Umbilical cord blood transplantation: The first 25 years and beyond

Karen K. Ballen, Eliane Gluckman and Hal E & Broxmeyer
blood-2013-2013 122: 491-498

Bibishahin Shamsian. MD
REVIEW:
Umbilical cord blood graft enhancement strategies: has the time come to move these into the clinic?
M Norkin 1, HM Lazarus 2 and JR Wingard 1
Bone Marrow Transplantation (2013) 48, 884–889
HSCT - definition

**Definition:**
Any procedure where hematopoietic stem cells of any donor and any source are given to a recipient with intention of repopulating/replacing the hematopoietic system in total or in part.
Stem cells

population of undifferentiated cells which are able:

• to divide for indefinite period
• to self renew
• to generate a functional progeny of highly specialised cells
HSC

Figure 3. Stem Cell Maturation Cascade

- Haematopoietic stem cell
- Differentiation
- Committed lymphoid precursor cells
- Committed myeloid precursor cells
- Cytokines
- Differentiated cells
Source
Figure 2. Bone Marrow Microenvironment\textsuperscript{20-22}
HSCs and MSCs CORD blood / source of

- Hematopoietic Stem Cells
- Mesenchymal Stem Cells
- Suppressed the effect of Graft Versus Host Disease
Hematopoietic stem cells

1 / 25 000 - 100 cells 000 of bone marrow

Characteristic:

- CD34
- CD133
- Lin−
- C-kit (CD117)
- BCRP

Blood, 15 Jan 2004
Highlights in Stem Cell Transplant

- 1957: marrow safely infused intravenously
- 1958: reports of successful identical twin transplants
- 1969: Cytoxan added to radiation
- 1970: bone marrow harvests for stem cells
- 1989: peripheral blood stem cells harvested
- 1990: first successful cord blood transplant
- 1996: first non-ablative transplant

Thomas et al J Clin Invest 1959
History of BM transplantation

- 1956 – 1\textsuperscript{st} marrow infusion
- 1968 – 1\textsuperscript{st} successful BMT
- 1981 – 1\textsuperscript{st} thalassaemia Tx
- 1988 – 1\textsuperscript{st} cord blood transplant
Nobel Prizes

- 1980: Jean Dausset, Baruj Benacerraf and George D. Snell for work on HLA system

- 1990: Dr E Donall Thomas – Seattle for clinical marrow transplantation
Indications

- Acute and chronic leukemias
- Lymphomas
- Solid tumors
- Aplastic anemia
- Congenital immunodeficiency diseases
- Metabolic disease of childhood
- Myelodisplasia
- Thalassemia
- HLH (Familial & Acq &)
- Autoimmune diseases
- .....................

http://www.ctsnet.org/home/eyevstratov
HSCT

- Allogeneic HSCT
  - sibling/related donor
  - Syngeneic
  - unrelated donor

- Autologous HSCT
- Cord Blood
Auto Transplant

The Autologous Transplant Process

1. Collection
   Stem cells are collected from the patient’s bone marrow or blood.

2. Processing
   Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.

3. Cryopreservation
   Blood or bone marrow is frozen to preserve it.

4. Chemotherapy
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. Reinfusion
   Thawed stem cells are reinfused into the patient.
Allotransplant

The Allogeneic Transplant Process

1. Collection
   Stem cells are collected from the patient's bone marrow or blood.

2. Processing
   Bone marrow or periferal blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process.

3. Cryopreservation
   Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.

4. Chemotherapy
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. Infusion
   Thawed stem cells are infused into the patient.
Complication

- **Allogeneic**
  - **Early**
    - infection
  - **Acute GVHD**
    - bleeding
    - Toxicity
    - Graft failure
  - **Late**
    - **Chronic GVHD**
      - infection
      - Relapse
      - gonadal failure
      - secondary malignancy
      - Toxicity

- **Autologous**
  - **Early**
    - infection
    - bleeding
    - toxicity
  - **Late**
    - **Relapse**
      - infection
      - gonadal failure
      - secondary malignancy
      - toxicity
Three sources of stem cells:

- Bone marrow
- Peripheral blood
- Umbilical cord blood
Bone marrow transplantation unit
Options for Stem Cell Transplant

- Obtain stem cells directly from bone marrow
- Obtained via invasive procedure in the operating room
- Are able to collect all the cells you need
Collection of hematopoietic stem cells
peripheral blood stem cell phrasis: Very often can obtain needed cell dose
Options for Stem Cell Transplant
Hematopoietic stem cell infusion
Options for Stem Cell Transplant

- Cord Blood
- Limiting factor is small cell dose
Cord blood Collecting Processes
J Clin Pathol 2010;63

My approach to the immunogenetics of haematopoietic stem cell transplant matching.

Factors influencing the outcome of HSCT:

- Disease factors; stage
- Patient, donor - related factors: Age & Sex
- Donor - related factors
  - Histopompatibility (HLA)
    The patient’s HLA type (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1 and in some cases HLA-DPB1) is generally defined using DNA-based HLA typing techniques.
    HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1 allele matched (10/10)
- Viral status (CMV positivity)
- CMV matching is preferable over a mismatch to limit the risk of CMV re-activation.
- the following ranking applies: 1. CMV status 2. male donor 3. age of donor 4. blood group compatibility
My approach to the immunogenetics of haematopoietic stem cell transplant matching.

- Factors influencing the outcome of HSCT
  - HLA
  - Peri-transplant factors
    - Conditioning
    - GVHD prevention
    - Stem cell source & content
      - BM, PBSC, CB
      - The desired recipient cell dose is $> 1.5 \times 10^6$ CD34 positive cells/kg of the recipient weight.

- Post-transplant factors
  - GVHD
HLA

HLA MHC Complex

HLA-A
HLA-C
HLA-B
HLA-DR
HLA-DQ
HLA-DP

21.32p
21.31p
21.2p
centromere

q arm

human chromosome 6
Family HLA Inheritance

Mother: A1, B8, DR17
Father: A11, B55, DR7
Children: A1, B7, DR17

For the second column:
Mother: A23
Father: A2
Children: A2, B60, DR4

For the third column:
Mother: A11
Father: DR4
Children: A11, B55, DR7

For the fourth column:
Mother: A2
Father: DR15
Children: A2, DR15

Legend:
A: A1, B: B8, C: B55, D: DR17
A: A23, B: B60, C: DR4, D: DR15
A: A11, B: DR7, C: B55, D: DR15
INHERITANCE OF HLA-ANTIGENS

<table>
<thead>
<tr>
<th>MOTHER’S ANTIGENS</th>
<th>FATHER’S ANTIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haplotype 1</td>
<td>Haplotype 2</td>
</tr>
<tr>
<td>HLA-A A-1</td>
<td>HLA-A A-2</td>
</tr>
<tr>
<td>HLA-B B-8</td>
<td>HLA-B B-7</td>
</tr>
<tr>
<td>HLA-DR DR-3</td>
<td>HLA-DR DR-7</td>
</tr>
<tr>
<td>Haplotype 1</td>
<td>Haplotype 2</td>
</tr>
<tr>
<td>HLA-A A-3</td>
<td>HLA-A A-24</td>
</tr>
<tr>
<td>HLA-B B-63</td>
<td>HLA-B B-12</td>
</tr>
<tr>
<td>HLA-DR DR-3</td>
<td>HLA-DR DR-6</td>
</tr>
</tbody>
</table>

CHILD 1: Mom A-1, Dad A-3
CHILD 2: Mom A-2, Dad A-3
CHILD 3: Mom A-2, Dad A-24
CHILD 4: Mom A-1, Dad A-3

http://www.ctsnet.org/home/eyevstratov
Human Leukocyte Antigens (HLA) are cell surface proteins involved in immune function.

HLA molecules present antigenic peptides to generate immune defense reactions.

Found on the short arm of chromosome 6

TYPING METHODS; Serology & Molecular
Major Histocompatibility Complex (MHC)

Human Leukocyte Antigens (HLA)

- **HLA-class I antigens - A, B, C:** Expressed on most nucleated cells in the body, including B-cells, T-cells, fibroblasts, etc. (Recognition of tumor and virus infected cells by T cells CD8+)
  - **HLA B most** polymorphic system and studies have shown is most significant followed by A and then C
  - **HLA-class II antigens HLA DR, DQ, DP** most significant
  - Expressed on B lymphocytes, activated T lymphocytes, macrophages, endothelial cells ie, (recognition of foreign antigens by CD4+ T cells)

- **HLA class III:** Complement, C2, C4, in Plasma, Lysis of extracellular pathogen
HLA complex
Donor-SCT

- HLA testing
- transmissible disease testing,
- completion of a health assessment questionnaire
- a complete medical history
- physical exam.

**Donors shall be tested at a minimum for HLA-A, B, DR type**

- HLA-C testing shall be performed for unrelated donors and related donors other than siblings.

**DNA high resolution molecular typing shall be used for Class II typing.**
Take-home messages

- HLA allele mismatches have an adverse effect on the outcome of haemopoietic stem cell transplantation.
- HLA matching strategies should aim for allele-level matching for HLA-A, HLA-B, HLA-C and HLA-DRB1. The benefit of matching for HLA-DQB1 and HLA-DPB1 remains uncertain.
- Alternative donors including single HLA allele-mismatched adult donors and cord blood (single and double units) should be considered in cases where a fully matched unrelated donor (10/10) is unavailable and clinical circumstances allow.
Choosing a Stem Cell Product

- Most important parameter: HLA match
  - Prefer a matched sibling donor (25%)
  - Want a “6 out of 6” match
  - HLA-A, HLA-B, and HLA-DR genes
  - Typically use PBSC, but can do marrow if unable to get enough cells via apheresis

- No matched sibling?
  - Unrelated HLA matched donor (30%)
  - Not enough donors (HLA type and race)
  - Many month delay before transplant

Choosing a Stem Cell Product

- HLA-matched unrelated cord blood
- Cell dose needed = (TNC) $2.5 \times 10^7$/Kg
- Only 25% of adults are small enough given typical cell doses in cord blood units
- Can increase the dose by using two cord blood units (double cord blood transplant)

HLA match and total nucleated cells/kg (TNC)recipient weight as Follows:

- Numeric fraction & Type TNC/kg ($10^7$)
- 6/6 match 1.5
- 5/6 (GvHD direction) –mismatch preferably = A or B rather than DRB1 3.0
- 4/6 (GvHD direction) –mismatches =preferably at A or B rather than DRB1 5.0
Summary of donor Search Strategy

- **HLA type patient**
  - **HLA type relatives**
    - Suitable related donor?
      - Yes: Proceed to transplant
      - No: Preliminary BMDW search, Contact registry - start search
    - Preliminary BMDW search
      - Select potential donors
        - Confirmatory type
          - Compatible?
            - No: Select further donors or select mismatched donors
            - Yes: Proceed to transplant

Perfect 6 antigen match; cells react only slightly against each other.

With a mismatch at one or more loci (in this case, DQ), cells will react viciously against each other.
Stem Cell Grafts are Complex

T Lymphocyte functions

Stem cell graft components

Facilitating Cells
Dendritic Cells
Stem Cells, progenitors
NK Cells
T and B Lymphocytes

GVHD
GVL, grafting
**GVHD Prophylaxis - How much?**

**Aggressive Prophylaxis**
- LESS GVHD
- MORE infection
- MORE relapse

**Minimal Prophylaxis**
- MORE GVHD
- LESS infection
- LESS relapse

**SURVIVAL**
Pathophysiology of GVHD

Essential factors necessary for GVHD to occur:

- Immunologically competent donor graft
- Histo-incompatibility between donor and host
- Immunologically incompetent host
Graft vs Host Disease/Graft Rejection

HLA differences stimulate detrimental immune responses

\[ \text{GvHD} \quad \rightarrow \quad \text{Rejection} \quad \rightarrow \quad \text{Donor Stem Cells} \]

Patient
GVHD Triad

Antigenic Differences:
- "Target"
- HLA mismatches
- Minor histocompatibility antigens

Immunosuppressed Host

Graft with Immunocompetent Cells

"Exceptions"
- Autologous GVHD
- Transfusion reactions similar to GVHD
Criteria for Development of GVHD

- Graft contains immunologically competent cells
- Host appears foreign to the graft; it has alloantigens that are capable of antigenically stimulating the graft
- Host is unable to mount an effective immunological reaction against the graft
Pathophysiology of GVHD – 3 stages

- Damaged host tissue \( \rightarrow \) cytokines (TNF\( \alpha \), IL\(_1\)) \( \rightarrow \) stimulate APCs \( \rightarrow \) recognition of host Ag by donor T cell
- Donor T cell activated \( \rightarrow \) cytokines (IFN\( \gamma \), IL\(_2\)) \( \rightarrow \) induce CTL, NKC, phagocytes
- Phagocytes release more cytokines \( \rightarrow \) cell lysis/apoptosis \( \rightarrow \) tissue destruction
Pathophysiology of Acute GVHD: adding more variables to the “triad”
New Classification: NIH Consensus

- Acute GVHD
  - <100 days
- Overlap Syndrome
- Chronic GVHD
  - ≥100 days

Persistent, Recurrent Or Late Onset aGVHD
ACUTE GVHD

SKIN

LIVER

GI TRACT
Risk Factors for Acute GVHD

- Degree of HLA match
- Conditioning intensity (high intensity)
- Donor type: Unrelated donor > related
- Graft source: PBSC > BM > Cord Blood
### Acute GVHD/ Glucksberg Staging/Grading Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (Bilirubin)</th>
<th>Intestinal Tract* (Diarrhea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>No rash</td>
<td>&lt;2.0 mg/dL or &lt;35 mmol/L</td>
<td>None or &lt;500 ml/day or &lt;280 ml/m²/day</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Maculopapular rash, &lt;25% of body surface</td>
<td>2.0–3.0 mg/dL or 35–52 mmol/L</td>
<td>&gt;500 but &lt;1,000 ml/day or 280–555 ml/m²/day</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Maculopapular rash, 25%–50% of body surface</td>
<td>3.1–6.0 mg/dL or 53–103 mmol/L</td>
<td>&gt;1,000 but &lt;1,500 ml/day or 556–833 ml/m²/day</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Generalized erythroderma</td>
<td>6.1–15.0 mg/dL or 104–236 mmol/L</td>
<td>&gt;1,500 ml/day or &gt;833 ml/m²/day</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Generalized erythroderma with bullae formation and desquamation</td>
<td>&gt;15.0 mg/dL or &gt;356 mmol/L</td>
<td>Severe abdominal pain, with or without ileus</td>
</tr>
</tbody>
</table>

*Use mL/day for adult patients and mL/m²/day for pediatric patients.

Acute GVHD Organ Staging
Acute GVHD Overall Grade

Grade I  Stage 1 to 2 skin rash; no gut involvement; no liver involvement; no decrease in clinical performance

Grade II  Stage 1 to 3 skin rash; Stage 1 gut involvement or liver involvement (or both); mild decrease in clinical performance

Grade III  Stage 2 to 3 rash; Stage 2 to 3 gut involvement or Stage 2 to 4 liver involvement (or both); marked decrease in clinical performance

Grade IV  Similar to Grade II with Stage 2 to 4 organ involvement and extreme decrease in clinical performance

IBMTR Acute GVHD Grading

<table>
<thead>
<tr>
<th>Organ Stage</th>
<th>Skin</th>
<th>Liver</th>
<th>Gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Stage 1</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Stage 2</td>
<td>Stage 1 or 2</td>
<td>Stage 1 or 2</td>
</tr>
<tr>
<td>C</td>
<td>Stage 3</td>
<td>Stage 3</td>
<td>Stage 3</td>
</tr>
<tr>
<td>D</td>
<td>Stage 4</td>
<td>Stage 4</td>
<td>Stage 4</td>
</tr>
</tbody>
</table>
Chronic GVHD

- Hepatic
- GI
- Pulmonary
- Skin
- Ocular
- Neuromuscular

Misc...
GVHD
Graft versus host disease (GVHD)
Graft versus host disease
What do we do for GVHD?

- GVHD prophylaxis (MTX, Methyl prednisolon, Cyclosporin, Tacrolimus)
- Change of conditioning regimen
- Source of stem cell transplantation
  PBSC, BM, CB

- GVHD Treatment:
  - Corticosteroieds, Cyclosporine, MMF, Anti-TNF antibodies, Pentostatin, Mesenchymal stem cells,
  - Sirolimus (Rapamycin), Alemtuzumab, Extracorporeal photopheresis (ECP), Pentostatin
HSCs and MSCs CORD blood / source of
There are several methods for collecting cord blood. The method most commonly used in clinical practice is the “closed technique”, which is similar to standard blood collection techniques.

With this method, the technician cannulates the vein of the severed umbilical cord using a needle that is connected to a blood bag, and cord blood flows through the needle into the bag.

On average, the closed technique enables collection of about 75 ml of cord blood.

Collected cord blood is cryopreserved and then stored in a cord blood bank for future transplantation.

A cord blood bank may be private (i.e. the blood is stored for and the costs paid by donor families) or public (i.e. stored and made available for use by unrelated donors).
What is cord blood?

- Another name: placental blood
- The blood that remains in baby's umbilical cord and placenta after birth
- A rich source of unique stem cells
Cord Blood

- CB transplants: 10 times less HSC than bone marrow (BM) transplants. So prolonged time to engraftment
- greater incidence of engraftment failure

- Cell dose was found to be the most important factor impacting engraftment and hence survival.

- While in general more is better, the recommended threshold was defined as $>3 \times 10^7$ NC/kg on collection and $>2 \times 10^7$ NC/kg on infusion, EuroCord group,

- Wagner et al. demonstrated a correlation between CD$_{34+}$ dose of $1.7 \times 10^5$ cell/kg and faster neutrophil recovery. Unfortunately, this measurement can still not be used for comparative studies because of the absence of standardization of the counting method between different centers.
Order: preference (choices from preceding tables):

- i. 6/6 unrelated cord blood
- ii. 8/8 living unrelated donor or 9/10 living unrelated donor or 5/6 cord or 4/6 cord
- iii. 7/8 living unrelated donor
CORD Blood

- significantly lower rates of acute and chronic graft versus host disease (GVHD) despite broader HLA disparity. The lower GVHD incidence may be explained by the lower number and mostly naïve repertoire of CB-derived T cells.

- Importantly, the graft versus leukemia (GVL) effect is preserved, most probably due to higher number and unique properties of NK cells in CB grafts.
2009 Blood Review

**umbilical** cord blood transplantation: Pros, cons and beyond
Anfisa Stanevsky

- HLA disparity was shown to be an additional factor affecting the outcome of CB transplants.
- Historically cord blood unit’s match is defined by **low resolution-A and HLA-B typing and high resolution- DR typing**.
- Increasing number of HLA mismatches was associated with delayed engraftment, higher TRM and chronic GVHD, and decreased risk of relapse.
- Gluckman et al. suggested that matching for **type II HLA may give better results**.
- Importantly, increasing the cell dose overcomes, at least partially, the HLA disparity impact.

- Furthermore, when an adequate cell dose was administered in children with leukemia, high resolution HLA-A, -B and -DR matching was not shown to improve survival, even in case of 10/10 matching.
Placental and Cord-Blood Stem Cell Transplants

After the birth of the baby, blood is collected into a special blood bag.

Stem cells transferred to a new bag.

Cryoprotectant added to minimize damage during freezing.

Virus-free, tissue-typed stem cells stored in liquid nitrogen for future transplant.
Umbilical cord blood transplantation: the first 25 years and beyond

- This year marks the 25th anniversary of the first umbilical cord blood (UCB) transplantation (UCBT) performed in France in a child with Fanconi Anemia (FA).
- Over the last 25 years, the field of UCB banking and transplantation has grown exponentially.
- Over 600,000 UCB units worldwide.
- 30,000 UCBTs have been performed. (Blood Review 2010: 14,000 in pediatric and adult)

- UCB serves as an alternative stem cell source; only 30% of patients who require an allograft will have a human leukocyte antigen (HLA)-matched sibling donor.
Umbilical cord blood transplantation: the first 25 years and beyond

- Despite 20 million adult volunteer donors in the National Marrow Donor Program and affiliated registries, many patients, particularly patients of diverse racial/ethnic backgrounds, will not have a suitably matched, unrelated volunteer donor identified in the required time period.

- UCB has extended access to transplantation, especially to patients of racial and ethnic minorities, and is rapidly available.
Umbilical cord blood transplantation: the first 25 years and beyond

- In this review:
  - review CB -SCT

- Strategies for future improvement include:
  - utilization of UCB expansion
  - ex vivo and in vivo homing techniques,
  - selection of the optimal UCB unit, and enhancement of immune recovery.
Using UCB as a source of transplantable hematopoietic stem (HSC) and progenitor (HPC) cells was suggested by Hal Broxmeyer 1982.

This meeting led to the formation a UCB company founded by Boyse et al., & at the Indiana University School of Medicine (IUSM), a 2-year grant to study the biology and cryopreservation of UCB cells.

UCB cells for study were obtained at the IUSM and later in larger numbers from Gordon Douglas at the New York University Medical Center.

These studies established the possibility of using UCB as a transplantable source of HSCs and HPCs, which then led to the first UCBT and subsequent UCBTs.
Scientific basis of cord blood transplantation

- UCB could be left for days at room temperature without significant loss of functional HPCs and that the UCB could be sent by overnight-express mail from New York to the Broxmeyer laboratory where these cells could be cryopreserved and later thawed with efficient recovery of HPC, it was realized that there were many more HPCs present in a single collection of UCB than previously appreciated.

- UCB can be stored cryopreserved for 20 years with efficient recovery of HSCs
The first cord blood transplant

- The first UCBT, performed in October 1988.

- UCB was collected by Dr. Douglas at the birth of a female baby, found by prenatal diagnosis using cultured amniotic fluid cells to be unaffected with FA and HLA-identical to a brother with FA, and the UCB was cryopreserved at the IUSM.
The first cord blood transplant

• The recipient was a 5-year-old patient with severe aplastic anemia due to FA, whose condition necessitated an urgent HCT.

• Conditioning Regimen:

• low-dose cyclophosphamide (20 mg/kg instead of 200 mg/kg) and 5 Gy total lymphoid irradiation.
The first cord blood transplant

- Results were similar to the counts before freezing.
- The first signs of **engraftment occurred on d 22**, with subsequent complete hematological reconstitution and donor chimerism.
- The patient had **no graft-versus-host disease (GVHD)** and is currently healthy with complete long-term hematological and immunological donor reconstitution 25 years after UCBT.
Pediatric UCBT

SO

- (1) a single UCB contained enough HSCs to definitively reconstitute the host lympho-hematopoietic compartment;
- (2) a UCB unit could be collected at birth without any harm to the newborn infant;
- (3) UCB HSCs could be cryopreserved and transplanted into a myeloablated host after thawing without losing their repopulating capacity.
Pediatric UCBT

• The main practical advantages of using UCB are:
  • the relative ease of procurement,
  • the absence of risk for mothers and donors,
  • the reduced likelihood of transmitting infections,
  • and the ability to store fully tested and HLA-typed UCB in the frozen state,
  • available for immediate use.
Pediatric UCBT

- UCB banks were established in order to collect and cryopreserve UCB for related and unrelated use.
- In Europe, the largest banks were in Dusseldorf, Milan, London, and Paris.
- In the US, the New York Blood Center, under the direction of Pablo Rubinstein, established the biggest unrelated UCB bank and reported the first largest cohort of unrelated UCBTs.
- For many years, most UCBTs were given to children, because it was thought that the low number of cells in a single UCB would not be sufficient to engraft an adult.
- Today, in the Eurocord registry, related UCBTs represent 8% of a total of 9419 UCBTs performed with European UCB units.

- Related UCBTs are not often performed, because most of the patients do not have a pregnant mother and because of the limited number of directed UCB banks for family use.
Pediatric UCBT

- In **2000**, in a Center for International Blood and Marrow Transplantation Research (CIBMTR)-Eurocord study comparing pediatric BMTs and UCBTs from HLA-identical siblings, UCBT was associated with:
  - delayed granulocyte and platelet engraftment
  - reduced acute and chronic GVHD,
  - but similar survival.

- This was the first analysis that demonstrated, that GVHD was reduced when UCB cells were used instead of BM.
Pediatric UCBT

- Results of related cord blood transplants for children with malignancies by Eurocord:
- In 147 patients, most with acute leukemia, the cumulative incidence of neutrophil recovery was 90%, & incidences of acute and chronic GVHD were 12% and 10% at 2 years, respectively.
- At 5 years, the cumulative incidences of nonrelapse mortality and relapse were 9% and 47%, respectively, DFS:44%.
- Cell dose and disease status: important factors for outcomes after related UCBT.
The first unrelated UCBTs in children were reported by Joanne Kurtzberg et al in 25 children with a variety of malignant and nonmalignant diseases. The 100-day overall survival (OS) was 64%, demonstrating the feasibility of unrelated mismatched UCBTs.

Comparison of unrelated HLA mismatched UCBTs to matched unrelated donor (MUD) transplants showed that UCBT resulted in a delayed engraftment, less acute and chronic GVHD, and similar relapse rate, OS, and leukemia-free survival (LFS) compared with MUD BM or peripheral blood stem cell transplant.
Pediatric UCBT

- In children with malignant diseases, 2 studies compared the outcomes of matched unrelated BMT (HLA 6 of 6) either unmanipulated or T-depleted to mismatched UCBT.
- After UCBT, engraftment was delayed,
- GVHD was similarly reduced to T-cell–depleted BMT
- Relapse and LFS were similar.
A meta-analysis of studies of UCBT and UBMT in children found that the incidence of chronic GVHD was lower with UCBTs, but the incidence of grade III–IV acute GVHD did not differ.

There was no difference in 2-year OS in children.

In children with nonmalignant diseases transplanted with HLA-mismatched UCBT, the results showed a survival rate of 40%.

This high failure rate was due to increased risk of rejection and delayed immune recovery.
Factors associated with better survival were a:
- higher TNC/kg and better HLA matching.
- A preliminary analysis of a randomized study comparing double and single UCBT in children did not show any survival advantage to using double UCBT.
- Progress has been made over the years in patient selection, modification of the conditioning regimen, and better choice of the UCB according to cell dose and HLA typing, factors contributing to the improvement of pediatric UCBT results and an increased demand for high-quality UCB units.
Pediatric UCBT

- In the future, new indications for UCBT might be developed in nonhematologic diseases, such as autoimmune diseases or degenerative diseases.
- Increasing the quality and diversity of UCB units may help to improve results for black patients, whose survival has been inferior to white patients in a large registry study.
However, increased transplantrelated mortality (TRM) was observed in children transplanted: with a low-UCB cell dose total nucleated cells [TNCs]/kg) and 1 HLA-disparate UCB graft or in children given a 2 HLA-disparate UCBT independently of the cell dose infused.
C&D ; adults

OS at 2 y after UCBT for patients with acute myeloid leukemia, acute lymphoid leukemia, and myelodysplasia in Europe and North America.
A&B Children < 16 y old
OS at 2 y after UCBT for patients with acute myeloid leukemia, acute lymphoid leukemia, and myelodysplasia in Europe and North America.
In an analysis of 1061 single adult and pediatric UCBT recipients for leukemia or myelodysplasia, the lowest TRM was seen in recipients of 6/6 HLA-A,-B antigen, -DRB1 allele-matched units, regardless of cell dose.

In recipients of mismatched units: the greater the mismatch, the greater the requirement for TNC dose.
HLA and selection of the best UCB unit

- Units that were:
- 4/6 HLA-matched to the recipient required a TNC >5.0 × 10^7/kg to achieve a similar TRM
- as 5/6 units with a TNC >2.5 × 10^7/kg.
- The presence of HLA antibodies against the UCB units has been shown to be a negative prognostic factor for both single and double UCBT.
- Preliminary studies suggest that matching the UCB unit and patient at HLA-C may be beneficial.
- Finally, the impact of donor killer immunoglobulin receptor ligand matching is unclear.
Future directions and the scientific basis of HSC function revisited

- perfusion of the placenta to collect more cells at the birth of a baby.
- Combining a haplo family or MUD with a single UCBT
- Intra-marrow injection to bypass the homing process known to be highly efficient after IV cell delivery has been attempted, with conflicting results.
- In a European study, intrabone injection had a significant advantage on engraftment with decreased GVHD.
- The MD Anderson group used a co-culture ex vivo with mesenchymal progenitor cells in 1 of 2 UCB units in 31 patients, reporting a 30-fold expansion in CD34 count and median time to engraftment of 15 days.
The most advanced ex vivo UCB enhancement strategies include the following:
- culture in the presence of stimulatory cytokines and hematopoietic growth factors;
- Notch ligand-mediated expansion;
- culture with mesenchymal stem cells
- culture in the presence of various agents, such as copper chelators, prostaglandins
- complement components, nicotinamide
- CD26/DPPIV (CD26/dipeptidyl peptidase IV) inhibitors.
Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling.

- 485 B thalassemia major (TM) or sickle cell disease (SCD) receiving HLA-identical sibling cord blood transplantation (CBT, n=96) or bone marrow transplantation (BMT, n=389).

- Compared to patients given BMT, CBT recipients were significantly younger (median age 6 versus 8 years, p=0.02), and were treated more recently (median year 2001 versus 1999, p<0.01).

- A higher proportion of patients with TM belonging to classes II-III of the Pesaro classification received BMT (44%) compared to CBT (39%, p<0.01).

- Patients receiving BMT (n=259, TM; n=130, SCD), those given CBT (n=66, TM; n=30, SCD) had slower neutrophil recovery, less acute graft-versus-host disease (GVHD) and none had extensive chronic GVHD.
Outcome of patients with hemoglobinopathies given either cord blood or bone marrow. Blood 2013.

transplantation from an HLA-identical sibling

- With a median follow-up of 70 months, the 6-year overall survival was 95% and 97% after BMT and CBT, respectively (p=0.92).
- The 6-year disease-free survival (DFS) was 86% and 80% in TM patients after BMT and CBT, respectively, while DFS in SCD patients was 92% and 90%, respectively. The cell dose infused did not influence outcome of patients given CBT.
- In multivariate analysis, DFS did not differ between CBT and BMT recipients. Patients with TM or SCD have excellent outcomes after both HLA-identical sibling CBT and BMT.
The patient is for us central to everything
HSCT in children needs pediatric multidisciplinary teamwork:

- Intensive Care including apheresis
- Immunology
- Surgery
- Pulmonary Medicine
- Gastroenterology
- Nephrology
- Cardiology
- Psychiatry
- Radiation Oncology
- Infection
- Endocrinology
- Parents & siblings
The Nobel Prize, 1990
E. Donnall Thomas

first successful HSCT in treatment of acute leukemias

Take-home messages

- HLA allele mismatches have an adverse effect on the outcome of haemopoietic stem cell transplantation.
- HLA matching strategies should aim for allele-level matching for HLA-A, HLA-B, HLA-C and HLA-DRB1. The benefit of matching for HLA-DQB1 and HLA-DPB1 remains uncertain.
- Alternative donors including single HLA allele-mismatched adult donors and cord blood (single and double units) should be considered in cases where a fully matched unrelated donor (10/10) is unavailable and clinical circumstances allow.