SUPPLEMENTARY FIGURES

Figure Legends S1-S4.

Data are representative of three independent experiments and the viSNE maps are the same as described in Figure 4. Expression of each signaling protein in all cell subsets are shown after stimulation with increasing concentrations of IL-2 (0-1,000 IU/ml) and results were analyzed as in Figure 4.

Figure S1: Effect of IL-2 stimulation in vitro on pSTAT3 activation in lymphocyte subsets

<table>
<thead>
<tr>
<th>CD4Treg</th>
<th>0 U</th>
<th>1 U</th>
<th>5 U</th>
<th>10 U</th>
<th>100 U</th>
<th>1000 U</th>
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<tbody>
<tr>
<td>Helios positive naive CD4Treg</td>
<td></td>
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<tr>
<td>Helios negative naive CD4Treg</td>
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<tr>
<td>Helios positive memory CD4Treg</td>
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<tr>
<td>Helios negative memory CD4Treg</td>
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<table>
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<tr>
<th>CD4Tcon</th>
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<tbody>
<tr>
<td>Naive CD4Tcon</td>
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<tr>
<td>Central memory CD4Tcon</td>
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<tr>
<td>Effector memory CD4Tcon</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CD8 T cell</th>
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</thead>
<tbody>
<tr>
<td>Naive CD8 T cell</td>
</tr>
<tr>
<td>Central memory CD8 T cell</td>
</tr>
<tr>
<td>Effector memory CD8 T cell</td>
</tr>
<tr>
<td>TEMRA CD8 T cell</td>
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<table>
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<th>NK cell</th>
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<tbody>
<tr>
<td>CD56brightCD16+ NK cell</td>
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<tr>
<td>CD56dimCD16- NK cell</td>
</tr>
<tr>
<td>CD56+CD16- NK cell</td>
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</tbody>
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<table>
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<tr>
<th>B cell</th>
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<tbody>
<tr>
<td>Naive B cell</td>
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<tr>
<td>Transitional B cell</td>
</tr>
<tr>
<td>Memory B cell</td>
</tr>
<tr>
<td>Plasmablast</td>
</tr>
</tbody>
</table>

Low expression | High expression
Figure S2: Effect of IL-2 stimulation in vitro on pAKT activation in lymphocyte subsets

**CD4Treg**
- Helios positive naive CD4Treg
- Helios negative naive CD4Treg
- Helios positive memory CD4Treg
- Helios negative memory CD4Treg

**CD4Tcon**
- Naive CD4Tcon
- Central memory CD4Tcon
- Effector memory CD4Tcon

**CD8 T cell**
- Naive CD8 T cell
- Central memory CD8 T cell
- Effector memory CD8 T cell
- TEMRA CD8 T cell

**NK cell**
- CD56^{bright}CD16^- NK cell
- CD56^{bright}CD16^+ NK cell
- CD56^{dim} NK cell

**B cell**
- Naive B cell
- Transitional B cell
- Memory B cell
- Plasmablast

Legend:
- Low expression
- High expression
Figure S3: Effect of IL-2 stimulation in vitro on pERK activation in lymphocyte subsets

- **CD4Treg**
  - Helios positive naive CD4Treg
  - Helios negative naive CD4Treg
  - Helios positive memory CD4Treg
  - Helios negative memory CD4Treg

- **CD4Tcon**
  - Naive CD4Tcon
  - Central memory CD4Tcon
  - Effector memory CD4Tcon

- **CD8 T cell**
  - Naive CD8 T cell
  - Central memory CD8 T cell
  - Effector memory CD8 T cell
  - TEMRA CD8 T cell

- **NK cell**
  - CD56dimCD16+ NK cell
  - CD56dimCD16- NK cell
  - CD56bright NK cell

- **B cell**
  - Naive B cell
  - Transitional B cell
  - Memory B cell
  - Plasmablast

Color scale: Low expression (green) to High expression (red)
Figure S4: Effect of IL-2 stimulation in vitro on pS6 activation in lymphocyte subsets

**CD4Treg**
- Helios positive naive CD4Treg
- Helios negative naive CD4Treg
- Helios positive memory CD4Treg
- Helios negative memory CD4Treg

**CD4Tcon**
- Naive CD4Tcon
- Central memory CD4Tcon
- Effector memory CD4Tcon

**CD8 T cell**
- Naive CD8 T cell
- Central memory CD8 T cell
- Effector memory CD8 T cell
- TEMRA CD8 T cell

**NK cell**
- CD56brightCD16low NK cell
- CD56dimCD16+ NK cell
- CD56dimCD16 bright NK cell

**B cell**
- Naive B cell
- Transitional B cell
- Memory B cell
- Plasmablast

Legend:
- Low expression
- High expression
Figure S5. Effect of low-dose IL-2 therapy on CD4Tcon, CD8 and B cell subsets. (A-C) Summary of CD4Tcon, CD8 T cell and B cell subset distribution from the 14 patients receiving IL-2 shown in Figure 5. Results at each time point are expressed as percentages of (A) total CD4Tcon, (B) total CD8 T cells and (C) total B cells.

Pending Patents: Methods for preventing or treating GVHD (UNC-CH file no. 03-43, no. 20050208036); MAPC Generation of Lung Tissue, April 21, 2004 (U/M No. Z04056) [with Athersys]; Indoleamine 2,3-dioxygenase pathways in the generation of regulatory T cells, January 6, 2006 (priority date, January 5, 2007 filing date) [licensed to New Links]; Indoleamine 2,3-dioxygenase and PD-1/PD-L pathways in the activation of regulatory T cells, filing of provisional patent, February 14, 2007 [licensed to New Links]; Use of PGE2-expressing cells to reduce inflammation, US Provisional Patent, filed November 19, 2009 [with Athersys]; Large-scale expansion approaches for regulatory T cells (UMN no. 20100109), January, 2009; Methods to expand a T regulatory cell master cell bank, (UPenn/UMN no. 61322186), April 8, 2010; Generation of natural killer cells and lymphoid tissue inducer-like (LTI-like) NK-22 cells, December 2, 2011; Methods for accelerating immune regeneration, October 4, 2012; TALEN based gene correction, March 1, 2013; Methods of treating and preventing alloantibody driven chronic graft-versus-host diseases, December 2, 2013 [with Pharmacyclics, Inc]; Treatment of graft-versus-host disease disorders using RAR antagonists, January 8, 2014 [with Ito Therapeutics, Inc]; Role of ROCK2 inhibitors in chronic GVHD, April 9, 2014 [with Kadmon Pharmaceuticals, Inc]; Activated Protein C therapy for chronic graft versus host disease related to
allogeneic hematopoietic stem-cell transplantation, 2014 [disclosure]; Fanconi Anemia Gene Editing by CRISPR/Cas9 System, 2014 [licensed, PlasmaTech]; Use of compositions modulating chromatin structure for graft versus host disease (GVHD), November 6, 2014; GvHD-associated, Inflammasome-mediated Loss of Function in Adoptively Transferred Myeloid-derived Suppressor Cells, August 6, 2015; Methods and Compositions for Increasing the Suppressive Function of Regulatory T-cells (TREGS), September 4, 2015; Chimeric Antigen Receptor (CAR) T Cells as Therapeutic Interventions for Auto- and Allo-immunity, September 28, 2015; Methods Involving Editing Polynucleotides That Encode T Cell Receptor, October 22, 2015; Derivation of human T-Progenitor cells from human T cells derived induced pluripotent stem cells (T-IPSCs), December 5, 2015; Optimizing Human Regulatory T Cell Therapy through Identification of Active miRNA/mRNA Complexes, in progress, 2015.