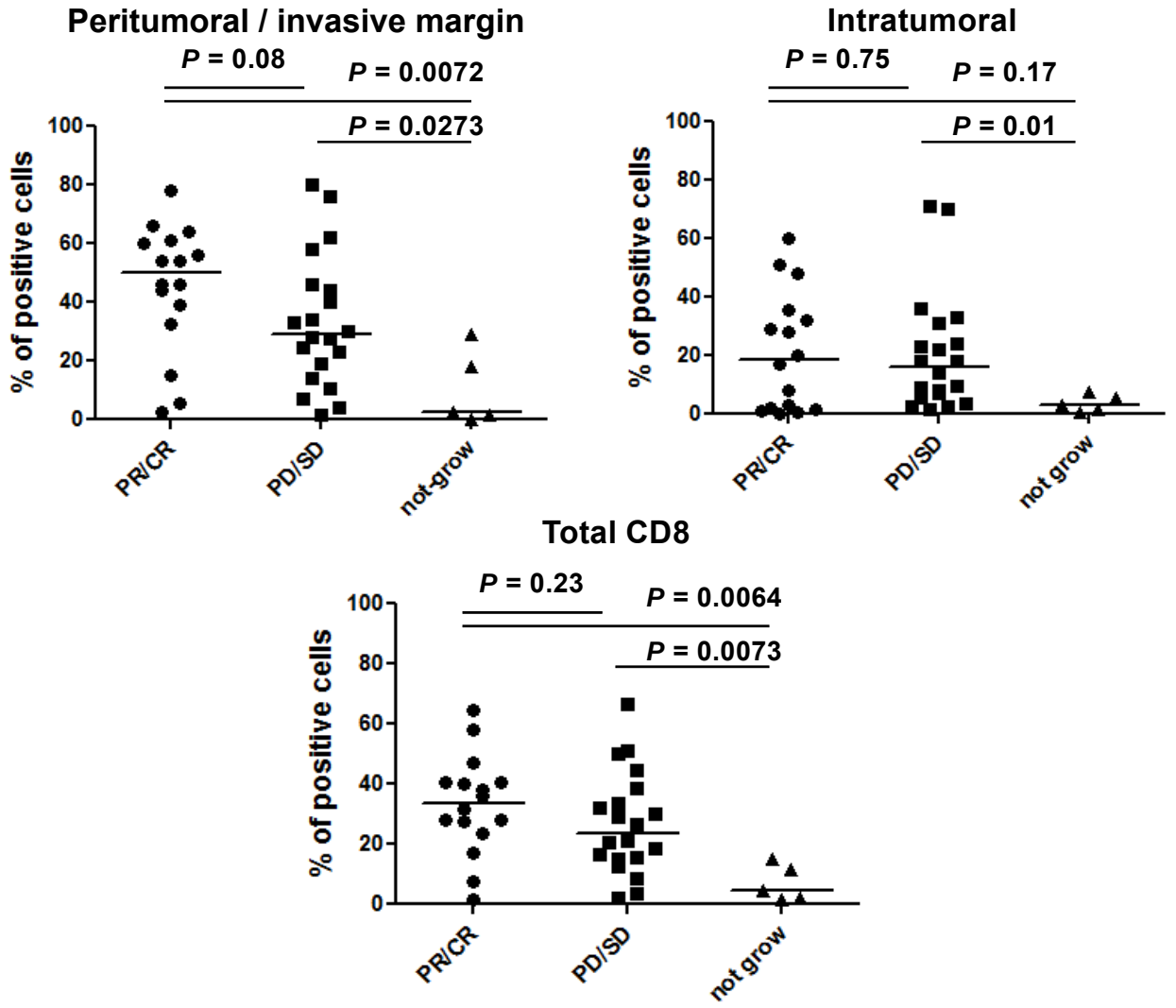


$P = 0.049$, $r^2 = 0.305$

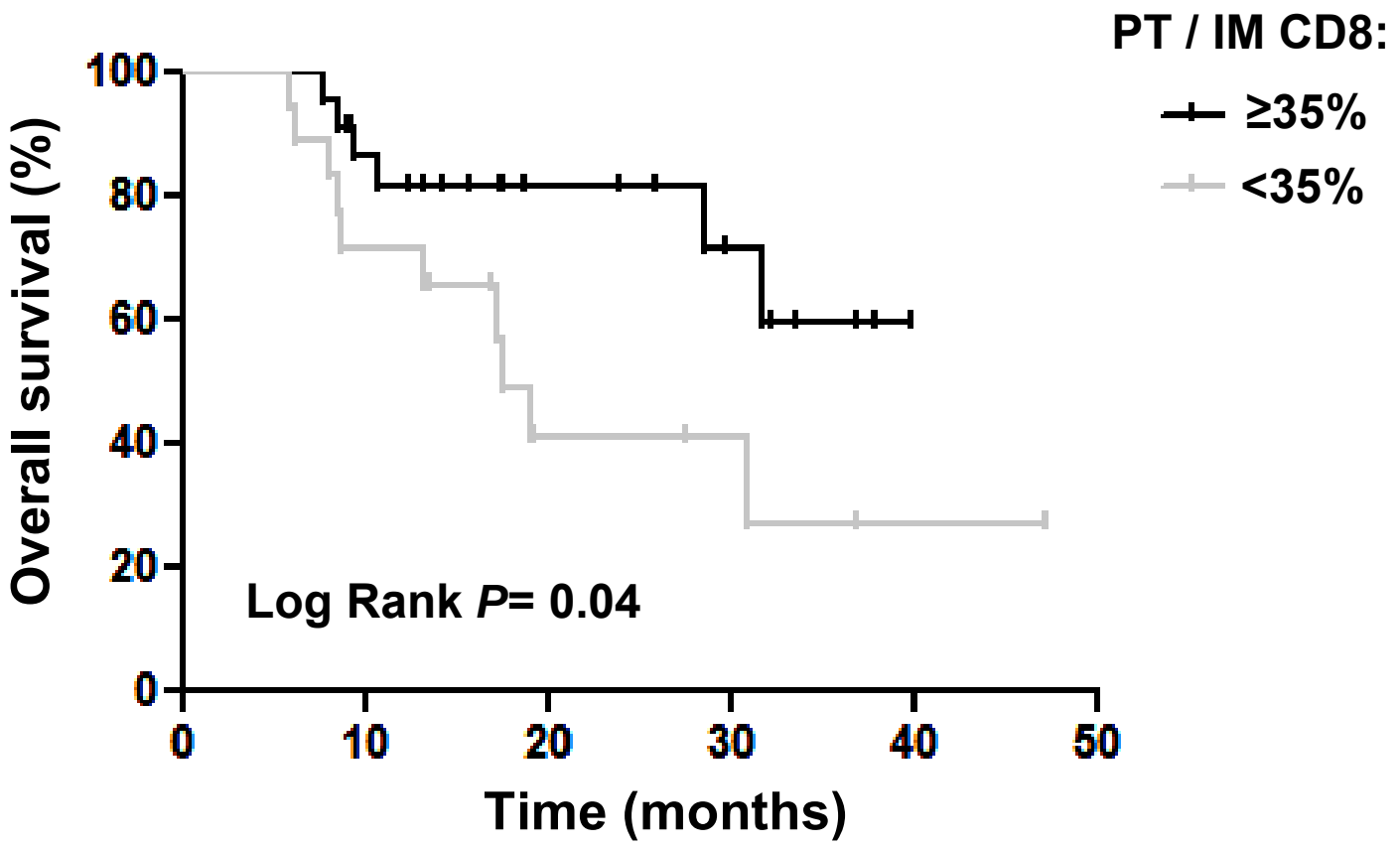


$P = 0.046$, $r^2 = 0.310$

Association between CD8 expression by IHC in tumor and TIL clinical response

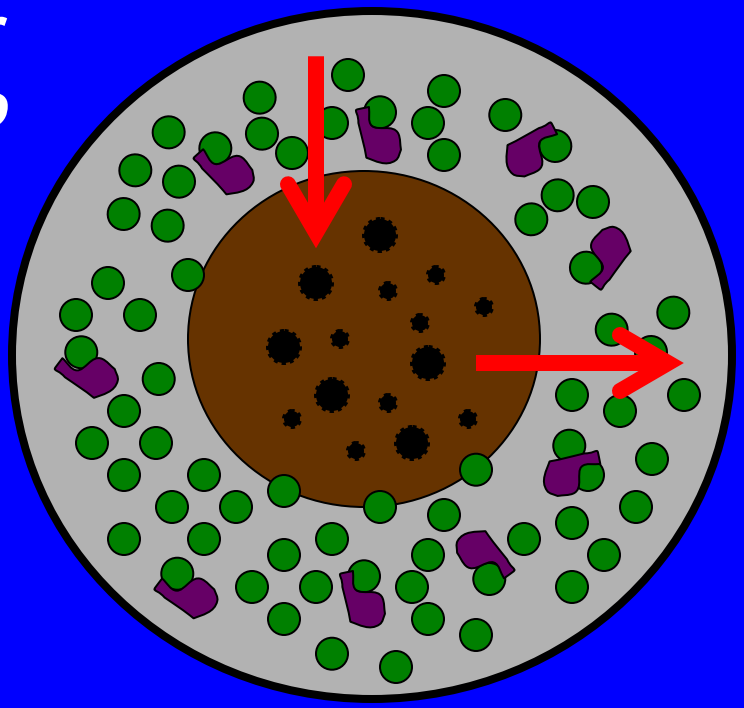


Association between higher CD8 % at invasive margin tumor and survival



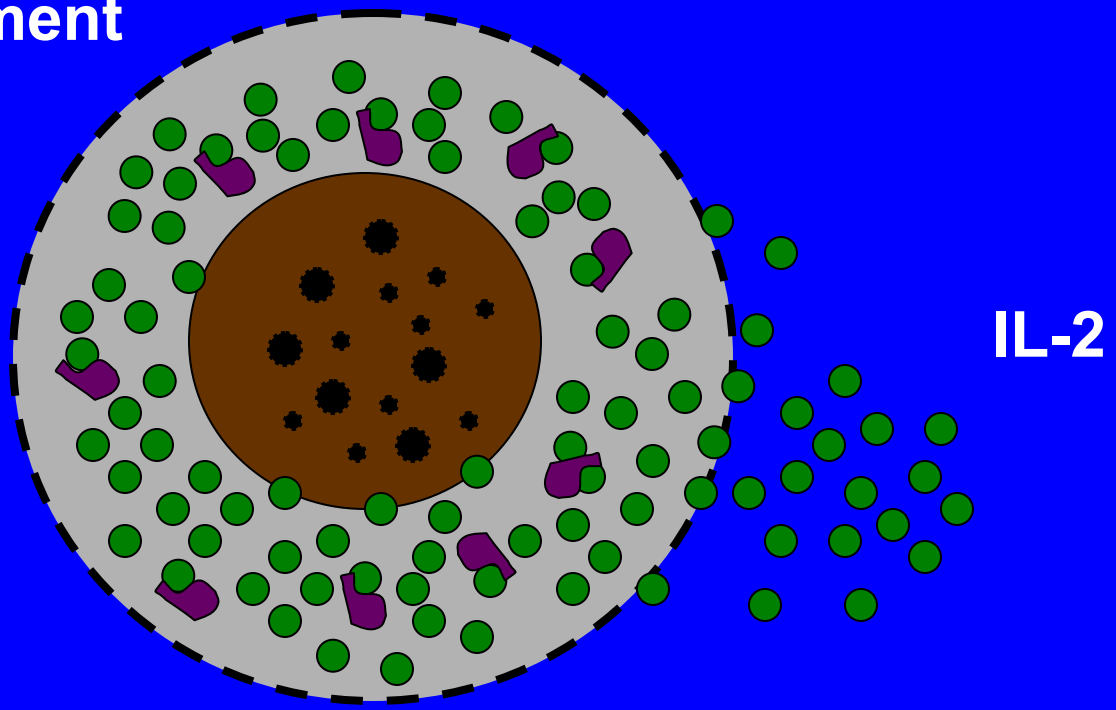
Relevance of TIL at the invasive margin (peri-tumoral)

Tumor
in vivo

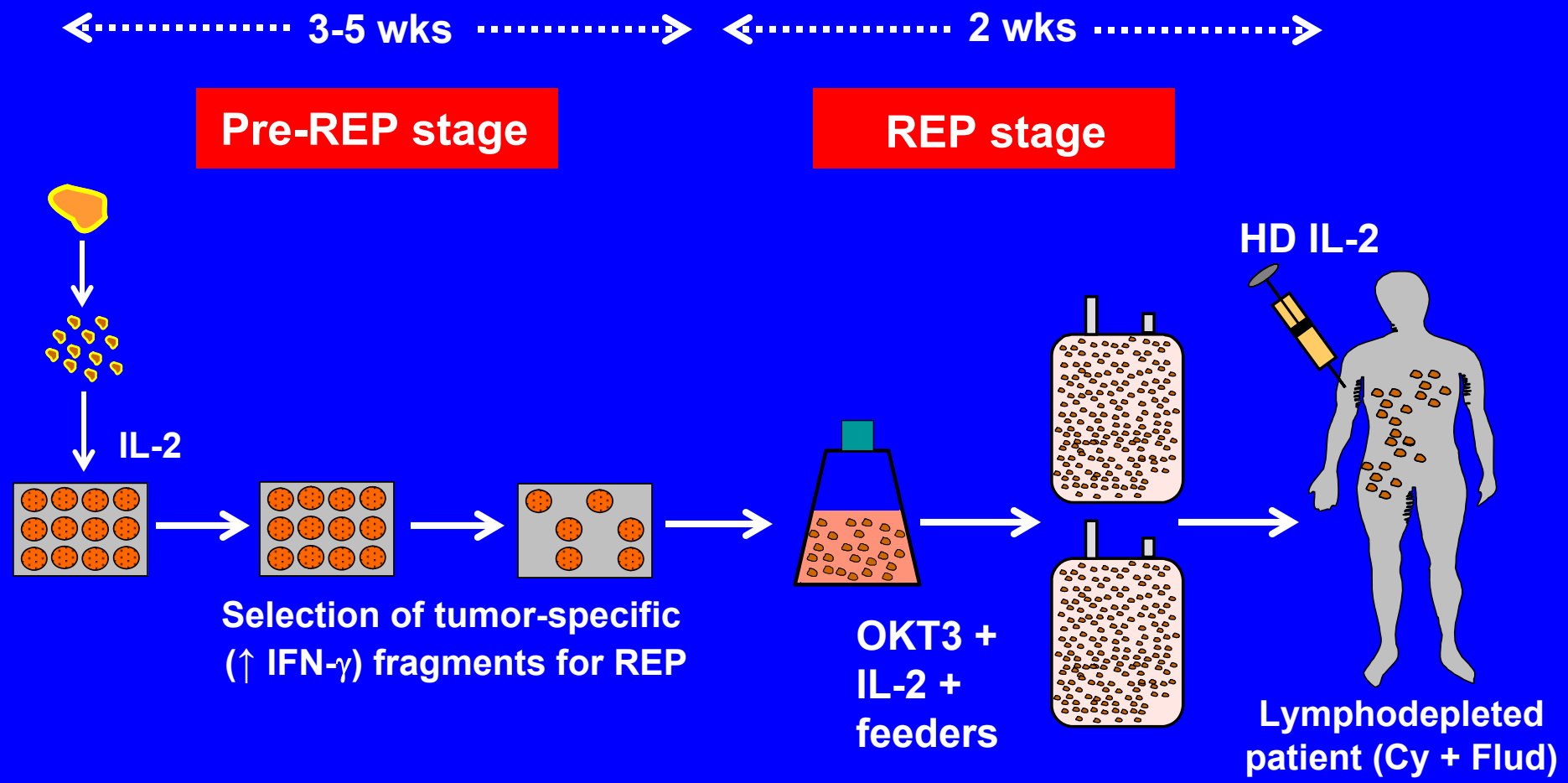


Relevance of TIL at the invasive margin (peri-tumoral)

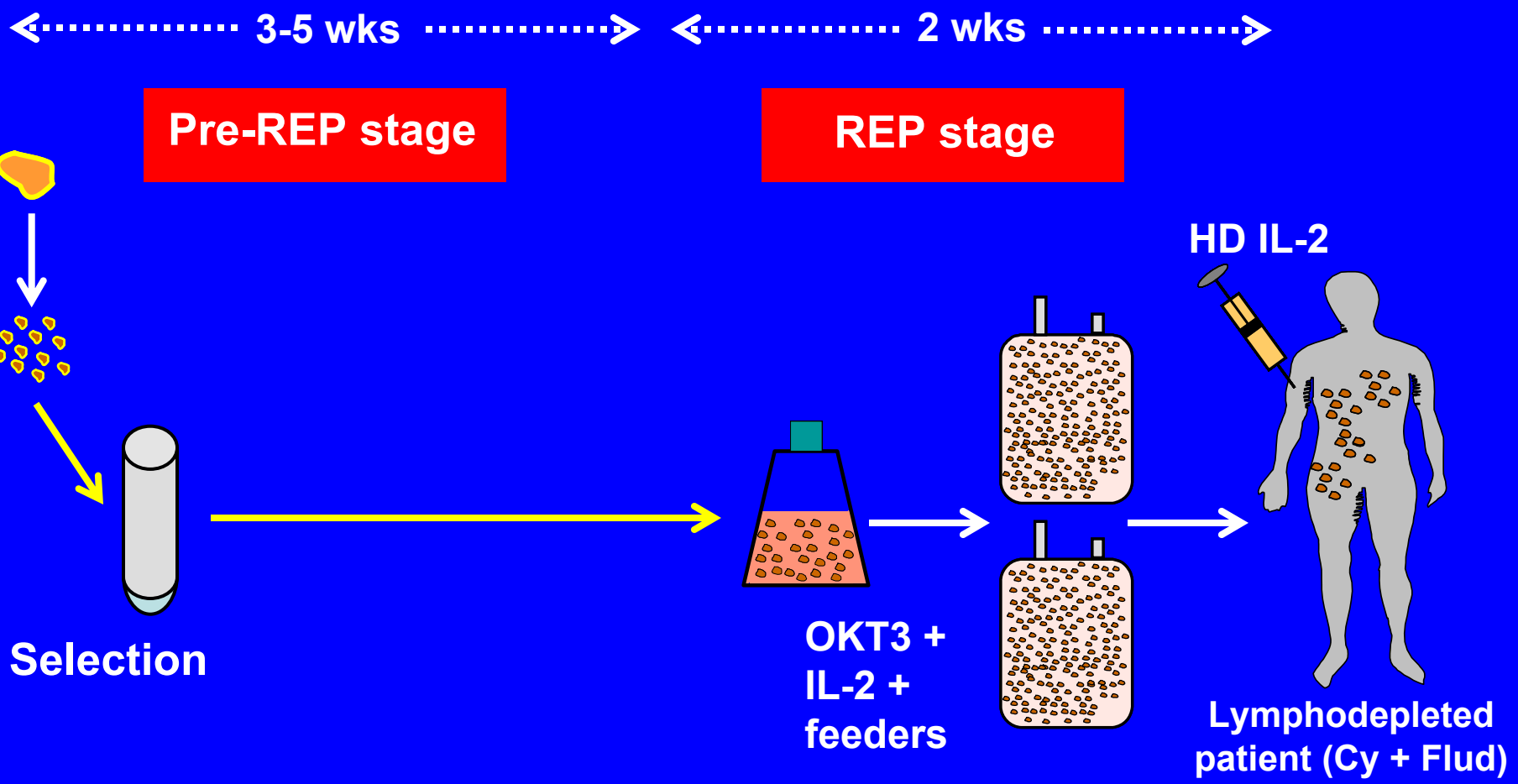
Tumor fragment
ex vivo



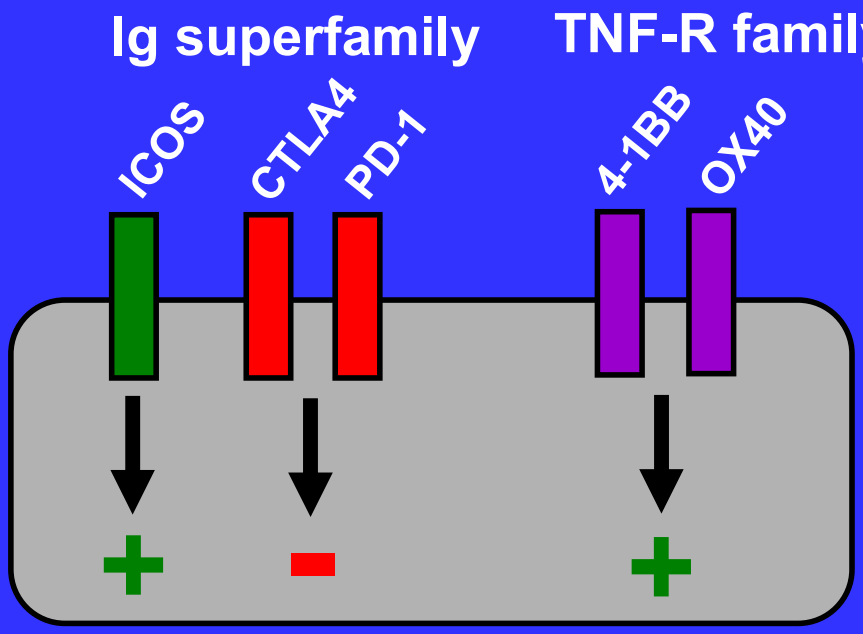
Can we select up-front tumor-specific TIL for expansion?



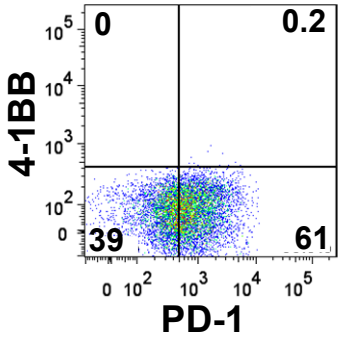
Can we select up-front tumor-specific TIL for expansion?



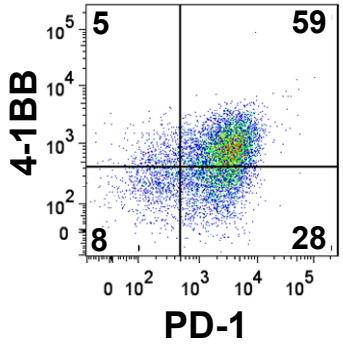
TCR activation induced costimulatory molecules (Ig and TNF-R families)



4-1BB and PD-1 induction

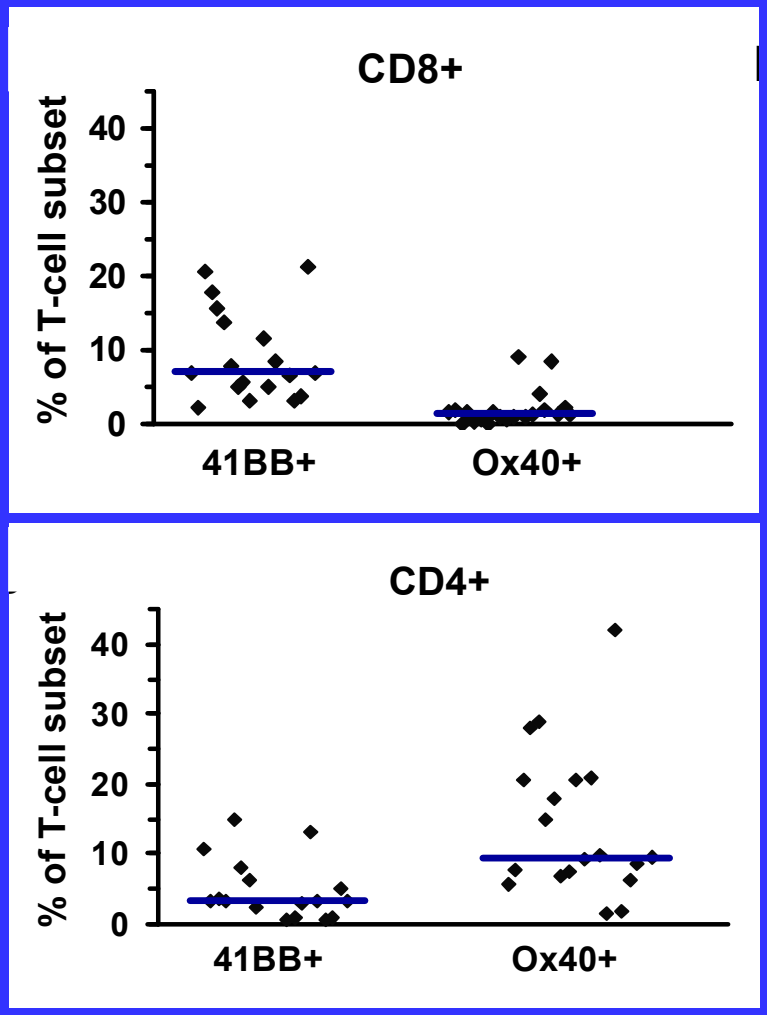


No tumor cells

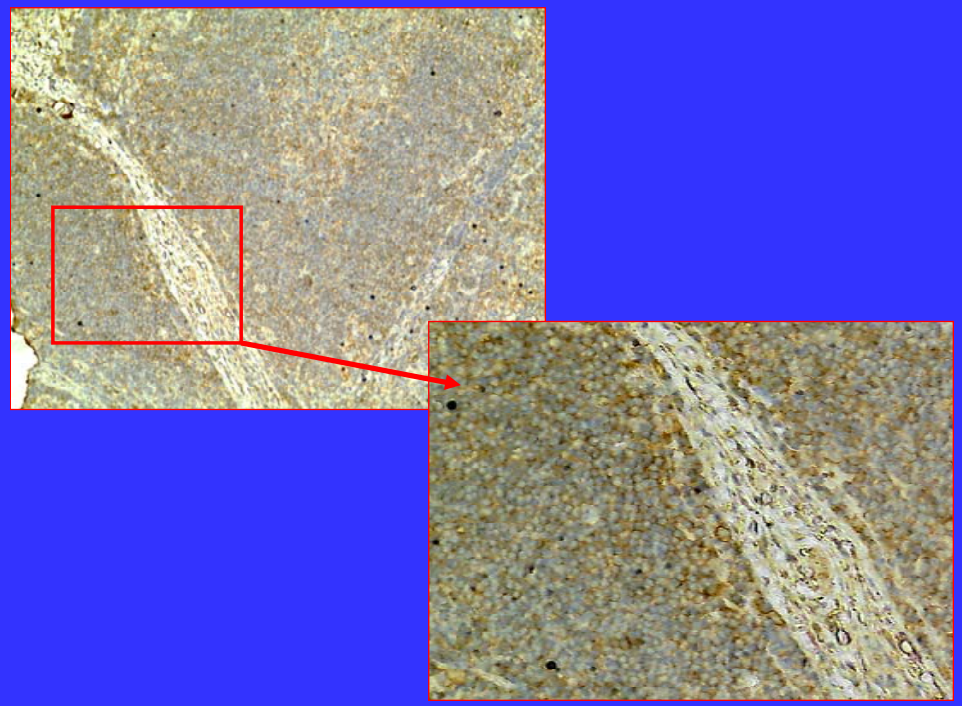


Plus tumor cells (24 h)

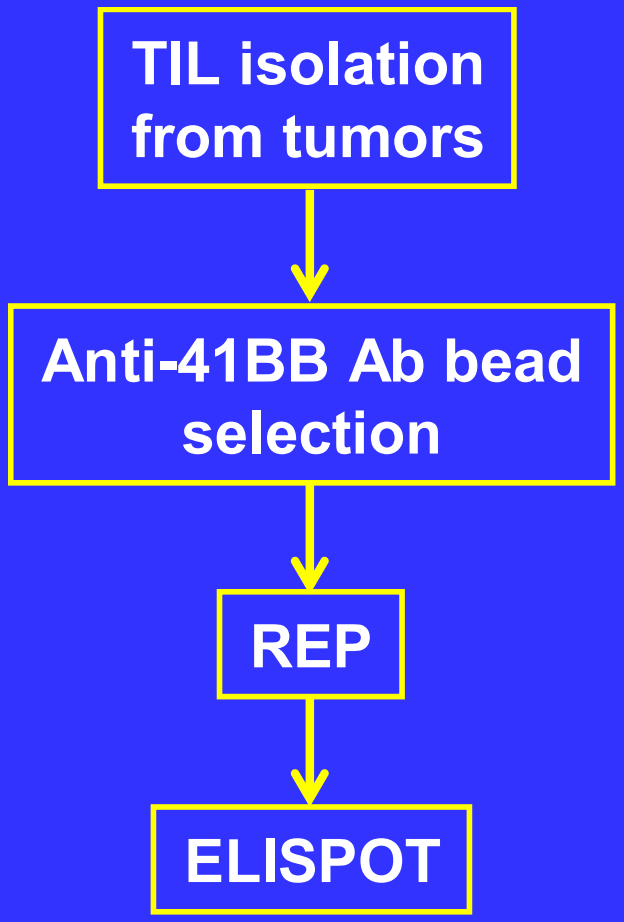
Presence of recently activated 4-1BB+ and OX40+ T cells in tumor isolates



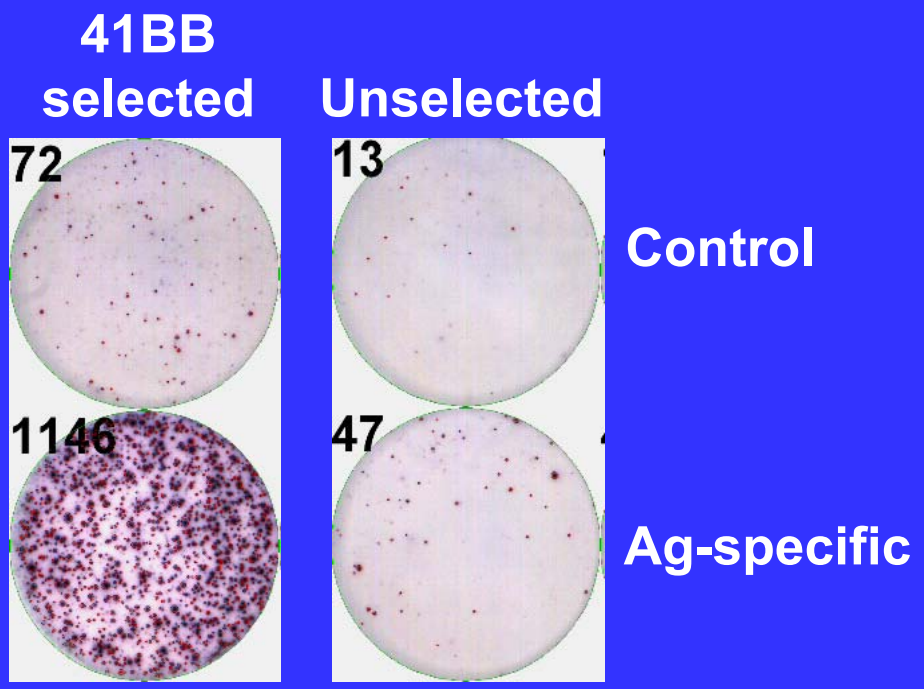
4-1BB staining by IHC



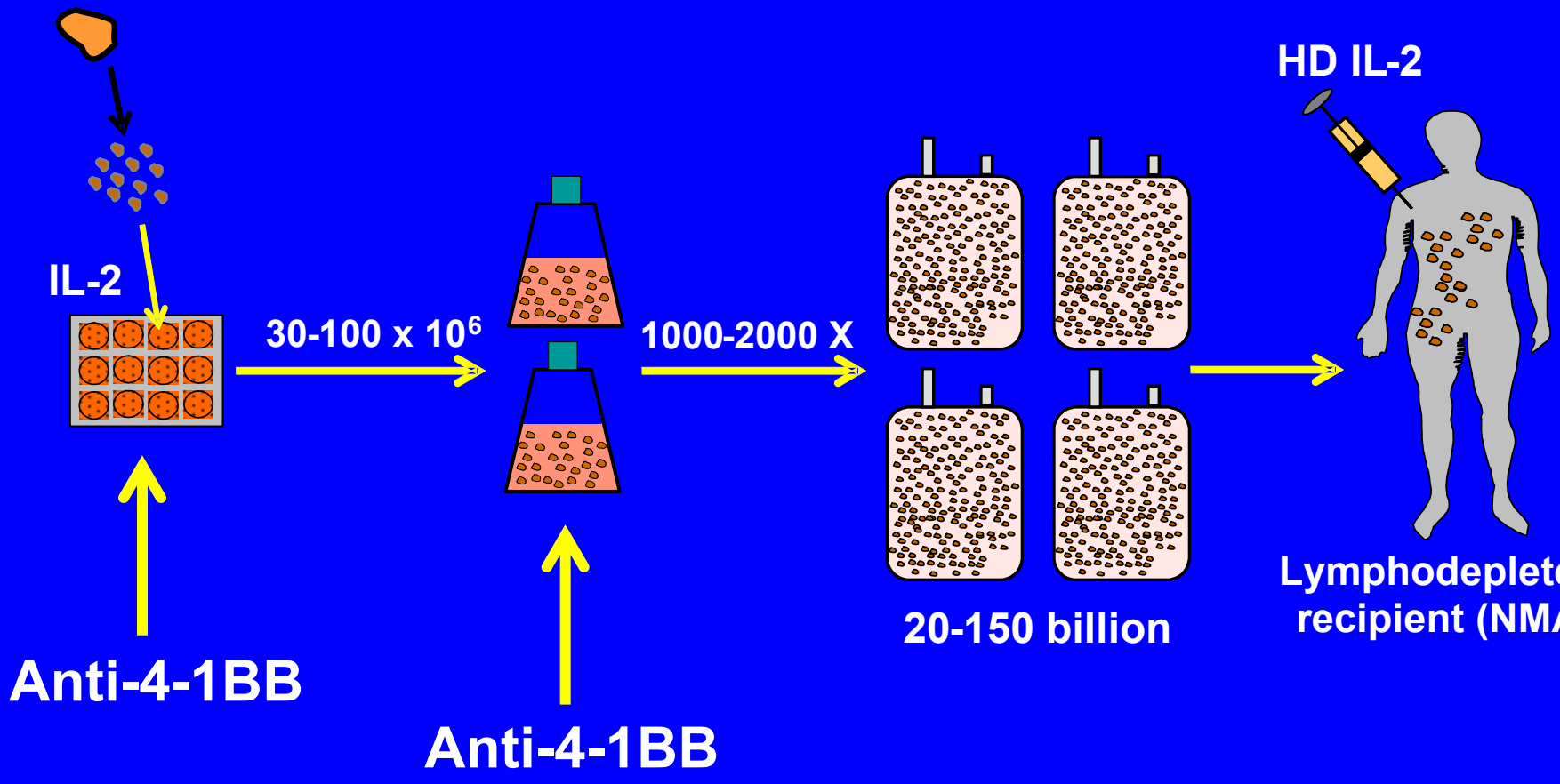
Selection of 4-1BB+ CD8+ T cells highly enriches tumor Ag-specific cells



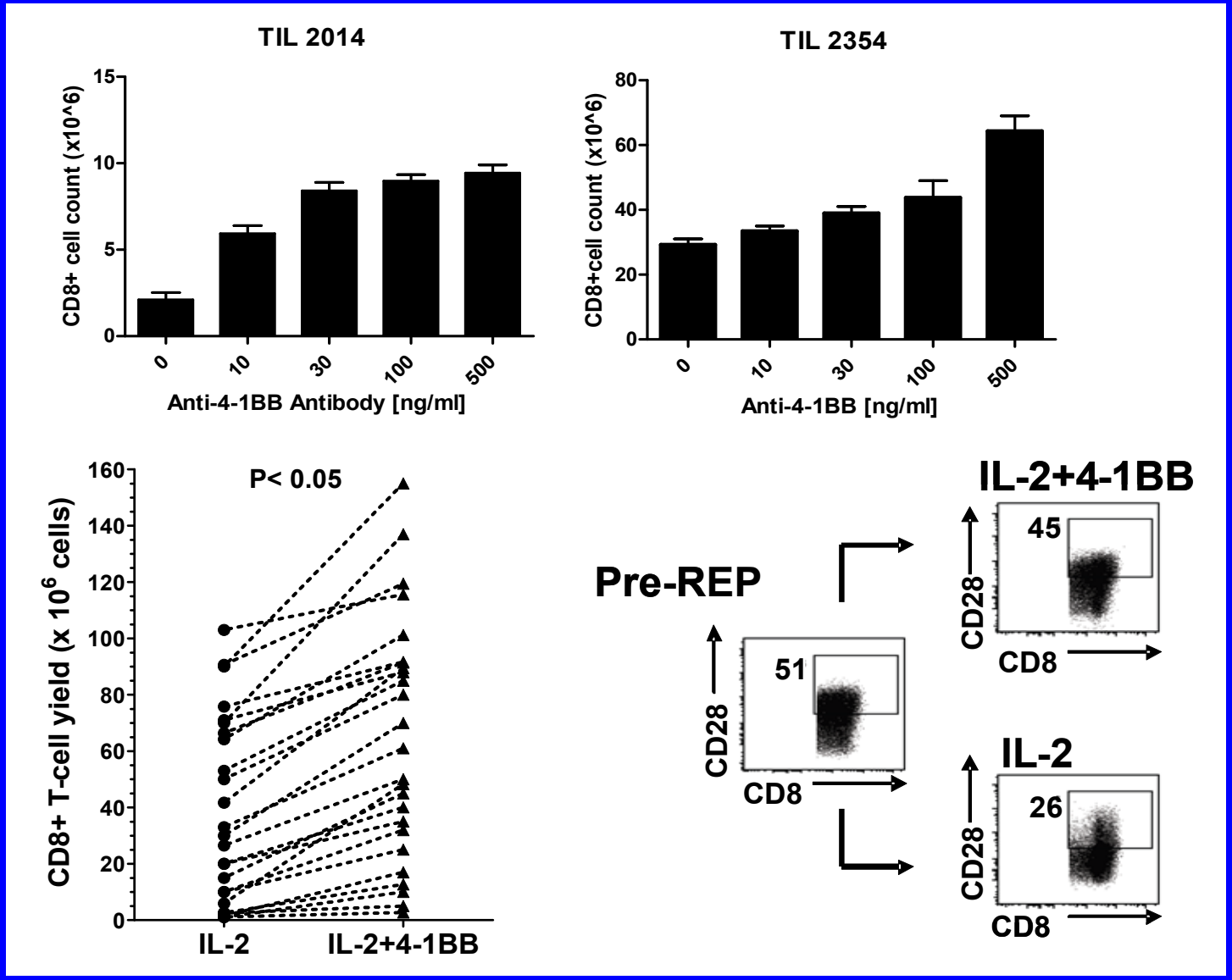
Handling before REP



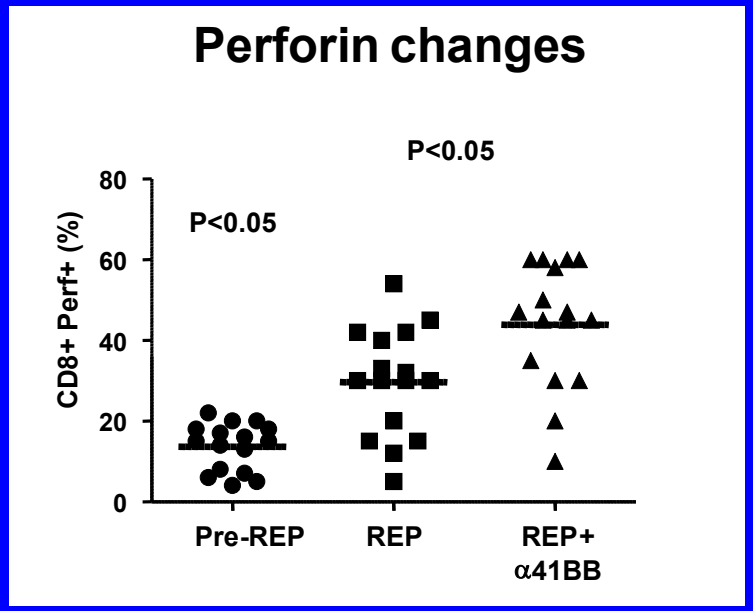
Addition of agonistic anti-4-1BB Abs during TIL production

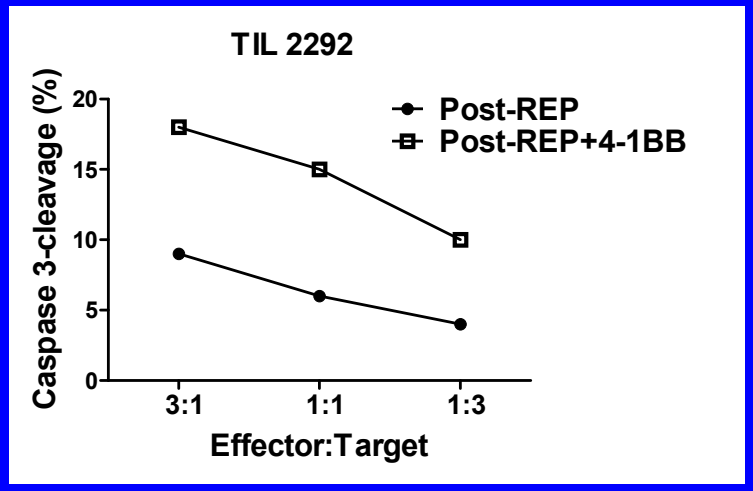


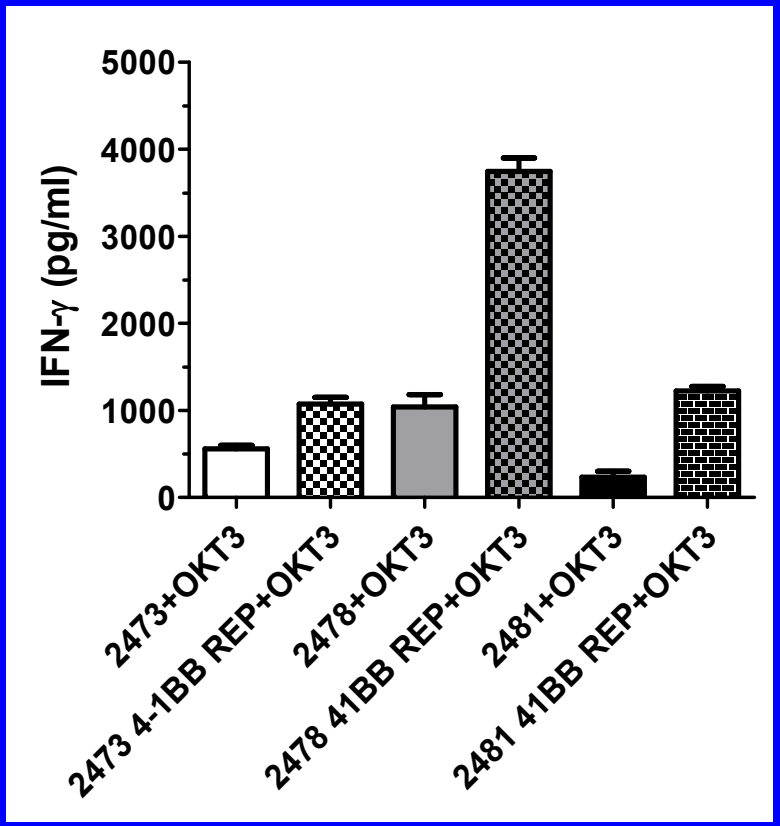
Anti-4-1BB Ab increases CD8+ T-cell yield and preserves CD28 expression



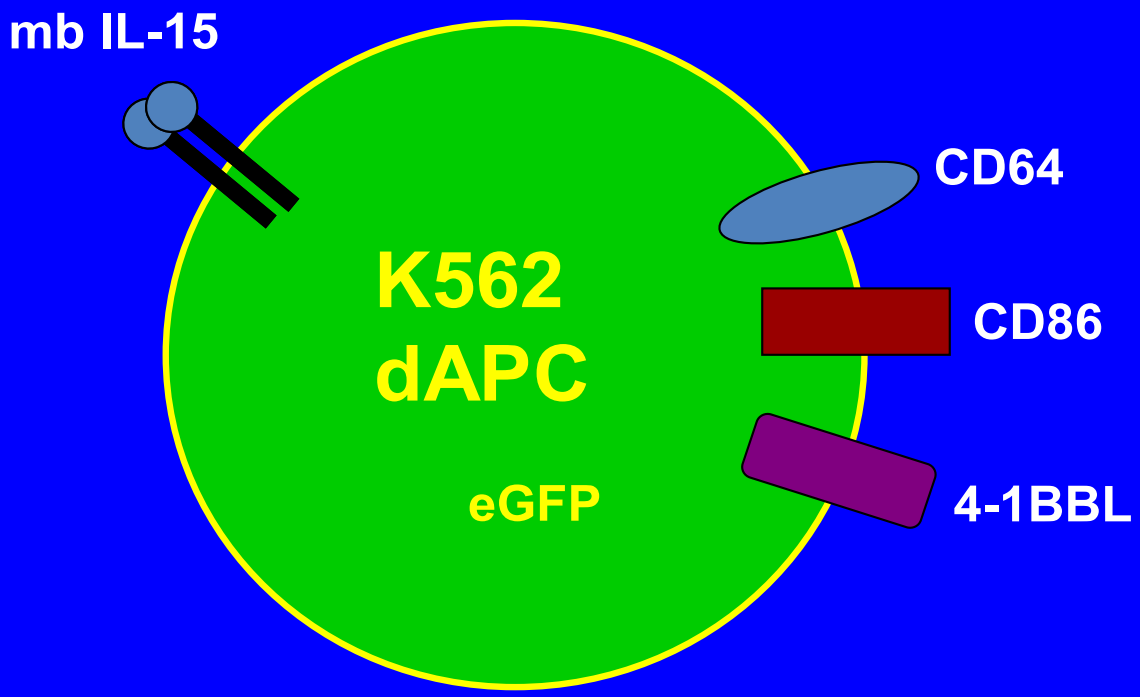
Anti-41BB during TIL expansion increases GB and Perforin expression







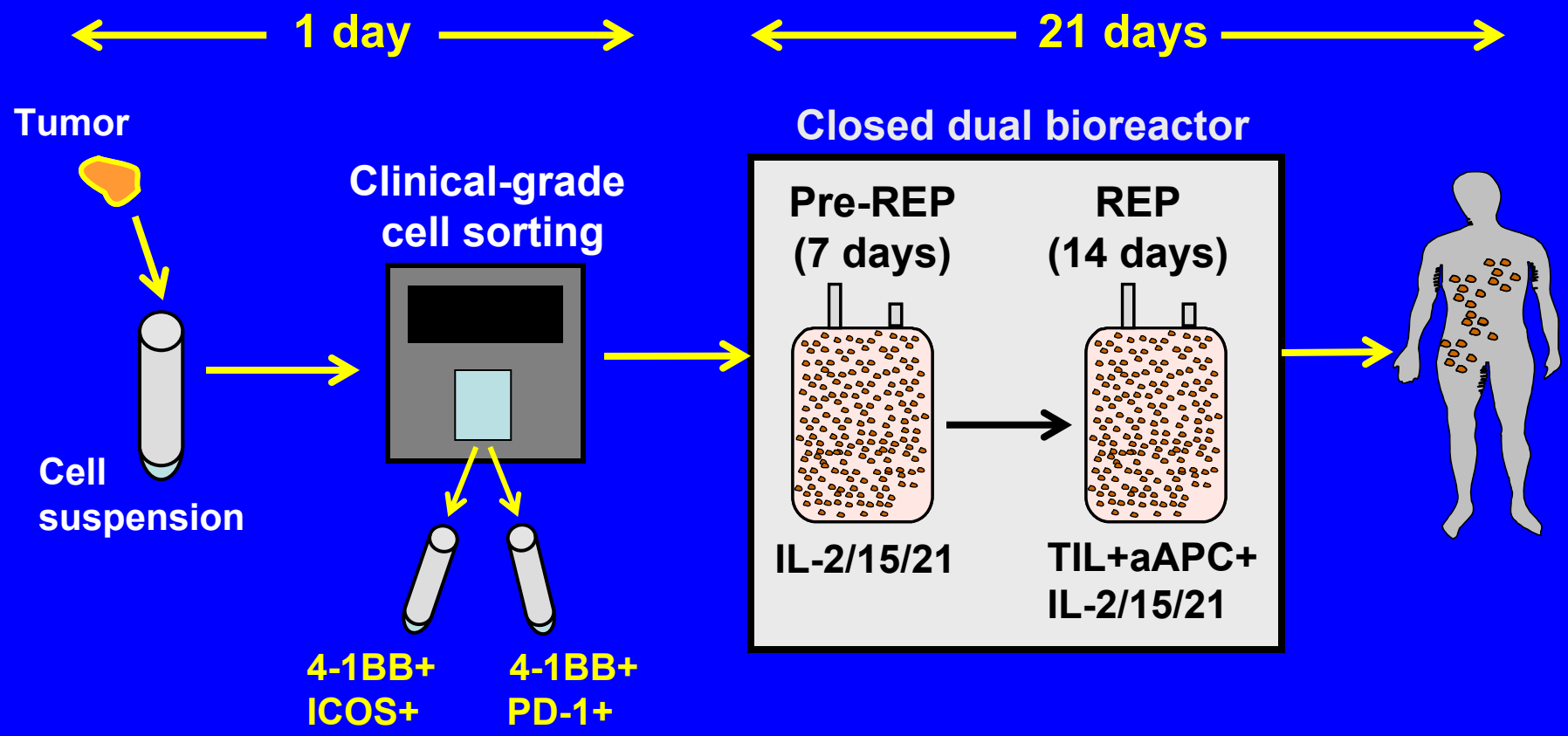
“Off-the-shelf” APCs for TIL REP: Engineered K562 cells



Generation #1 aAPC
(master cell bank made)

Problem	Solution
• No reliable biomarkers of infused TIL potency predictive of response	• Phenotypic biomarker analysis: - T-cell EM subsets (CD8) - Novel markers - Function (Ag-specific / polyclonal)
• No predictive biomarkers for patient selection for therapy: - clinical response - initial TIL outgrowth - expanded TIL phenotypes	• Predictive tests before tumor resection for TIL outgrowth: - IHC biomarkers in tumors - gene expression in tumors - systemic/genetic markers (blood)
• No method to isolate tumor-specific TIL up-front for expansion (save time)	• Selection from fresh TIL isolates using activation markers?
• PBMC feeder problem and availability (costs)	• Off-the-shelf APCs with defined stimulatory molecules
• Open systems → too much manual handling (labor/cost)	• Automated closed systems for selection and expansion

What the future TIL expansion protocol will look like (21-day process)?



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