TCR Alpha, Beta and CD19+ Cell Depleted Haploidentical Transplant for Primary Immunodeficiency Disorders
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Human Immune System

Immune System

Acquired
- T-cell immunity
  - (cell-mediated immunity)
  - Whole T-cells released into:
    - Suppressor T-cells
    - Helper T-cells
    - Cytotoxic T-cells
  - Death of the body's cells that are infected with a virus or otherwise damaged

B-cell immunity
  - (humoral immunity)
  - Antigen exposure
  - Lymphoblasts
  - Plasma cells
    - Antibodies
      - Complement cascade
        - Classical pathway

Clonal B-cells
  - Memory B-cells

Innate
- Bloodbourne
  - Complement cascade
  - Alternative pathway

- Phagocytes
  - Neutrophils
  - Macrophages
  - Basophils
  - Eosinophils
  - Natural killer cells
  - Death of dangerous organisms
  - Direct killing of bacteria

Physical barriers
- 1. Skin
- 2. Mucous membranes
- 3. Saliva
- 4. Flushing action of urine and tears
- 5. Stomach acid
  - Stops infection before it enters the body
Hematopoiesis in the Bone Marrow

Self-renewing Pluripotent Stem Cell

Lymphoid Stem Cell

Myeloid Stem Cell (CFU-GEEM)

Pre-T

Pre-B

BFU-Meg

CFU-Meg

CFU-GM

CFU-M

CFU-E

CFU-G

Megakaryocyte

Monocyte

Reticulocyte

Mast Cell

Neutrophil (PMN)

T Cell

B Cell

Platelets

Macrophage

Baxter Healthcare Corporation
Biotech Group
Primary Immunodeficiency Disorders

- Primary immunodeficiency diseases (PID) are chronic disorders in which part of the body’s immune system neutrophils, macrophages, dendritic cells, natural killer cells, T and B lymphocytes and complement components is missing or functions improperly.
- These diseases are caused by hereditary or genetic defects.
- These disorders present at birth or in early childhood, Some affect a single part of the immune system; others may affect more than one components of the immune system.
- More than 300 distinct PID disorders have been identified and 400 genes have been associated with these diseases.
- Spectrum of these diseases can vary from mild presentation to lethal disorders. Lethality is due to increase susceptibility to infections and malignancies.
- Aberration Immune Cells, vigorously reacting to self antigens resulting in high prevalence of autoimmune diseases.
Hematopoiesis in the Bone Marrow

Self-renewing Pluripotent Stem Cell

SCF

Lymphoid Stem Cell

IL-3, SCF

Myeloid Stem Cell (CFU-GE MM)

IL-3, SCF

CFU-GM

IL-3, GM-CSF, G-CSF

BFU-E

IL-3, SCF, EPO

CFU-E

IL-3, GM-CSF, EPO

CFU-G

EPO

Monocyte

Reticulocyte

Mast Cell

Neutrophil (PMN)

Megakaryocyte

Platelets

T Cell

Pre-T

SCF + IL-7

B Cell

Pre-B

BFU-Meg

IL-3, SCF

CFU-Meg

IL-3, SCF, GM-CSF

CFU-M

IL-3, GM-CSF, M-CSF

Macrophage

Baxter Healthcare Corporation
Biotech Group
Since 1968 bone marrow transplantation from a HLA matched sibling donor became the Gold standard.
# Primary Immune Deficiency Disorders Receiving Allogeneic BMT
**CHLA 1/1/1983 to 9/30/2017**  
**n=210**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>BMT #</th>
<th>Diagnosis</th>
<th>BMT #</th>
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<tbody>
<tr>
<td>ADA Deficiency</td>
<td>1</td>
<td>Bare Lymphocyte Syndrome</td>
<td>4</td>
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<tr>
<td>CD40 Ligand Deficiency</td>
<td>7</td>
<td>Chediak-Higashi Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Granulomatous Disease</td>
<td>23</td>
<td>Combined Immunodeficiency Disease</td>
<td>2</td>
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<tr>
<td>Common Immune Variable Deficiency</td>
<td>1</td>
<td>Hemophagocytic Lymphohistiocytosis</td>
<td>23</td>
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<td>Histiocytosis-X</td>
<td>1</td>
<td>I Cell Disease</td>
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<tr>
<td>Immune Deficiency</td>
<td>2</td>
<td>Kostmann’s Syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Leukocyte Adhesion Deficiency</td>
<td>2</td>
<td>Neutrophil Defect</td>
<td>1</td>
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<tr>
<td>Omenn Syndrome</td>
<td>1</td>
<td>Shwachman-Diamond Syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Severe Combined Immunodeficiency</td>
<td>114</td>
<td>Severe Congenital Neutropenia</td>
<td>1</td>
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<tr>
<td>Wiskott-Aldrich Syndrome</td>
<td>18</td>
<td>X-linked Lymphoproliferative Syndrome</td>
<td>3</td>
</tr>
</tbody>
</table>
Primary Immune Deficiency Disorders
CHLA 1/1/83 to 12/31/17
n=210

- ADA Deficiency
- Bare Lymphocyte Syndrome
- CD40 Ligand Deficiency
- Chediak-Higashi Syndrome
- Chronic Granulomatous Disease
- Combined Immunodeficiency Disease
- Common Immune Variable Deficiency
- Hemophagocytic Lymphohistiocytosis (HLH) (Familial)
- Histioyctosis-X
- I-cell disease
- Immune Deficiency
- Kostmann’s Syndrome
- Leukocyte adhesion deficiencies
- Neutrophil defect
- Omenn syndrome
- Shwachman-Diamond Syndrome
- Severe Combined Immunodeficiency (SCID)
- Severe Congenital Neutropenia
- Wiskott-Aldrich Syndrome
- X-linked Lymphoproliferative Syndrome
Essential steps for Blood Stem cell transplant from another individual (Allogeneic Transplant)

- **Identification of the disease correctable with allo BMT or auto BMT.**
- **Identification of suitable HPC donor**
- **Conditioning regimen with Myeloablation and immunosuppression**
- **Making recipient immuno-incompetent to accept the graft (Immunosuppression)**
- **Histo-compatible donor HSC graft (HLA matched)**
- **Post transplant immuno-suppression to prevent graft versus host disease (short duration)**
- **Recovery of lympho-hematopoiesis**
Post Transplant survival

n=118, Sib n=22 (17%) Unrelated Marrow n=66 (51%) UCB n=39 (30%)
Essential steps for Blood Stem cell transplant from another individual (Allogeneic Transplant)

- Identification of the disease correctable with allo BMT or auto BMT.
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- Making recipient immuno-incompetent to accept the graft (Immunosuppression)
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- Recovery of lympho-hematopoiesis
Availability of Donor

- For a patient with non genetic disease, there is 35% chance to have histocompatible donor within siblings.
- For a patient with genetic disease, there is <25% chance to have histocompatible sibling who is also healthy.
- Less than 5% have other related matched donor.
- **60 to 75% must have alternative Stem cell donor graft**
  - ✓ Unrelated donor marrow, PBSC or cord blood
  - ✓ Haploidentical donor
A patient’s likelihood of having a donor on the Be The Match Registry who is willing and able to help save a life is estimated to range from 66% to 93%, depending on race and ethnicity. Cord blood improves likelihood of finding an appropriate cell source. In 2012, 39 percent of minority patients who received a transplant used cord blood.

<table>
<thead>
<tr>
<th>All patients, depending on race and ethnicity</th>
<th>66-93%</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American or Black patients</td>
<td>66%</td>
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<tr>
<td>American Indian and Alaska Native</td>
<td>82%</td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>73%</td>
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<tr>
<td>Hispanic or Latino</td>
<td>72%</td>
</tr>
<tr>
<td>White</td>
<td>93%</td>
</tr>
</tbody>
</table>

Source: NMDP Bioinformatics, 2010
Note: Percentages are based on matching an adult donor only. Cord blood further increases the chance of finding a match for some patients.

For 10-45% of patients there are no matched sibling or unrelated donor Option for those Patients: Haploidentical donor transplants
Haplo matched transplantation

- In late 70’s and early 80’s, option of haplo-matched donor transplantation “from the donors who were readily available but over looked” was entertained.

- The major issues related to these transplant was **Graft versus Host disease** and the primary cells which cause this reaction were identified “**immuno-competent T cells**” present in the graft.

- Studies showed that in vitro or in vivo **T cell depletion** from the graft is essential to remove allo reactive post thymic T cells to prevent graft versus host disease.
In late 70’s and early 80’s, option of haplo-matched donor transplantation “from the donors who were readily available but over looked” was entertained.
Haploidentical transplants

- **Techniques used for depletion of T cells**
  - T depletion with Soy Bean Lectin agglutination and E rosette
  - OKT3 monoclonal antibodies depletion.
  - T cells depletion with use of Campath in the Bag
  - CD34+ cell selection
  - Post graft Cyclophosphamide (In vivo depletion)
  - TCR Alpha, Beta and CD19+ Cell Depletion
Sources of Hematopoietic Stem Cells

For TCR Alpha, Beta and CD19+ Cell Depletion

Bone Marrow

Peripheral Blood Stem Cells (PBSC)

-Preferred source is mobilized peripheral blood Stem cells as machine is validated for it.
-Larger number of stem cell are procured
TCRαβ/CD20 depletion by CliniMacs

Pre Column

TCR αβ Depletion
(4.5 log)

Post Column

TCR γδ Enrichment

B cell Depletion
(2.6 log)
Strategy for depletion of $\alpha/\beta^+$ CD19+ cells

1. biotin-anti-$\alpha/\beta$ and CD19 mAb
2. microbeads with anti-biotin mAb

Waste ($\alpha/\beta$ T cells)

Graft

CD34+ and CD34- progenitors
NK cells
Dendritic cells
$\gamma/\delta$ T-cells
**Key points**

*TCR α β and CD19 cells Depletion for haplo-identical transplantation*

- Prompt donor availability
- Graft depleted of allo-reactive T cells
- Graft enriched for CD34^+ cells, innate immune cells including TCR γδ cells, NK cell, Dendritic cells to provide bridging immunity while new immune cells are growing from stem cells
- No post transplant immunosuppression needed

*Issues associated with the T cell depletion or Stem cell Selection*

- Stem cell loss during procedure
- Graft failure
- *Delayed recovery of lymphocytes and immunity*
- Infections and re-occurrence of disease
- PTLD
All lethal events were due to uncontrollable viral infections

- Infusion of BPX-501 T cells to improve immune reconstitution
- BPX-501 T cells contain the iCasp9 suicide gene to provide safety
TCR αβ and CD19 cells Depletion for haplo-identical transplantation

BP-U-004 Bellicum study

- Haplo-identical stem cell transplant following αβ T cell & CD19 B cell depletion and retention of NK cells and γδ T cell

- γδ T cells are non allo-reactive, recognize conserved non peptide antigen which is up regulated by transformed or viral infected cells and is able to kill those cells. NK cells provide innate immunity with out GVHD.

- Potentiate immunity by infusing donor T cells genetically modified with retroviral vector containing iCasp suicide gene.

- This chimeric protein is quiescent in the cells till triggered by small molecule dimerizer drug Rimiducid.

- These T cells are given 21± 14 days post transplant

- No immunosuppressive treatment post transplant
**Engineered T-cells with iC9 “safety switch” and CD19 marker**

Inducible caspase 9 binding site; rimiducid binding starts caspase apoptosis cascade

**Truncated CD19 marker allows selection for purity and tracking in blood**

- MNC obtained from donor leukapheresis, produced in GMP facilities in Europe and US
- Activated and expanded in culture, transduced with the iC9 suicide gene and selected for CD19+ cells
- Cryopreserved and stored in liquid nitrogen
- Normal T-cell characteristics are maintained
  - Broad T-cell repertoire of immunity
  - Antiviral and antigen-specific activity

**Sponsor:** Bellicum Pharmaceuticals
ClinicalTrials.gov identifier: NCT02065869
EUDRACT number: 2014-000584-41
A. 
- Caspase 9 gene with FKBP mutant-with rimiducid binding domain (iCasp9)
- Rimiducid specifically designed to bind FKBP variant

B. 
- Rimiducid induces dimerization of the FKBP-caspase 9
- Caspase cascade activated
- Resulting in rapid apoptosis and cell-death (clinical symptoms start to resolve in 1 hour, generally resolved in 24 hours)

C. 
- iCasp9 gene containing truncated CD19 marker, integrated into T cells through retroviral vector
BPX-501 After αβ T-cell–depleted Haploidentical HSCT: To provide bridging immunity

- Clinical research to date suggests that depleting TCR αβ+ cells from the allograft and then infusing donor T-cells transduced with iCaspase9 suicide gene (BPX-501) can provide
  - More refined T-cell depletion (depletion of allo-reactive T cells), with graft containing only cells of innate immunity
  - Enhanced immune reconstitution with genetically-modified, adoptively-transferred T-cells
- In the event of uncontrolled GvHD due to BPX-501 (CD3+CD19+ T-cells), rimiducid administration induces the suicide gene, eliminating the BPX-501 cells and resolving GvHD quickly and effectively
# PID Patient population on BP-U-004 study

### Jan 2018

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EU (N=42)</th>
<th>US (N=17)</th>
<th>Overall (N=59)</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (57.1)</td>
<td>10 (58.8)</td>
<td>34 (57.6)</td>
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<tr>
<td>Female</td>
<td>18 (42.9)</td>
<td>7 (41.2)</td>
<td>25 (42.4)</td>
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<tr>
<td><strong>Age at HSCT (yrs)</strong></td>
<td>Mean (S.D.)</td>
<td>7.26 (6.99)</td>
<td>4.61 (5.29)</td>
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<td></td>
<td>Median</td>
<td>4.02</td>
<td>1.85</td>
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<tr>
<td></td>
<td>Min - Max</td>
<td>0.27 - 17.55</td>
<td>0.21 - 17.55</td>
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<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SCID</td>
<td>15 (35.7)</td>
<td>4 (23.5)</td>
<td>19 (32.2)</td>
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<tr>
<td>WAS</td>
<td>9 (21.4)</td>
<td>0</td>
<td>9 (15.3)</td>
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<tr>
<td>CGD</td>
<td>3 (7.1)</td>
<td>4 (23.5)</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>CID</td>
<td>3 (7.1)</td>
<td>1 (5.9)</td>
<td>4 (6.8)</td>
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<td>XIAP-deficiency</td>
<td>1 (2.4)</td>
<td>0</td>
<td>1 (1.7)</td>
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<td>IL-2 Receptor Deficiency</td>
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<td>1 (5.9)</td>
<td>1 (1.7)</td>
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<tr>
<td>IFNgamma-receptor 1 deficiency</td>
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<td>1 (5.9)</td>
<td>1 (1.7)</td>
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<tr>
<td>HLH</td>
<td>4 (9.5)</td>
<td>2 (11.8)</td>
<td>6 (10.2)</td>
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<td>IL-10 RB deficiency</td>
<td>1 (2.4)</td>
<td>0</td>
<td>1 (1.7)</td>
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<td>C4 deficiency</td>
<td>0</td>
<td>1 (5.9)</td>
<td>1 (1.7)</td>
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<tr>
<td>CD40 LIGAND DEFICIENCY</td>
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<td>1 (5.9)</td>
<td>1 (1.7)</td>
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<td>MHC CLASS II DEFICIENCY</td>
<td>3 (7.1)</td>
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<td>HYPER IG SYNDROME</td>
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<td>2 (3.4)</td>
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<td>IKBetaAlfa GAIN OF FUNCTION</td>
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<td>MUTATION</td>
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<td>DOCK 8 DEFICIENCY</td>
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<td>1 (1.7)</td>
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<td>SEVERE CONGENITAL NEUTROPENIA</td>
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<td>1 (5.9)</td>
<td>1 (1.7)</td>
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## Donor and graft characteristics

**BP-U-004 study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>EU (N=42)</th>
<th>US (N=17)</th>
<th>Overall (N=59)</th>
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<td><strong>Conditioning Regimen</strong></td>
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<tr>
<td>Treosulfan-based</td>
<td>n (%)</td>
<td>28 (66.7)</td>
<td>0</td>
<td>28 (47.5)</td>
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<tr>
<td>Busulfan-based</td>
<td>n (%)</td>
<td>10 (23.8)</td>
<td>13 (76.5)</td>
<td>23 (39.0)</td>
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<tr>
<td>Other: TBI</td>
<td>n (%)</td>
<td>2 (4.8)</td>
<td>1 (5.9)</td>
<td>3 (5.1)</td>
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<tr>
<td>Other</td>
<td>n (%)</td>
<td>1 (2.4)</td>
<td>3 (17.6)</td>
<td>4 (6.8)</td>
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<tr>
<td><strong>Type of Donor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>n (%)</td>
<td>40 (95.2)</td>
<td>16 (94.1)</td>
<td>56 (94.9)</td>
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<td>Sibling</td>
<td>n (%)</td>
<td>2 (4.8)</td>
<td>1 (5.9)</td>
<td>3 (5.1)</td>
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<tr>
<td><strong>Donor Age (yrs)</strong></td>
<td>Mean (S.D.)</td>
<td>33.19 (7.42)</td>
<td>35.06 (7.93)</td>
<td>33.73 (7.55)</td>
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<td>Median</td>
<td>34.00</td>
<td>35.00</td>
<td>34.00</td>
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<tr>
<td></td>
<td>Min - Max</td>
<td>22.00 - 49.00</td>
<td>21.00 - 52.00</td>
<td>21.00 - 52.00</td>
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<tr>
<td><strong>Cell Dose: CD34 10^6/kg</strong></td>
<td>Mean (S.D.)</td>
<td>22.32 (10.24)</td>
<td>17.75 (14.32)</td>
<td>21.04 (11.58)</td>
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<td>Median</td>
<td>23.00</td>
<td>18.50</td>
<td>22.00</td>
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<td>4.00 - 57.00</td>
<td>1.00 - 42.00</td>
<td>1.00 - 57.00</td>
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<tr>
<td><strong>Cell Dose: TCR 10^5/kg</strong></td>
<td>Mean (S.D.)</td>
<td>0.40 (0.29)</td>
<td>0.55 (0.34)</td>
<td>0.44 (0.31)</td>
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<tr>
<td></td>
<td>Median</td>
<td>0.35</td>
<td>0.49</td>
<td>0.40</td>
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<tr>
<td></td>
<td>Min - Max</td>
<td>0.01 - 1.11</td>
<td>0.01 - 1.00</td>
<td>0.01 - 1.11</td>
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<tr>
<td>BP-004 PID Transplant Characteristics</td>
<td>TOTAL (N=23)</td>
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<td>-----------------------------------------------------------------</td>
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<td>Conditioning Regimen</td>
<td>N (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Treosulfan-based</td>
<td>14 (60.9)</td>
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<tr>
<td>Busulfan-based</td>
<td>8 (34.8)</td>
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<tr>
<td>Other</td>
<td>1 (4.3)</td>
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<tr>
<td>Median CD34 Cell Dose (10^6cells/kg)</td>
<td>21.00 (11.0 - 35.0)</td>
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<tr>
<td>Median TCR TCRγδ Cell Dose (10^6cells/kg)</td>
<td>0.05 (0.00 - 0.10)</td>
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<tr>
<td>Median NK Cell Dose (10^6cells/kg)</td>
<td>42.8 (19.4-171.0)</td>
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<tr>
<td>Median TCR γδ Cell Dose (10^6cells/kg)</td>
<td>16 (5.68-60.4)</td>
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<tr>
<td>Median Donor Age (yrs)</td>
<td>33.0 (21.0 - 45.0)</td>
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<tr>
<td>Type of Donor</td>
<td>N (%)</td>
<td></td>
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<td></td>
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<tr>
<td>Parent</td>
<td>22 (95.7)</td>
<td></td>
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</tr>
<tr>
<td>Sibling</td>
<td>1 (4.3)</td>
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<tr>
<td>Median Time to BPX-501 infusion (days)</td>
<td>17.00 (3.00 - 56.0)</td>
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</tr>
<tr>
<td>Parameter</td>
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<td>------------------------------------------</td>
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<td>-----------</td>
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<td>----------------</td>
</tr>
<tr>
<td><strong>Time to Neutrophil Recovery (days)</strong></td>
<td>Mean (S.D.)</td>
<td>16.64 (4.55)</td>
<td>14.29 (2.79)</td>
<td>16.02 (4.26)</td>
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<tr>
<td></td>
<td>Median</td>
<td>17.00</td>
<td>14.50</td>
<td>16.00</td>
</tr>
<tr>
<td></td>
<td>Min - Max</td>
<td>8.00 - 32.00</td>
<td>9.00 - 20.00</td>
<td>8.00 - 32.00</td>
</tr>
<tr>
<td><strong>Time to Platelet Recovery (days)</strong></td>
<td>Mean (S.D.)</td>
<td>11.44 (5.13)</td>
<td>17.14 (8.63)</td>
<td>13.10 (6.78)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>10.00</td>
<td>15.00</td>
<td>11.00</td>
</tr>
<tr>
<td></td>
<td>Min - Max</td>
<td>1.00 - 31.00</td>
<td>8.00 - 42.00</td>
<td>1.00 - 42.00</td>
</tr>
<tr>
<td><strong>Time to BPX infused (days)</strong></td>
<td>Mean (S.D.)</td>
<td>18.85 (9.90)</td>
<td>19.81 (5.92)</td>
<td>19.12 (8.92)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>15.00</td>
<td>19.00</td>
<td>15.00</td>
</tr>
<tr>
<td></td>
<td>Min - Max</td>
<td>11.00 - 56.00</td>
<td>12.00 - 33.00</td>
<td>11.00 - 56.00</td>
</tr>
</tbody>
</table>
N=59, E=10, Cum. Incidences of aGvHD Grade II - IV
aGvHD Grade II - IV 17.0% (95% CI 7.4 - 26.6.6)
N=59, E=3, Cum. Incidences of aGvHD Grade III - IV
aGvHD Grade III - IV 5.5% (95% CI 0 - 11.6)
N=59, E=2, Cum. Incidences of cGvHD Mild-Severe

cGvHD Mild - Severe 5.1% (95% CI 0 - 12.2)
N=59, E=3, Cum.Incidence of TRM
TRM 9.6% (95% CI 0 - 20.0)
N=59, E=7, Disease Free Survival
DFS 88.1% (95% CI 79.9 - 96.3)
<table>
<thead>
<tr>
<th>WBC</th>
<th>Lymphs abs</th>
<th>Lymphs %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3480</td>
<td>399</td>
<td>11.46</td>
</tr>
<tr>
<td>5530</td>
<td>789</td>
<td>14.26</td>
</tr>
<tr>
<td>6410</td>
<td>2470</td>
<td>38.54</td>
</tr>
<tr>
<td>5410</td>
<td>2700</td>
<td>49.9</td>
</tr>
<tr>
<td>4040</td>
<td>2798</td>
<td>69.26</td>
</tr>
</tbody>
</table>

**Bellicum subject 004-015-001**

**WBC and absolute Lymphocyte numbers/mm³**

- **WBC**
- **Lymphs abs**

Day 0: 0
Day +19: 1000
Day +26: 2000
Day +52: 5000
Day +63: 4000
Day +70: 3000

Post HAPLO transplant.
<table>
<thead>
<tr>
<th>Day</th>
<th>TCRαβ</th>
<th>TCRγδ</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>98.81</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>97.63</td>
<td></td>
</tr>
<tr>
<td>79.96</td>
<td>12.42</td>
<td></td>
</tr>
<tr>
<td>71.53</td>
<td>18.2</td>
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<tr>
<td>72</td>
<td>19.74</td>
<td></td>
</tr>
</tbody>
</table>

Bellicum subject 004-015-001

% TCRαβ and TCRγδ of CD3 + cells

Day: +19, +26, +52, +63, +70

post HAPLO Transplant
Reconstitution of Humoral Immunity (N=23) post BPX-501 T Cells infusion
Expansion of T Cell Subsets / Viral-specific BPX-501 T Cells

**Immune reconstitution**

- **TcRγδ**
- **TcRαβ**

- **CD3+CD19+CD8+**
- **CD3+CD19+CD4+**
- **CD3+CD19**

- **CD3+CD19+ CMV-**
- **CD3+CD19+ CMV+**

**Time from HSCT (days):**

- 30
- 90
- 180
- 270
- 360

**cells/mL:**

- 0
- 50
- 100
- 150
- 200
- 2500
Expansion of BPX-501 T Cells in SCID Patient

CD3+/CD19+ and CMV reactivation

Days post HSCT

CD3+/CD19+ (/mL)

CMV DNA (copies/ml)

IFNγ, SFC/10⁵ PBMC

CMV proteins
### Immune re-constitution: Six months post haplo-identical Transplant

<table>
<thead>
<tr>
<th>Charge #</th>
<th>Reagent (Dilution)</th>
<th>Mean CPM</th>
<th>SI</th>
<th>Normal</th>
<th>Low</th>
<th>CONTROL Mean CPM</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td>Background</td>
<td>594</td>
<td>N/A</td>
<td></td>
<td></td>
<td>1092</td>
<td>N/A</td>
</tr>
<tr>
<td>19045</td>
<td>PHA (1:25) - Phytohemagglutinin</td>
<td>64583</td>
<td>109</td>
<td>✔️</td>
<td></td>
<td>262510</td>
<td>240</td>
</tr>
<tr>
<td>19052</td>
<td>PHA (1:125)</td>
<td>81750</td>
<td>138</td>
<td></td>
<td></td>
<td>486647</td>
<td>446</td>
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<tr>
<td>19060</td>
<td>PHA (1:625)</td>
<td>8670</td>
<td>15</td>
<td></td>
<td>✔️</td>
<td>349958</td>
<td>320</td>
</tr>
<tr>
<td>19029</td>
<td>PWM (1:40) - Pokeweed Mitogen</td>
<td>34993</td>
<td>59</td>
<td>✔️</td>
<td></td>
<td>115691</td>
<td>106</td>
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<tr>
<td>19037</td>
<td>Con A (1:10) - Concanavalin A</td>
<td>23119</td>
<td>39</td>
<td>✔️</td>
<td></td>
<td>82635</td>
<td>76</td>
</tr>
</tbody>
</table>

**IgE Total**: 21 kU/L, 15 kU/L
**IgG Level**: 1,040 mg/dL, 972 mg/dL
**IgM Level**: 52 mg/dL, L 36 mg/dL
**IgA Level**: 68 mg/dL, 67 mg/dL

1+RA+4+3+ = 16% Absolute # = 104
2L+RA+4+3+ = 18% Absolute # = 116
Key points need to be captured

- Disease and disease status, comorbid features
- Conditioning regimen myeloablative / reduced intensity myeloablative
- Donor, Donor’s age and sex
- Graft characteristics ..... Composition of the graft and dose/kg of CD34+ cell dose, TCR αβ, CD 19+ cells TCR γδ, NK cells, TNC
- Recovery of ANC, Platelet
- Chimerism
- Assessment of recovery of immune cells in number and function
- Graft versus host disease acute and chronic
- Graft failure
- Documentation of correction of the original disease for which transplant was performed
- Monitoring for genetically modified cells and their role in providing immunity
In Summary

- T cell depletion had allowed us to offer hematopoietic stem cell transplant to patient who lacked Histocompatible related unrelated donor (every patient potentially has a donor)
- No immunosuppression is needed post transplant
- Down side of Haplo transplant is risk of GVHD with some technique and very delayed recovery of immune system with other
- TCR αβ, CD 19+ cells depletion technique leaves behind non allo-reactive innate immune cells TCR γδ, NK Cells and dendritic cells and provide some immunity
- The study results I presented is to boost the immune system with donor’s genetically engineered T cells with suicide gene, which provide bridging immunity, while new immune system grows under the influence of host thymus, thus producing haploidentical T cells tolerant to the host but reactive all other foreign antigens
- Long term follow up is needed to establish the benefit of such procedure and its applicability to other type of transplantation
• Patients and families, who bestow their trust in all of us and give us opportunities to explore new therapeutic modalities
• Clinical and Laboratory teams whose dedication and tireless efforts make it possible to offer these very complex and challenging therapeutic options to our patients
• Data management staff, clinical research staff, regulatory staff, quality and compliance staff, with out their help, we would not be able to tell you, what we did over the years
• Bellicum Pharmaceutical staff for helping us to undertake this multi-institutional study
• I want to thank my mentors, who instilled the interest in this field of haplo transplant in me
Collaborators:

**USA**
1. Children's Hospital Los Angeles
2. Baylor College of Medicine CAGT, Feigin Center
3. Children's Healthcare of Atlanta at Egleston
4. Boston Children's Dana Farber
5. Children's National Medical Center
6. Seattle Children’s Hospital/UW/FHRCC
7. Children's Hospital - OHSU
8. Children’s Hospital UTSW
9. The Children's Hospital at Montefiore
10. Stanford University - Lucille Packard Children’s Hospital

**Europe**
1. Ospedale Pediatrico Bambino Gesù
2. Great Ormond Street Hospital
3. Great North Children's Hospital Research Unit