The Future of Cord Blood Derived Therapies

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Disclosures

The following faculty and planning committee staff have no financial disclosures:

<table>
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<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Merry Duffy</td>
<td>NMDP/Be The Match</td>
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<td>Wendy Hearn, RN, BSN,</td>
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<td>John E Wagner, MD</td>
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<td>Novartis PI Magenta Therapeutics (in development)</td>
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Learning objectives

At the conclusion of this session, attendees will be able to:

- List the obstacles to successful allogeneic hematopoietic cell transplantation
- Describe how cord blood-derived cell therapeutics could enhance immune reconstitution regardless of hematopoietic stem cell source
- Identify future potential applications of cord blood-derived cell therapeutics
Increasing Use of HSC Transplantation

Transplant Activity in the US

20,000 per year
autoHSCT
alloHSCT

CIBMTR
Obstacles to Successful Allogeneic Hematopoietic Stem Cell Transplantation

- Rapid and sustained lympho-hematopoietic reconstitution [non-malignant diseases]
- Rapid immune reconstitution
- Absence of acute and chronic GVHD
- Low risk of relapse [malignant diseases]
- Immediately available HLA matched donor
HLA match donors are not available for many

Proportion with Adult URD

- 75% chance of finding 8/8 match for White Europeans
- <20% for African Americans or other African descent
- ~40% for most everyone else

Other Obstacles
[other than HLA match]

- Time to graft acquisition
- Reliability of the donor’s availability
- Possible donor preference for mPB
- Regulatory burden and cost of graft acquisition

I want a graft that provides reliable engraftment, low risk of chronic GVHD and a potent GVL effect, and I want it within 21 days of when I deem the patient is ready for transplant.
Overcoming Barriers

Lesson

Brick walls are there for reasons—not to keep YOU out but to give you a chance to show how badly you want to succeed........ [in overcoming it].

the last lecture

Randy Pausch
Overall Survival with UCB can be Comparable to Other Graft Sources

Survival by Donor Type

Cumulative Proportion

UCB
MUD
MMURD
SIB

Years post-transplantation

0.0
0.2
0.4
0.6
0.8
1.0

Brunstein et al.
Blood 2010; 116: 4693-4699
Relapse Risk with UCB is Relatively Low

Cumulative Incidence

P < 0.01

Years post-transplantation

Brunstein et al.  
Blood 2010; 116: 4693-4699
Enhanced GVL particularly in the state of MRD

Survival

Relapse

Milano and Delaney
Advantages of UCB
High Survival and Low Relapse Risk

Overall Survival
Adjusted for disease, disease status, CMV serostatus, age

BMT CTN 0501 Children with Acute Leukemia

70% [95% CI 60-77] at 5 years

24% [95% CI 15-33
16% [95% CI 10-23])

Cy 120 Flu 75 TBI 1320
and Single UCB

Conditioning Impacts High Survival and Low Relapse Risk after UCBT

Overall Survival
Adjusted for disease, disease status, CMV serostatus, age

At 5 years
TRM 16% [95% CI 10-23]
Relapse 24% [95% CI 15-33]

What happened to the 30% who died
70% [95% CI 60-77] at 5 years
Neutrophil recovery by HSC source
PBSC > BM > UCB (Disadvantage for UCB)

PBPC matched, 96%
PBPC mismatched, 96%
13 days

BM matched, 92%

UCB mismatched, 79%
25 days

BM mismatched, 94%
18 days

0 20 50 10 30 40 50 60 70 80 90 100

Incidence, %

0 10 20 30 40 50 60 70 80 90 100

Days

Adults

Eapen et al.
Lancet Oncol 2010; 11: 653-660

-15%
Lesson

‘When they go low, we go high!’
Higher UCB CD34+ cell dose is associated with faster recovery

Interpretation:

Increase in HSC number could improve engraftment and speed of hematopoietic recovery

Wagner et al.  
Blood 2002; 100: 1611-8
New Cell Dose Threshold is $1.0 \times 10^7$ TNC/kg
Greater Number of Availability of Useable UCB Units

75% of CBUs have a TNC dose $>1.0 \times 10^7$/kg for a 80 kg adult

4.3% of CBUs have a TNC dose $>2.5 \times 10^7$/kg for a 80 kg adult

NMDP Cord Blood Searchable Inventory
MGTA-456 – Provides neutrophil recovery and engraftment rates comparable to GCSF mobilized PBPC

- **PBPC**
  - Engraftment: 96%
  - Median 13 days

- **UCB**
  - Engraftment: 79%
  - Median 25 days

- **UCB**
  - Engraftment: 100%
  - Median 12 days

+4%
T regulatory cell

CD8 Teff

Placenta

Trophoblasts

T cells proliferate but don't kill
Liver Destruction of the Bile Ducts

Gut Crypt Cell Necrosis

Skin
Strategies to Enhance Immune reconstitution after Allogeneic HSCT

High Risk of GVHD Regardless of HSC Source

Cumulative Incidence
Grade II-IV Acute GvHD
by Donor Type

- SIB
- MMUD
- MUD
- DUCB

Cumulative Incidence
Grade III-IV Acute GvHD
by Donor Type

- SIB
- MMUD
- MUD
- DUCB

Brunstein and Delaney et al. Blood 2010; 116: 4693-4699
Maternal-Fetal Tolerance Modulating the Immune Response

T regulatory cell

CD8 Teff → T regulatory cell

Trophoblasts

Placenta
Thymic T regulatory cells

- Specialized subpopulation of CD4+ T cells that co-express CD25 (IL-2Rα chain) emanating from the thymus
- Preferentially migrate to secondary lymphoid organs, the putative site of allopriming and GVHD initiation
- Markedly impair activation and expansion of alloreactive CD4+ and CD8+ T cells; prevents GVHD in GVHD models
- In nature, tTreg are specific for self antigens and important for self tolerance and prevention of autoimmunity
tTreg Proof of Concept

Dose Target

**Experiment 1**
- Effect of Treg (CD25+Lsel$^{hi}$ cells)
- 1-3 Treg : Teff cell ratio
- No GVHD; complete survival

**Experiment 2**
- Human T cells into NSG mice
- Effect of human Treg (CD4+CD25+FoxP3+)
- 1 Treg : Teff ratio
- No GVHD in ileum or colon

**Target**
- 1 Treg : 1 Teff
- $>15$ million/kg
- (6-8 x 10$^6$ CD3 per kg per UCB unit in adults)
Optimization of UCB CD25 Selection and Expansion Culture

**CD25+ selection**
- Culture in X-VIVO 15
- Human AB serum 10%
- Supplemented with IL-2 300 IU/mL

**Flask culture**
18 +/- 1 days in culture

**Lot Release**
- Gram stain negative
- Endotoxin <5 EU/kg
- Viability ≥70%
- CD4+/CD25+ ≥70%
- CD3+/CD8+ ≤10%
- Sterility negative
- Mycoplasma negative
- Bead count <100/3x10⁶ cells
Strategy 1
CD3/28 bead based expansion

CD25++ → Culture 18-21 days

Rationale
- Track record in humans
- Available GMP reagents
- Standardized protocols
Strategy 2
Artificial APC based expansion

Considerations
- Ability to natural ligands
- Multiple costimulatory signals
- Stable expression
- Secretion of cytokines
- Antigen specific expansion

CD25++
Culture 18-21 days
Safety and Efficacy of UCB Treg Phase I/II Clinical Trial

CD4/CD25 Expansion

Chimerism Studies

Days Relative to UCB Transplant

Brunstein, Blazar and Wagner et al. Blood 2016
tTreg Pharmacokinetics
Dose Effect

HLA A2, B8 tracking

Dose Effect

<table>
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<th>Dose (x10^6)</th>
<th>0</th>
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<td>28 days</td>
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UCB tTreg
Impact on Acute GVHD

Steroids used for Engraftment Syndrome

- CsA/MMF 62%  n=108
- Siro/MMF 48%  n=19
- Treg/Siro/MMF 12%  n=12

P=0.03

Brunstein and Wagner et al. Blood 2015
UCB tTreg Impact on NRM and Relapse

**NRM**

- Cumulative Incidence
- Months: 0, 1, 2, 3, 4, 5, 6
- Tregs
- Siro/MMF
- P = 0.63

**Relapse**

- Cumulative Incidence
- Months: 0, 2, 4, 6, 8, 10, 12
- Tregs
- Siro/MMF
- P = 0.15
UCB tTreg Impact on DFS

Cumulative Proportion vs. Months

- KT64/86
- No Tregs

P = 0.36
UCB tTreg
Potentially Faster Immune Recovery

CD4+

Days After UCBT

Cells/mm^3

CD3^+CD4^+
P=0.045

n=10

n=7

Siro/MMF

siro/MMF/Treg

TCR diversity at d100

P value 0.0273

Simpson's index of diversity
UCB tTreg + Ultra Low Dose rh-IL2 Pilot Study (10 patients)

**Phase I/II Trial**

**Primary Endpoint**
1. Safety (absence of GVHD)

**Secondary Endpoints**
1. risk of gr 3-4 acute GVHD
2. immune reconstitution
3. transplant outcomes

**Treg expansion culture**

- UCB 1
- UCB 2
- UCB 3

- HLA < 2 loci mm
- NC > 1.5 x 10^7/kg

**Inject Treg at 1:1 Treg to Teff ratio**

- Ultra low IL2
  - 200,000 IU/m^2 MWF

**Days Relative to UCB Transplant**

-18 -12 -8 -7 -6 -5 -4 -3 -2 -1 0 7 14 21 28 60 100 360
**Next Steps**

- Develop off-the-shelf tTreg products for prophylaxis and GVHD treatment
  - Determine impact of HLA match
  - Determine the effect of prior cryopreservation
- Evaluate tTreg in treatment of autoimmune disease.
  - Type I diabetes (autologous UCB)
  - Solid organ transplants
UCB tTreg
Clinical Summary

• UCB tTreg are potent modulators of the alloreactive response

• UCB tTreg at high doses are safe and have not increased the risk of opportunistic infection or relapse

• Safety and effectiveness of ultra-low dose rh-IL2 + UCB tTreg are under evaluation; if results are positive, it will markedly reduce tTreg manufacturing costs

• Usefulness in autoimmune diseases have broad applicability
Reconstitution of the T cell Compartment after UCB Transplantation

Increase graft HSC
Reduce thymic injury
Eliminate GVHD
Increase T progenitors
Summary

UCB has uses beyond hematopoietic stem cell rescue

- Source of potent tTregs
- Source of thymic progenitors
- Source of NK cells
- Source of HPCs
The new ‘bench mark’

Overall Survival
Adjusted for disease, disease status, CMV serostatus, age

BMT CTN 0501 Children with Acute Leukemia

70% [95% CI 60-77] at 5 years