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

--or--

From IL-2 to IL-7

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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

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**Duodenal biopsy**

Before Bone Marrow Transplantation
- flattened mucosa, absence of crypts

After Bone Marrow Transplantation
- restoration of duodenal villi/crypts

Baud, NEJM, 2001
CD4+CD25+ Regulatory T Cells Increase after chemotherapy ± IL2

No IL-2

Zhang, 2005, Nat Med
CD4+CD25+ Regulatory T Cells Proliferate In Response to Lymphopenia and/or IL-2

Zhang 2005, Nat Med
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 \textit{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

- Immunity to male antigens
- Rejection of a tumor expressing male antigens

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**FEMALE C57BL/6**

**Day:**
- 1
- 14
- 21
- 28

**CYTOKINE**
- sham
- IL7
- IL2
- IL15
- IL7+IL15

**GATED CD8+ SPLENOCYTES (D28)**

**Immunodominant Tetramer**

**CD44**

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**Overall survival**

- IL-7 (p=0.0006)
- IL-15
- DC
- control

(p compared to control)

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*Melchionda, J Clin Invest, 2005*
IL7 Therapy In Humans Induces Widespread T Cell Cycling and Increases Lymphocyte Mass

IL7 Dose (↑): QOD SQ x 7 doses
- 3 ucg/kg
- 10 mcg/kg
- 30 mcg/kg
- 60 mcg/kg

Peripheral Blood CD4+ T cells
- Cells/mL peripheral blood

Peripheral Blood CD8+ T cells
- % of cell subset Ki-67+

Peripheral Blood IL7Rα mean Fluorescence intensity

Spleen & Lymph Node Size
- % increase over baseline (2D)
  - Solid line = spleen
  - Dashed line = LNs
IL7 Therapy in Humans Does Not Expand CD4+ Treg Cells

**IL-2 Study**

**IL-7 Study**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Normal</th>
<th>Pt. Baseline</th>
<th>Post-IL2</th>
<th>Pt. Baseline</th>
<th>Post-IL7</th>
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</thead>
</table>

Foxp3 copy number in CD4+ cells/1000 copies beta-actin

0 10 20 30 40 50
IL7 Therapy Increases Thymic Emigrants and Increases TCR Repertoire Diversity

Thymopoiesis

Homeostatic Peripheral Expansion

CD4+ Recent thymic Emigrants: CD45RA+/CD31+

TRECs/mm³ peripheral blood

Days

CD4+

CD31

CD45RA

CD31

CD45RA

ki67

ki67

100,000 Purified CD4+ T Cells
BV1 Spectrotype

before rhIL7 therapy

after rhIL7 therapy

IL7 Therapy Increases Thymic Emigrants and Increases TCR Repertoire Diversity
Regulation of IL7rα Expression During T Cell Differentiation Dictates Effects of IL7 Therapy

Thymopoiesis → Recent Thymic Emigrants → Naïve T Cells → Effector T Cells → "Early" Antigen Experienced → "Late" Antigen Experienced

Memory T Cells

γc Receptor Expression

IL7rα Expression

Expanded with IL7 Therapy
IL-7: Necessary and Sufficient Growth Factor for T Cells

- **B Cell**
- **T Cell Progenitor**
- **NK Cell**
- **Lymphoid progenitor**
- **THYMUS**
- **Hematopoietic pluripotent progenitor cell**
- **Myelomonocytic progenitor**
- **Erythroid progenitor**
- **Platelet progenitor**
- **IL-11, thrombopoietin**
- **M-CSF, GM-CSF, G-CSF**
- **EPO**
- **IL-7, IL-15**
- **T Cell naive**
- **T Cell memory**
- **Neutrophils**
- **RBCs**
- **Platelets**
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Activation vs. Homeostatic Cytokines

**Activation Prototype**
- IL-2

**Homeostatic Prototype**
- IL-7

**Naive cell**
- T cell
- TCR Activation
- IL-2

**Effector Cell**
- T cell
- TCR Activation
- IL-7
- Effector to Memory Transition

**Memory Cell**
- T cell
- Effector to Memory Transition

**IL-2**
- IL-2rα
- IL-2rβ

**IL-7**
- IL7rα

**IL-15**