Bone Marrow Transplantation for Diamond Blackfan Anemia

Lauri Burroughs, M.D.

Director, Non-Malignant Transplant Program

Fred Hutchinson Cancer Research Center,

Seattle Children's Hospital

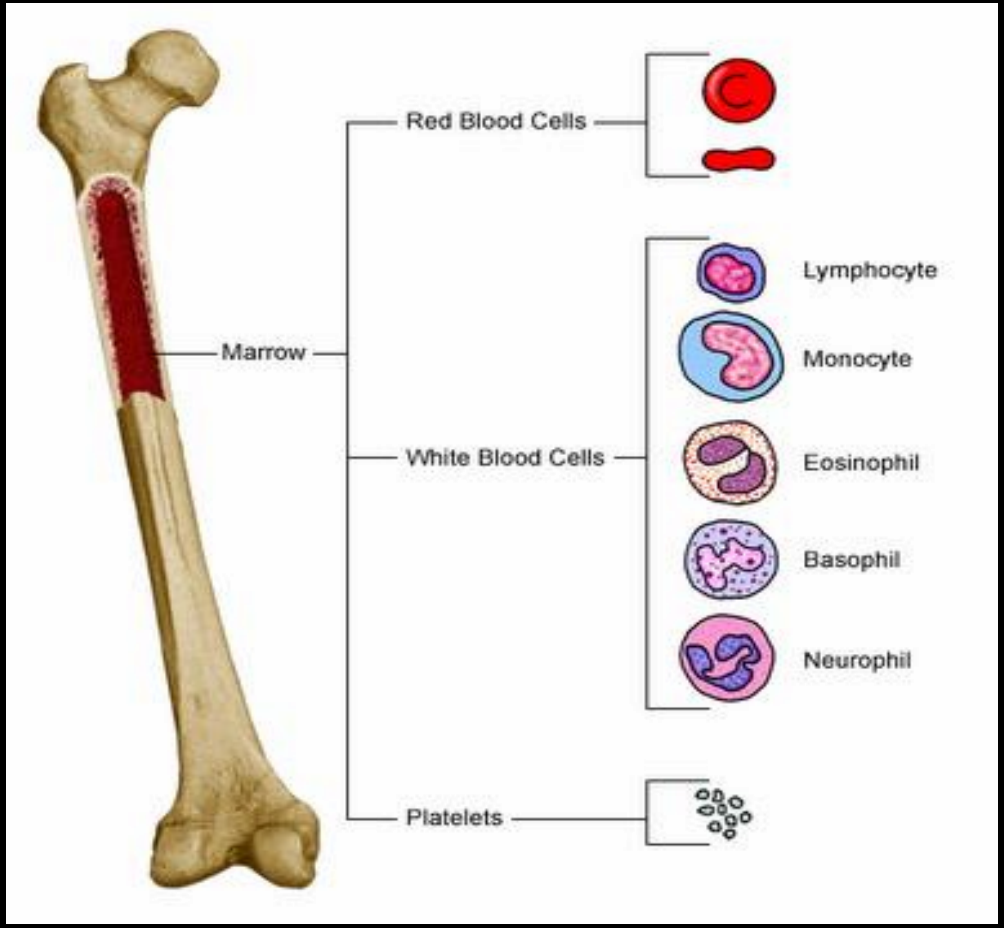
Outline

- What is the Bone Marrow
- Treatment Options for DBA
- Goals/Basic Principles of Transplantation
- Historic Transplantation Outcomes for DBA
- New Transplant Strategies
- Final Thoughts

What is Bone Marrow?

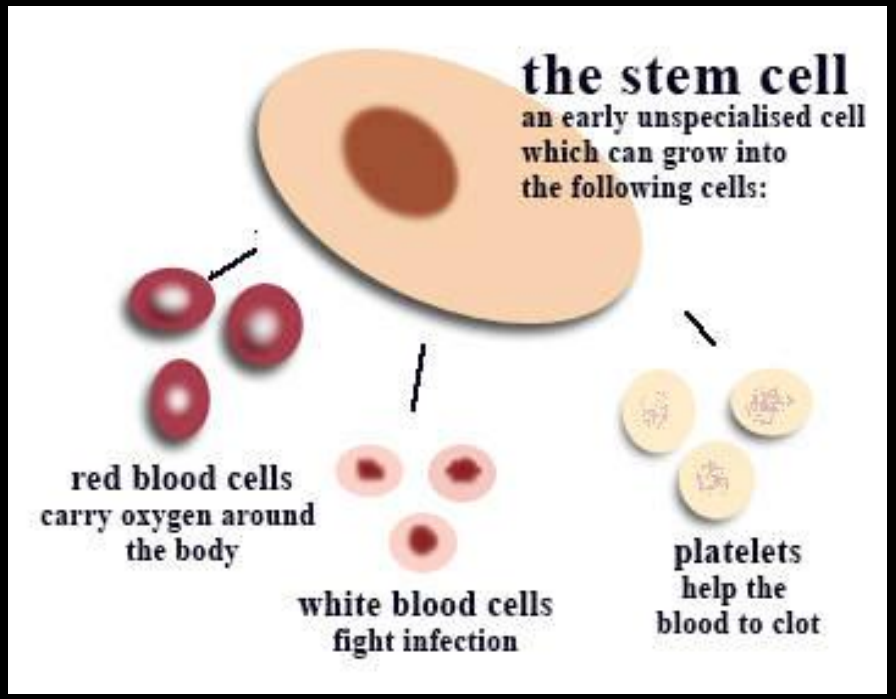
Bone marrow

- **Located**
  - **Inside bones**
- **Produces**
  - **Red blood cells**
  - **White blood cells**
  - **Platelets**
  - **Immune system**



Bone Marrow Stem Cells

- Bone marrow grows from stem cells that live in bones.
- We can collect stem cells from the bones with needles, just like when your child has a bone marrow test.
- Stem cells are like seeds.
- Stem cells can grow a whole new bone marrow in a different person over time



Treatment Options: Patients with DBA

Mainstay Therapies:

- Steroids
- Red blood cell transfusions/chelation therapy

Definitive long term cure

- Hematopoietic cell transplantation
  (Bone marrow transplantation)

Goals of Transplantation for patients with DBA

- Normalize the red blood count
- Achieve full engraftment (avoid graft rejection)
- Minimize short and long-term toxicities
- Minimize risk of infections
- Prevent Graft *vs* Host Disease (GVHD)
- Destroy any clones, MDS or leukemia

Multiple Factors Go Into Whether or Not a Patient Should Go to Transplant

…..It is not always an easy decision

1. How healthy are you?
   - Age
   - Organ function – heart, liver, lungs, kidneys?
   - Any complications - from steroids or blood transfusions?
2. Do you have a donor?
   - Matched siblings >> unrelated donors
3. What stem cell source do you have?
   - Bone marrow >> “other” sources (peripheral or cord blood)
4. What kind of conditioning can be used?
   - Full Intensity >> Moderate Intensity >> Minimal Intensity

What if You Need a Transplant?

1. Identify a Donor
    a. Matched Sibling
    b. Unrelated Donor
    c. Parent

Identifying a Donor

- Preference is a fully HLA-matched unaffected brother or sister
- “HLA” are proteins on the surface of a cell that identify who it belongs to
- There is a 1 in 4 chance that any brother or sister will be an HLA match to each other

What Do We Do If You Don't Have a Matched Sibling Donor?

- Unrelated donors are volunteers who have agreed to be tissue typed
- The tissue types are stored in a large computer belonging to the National Marrow Donor Program
- When a donor is needed the patient's tissue type is entered into the computer to see if there is match- called running a search

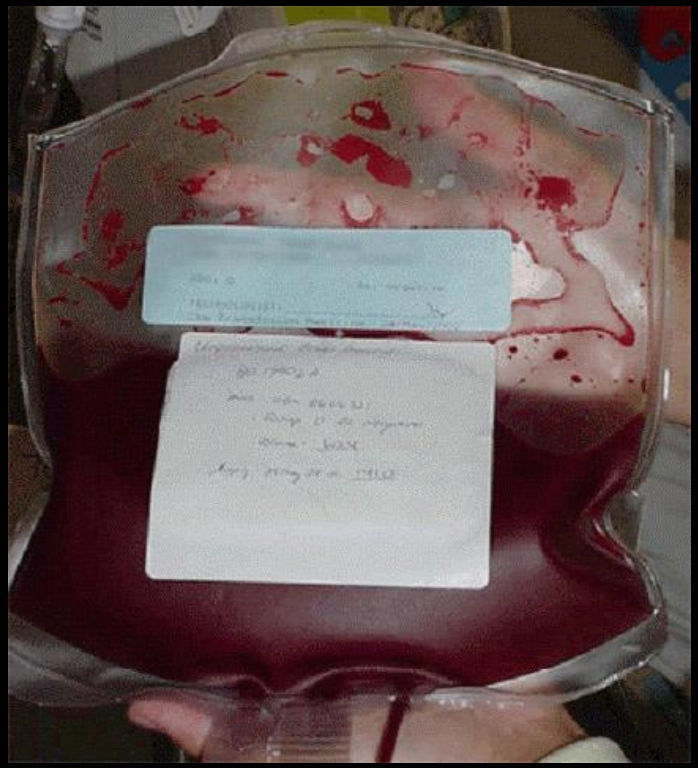
Finding an Unrelated Donor: Bone Marrow Registries

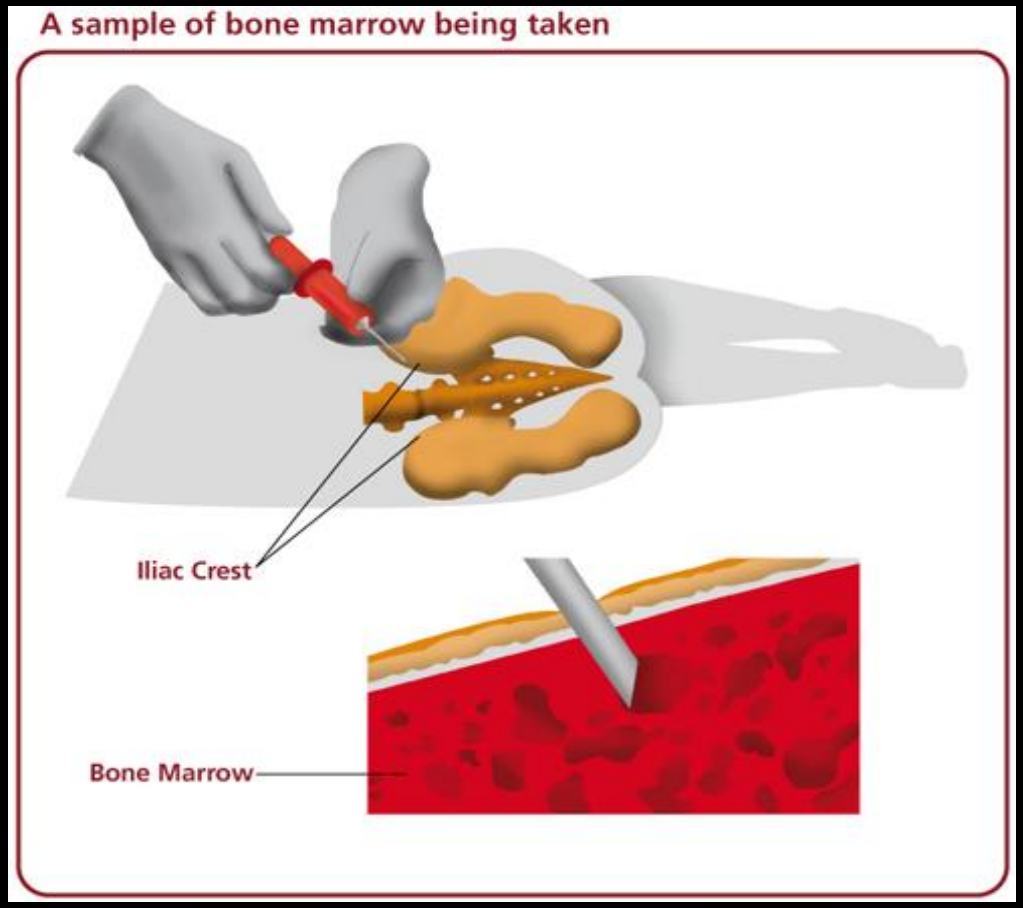
- Over 11 million unrelated donors in the US registry
- We also look for donors in registries in other countries via the internet; we are all linked – almost 24 million donors worldwide
- Donations are anonymous; you don't know who your donor is until at least 1 year after a transplant

What if You Need a Transplant?

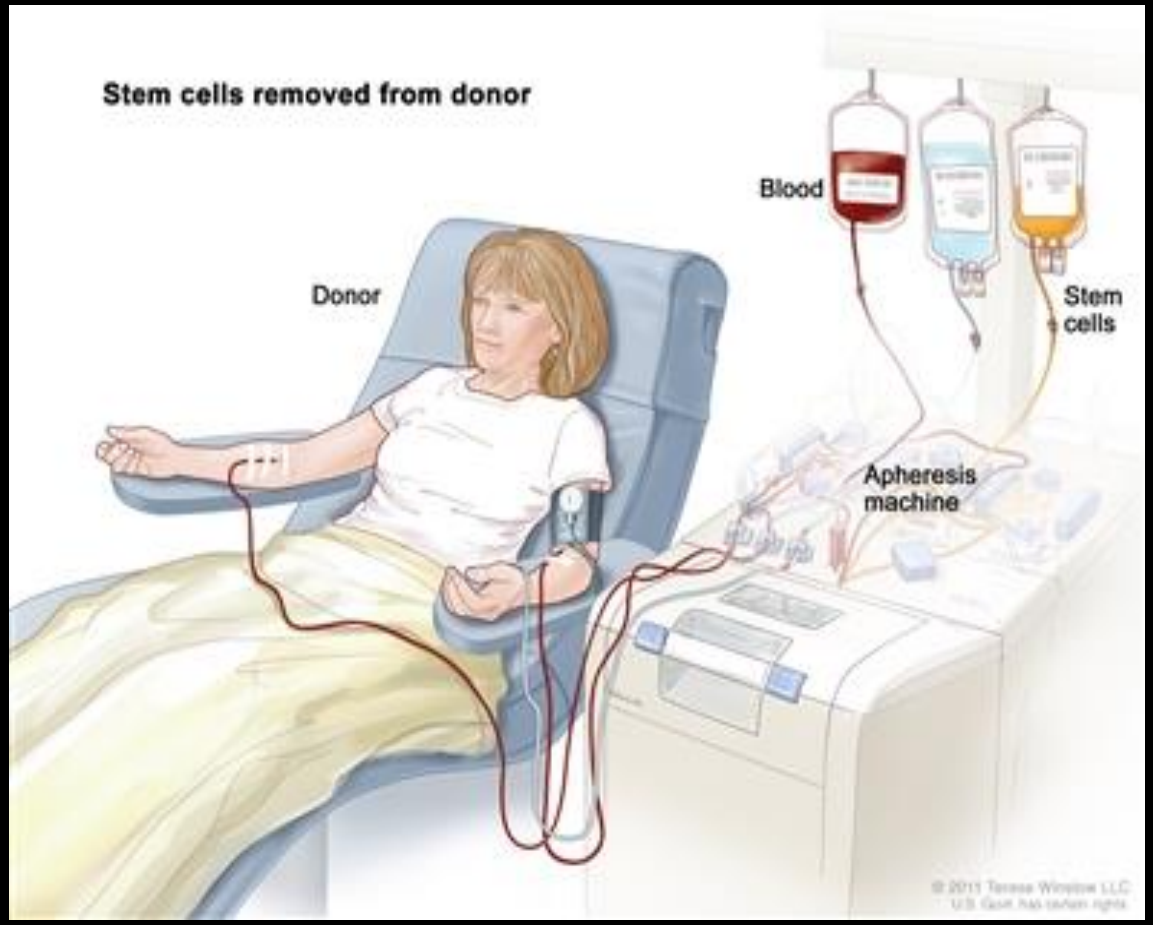
2. Select the stem cell source
    a. Bone Marrow
    b. Peripheral Blood Stem Cells
    c. Umbilical Cord Blood

Bone Marrow Harvest





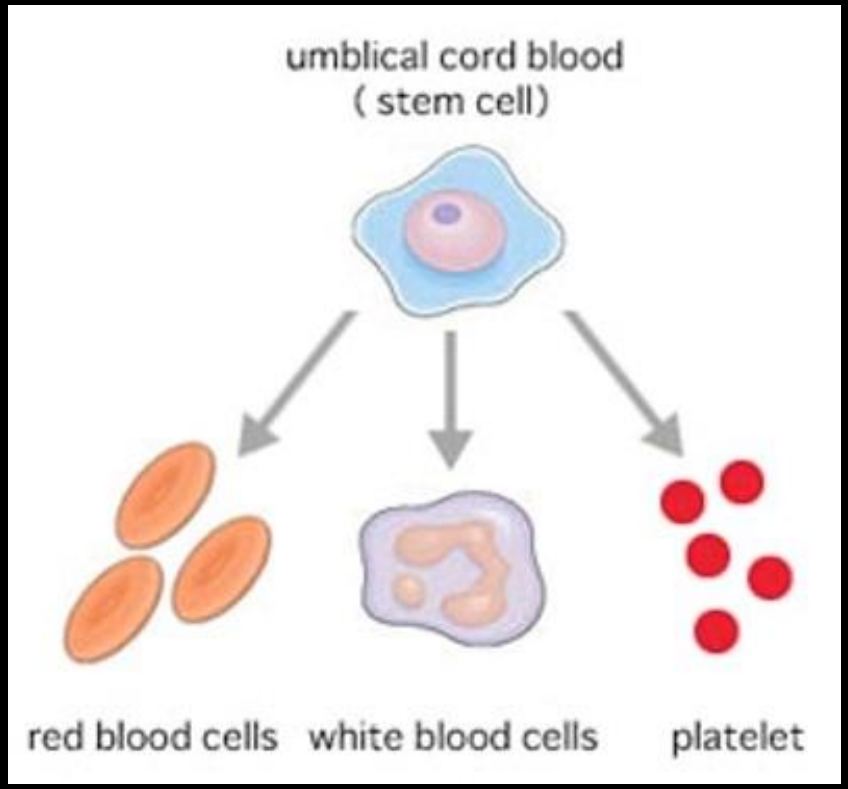
Peripheral Blood Stem Cell Harvest



Advantages:
Decreased risk
Rejection

Disadvantage:
Increased risk
GVHD

Umbilical Cord Blood Contains Bone Marrow Stem Cells



- Cord blood doesn't have to be as well matched as marrow; therefore we can often find a cord blood donor
- > 610,000 cord bloods are frozen in banks worldwide

What if You Need a Transplant?

3. Select the Transplant Conditioning Regimen

a. Myeloablative (Full Intensity)

- Busulfan/Cyclophosphamide
- TBI/Cyclophosphamide

b. Reduced Intensity/Reduced Toxicity

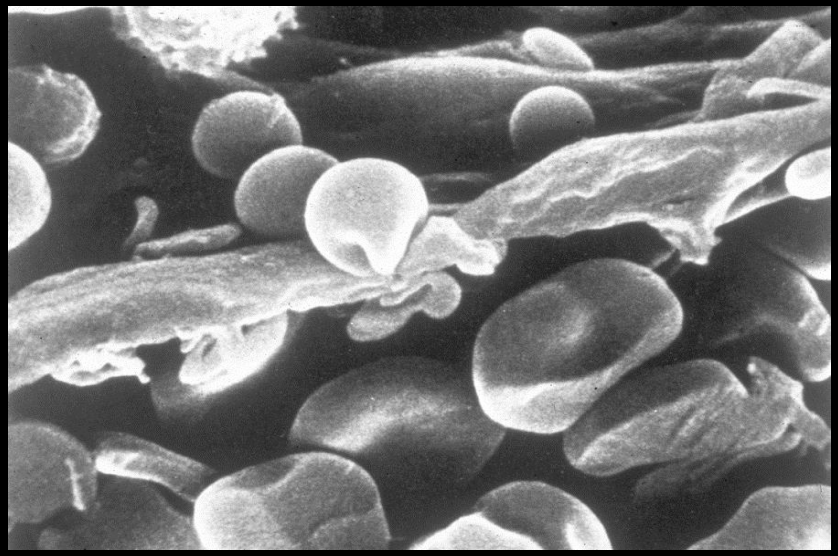
- Treosulfan//Fludarabine
- Busulfan/Fludarabine
- Fludarabine/Melphalan/Campath

c. Non-myeloablative (Low Intensity/Toxicity)

- Low dose TBI/Fludarabine

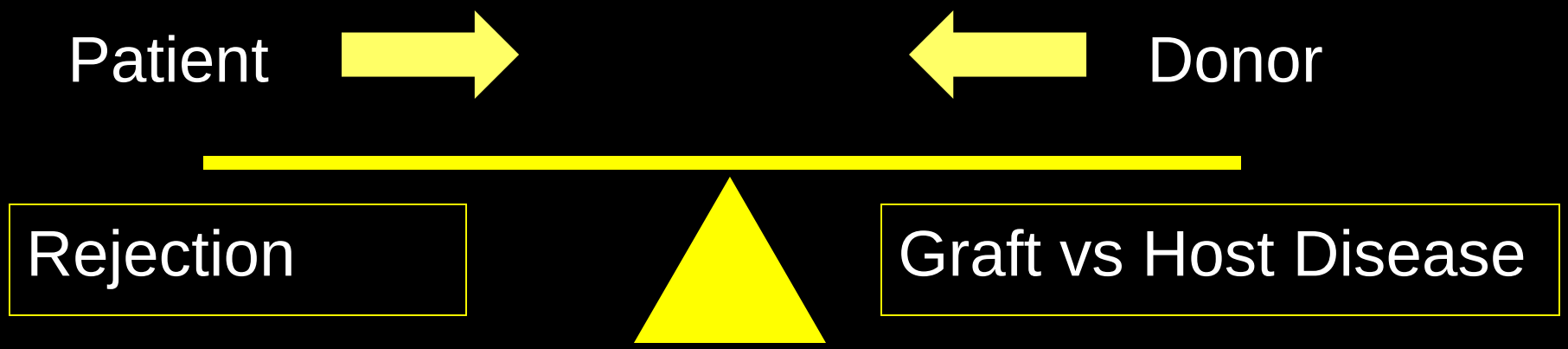
Basic Principles of Transplantation

1. Patient given drugs (called conditioning) destroys abnormal marrow & makes room for new healthy marrow
2. Healthy donor marrow infused into patient & finds its way to the empty marrow space & begins to attach, grow, and divide



3. Patient given drugs (called immune suppression) to prevent graft rejection and graft versus host disease

Two competing forces

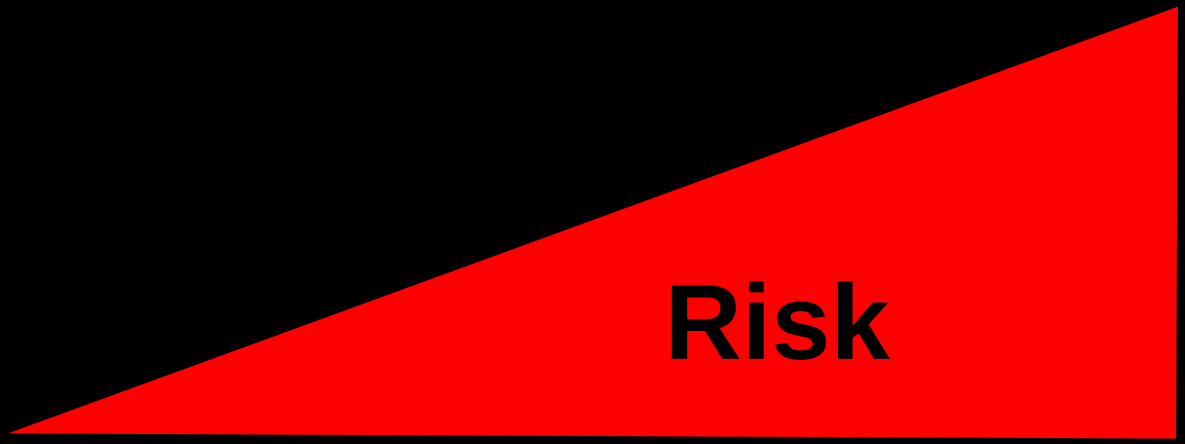


Patient doesn't recognize the donor's marrow and "rejects" it

Donor doesn't recognize the patient and attacks the patient

…we don't want either of these to happen

Transplant Risk



Higher risk
GVHD
Toxicity
Death

Donor	Matched Sibling	Matched Unrelated	Not Matched
Cell Type:	Bone Marrow	Cord Blood ⟷	Peripheral Blood
Conditioning	Minimal Intensity	Moderate Intensity	Full Intensity

Short-Term Toxicities of Transplant

- Nausea, vomiting, diarrhea
- Fatigue
- Drop in blood counts – transfusions
- Mucositis (mouth sores)
  - Often require nutritional support and pain meds
- Infections
- Organ toxicity – liver and lungs most sensitive
- Specific toxicities based on the chemo used

Long-Term Toxicities of Transplant

Likely depends on the intensity of the regimen with more intense regimens having greater long-term risks

- Infertility – inability to have children
- Impact on growth
- Delayed puberty or lack of puberty
- Other hormone problems
- Long-term organ damage
- Secondary cancers

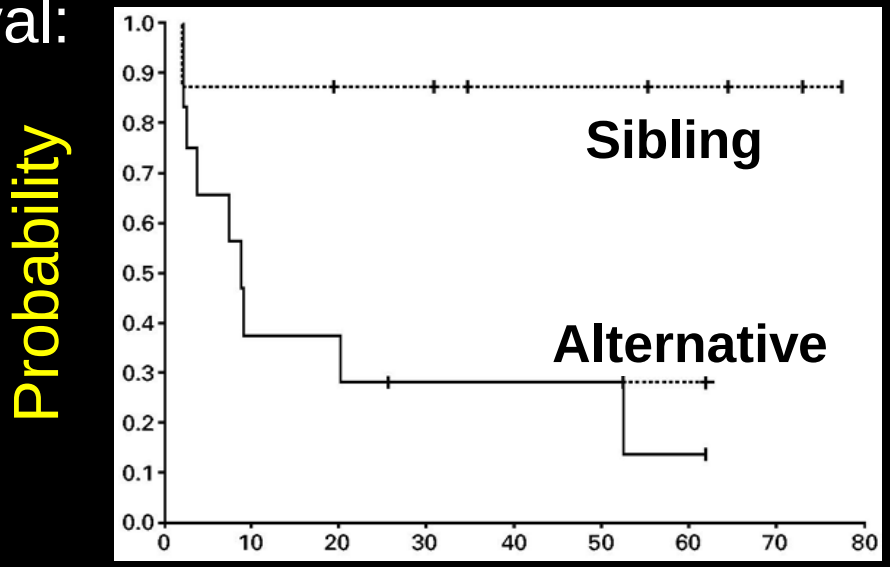
Transplant for Patients with DBA

Unfortunately:

- Due to rarity of disease, there have not been a lot of protocol driven studies to evaluate the best regimen for patients with DBA
  - Retrospective analyses of different regimens
  - Case reports
- Old data

Transplant studies: DBA #1

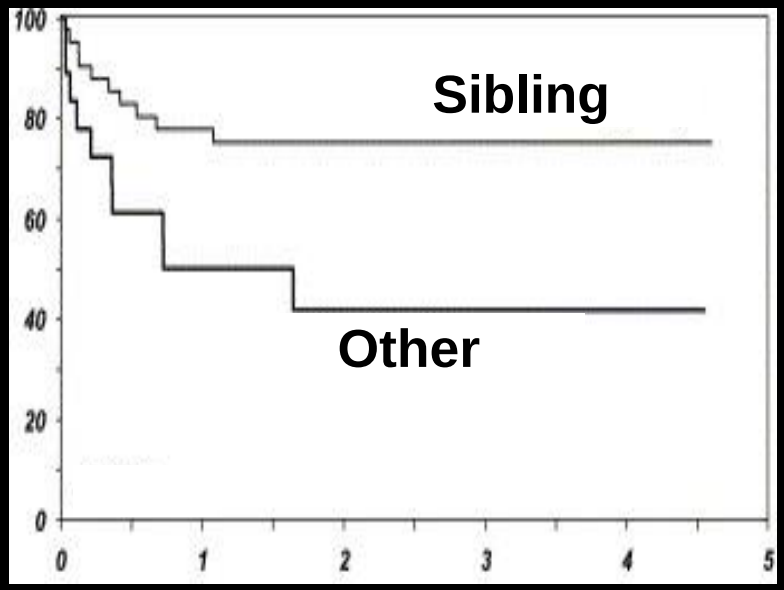
- Diamond Blackfan Anemia Registry (1993-1999)
  - 20 patients, ages 1- 23 years old
  - Transfusion dependent
  - Conditioning:
    - Busulfan-based, TBI-based
  - Survival:

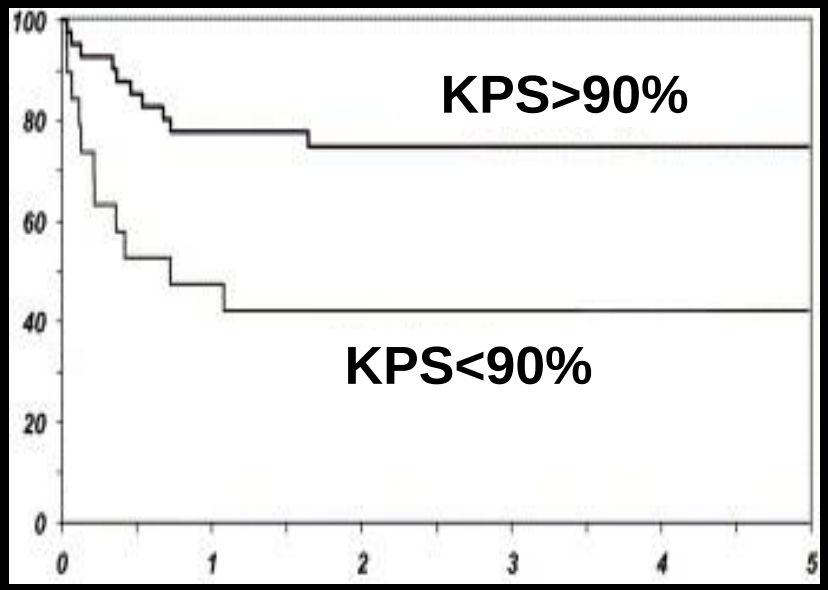


Vlachos, et al., BMT 2001

Transplant studies: DBA #2

- International Marrow Transplant Registry (1984-2000)
  - 61 patients, Median age 7 years
  - Transfusion dependent
  - Conditioning:
    - Busulfan/Cyclophosphamide, TBI/Cyclophosphamide
  - Survival:



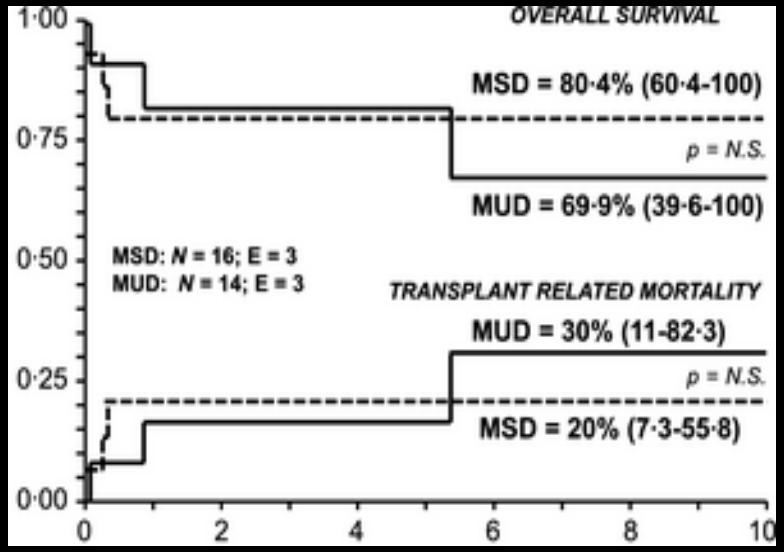


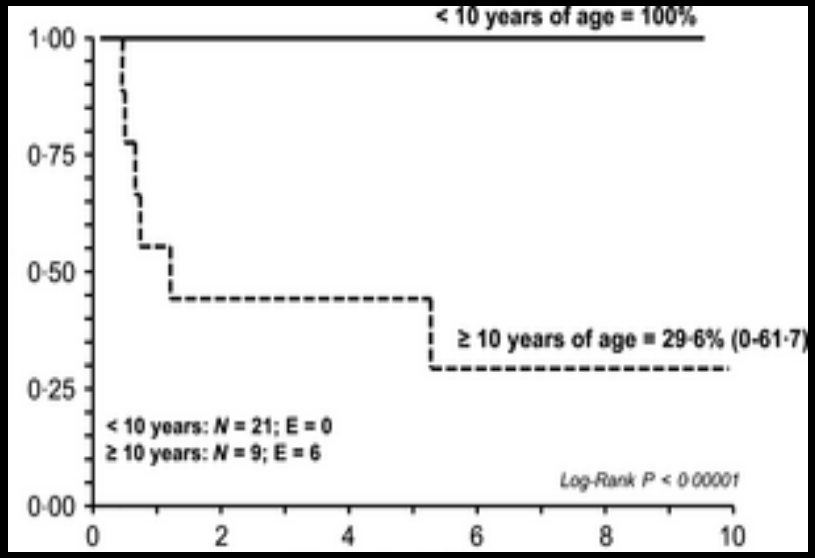
Years after Transplant

Roy, et al., BBMT 2005

Transplant studies: DBA #3

- Italian Association of Pediatric Hematology and Oncology Registry (1990-2012; n=30)
  - Transfusion dependent
  - Conditioning: Primarily Busulfan based
  - Match sibling (n=16), matched unrelated donor (n=14)
  - Survival:





Percent

Years after Transplant

Fagioli et al., BJH 2014

2008 Consensus Conference

Recommend Transplant:

- Matched sibling- transfusion dependent
  - Careful evaluation of the sibling donor
- Unrelated donor
  - Iron overload despite chelation therapy
  - Severe cytopenias: decreased RBC, WBC, or platelets
  - Development of leukemia or MDS

Debatable

- Alternative donor
  - Mismatched unrelated donor, Cord blood, Haplo donor

***Recent data - better survivals with alternative donors
Survival 23% (before 2000) versus 86% (after 2000)

Vlachos, et al., Blood 2010

Important Points to Discuss

- Retrospective data & “Old Data”
- Improved survival following transplantation
  - Better matching between donor and patient
  - Better supportive care
- Need for
  - Prospective studies
  - Development of less toxic yet effective regimens
  - Expanded donor and stem cell sources
    - 25% related donor

Seattle Protocol: Treo/Flu/ATG

- **ATG:** immunosuppressive antibody which wipes out the cells which are responsible for graft rejection and reduces the risk of GVHD

- **Fludarabine**: immunosuppressive chemotherapy drug which helps prevent graft rejection

- **Treosulfan**: chemotherapy drug similar to Busulfan but without many of the toxicities

Treosulfan

- Medac International (Hamburg, Germany)
- Widely used in Europe
  - Chemotherapeutic agent -solid tumors
  - Transplantation for malignant and nonmalignant
- Full intensity, reduced toxicity
- Results are encouraging:
  - Successful engraftment
  - Decreased toxicity – less organ damage
  - Improved survival

Phase II Study – Treosulfan Based Nonmalignant Diseases

Hypothesis

- Treosulfan/Fludarabine
  - Overcome barriers to engraftment
  - Decreased toxicities and transplant related mortality

Patient/Disease Inclusions:

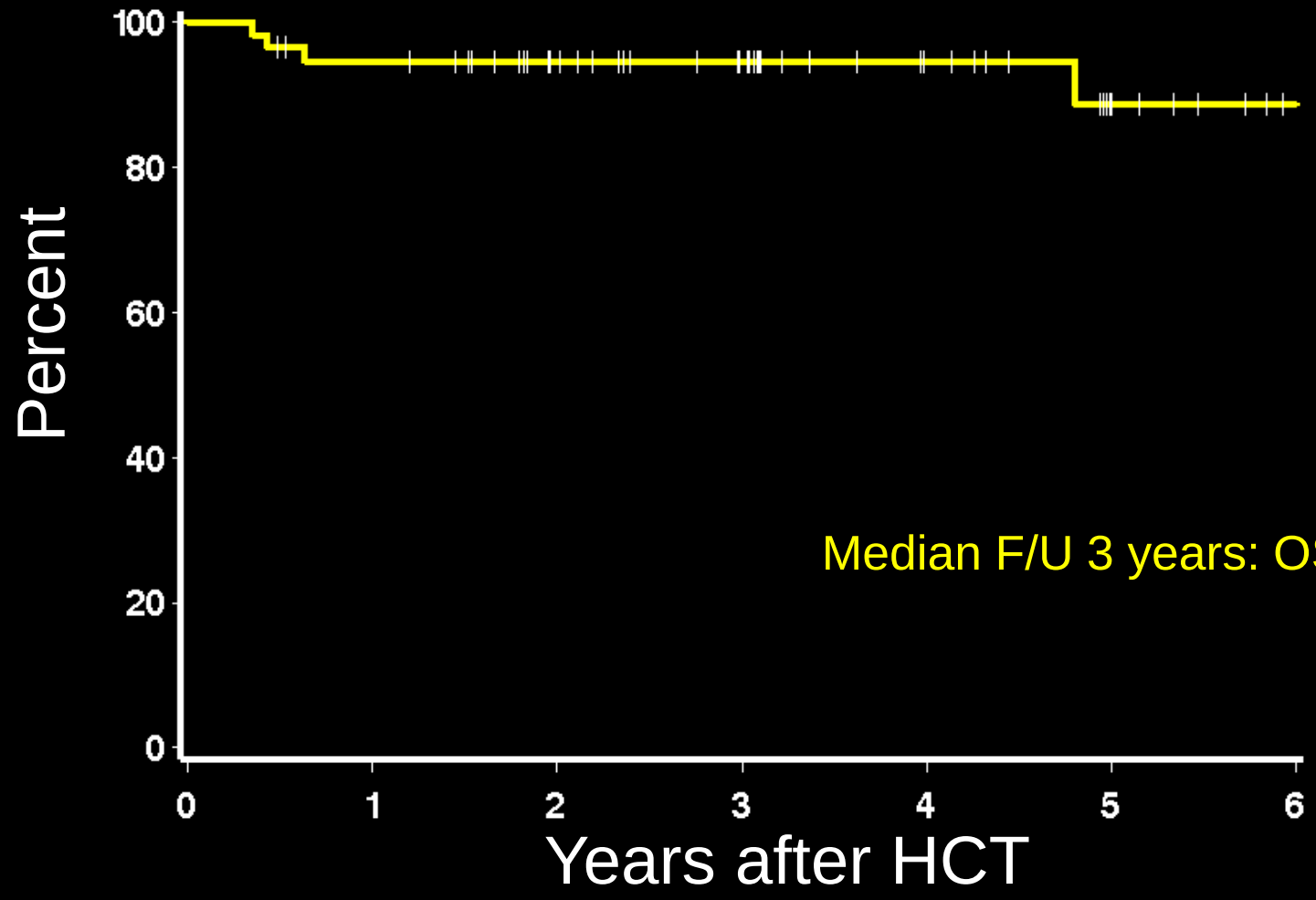
- High-risk of graft rejection
- High-risk of transplant related mortality
  - Marrow Failure - DBA

Fred Hutchinson Cancer Research Center/ Seattle Children's- only protocol in the U.S., IND

Seattle: Treosulfan Based Study Patient/Study Characteristics

- Diagnosis (n=64)
  - Bone Marrow Failure (17) → (DBA, n=5)
  - Immune Deficiencies (26)
  - HLH (13)
  - Red Blood Cell Disorders/metabolic (8)
- Median age 5.9 (range, 0.2 - 32.5) years
- Cell Source
  - BM (58)/PBSC (6) Unrelated (55) Related (9)
- 2nd HCT (7)
- Study Sites
  - FHCRC (48) MCW (12) VAND (2) OHSU (1) Colorado(1)

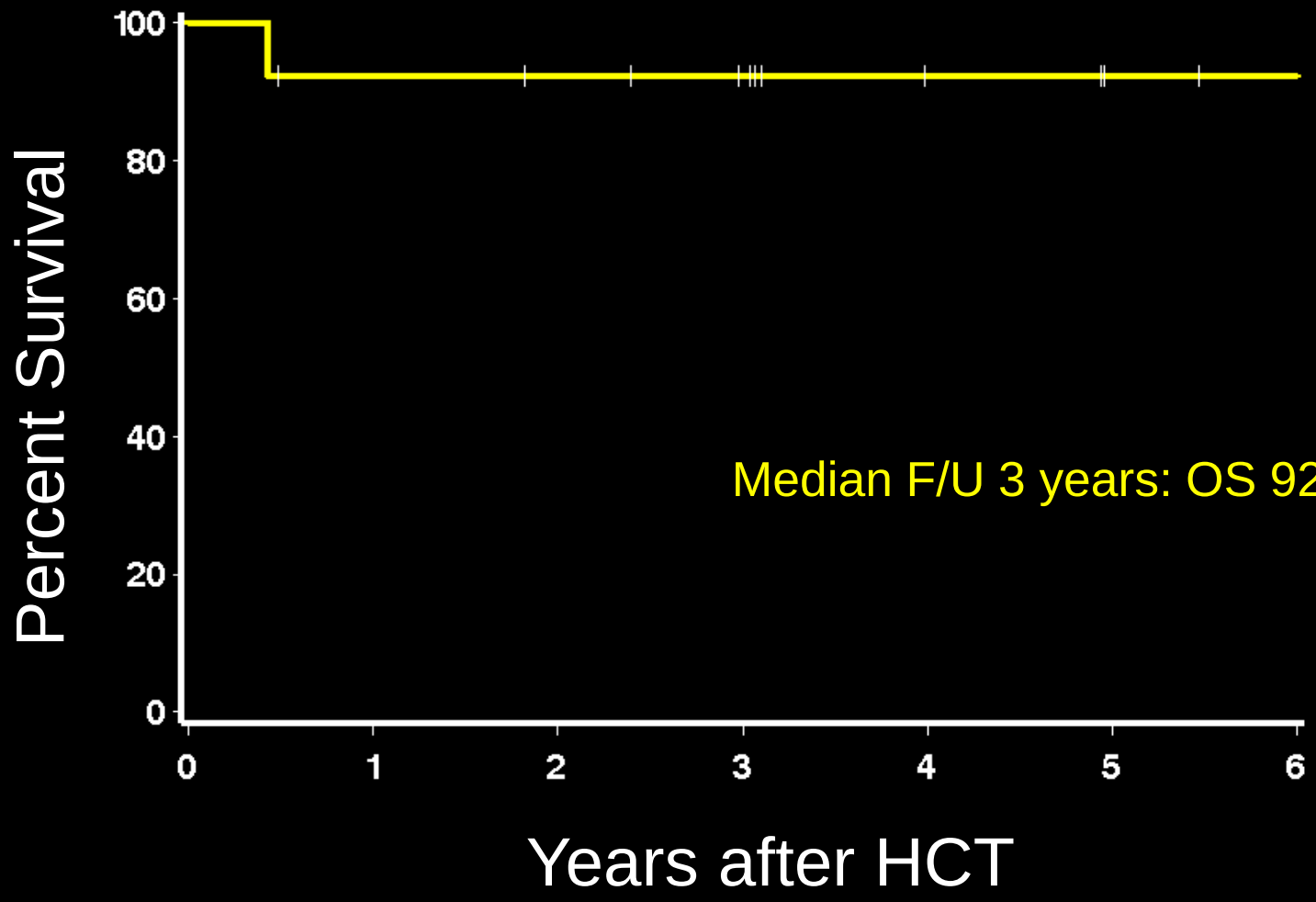
U.S. Treosulfan Study – Survival (n=64)



Median F/U 3 years: OS 95%

Burroughs et al, BBMT. 2014

U.S. Treosulfan Study
Survival BMF Patients (n=17)



Median F/U 3 years: OS 92%

Burroughs et al, BBMT. 2017

Future Directions

- FDA approval in United States
- Extended accrual (n=120) current trial
- National: BMT-CTN clinical trial
- New Protocol: Marrow Failure and MDS/AML
  - Treo/Flu/2 Gy TBI

Recommendations Transplant 2017

Recommend Transplant:

- Matched sibling- transfusion dependent
  - Careful evaluation of the sibling donor
- Unrelated donor
  - Iron overload despite chelation therapy
  - Severe cytopenias: decreased RBC, WBC, or platelets
  - Development of leukemia or MDS
  - Other complications - infections

**With improved URD transplant outcomes more discussion around doing a URD transplant if transfusion dependent.

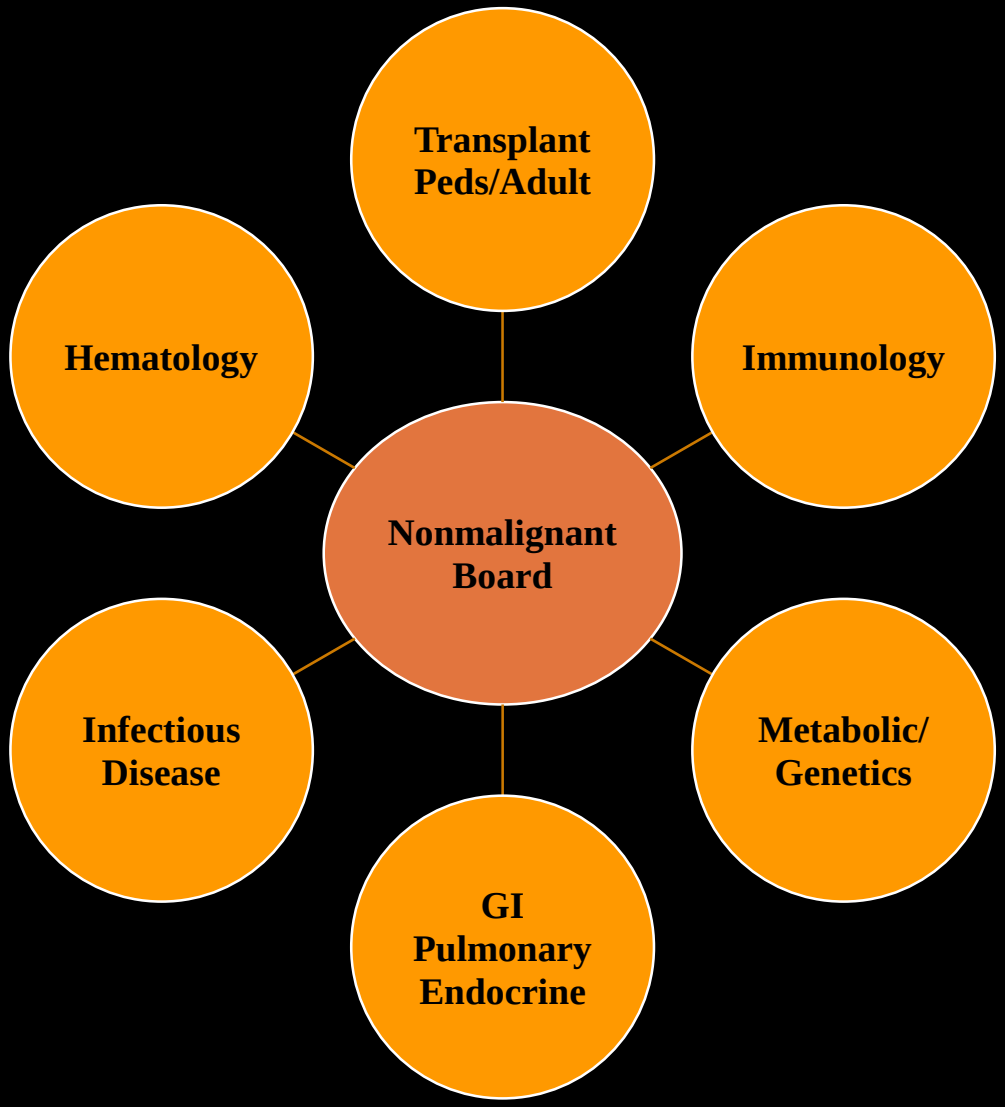
Still Debatable

- Alternative donor
  - Mismatched unrelated donor, Cord blood, Haplo donor

Important Points

- DBA is a rare disorder
- Better outcomes at centers familiar with the special care of patients with DBA
- Multi-system disease with complex medical issues requiring expertise multiple areas….Team approach!
  - Hematology, Transplant, Other Subspecialists
- Results following transplant are significantly better
  - Improved conditioning regimens
  - Better supportive care
- Expanded donor options: BM, PB, CB

Seattle's: Non-Malignant Board



Improves:

- Patient Care
- Outcomes
- Collaboration

Final Thoughts

- Meet with the transplant team early in the disease
  - Proactively plan
  - Continually assess risk/benefit ratio for YOU/YOUR CHILD
  - Improved survival the healthier you are!
- Transplant is an option for older and/or sick patients
- You are your child's best advocate!

Final Thoughts……

- Need for a greater understanding of DBA
  - Cause/Biology
  - Who and why do some patients go into remission
  - Predictors of failure of therapy
  - Who will benefit from transplant

- Prospective studies
  - Transplant
  - Non-transplant

Thank You!

Dr. Lauri Burroughs
Fred Hutchinson Cancer Research Center
Seattle Children's Hospital
Seattle, WA
206-667-2396 or
Lburroug@fredhutch.org

Bernie McLaughlin RN
206-667-4916, bmclaugh@fredhutch.org