

Interleukin-7: Preclinical and Clinical Development of a Potent Vaccine Adjuvant and Immunorestorative

--or--

From IL-2 to IL-7

Crystal L Mackall MD

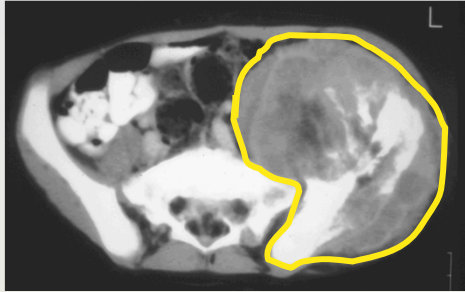
Acting Chief

Pediatric Oncology Branch

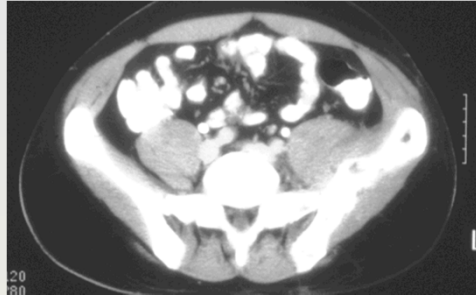
Center for Cancer Research, NCI



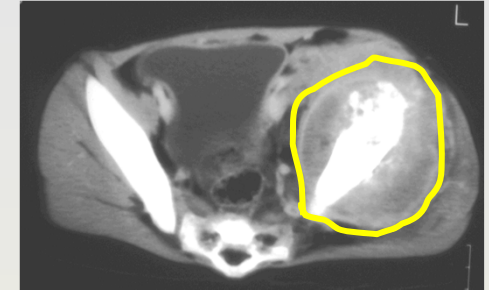
DIAGNOSIS



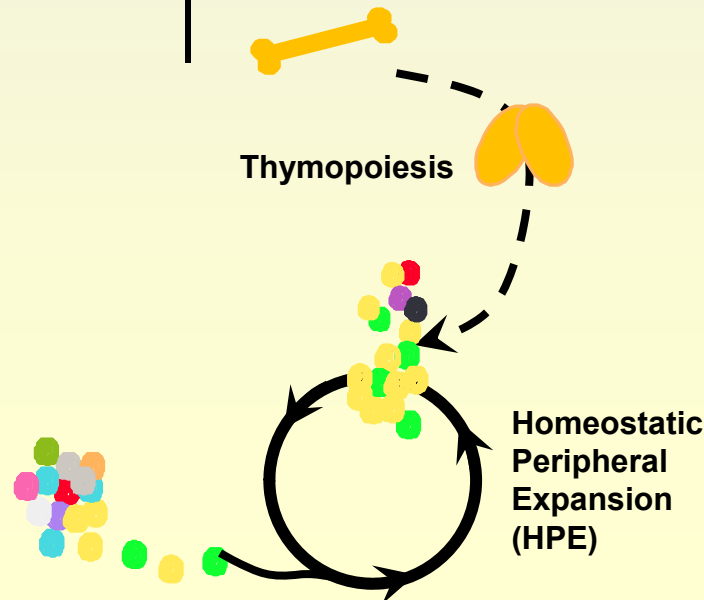
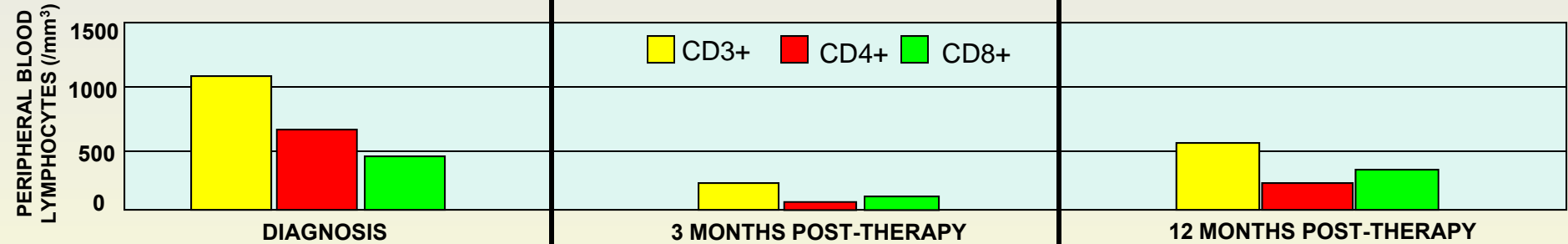
MINIMAL RESIDUAL DISEASE



RECURRENCE



Tumor burden



- thymopoiesis cannot rapidly restore T cells following chemotherapy (*Mackall, 1995*)
- HPE predominates during lymphopenia but does not normalize T cell number (*Mackall, 1994*)
- immunization during HPE can skew the T cell repertoire toward an antigen of interest (*Mackall 1996*)
- what about regeneration of regulatory T cell subsets (suppressor cells)?

Congenital Deficiency of CD4+CD25+ Regulatory T Cells

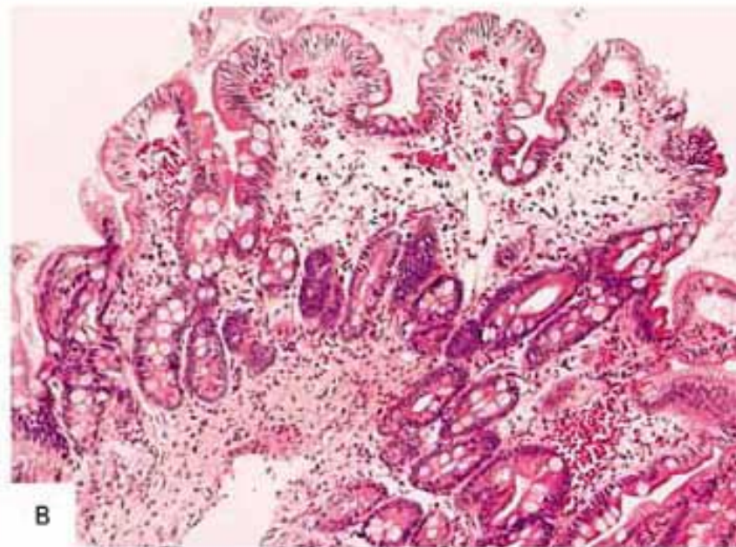
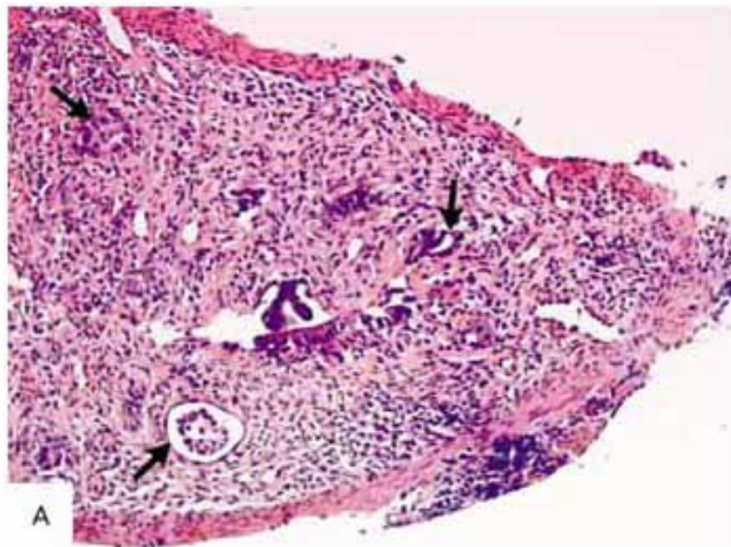
IPEX: fatal immune dysregulation, polyendocrinopathy, enteropathy, x-linked

➤ mutations in *FOXP3* in Xp11.23 which encodes for scurfin

Duodenal biopsy

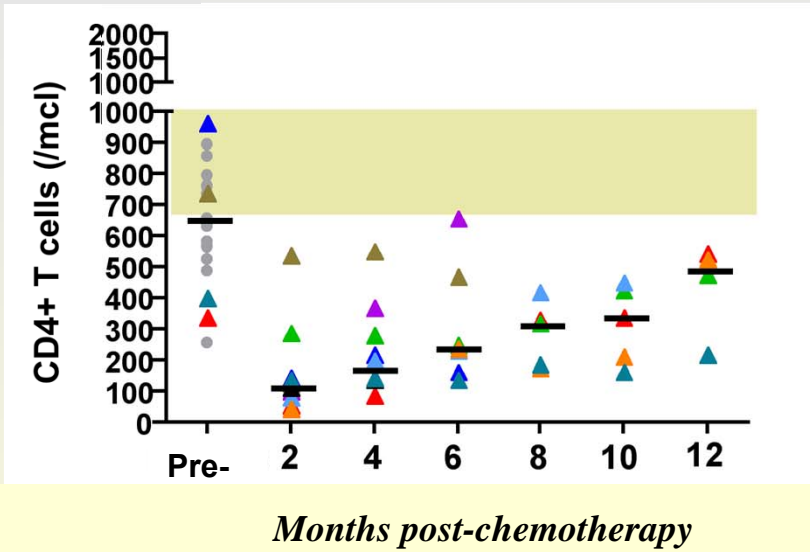
Before Bone Marrow Transplantation
-flattened mucosa, absence of crypts

After Bone Marrow Transplantation
-restoration of duodenal villi/crypts



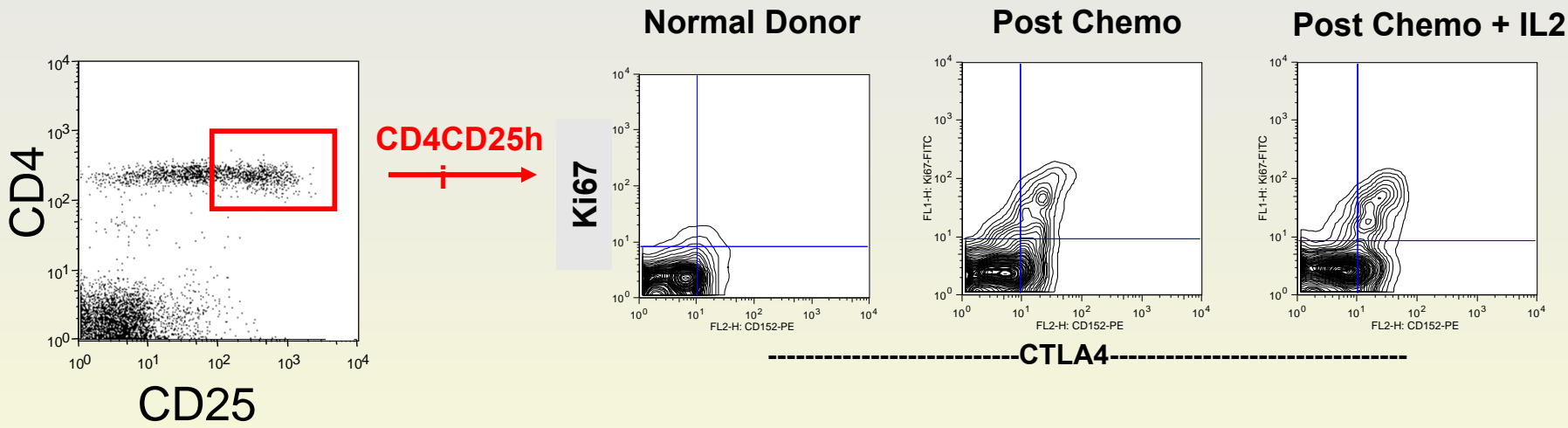
CD4+CD25+ Regulatory T Cells Increase after chemotherapy \pm IL2

No IL-2

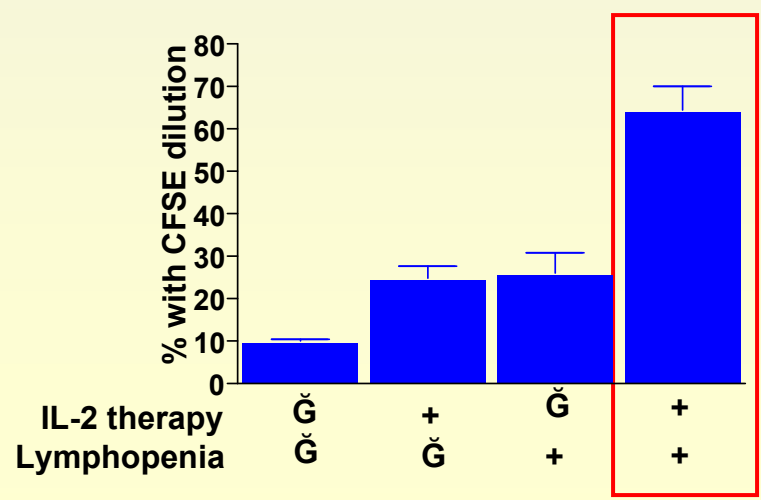
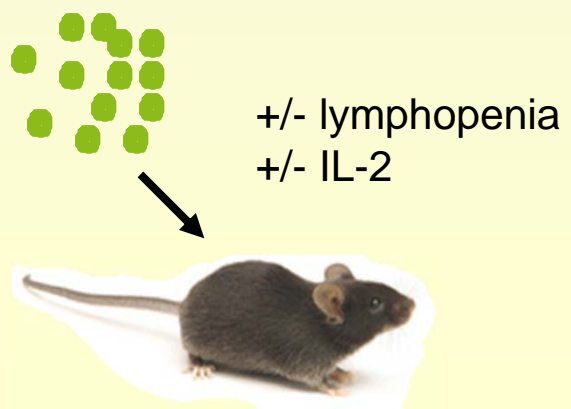


Months post-chemotherapy

CD4+CD25+ Regulatory T Cells Proliferate In Response to Lymphopenia and/or IL-2

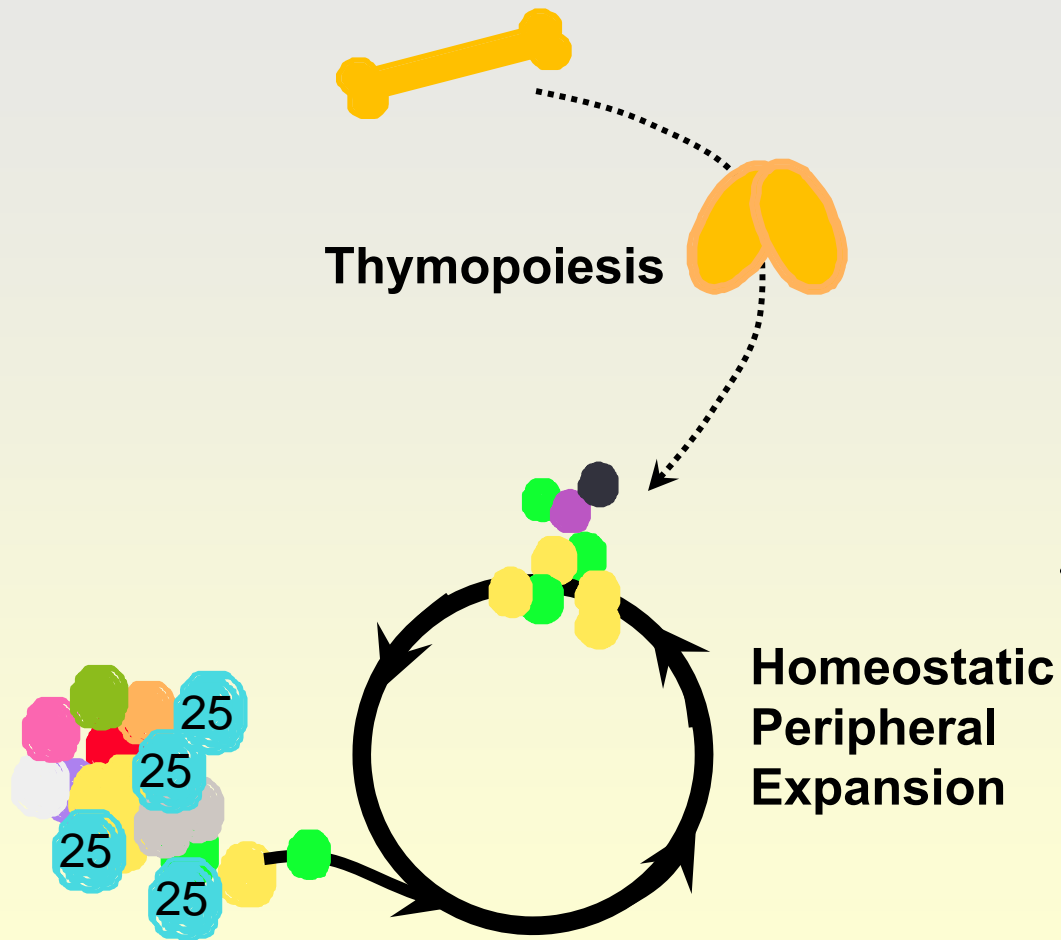


CFSE labeled Tregs



Zhang
2005, Nat Med

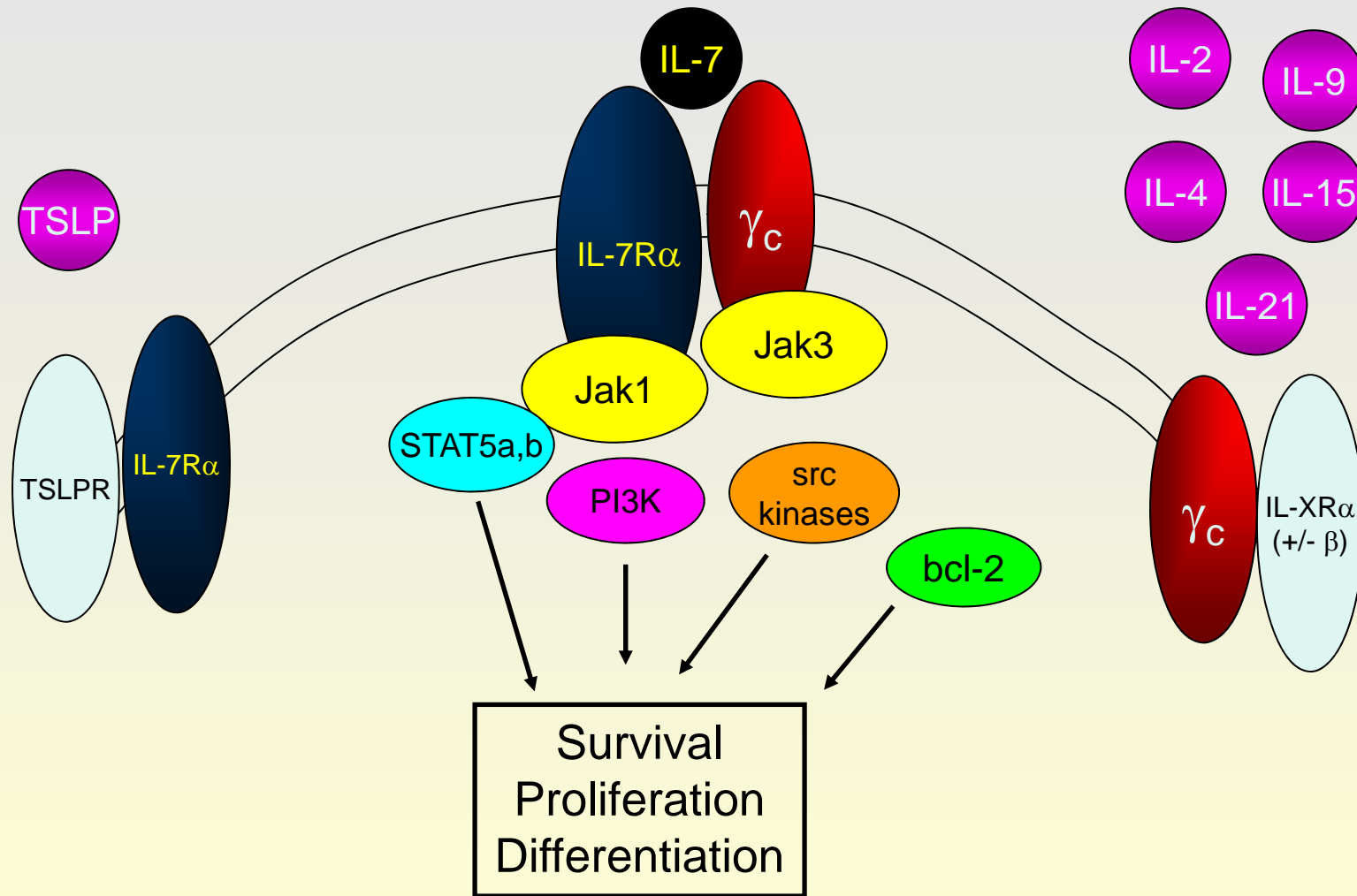
CD4+CD25+ Tregs and Immune Reconstitution



➤ Cyclophosphamide, in doses commonly administered to cancer patients, profoundly depletes the entire CD4 compartment with a relative increase in Tregs.

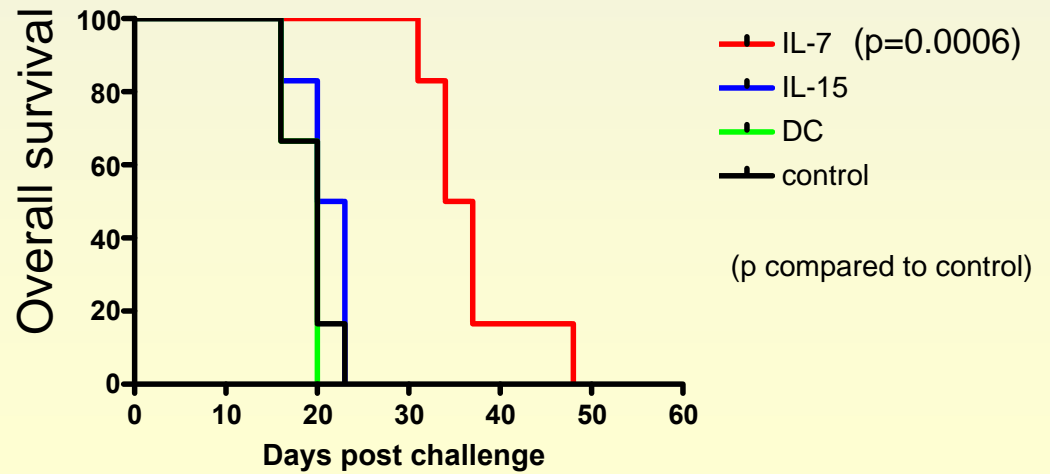
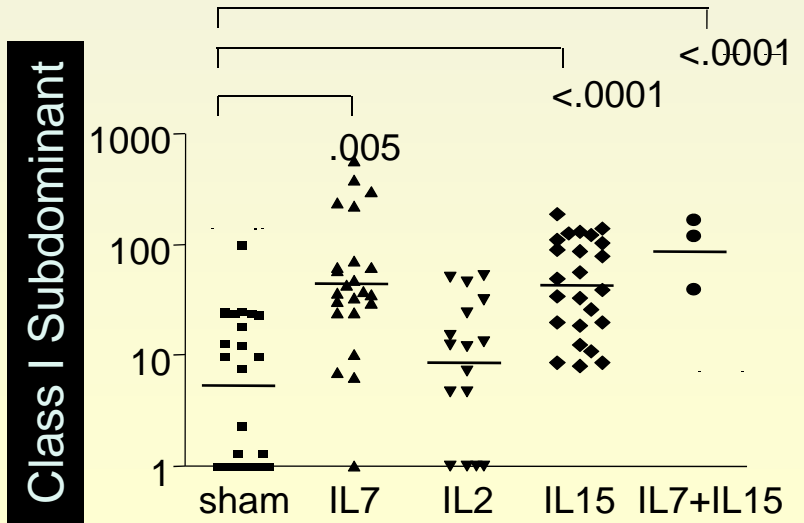
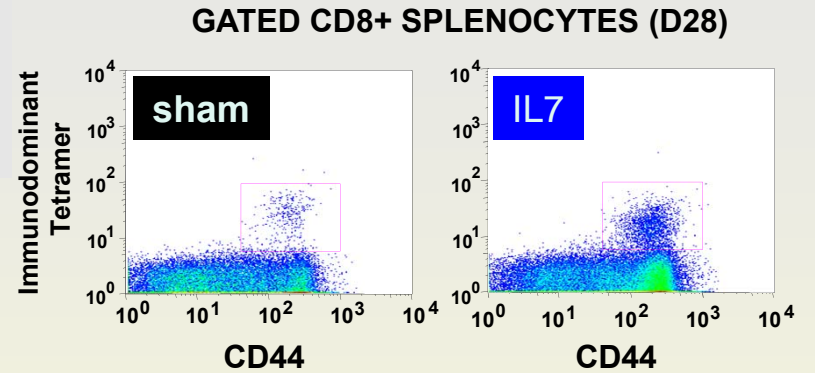
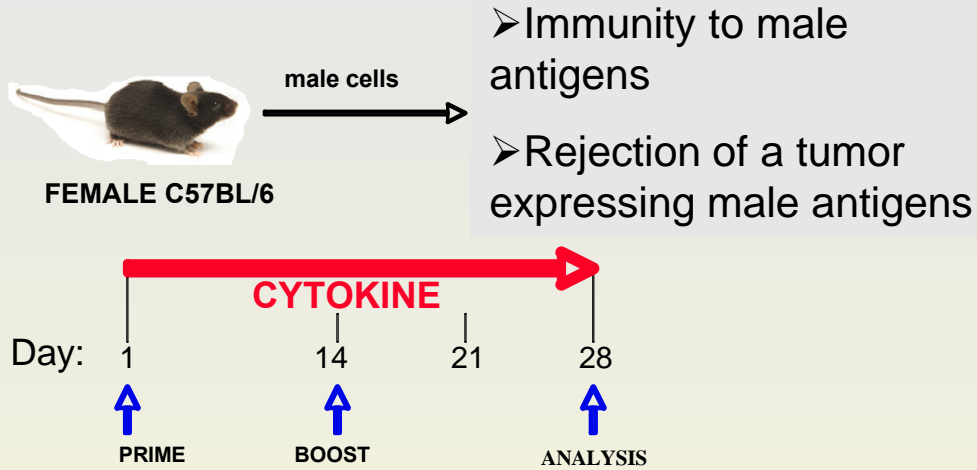
➤ **Regulatory T cells expand during lymphopenia** resulting in an increased frequency of CD4+CD25+Tregs compared to that observed in normal, T cell replete hosts.

➤ **IL2 therapy expands Tregs *in vivo*** and this effect is exaggerated during lymphopenia.

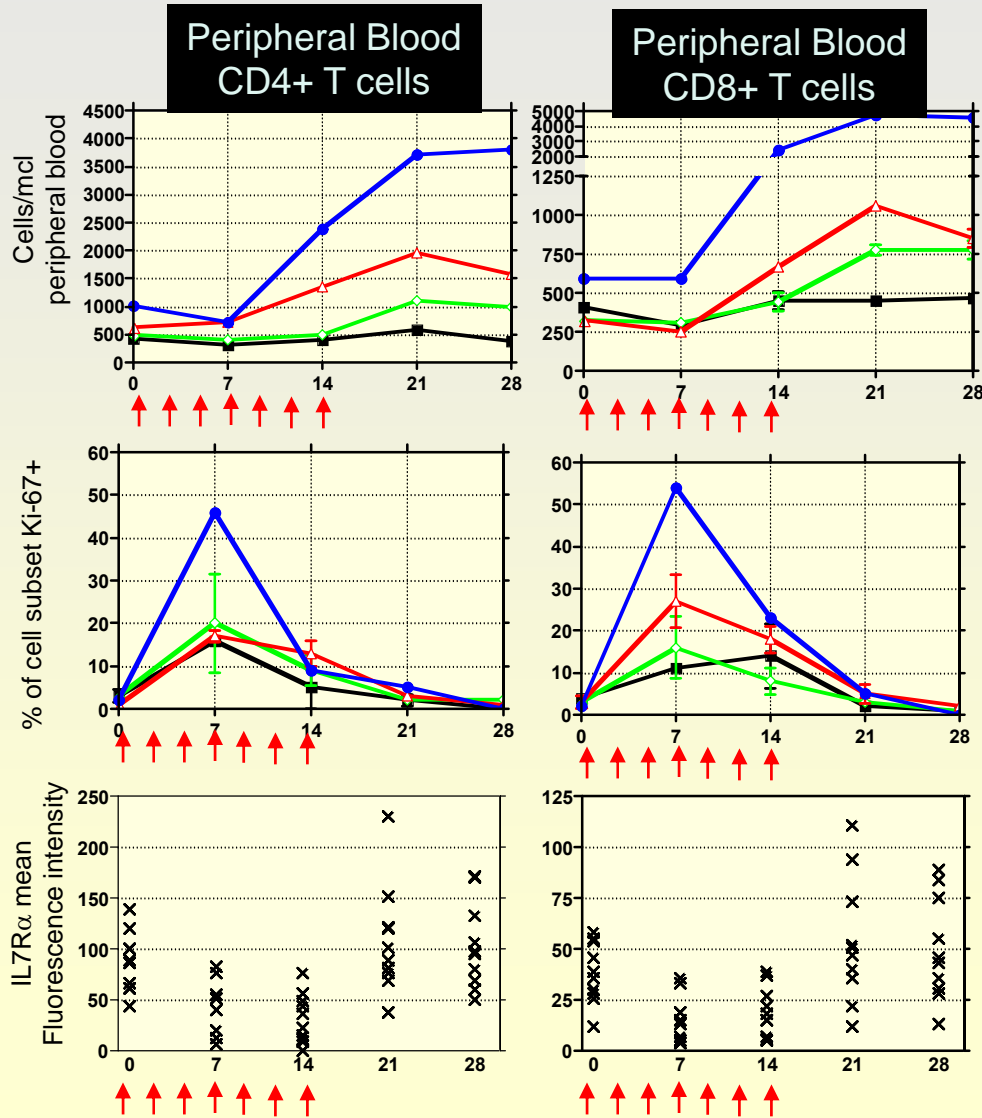


INTERLEUKIN-7 IS REQUIRED FOR T CELL DEVELOPMENT AND T CELL MAINTENANCE

IL7 Is A Potent Vaccine Adjuvant



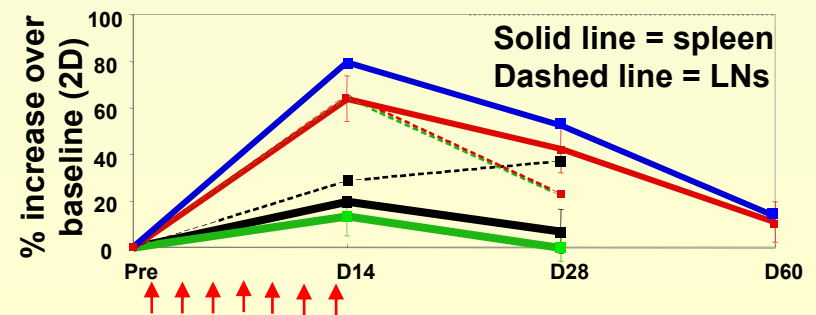
IL7 Therapy In Humans Induces Widespread T Cell Cycling and Increases Lymphocyte Mass



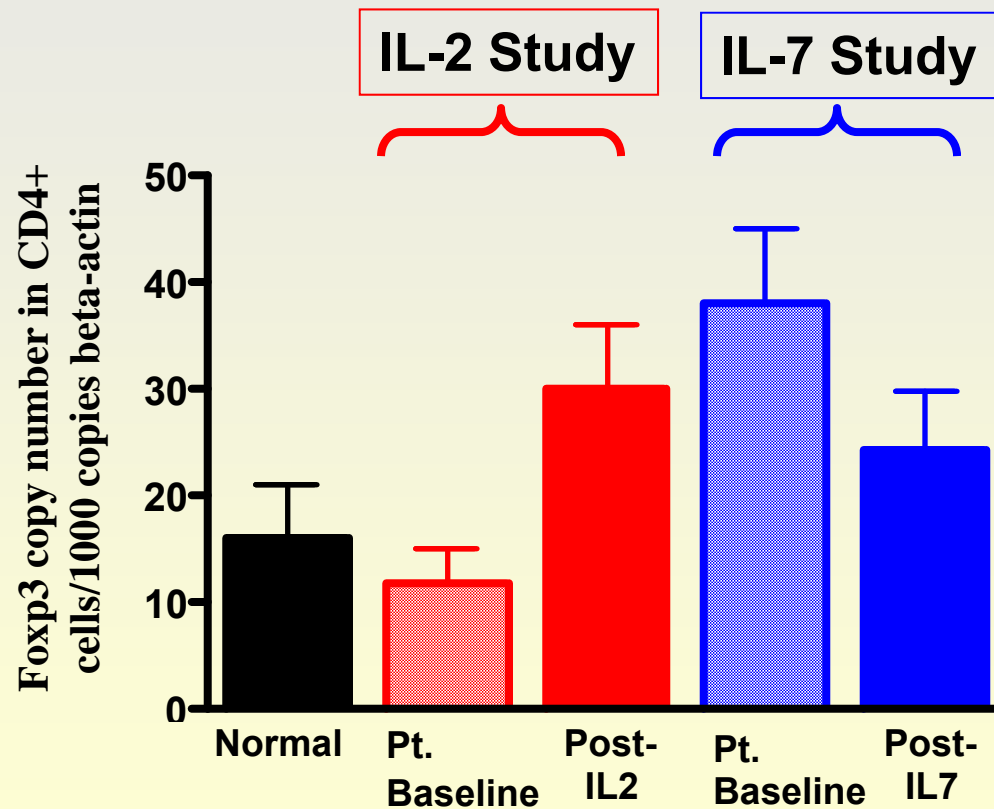
IL7 Dose (↑): QOD SQ x 7 doses

- 3 ug/kg
- ◆ 10 mcg/kg
- ▲ 30 mcg/kg
- 60 mcg/kg

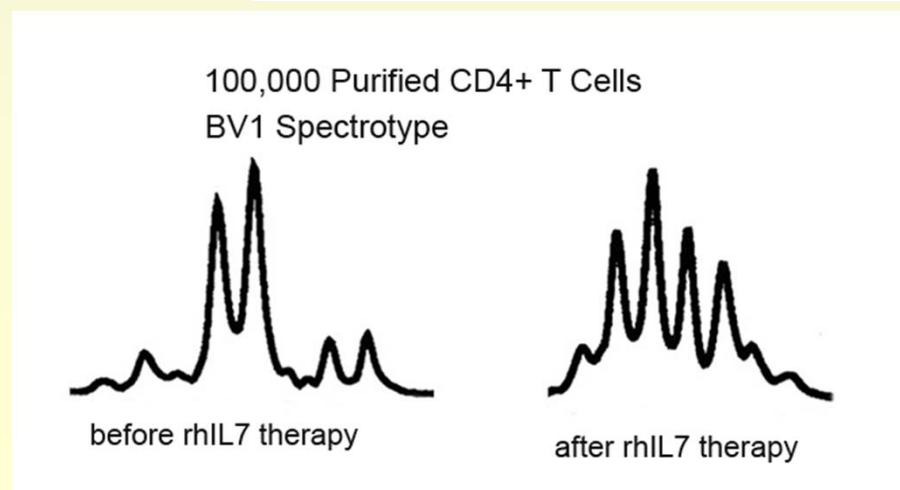
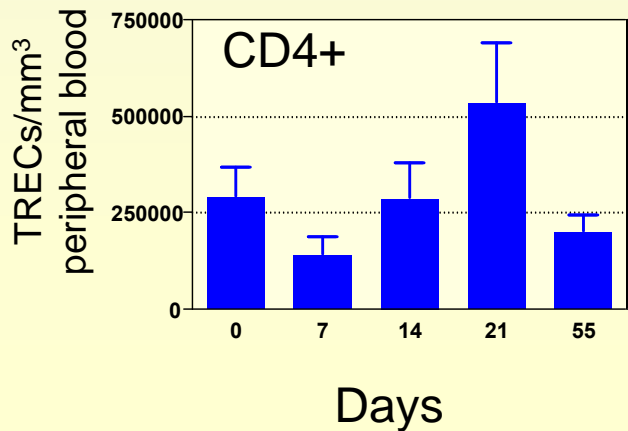
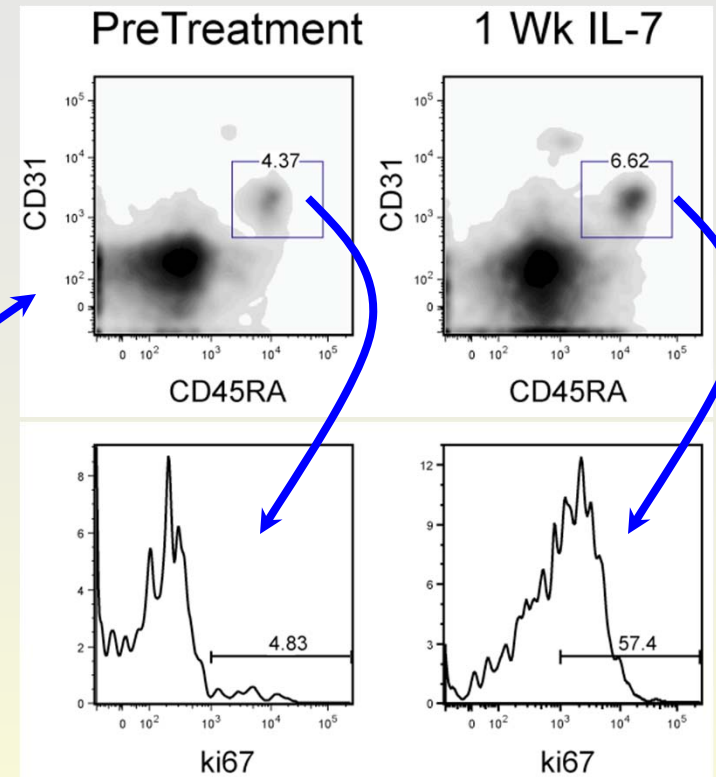
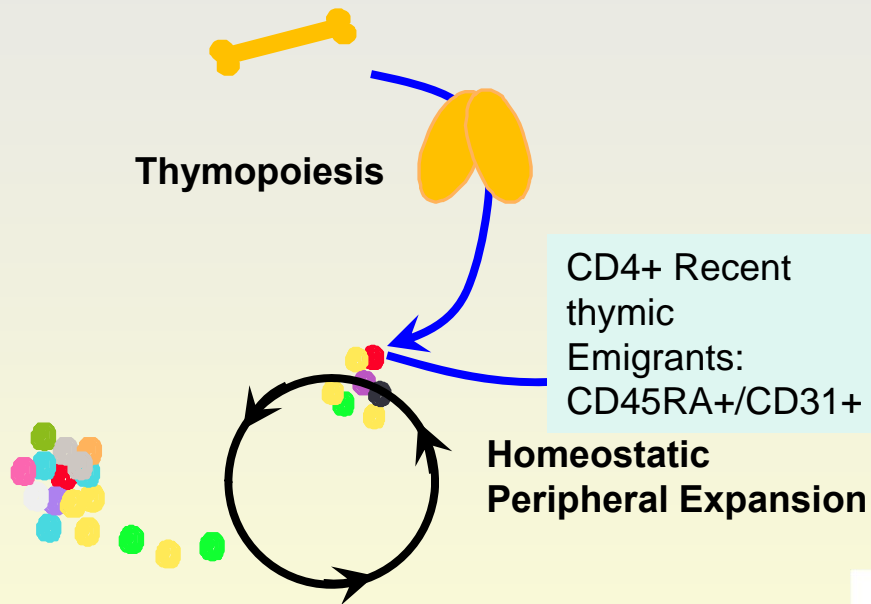
Spleen & Lymph Node Size



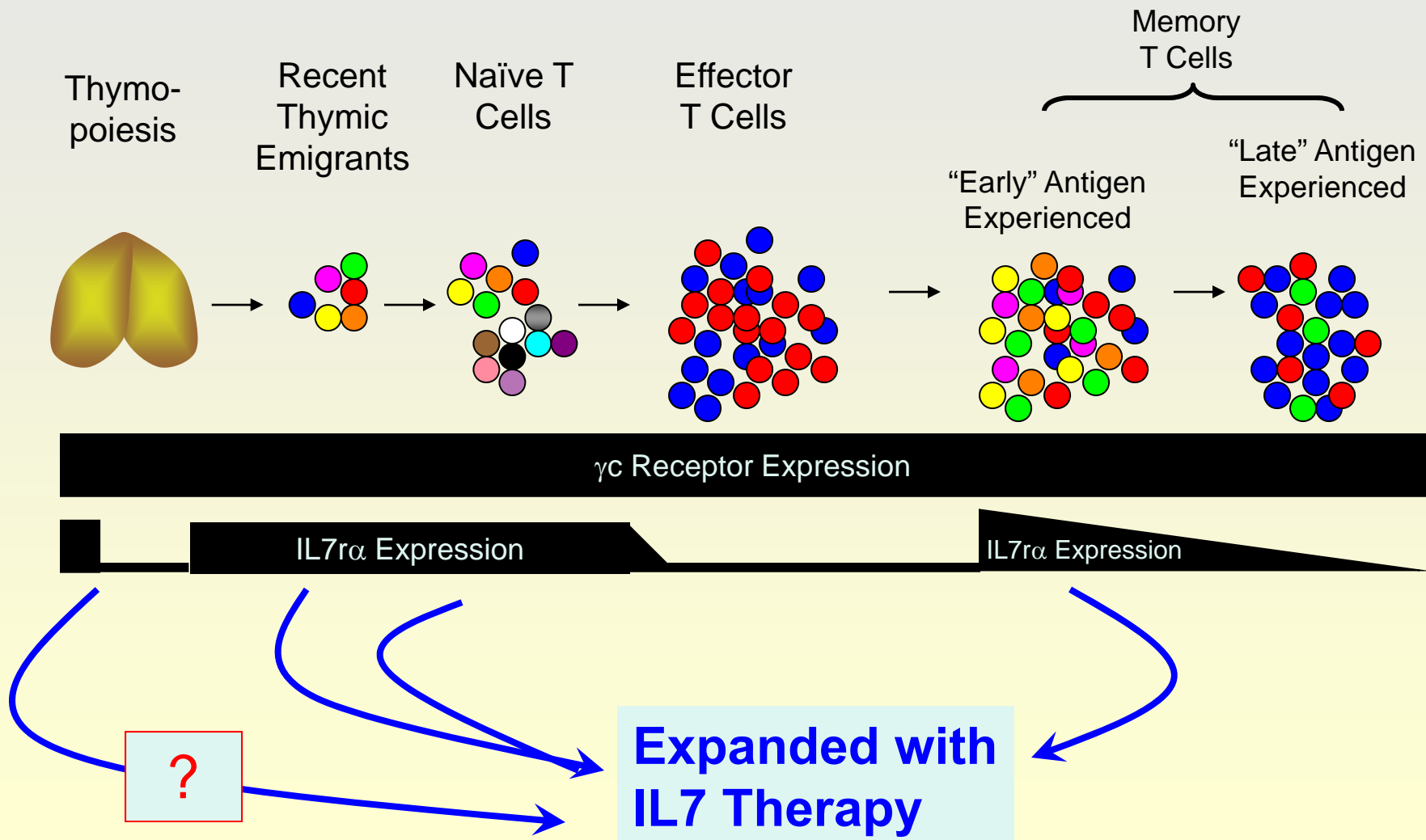
IL7 Therapy in Humans Does Not Expand CD4+Treg Cells



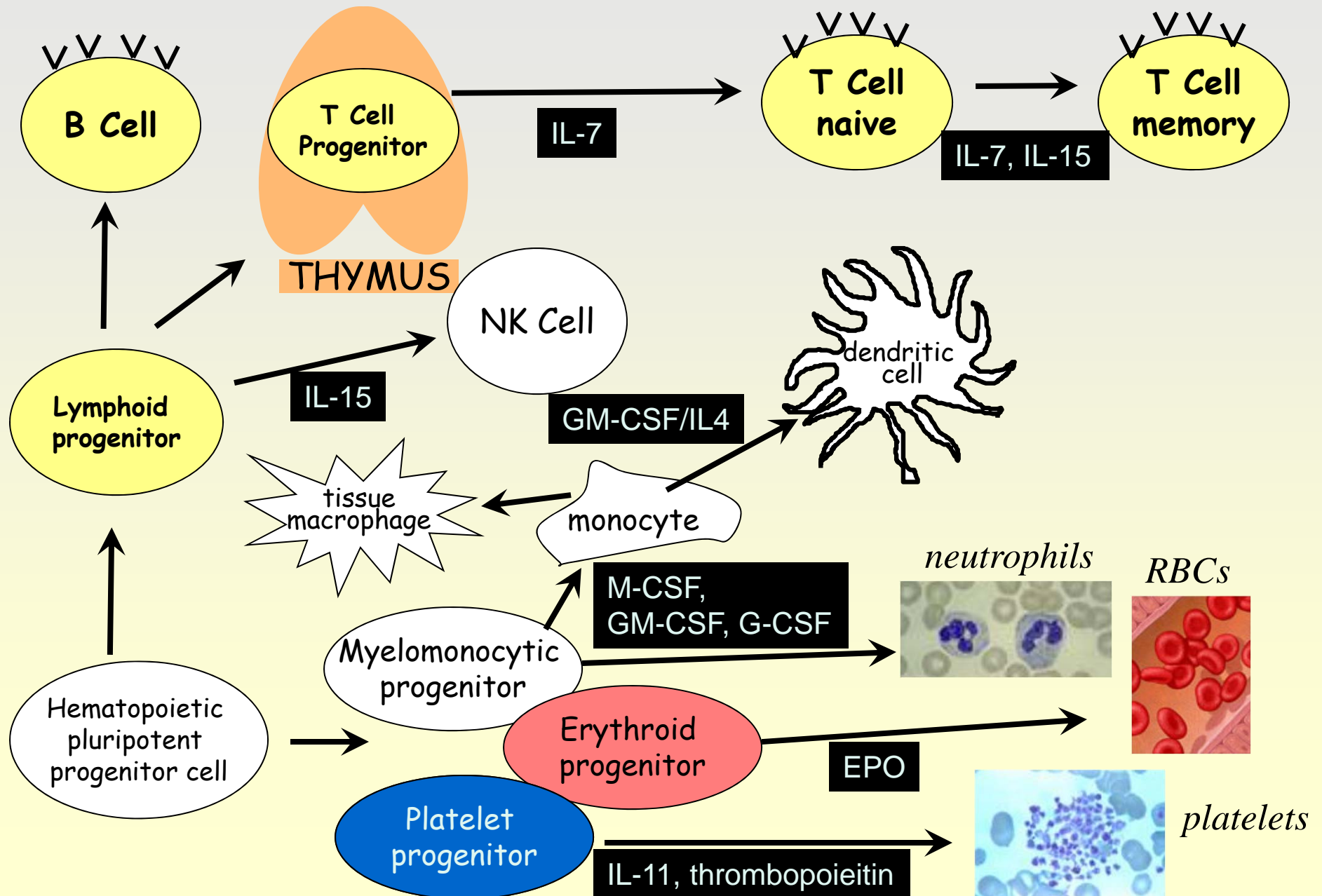
IL7 Therapy Increases Thymic Emigrants and Increases TCR Repertoire Diversity



Regulation of IL7 α Expression During T Cell Differentiation Dictates Effects of IL7 Therapy



IL-7: Necessary and Sufficient Growth Factor for T Cells



Acknowledgements

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Activation vs. Homeostatic Cytokines

