Cytokine Support for Gene Engineered T Cells

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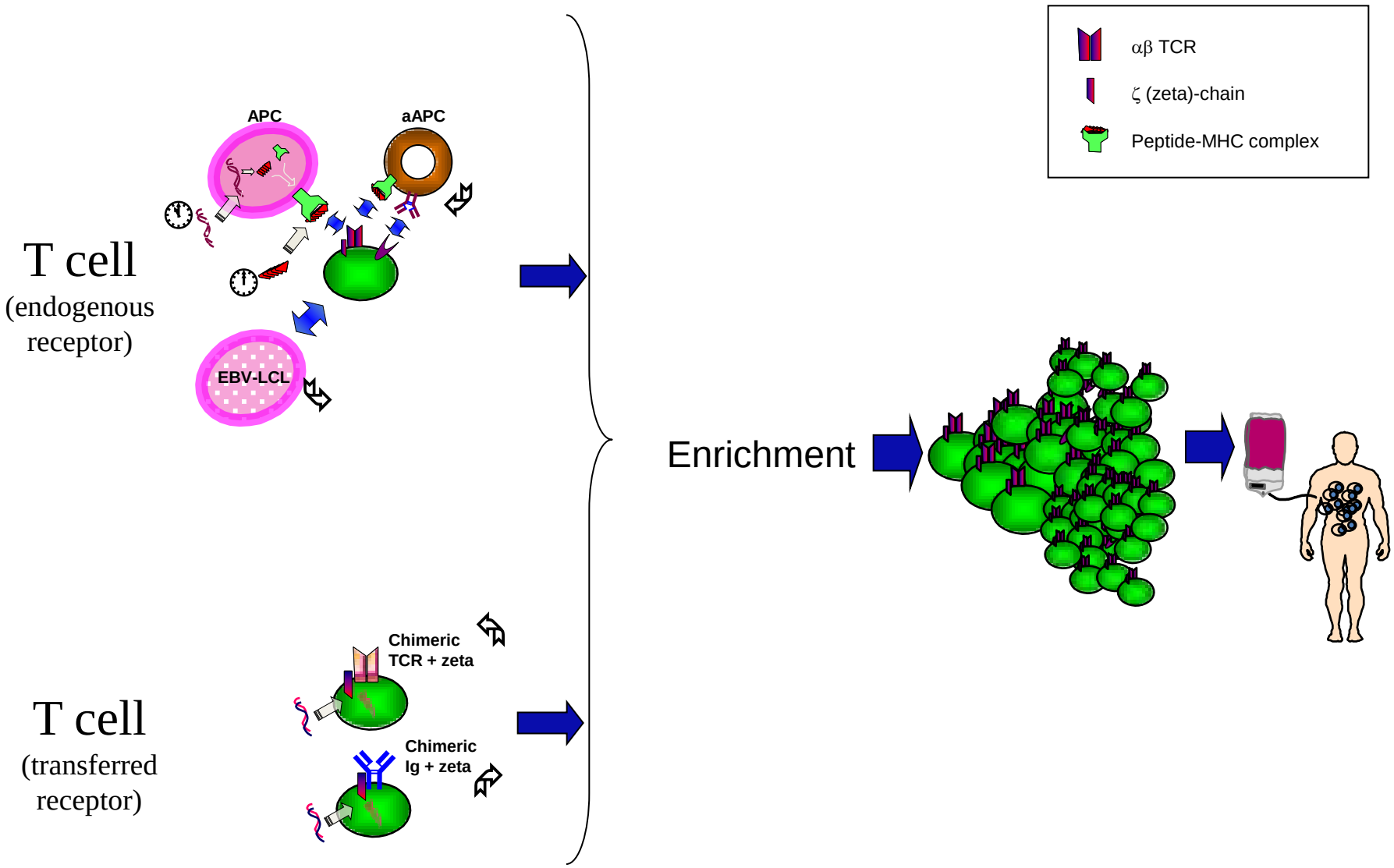
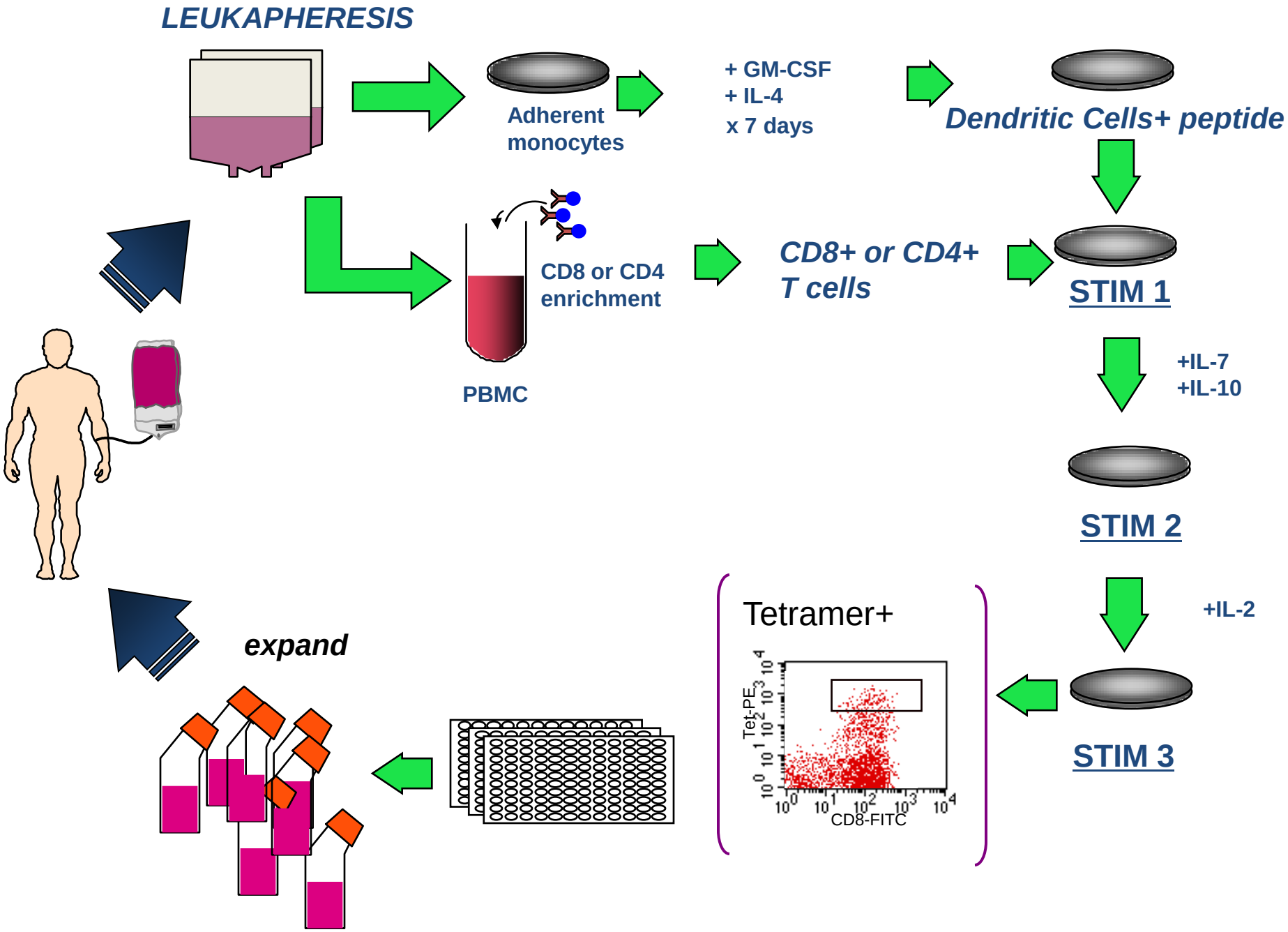
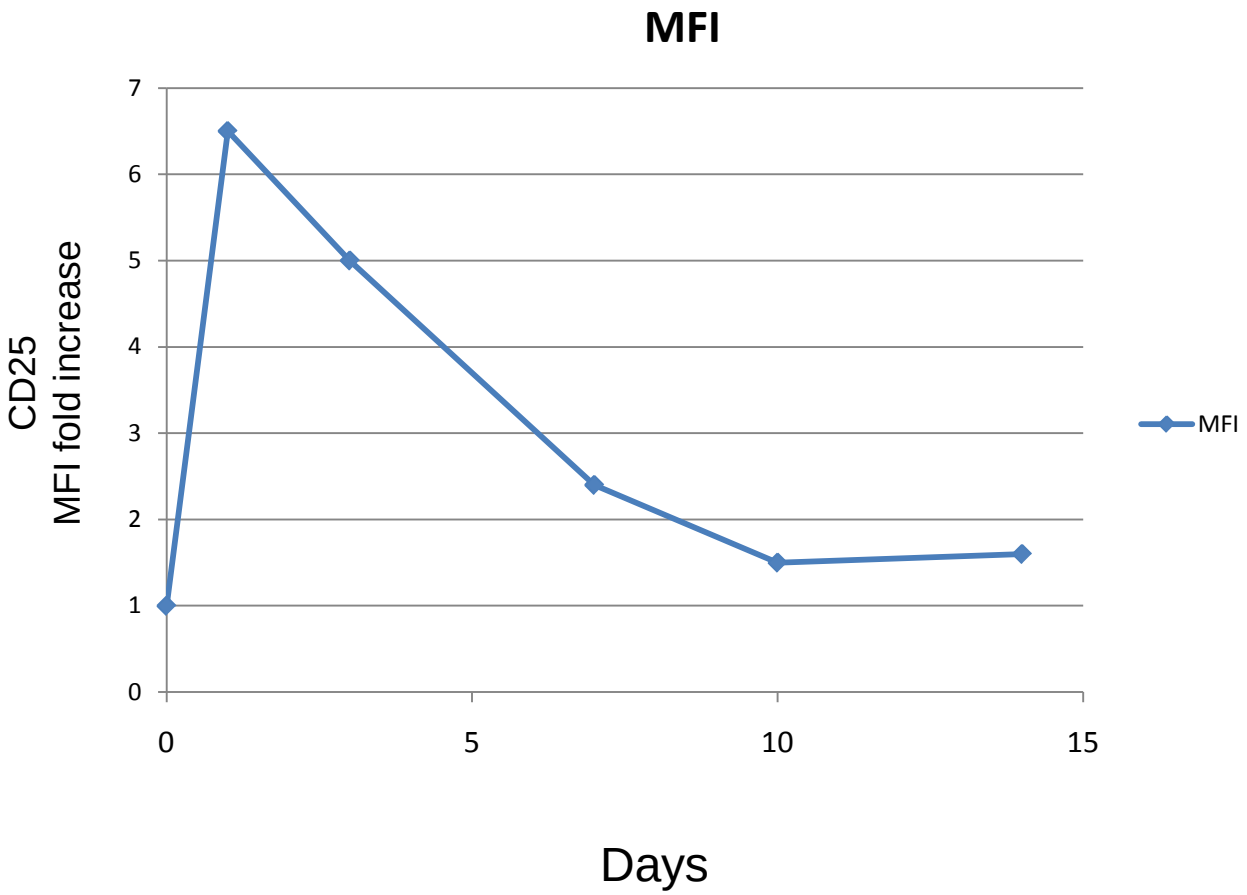


Antigen-specific T Cell Enrichment

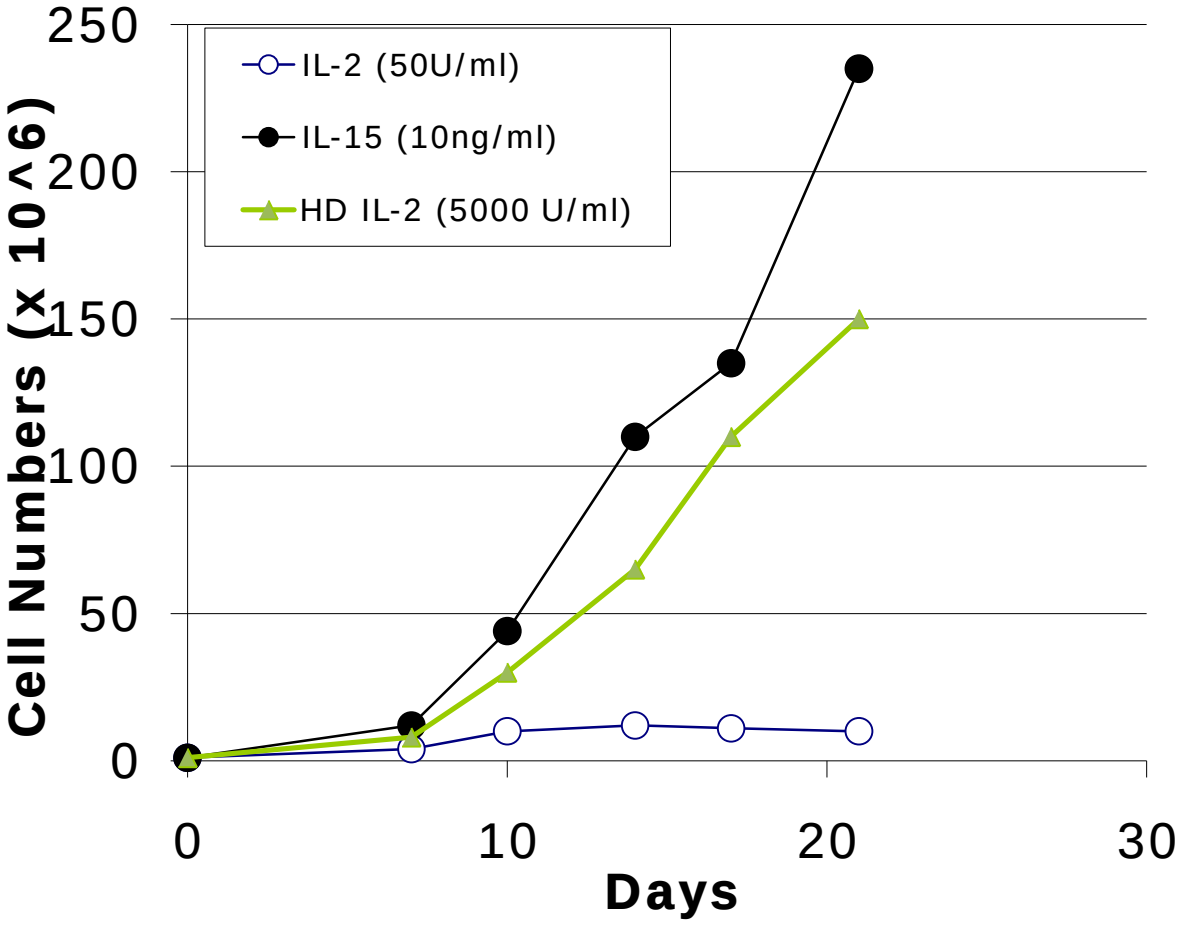
T Cell Expansion & Infusion


LEUKAPHERESIS
Adherent monocytes
+ GM-CSF
+ IL-4
x 7 days
Dendritic Cells+ peptide
CD8 or CD4 enrichment
PBMC
CD8+ or CD4+ T cells
STIM 1
+IL-7
+IL-10
STIM 2
+IL-2
STIM 3
Tetramer+
Tet-PE
CD8-FITC
expand

In vitro response

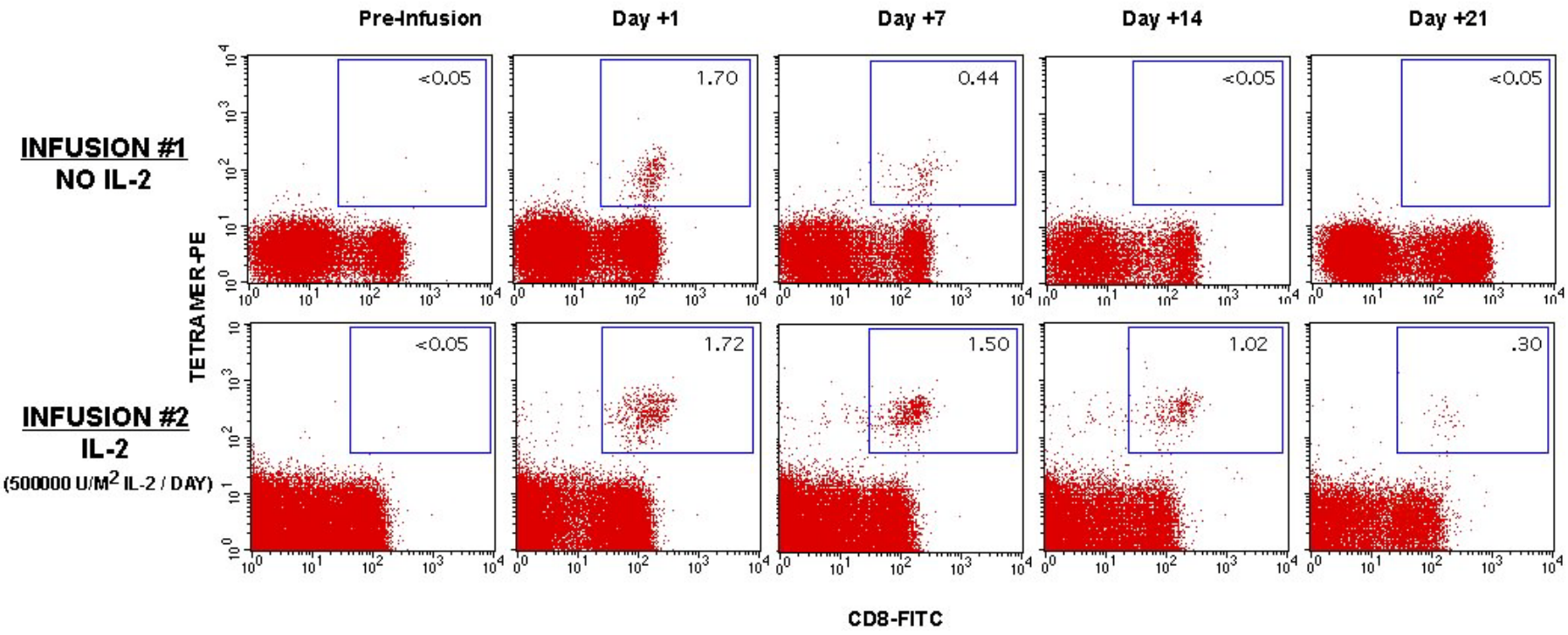


In vitro response



In vivo

- Low-dose IL-2 (250,000 U/m2 s.c. q12h x 14d)



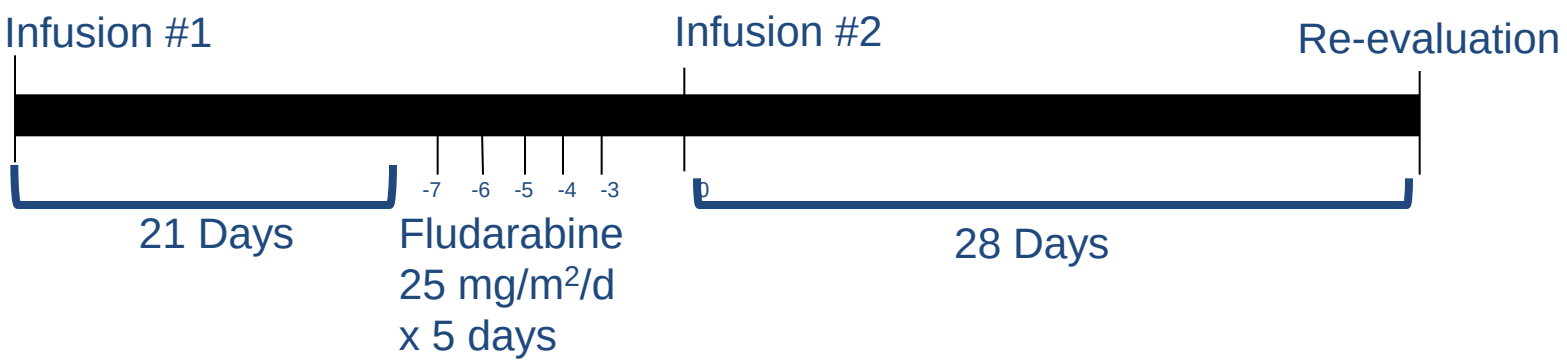
Low-dose IL-2 + Lymphodepletion

PROTOCOL # 1796
Adoptive T Cell Therapy following Lymphodepletion

Objectives :
- Evaluate Safety
- Evaluate T Cell Persistence
- Evaluate anti-tumor efficacy

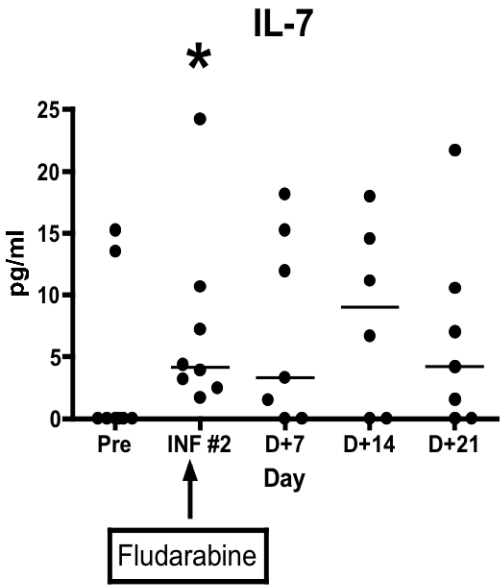
Eligibility Criteria :
- Stage IV (Metastatic)
- HLA-A2

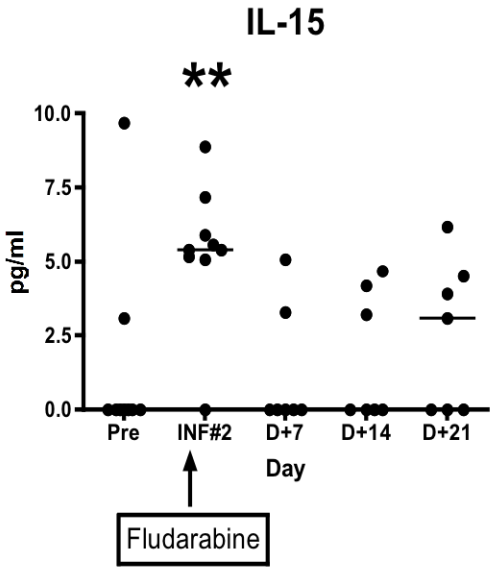
T Cell Infusion:
- Antigen-specific CD8+ T cell clones
- Targeting MART-1, gp100
- Dose: 10^{10} cells / m^2

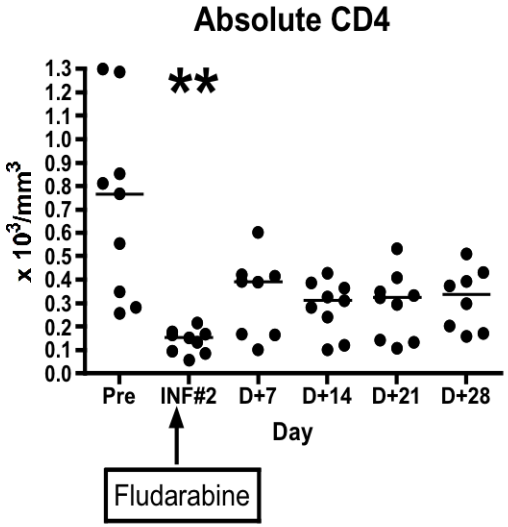


Low-dose IL-2 + Lymphodepletion

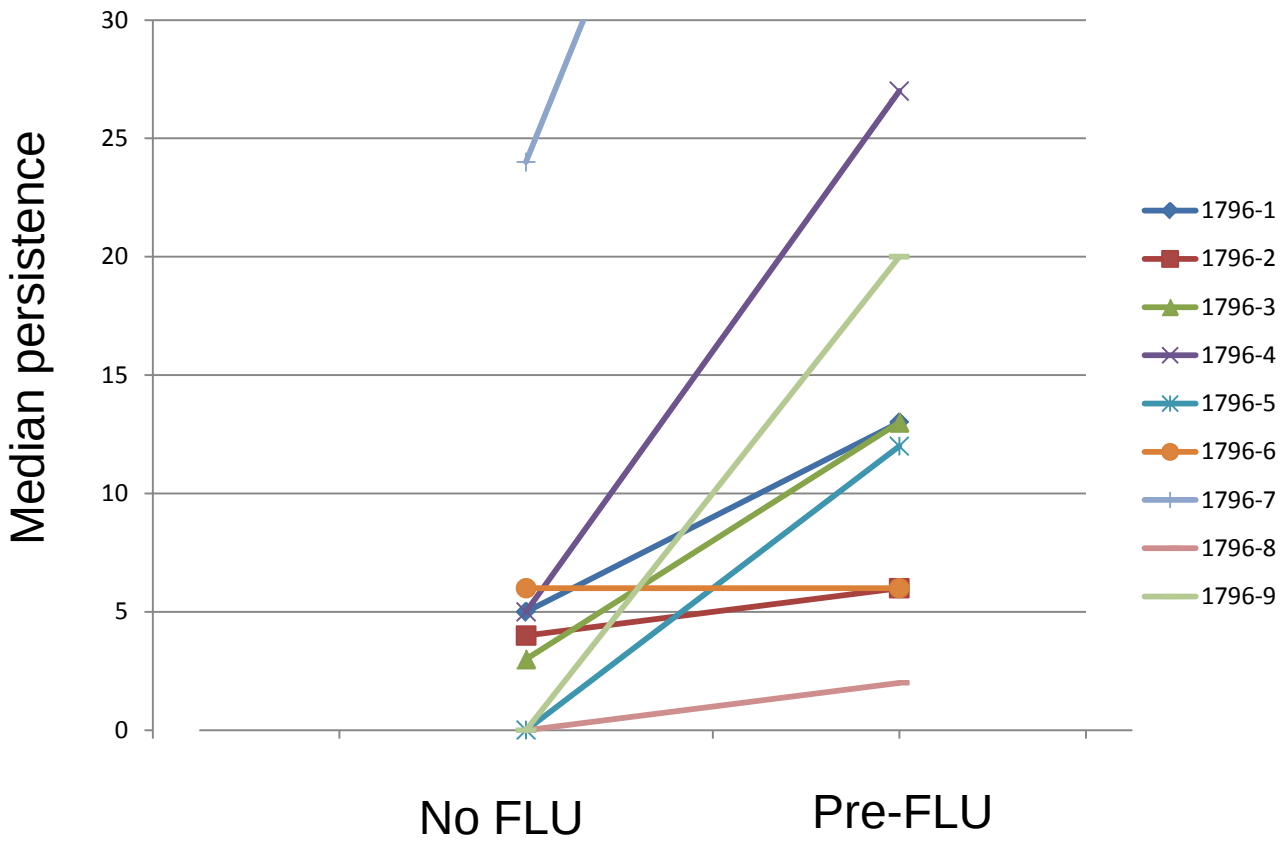
CD4 Lymphopenia Is Accompanied By Increase In Serum IL-7 And IL-15







Low-dose IL-2 + Lymphodepletion



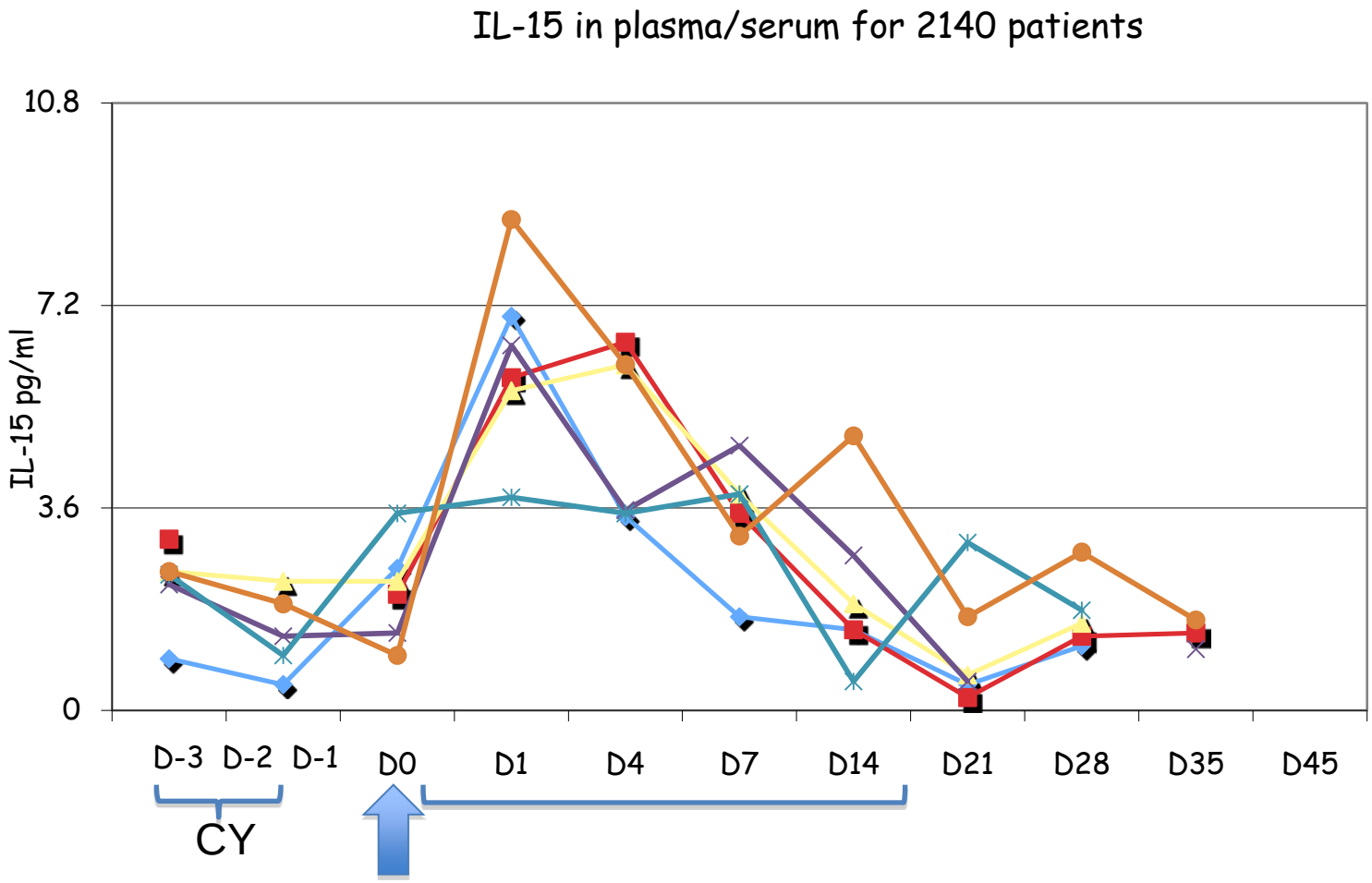
IL-2 + Lymphodepletion

PROTOCOL # 2140
Adoptive T Cell Therapy following Lymphodepletion

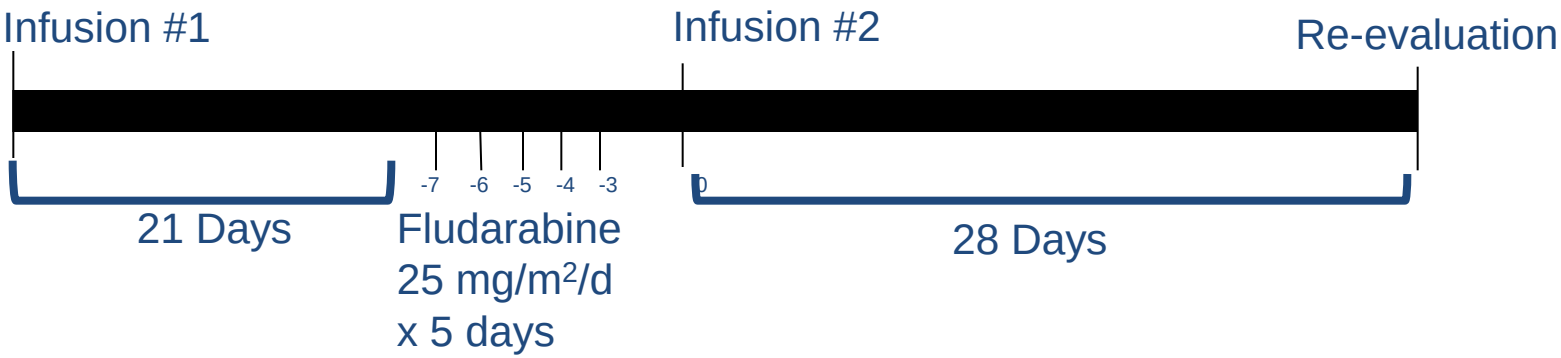
Objectives :
- Evaluate Safety
- Evaluate T Cell Persistence
- Evaluate anti-tumor efficacy

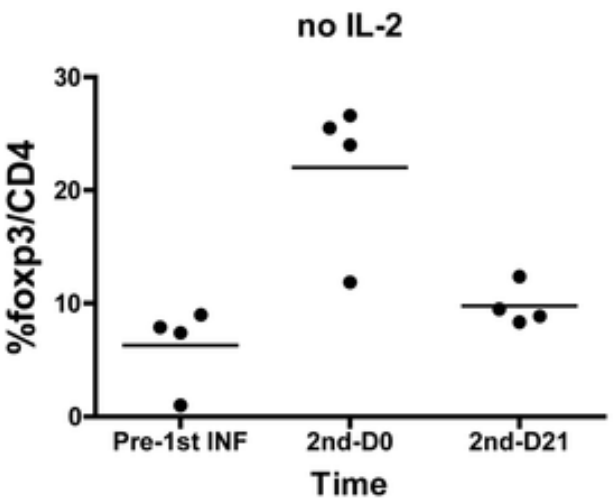
Eligibility Criteria :
- Stage IV (Metastatic)
- HLA-A2

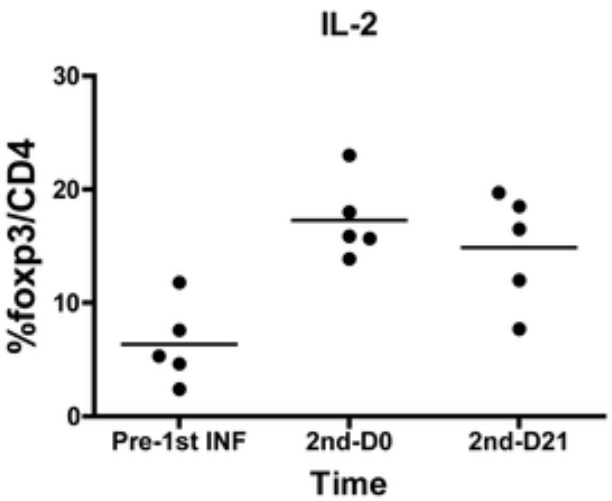
T Cell Infusion:
- Antigen-specific CD8+ T cell clones
- Targeting MART-1, gp100
- Dose: 10^{10} cells / m^2


IL-15 in plasma/serum for 2140 patients
10.8
7.2
3.6
0
IL-15 pg/ml
D-3
D-2
D-1
D0
D1
D4
D7
D14
D21
D28
D35
D45
CY

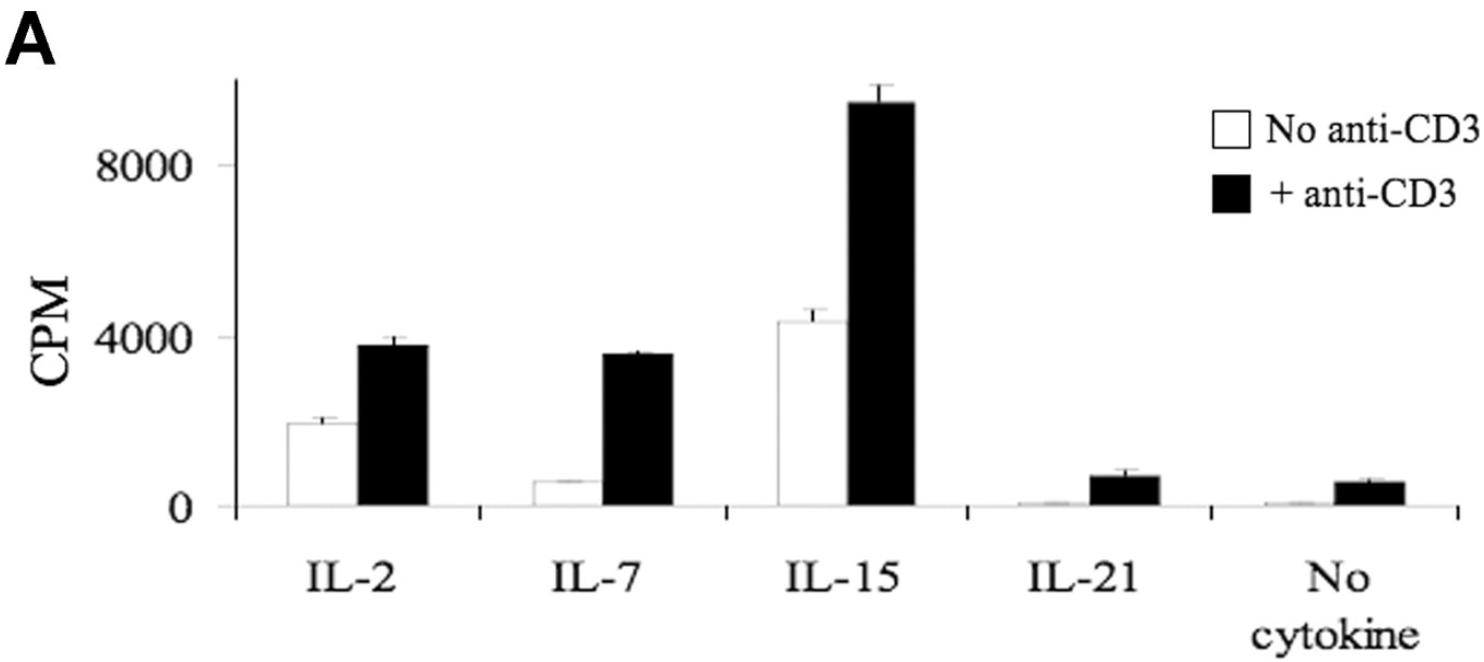
Tregs


Infusion #1
Infusion #2
Re-evaluation
-7
-6
-5
-4
-3
0
21 Days
Fludarabine
25 mg/m2/d
x 5 days
28 Days


no IL-2
%foxp3/CD4
30
20
10
0
Pre-1st INF
2nd-D0
2nd-D21
Time


IL-2
%foxp3/CD4
30
20
10
0
Pre-1st INF
2nd-D0
2nd-D21
Time

Tregs


A
CPM
8000
4000
0
No anti-CD3
+ anti-CD3
IL-2
IL-7
IL-15
IL-21
No cytokine

Conclusions

- Low dose IL-2 extends in vivo persistence of adoptively transferred CTL
- Lymphodepletion leads to increase in serum IL-7 and IL-15 levels
- High-dose IL-2 does not lead to an observed increase in peripheral in vivo persistence ? Trafficking
- Lymphodepletion + low-dose IL-2 extends survival
- However → clone-/patient- specific
- Highly persistent clones (re)-express CM phenotype
  - ?2nd generation CARs
- Tregs?