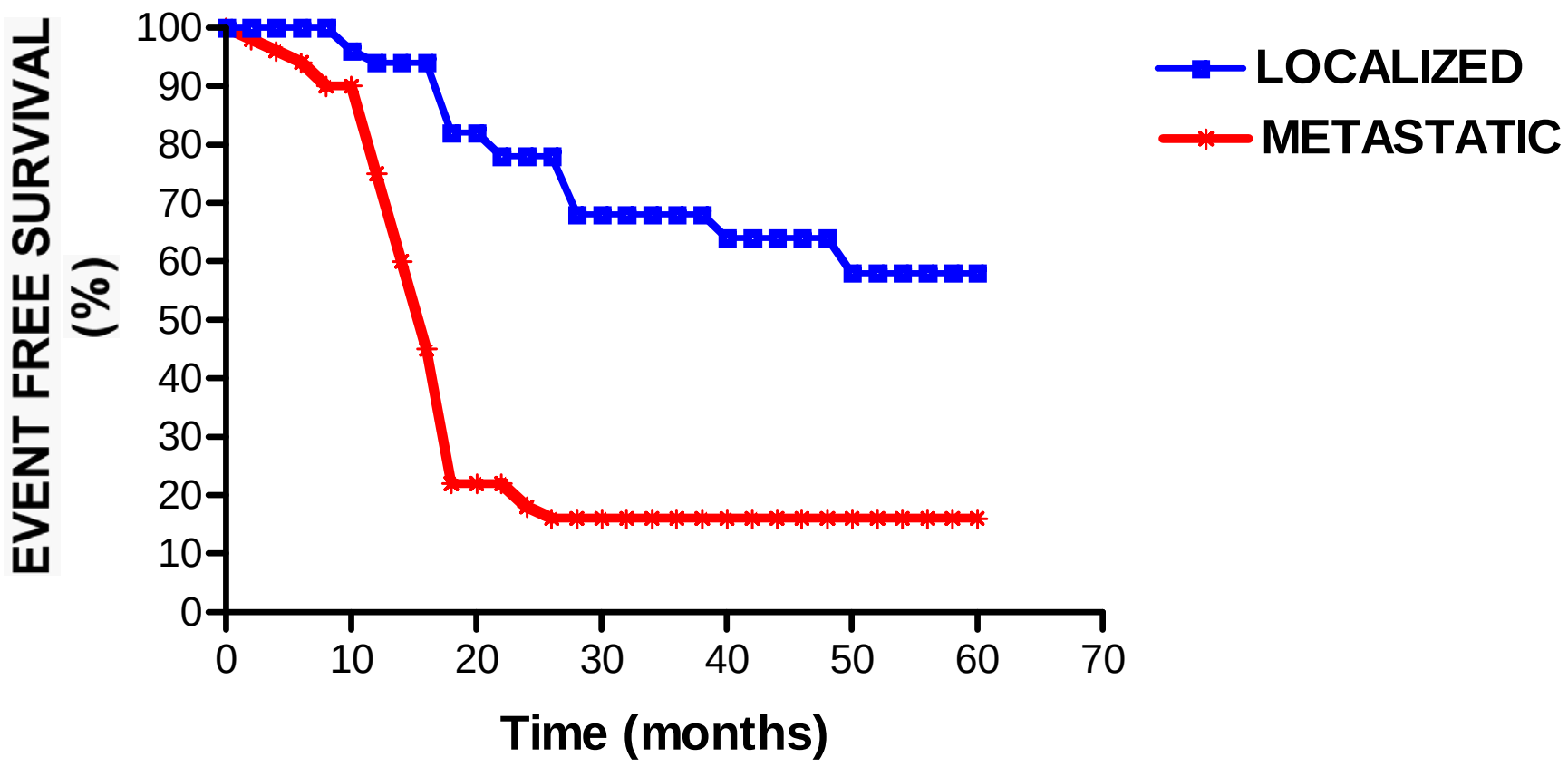
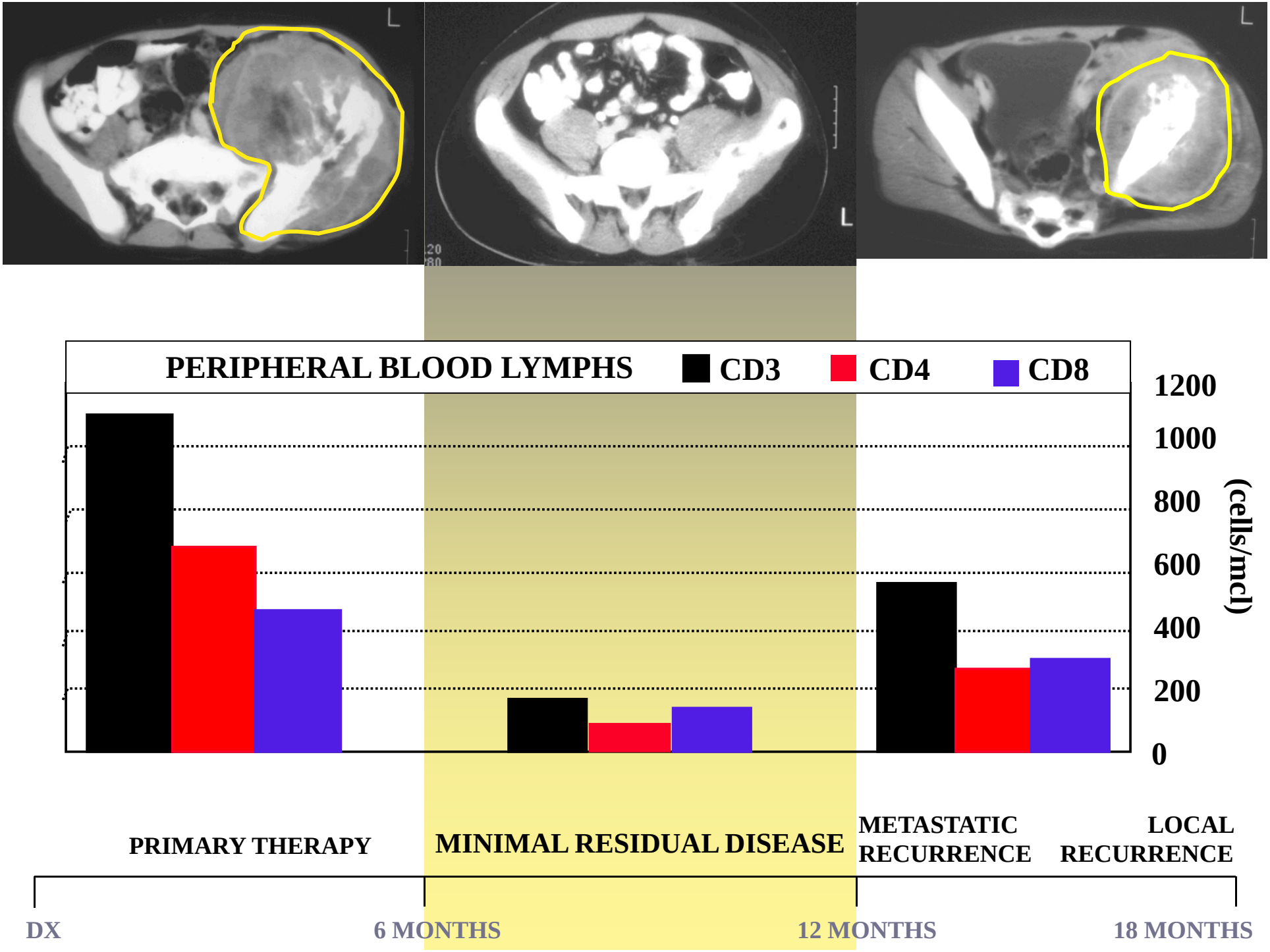
Survival in Pediatric Sarcomas

NCI POB Results: 86-C-169




PERIPHERAL BLOOD LYMPHS
CD3
CD4
CD8
1200
1000
800
600
400
200
0
(cells/mcl)
PRIMARY THERAPY
MINIMAL RESIDUAL DISEASE
METASTATIC RECURRENCE
LOCAL RECURRENCE
DX
6 MONTHS
12 MONTHS
18 MONTHS

Immunology Section

Pediatric ONCOLOGY BRANCH

Discovery

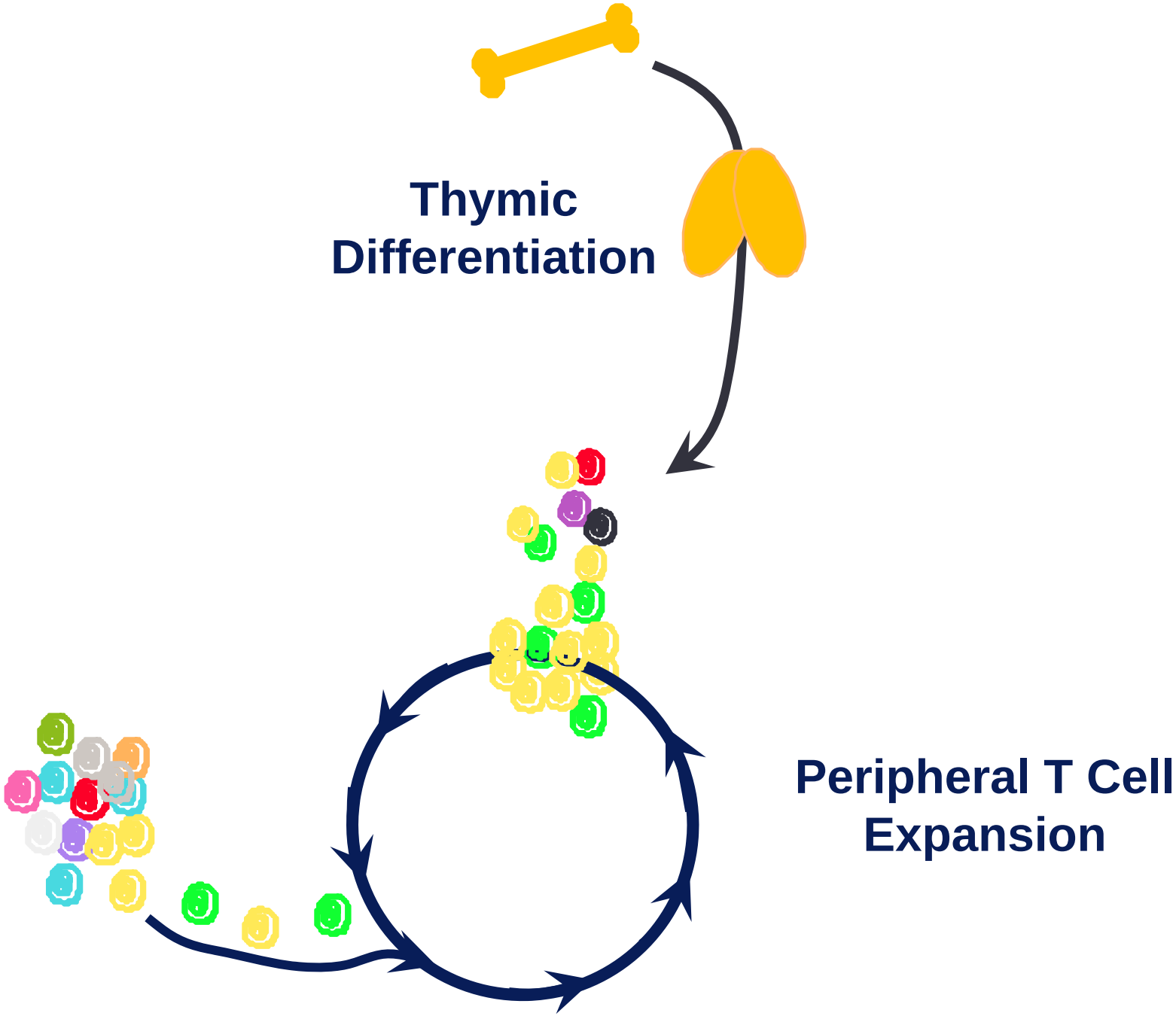
Development

Delivery

Biology of Immune Reconstitution --identify a critical role for IL7

Develop IL7 as an immunorestorative agent

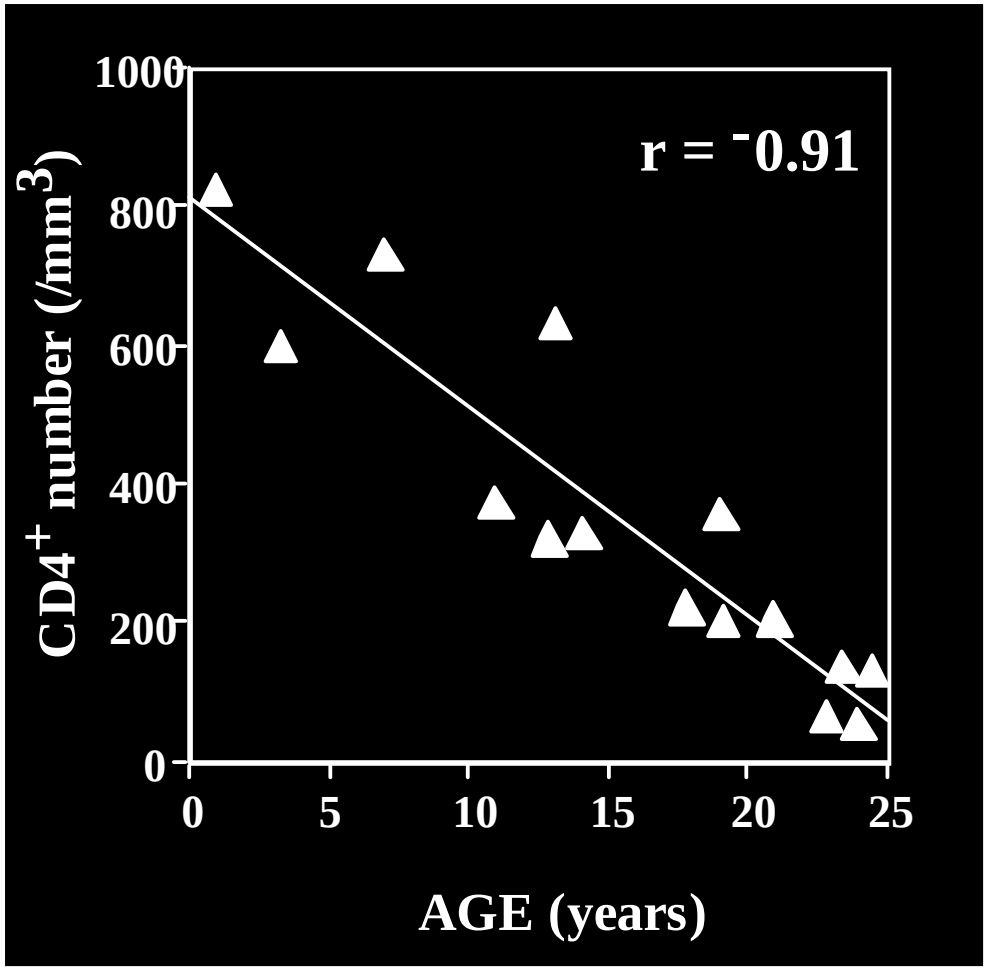
Integrate immunotherapy into multimodality regimens for cancer


Thymic
Differentiation
Peripheral T Cell
Expansion

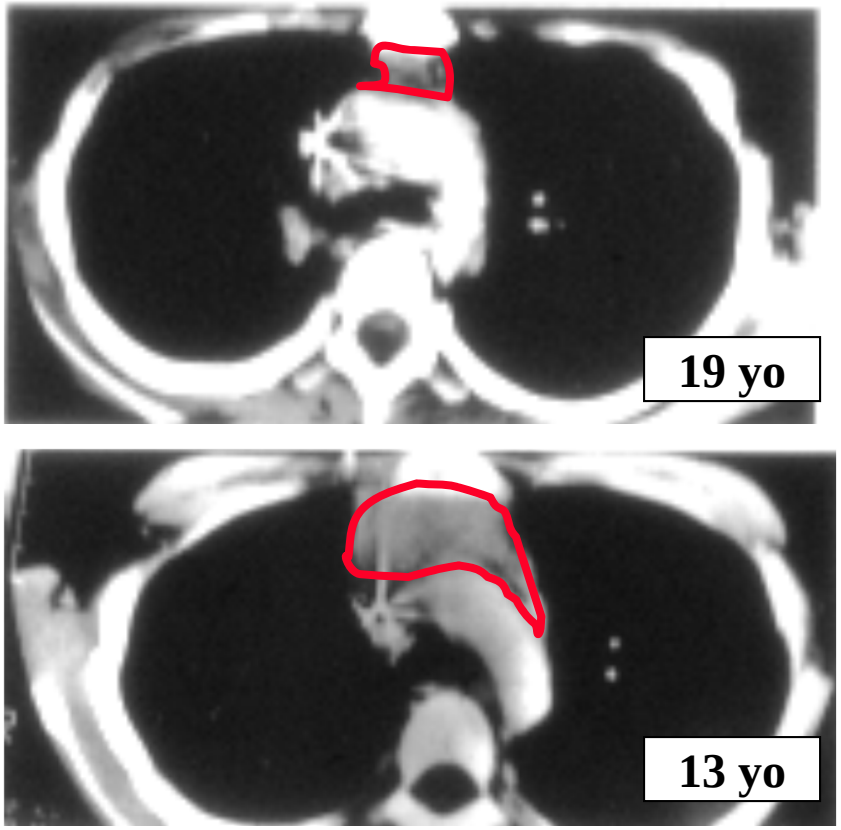
CD4+ T Cell Regeneration Is Age-dependent

6 Months Following Completion of Multiagent Chemotherapy

CD4 Count

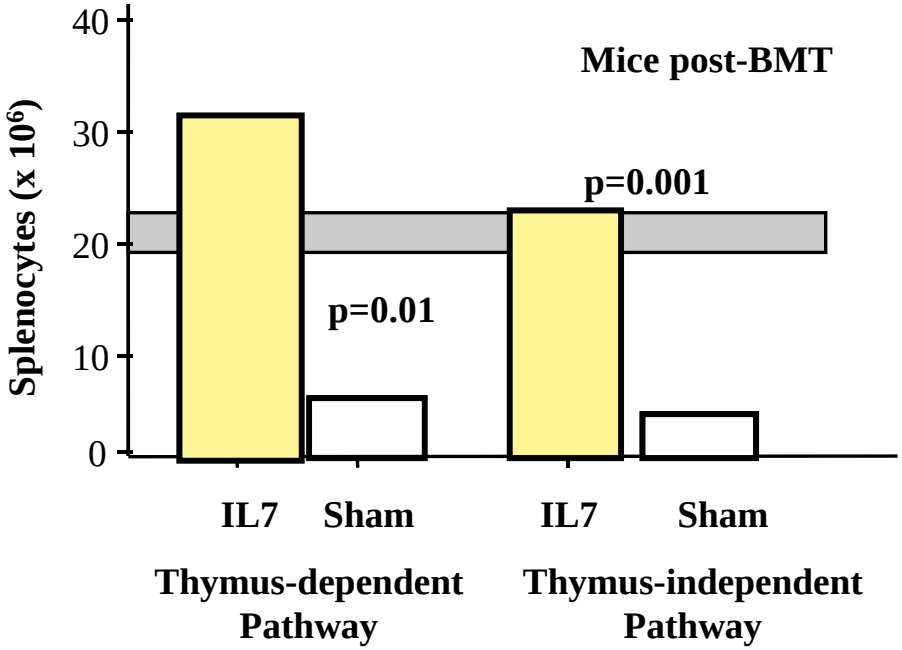


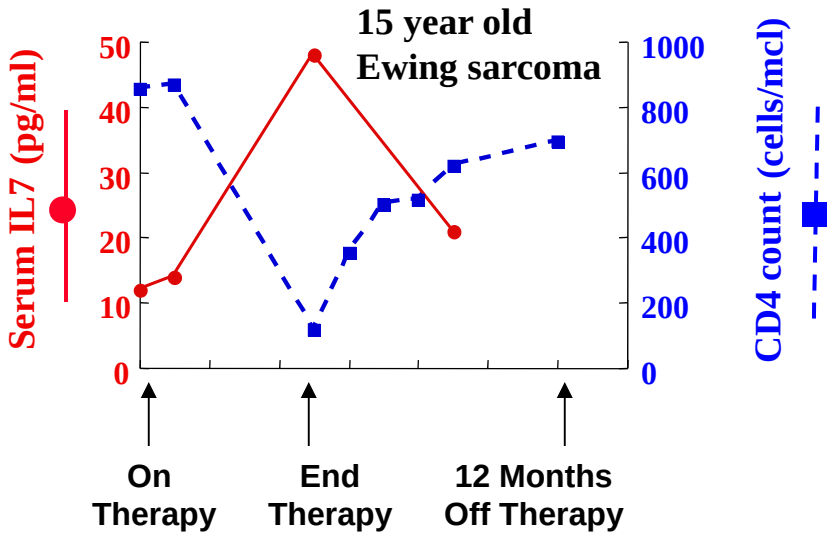
Thymic Size

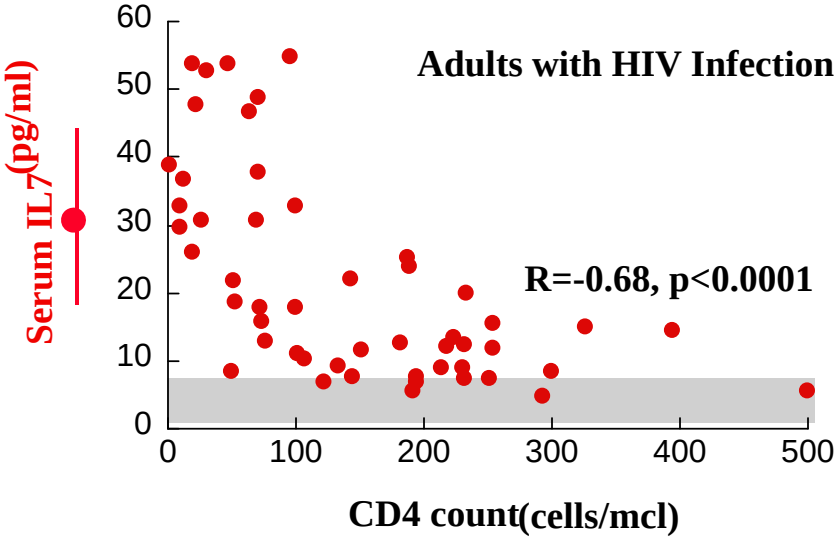


Mackall et al., NEJM, 1995

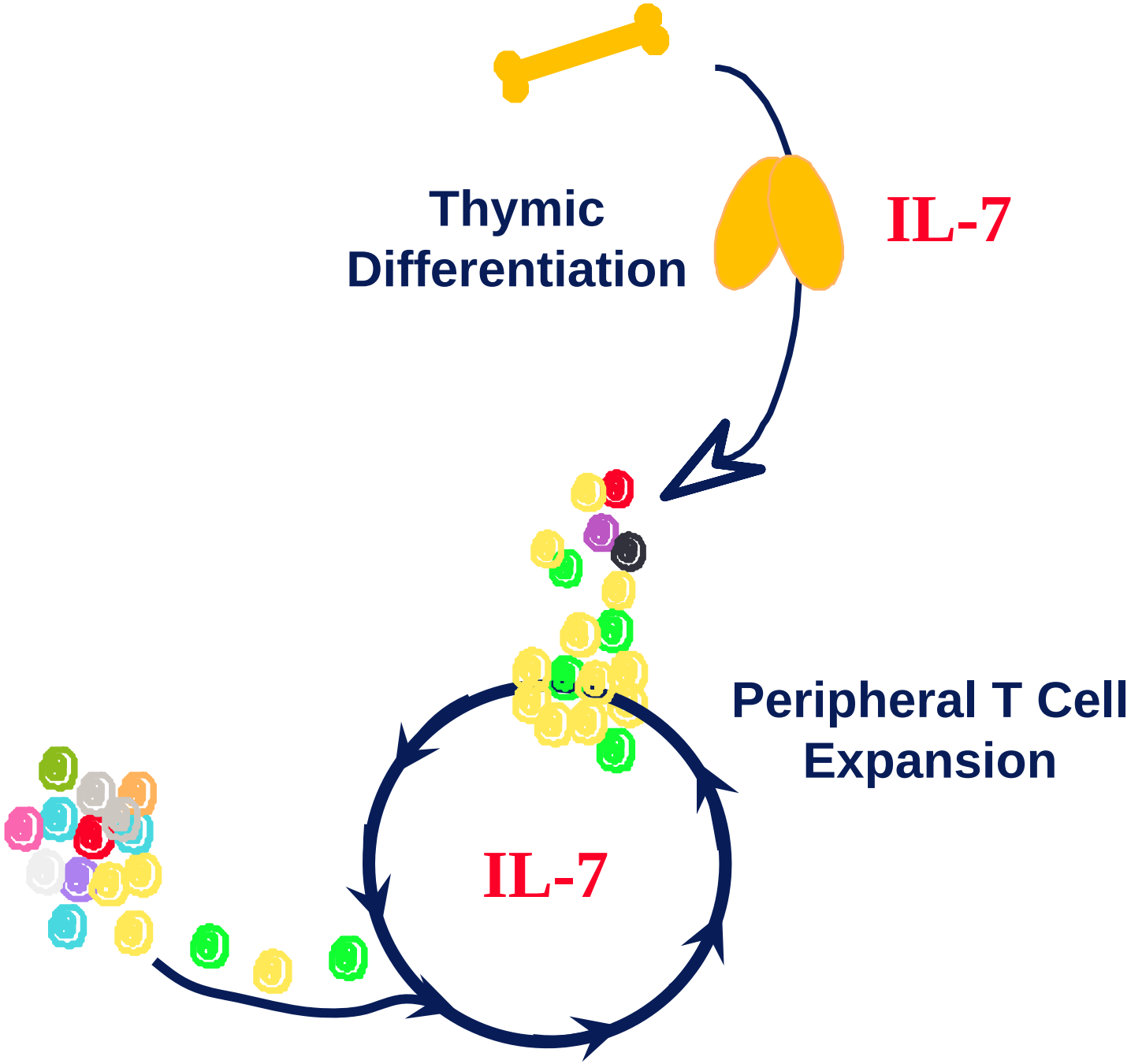
IL-7 Regulates T Cell Regeneration







Mackall et al., Blood, 2001
Fry et al., Blood, 2001


Thymic
Differentiation
IL-7
Peripheral T Cell
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IL-7

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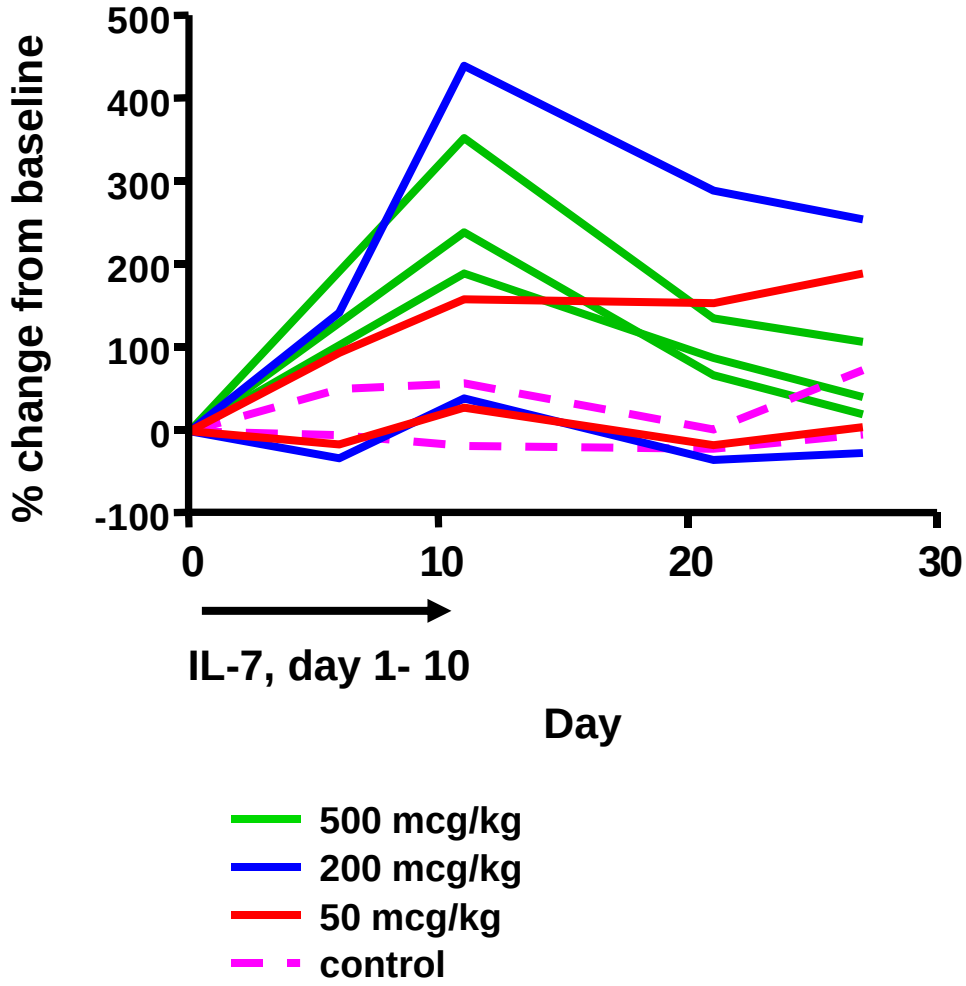
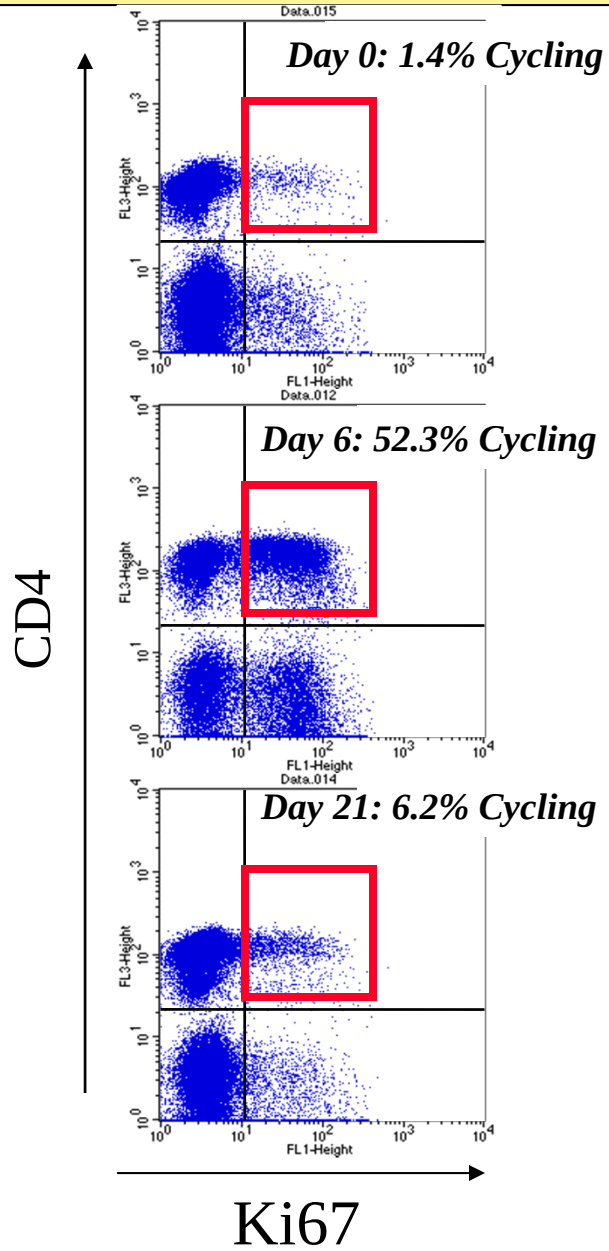
Preclinical Development History of Recombinant Human IL7

- 1989: Cloned by Namen et al., Immunex
- Sold to Sterling, Inc.
- Sold to Sanofi, Inc.
- 1996
  - NCI approaches Sanofi regarding development
  - NCI decides to produce rhIL7 for preclinical and early clinical development
- 2000-2001
  - Sanofi sells to Biotech Inflection Point, now Cytheris
  - NCI CRADA with Cytheris to develop manufacturing process
- 2003
  - Phase I Trial of rhIL7 at Clinical Center, sponsored by Cytheris

IL7 Therapy in Normal Non-Human Primates: Dramatic Reversible Increases in T Cell Numbers





Fry et al., Blood, 2003

Immunology Section

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Pilot Clinical Trials to Integrate Immunotherapy into Standard Therapy for Pediatric Sarcomas

Presentation →

- **Referral to Clinical Center**
- **Apheresis - T cells and monocytes are frozen**

↓

"Standard Therapy" →

- **Back to referring institution**
- **Multimodality therapy - multiagent chemotherapy, surgery and/or radiotherapy**

↓ ***6-10 WEEKS***

Immunotherapy →

- **Immune Reconstitution**
  - **Autologous T Cells**
  - **IL2 (platform for IL7)**
- **Tumor Vaccine**
  - **tumor specific translocation breakpoint peptide on dendritic cells**

Protocol 97-C-0052: Status of Patients Who Have Completed Immunotherapy

PT#	Referral Ctr.	Disease	CLINICAL STATUS
COHORT 1: Immature Dendritic Cells, Intermediate Dose IL2			
1	Private MD, SC	Recurrent EWS	PD 4 yrs., AWD
2	Univ. TX, Dallas	Recurrent EWS	PD 1 mo., AWD
3	Johns Hopkins Univ.	Recurrent ARMS	PD 1 mo., AWD
4	MD Anderson	Recurrent EWS	PD 24 mo., AWD
5	Oregon HSC	Metastatic ARMS	PD, 1 mo., DOD
6	University of MD	Recurrent Ewings	**NED, 4.0 yrs.**
7	Local	Metastatic ARMS	**NED, 4.0 yrs.**
8	Private MD, IL	Metastatic ARMS	PD, 1 mo., DOD
9	Hershey Med Center	Metastatic EWS	PD, 12 mos., DOD
10	William Beaumont, MI	Metastatic EWS	PD 6 mos., DOD
11	Riley, Indianapolis, IN	Metastatic EWS	PD 3 mos., DOD
COHORT 2: CD40 Ligand Matured Dendritic Cells, Low Dose IL2			
12	MD Anderson	Metastatic EWS	**NED, 2.0 yrs.**
13	Wash University, MO	Recurrent ARMS	PD, 3 mos., DOD
14	Phoenix Children's, AZ	Recurrent EWS	PD 1 mo., DOD
15	Texas Children's	Metastatic EWS	PD, 6 mos., AWD
16	Univ. Wisconsin	Recurrent EWS	PD, 1 mo., DOD
17	Univ. Nebraska	Metastatic EWS	**NED, 2.5 yrs..**
18	Hershey Med Center	Metastatic ARMS	PD, 1 mo., DOD
19	Local	Recurrent ARMS	**NED, 2.0 yrs.**
20	Meunster, Germany	Recurrent EWS	**NED, 1.5 yrs.**

Immunology Section

Pediatric ONCOLOGY BRANCH

Discovery

- Biology of Immune Reconstitution
- Identified that Tumor Lytic T Cells in Patients with Ewings Require a Unique Costimulatory Signal: 4-1BB

Development

- Develop IL7 As an Immunorestorative Agent

Delivery

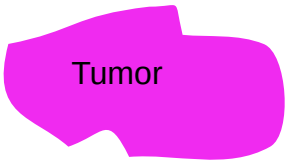
- Integrate Immunotherapy into Multimodality Regimens
- Tissue samples from patients are acquired for research

Adoptive Immunotherapy Using Autologous CD8 T Cells in A SCID/human PBL Xenograft Model

Leukopheresis → PBL → CD8 Enrichment → CD8 T cells ✚

- **@CD3/4-1BBL**
- @CD3/CD28
- None

Tumor Cell Line from the Patient



Implant → Lower Extremity

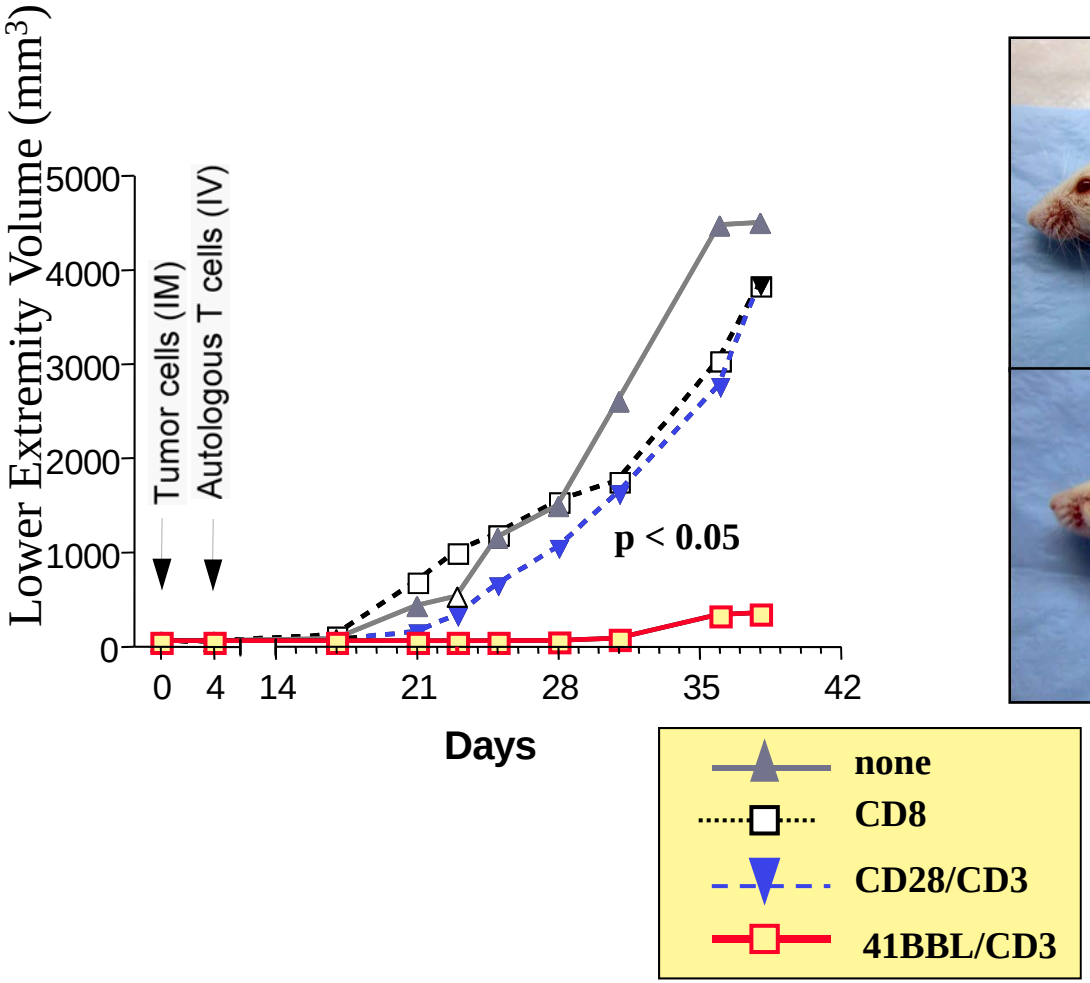
Autologous T Cells

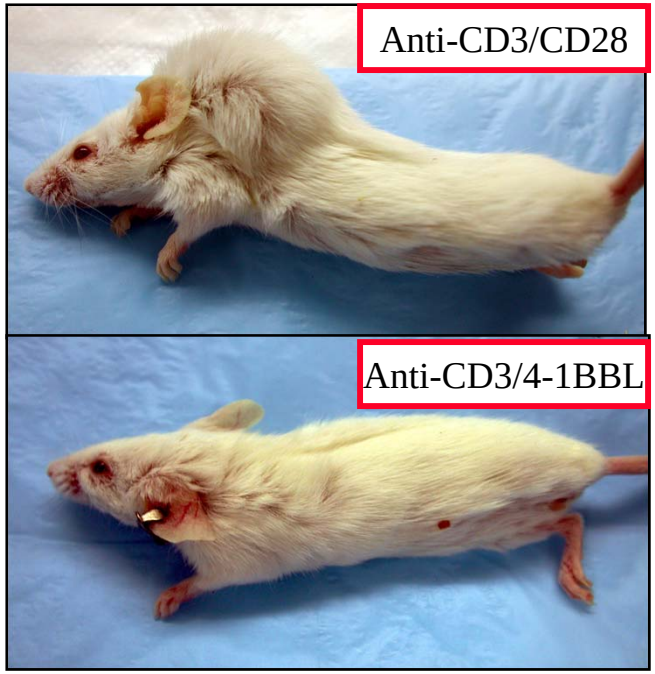
Primary Tumor

Amputation →

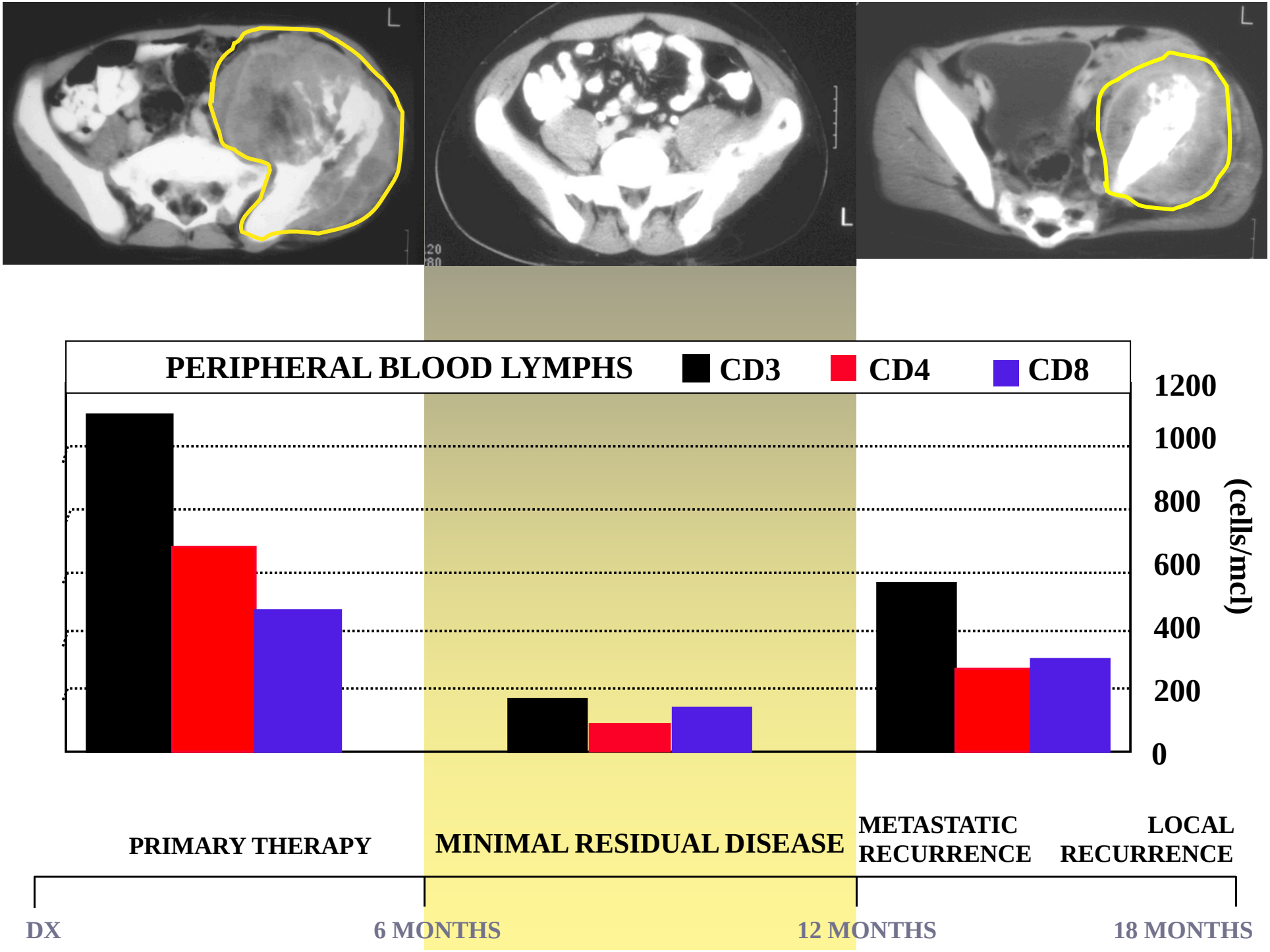
Minimal Residual Disease

Autologous CD3/4-1BBL Expanded Cells Control Growth and Metastasis of Ewings Xenografts





Zhang et al., Cancer Biology and Therapy, 2003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