The Future of Cord Blood Derived Therapies

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Disclosures

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

Name	Institution
Merry Duffy	NMDP/Be The Match
Wendy Hearn, RN, BSN,	NMDP/Be The Match

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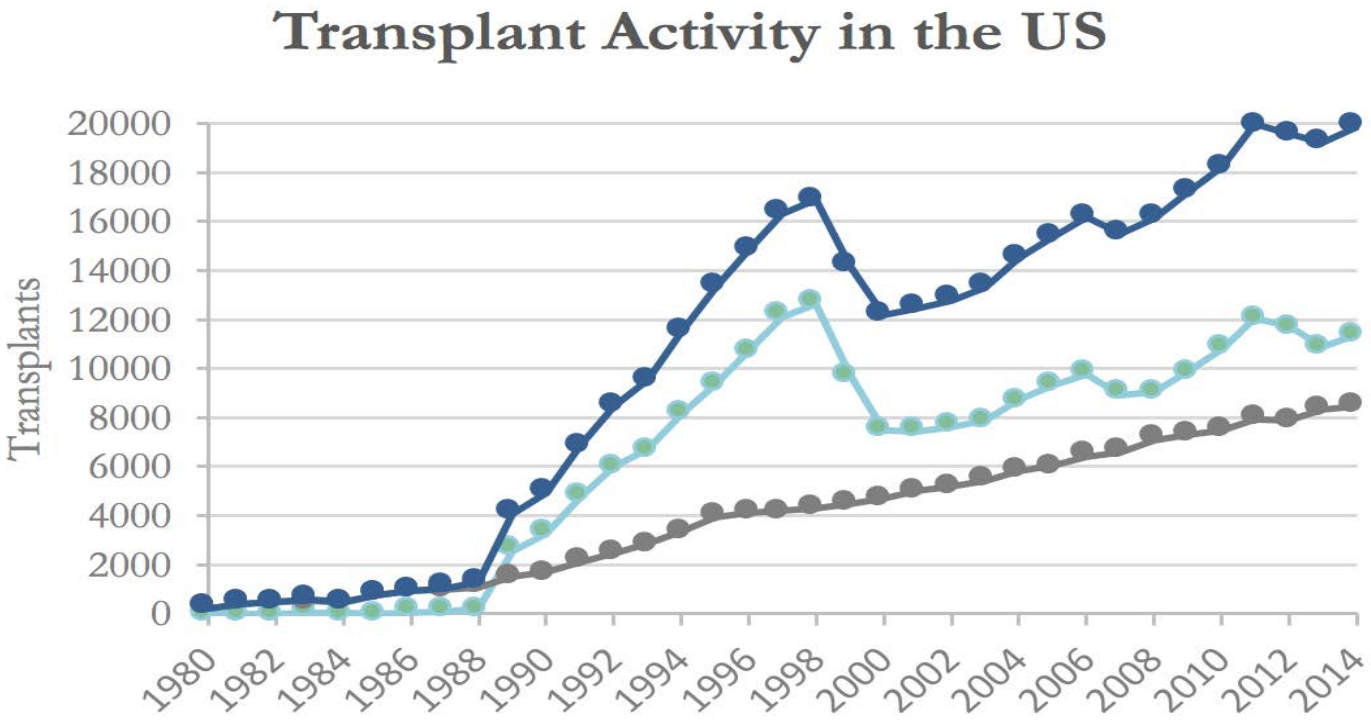
John E Wagner, MD	University of Minnesota	Novartis PI Magenta Therapeutics (in development)

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



20,000 per year

autoHSCT

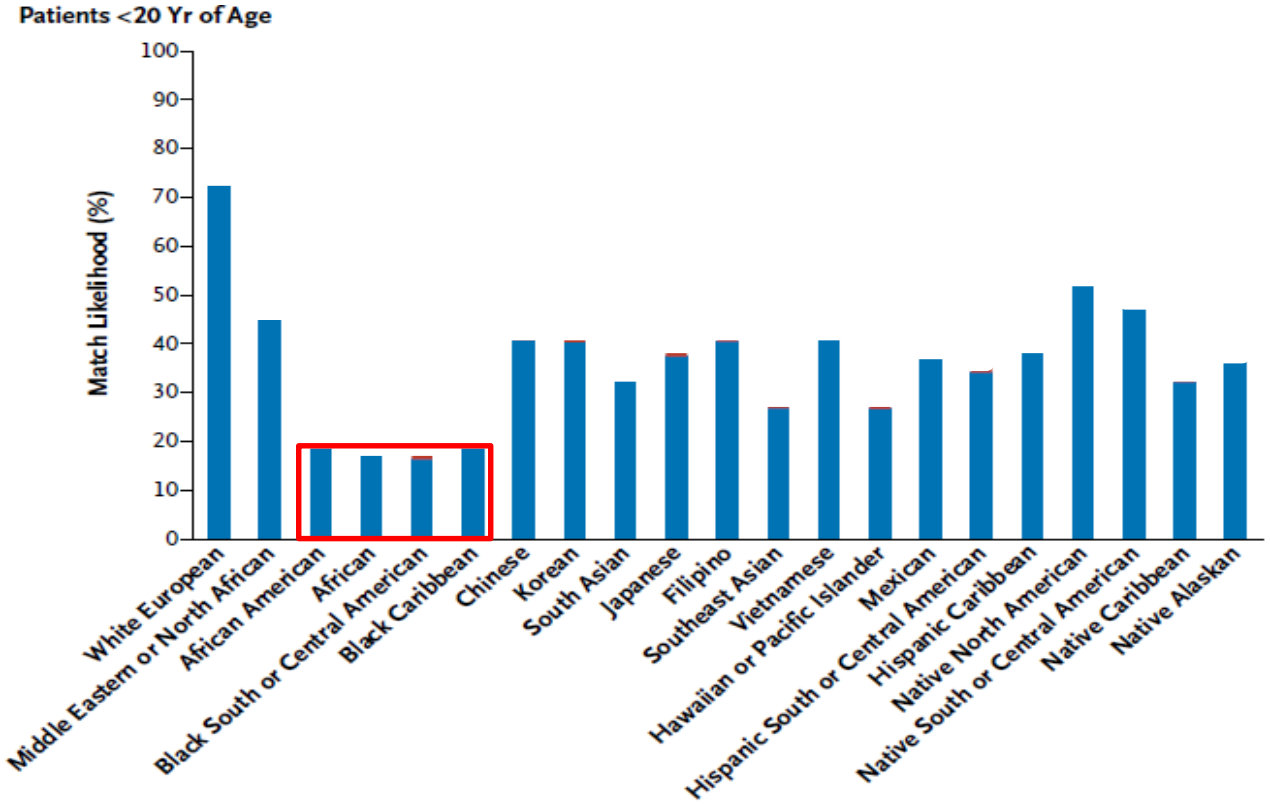
alloHSCT

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



N Engl J Med 2014;371:339-48.

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

Berlin Wall

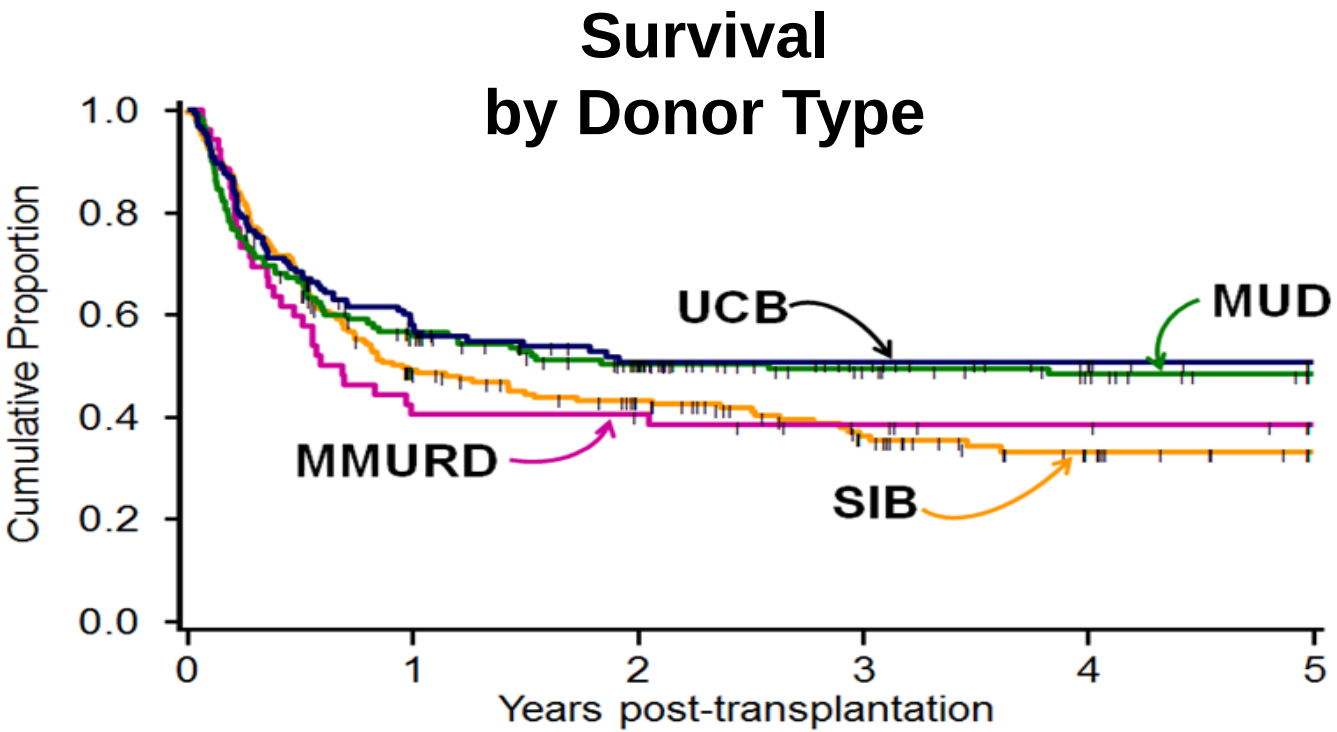
Lesson

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 ovecoming it].

the last lecture

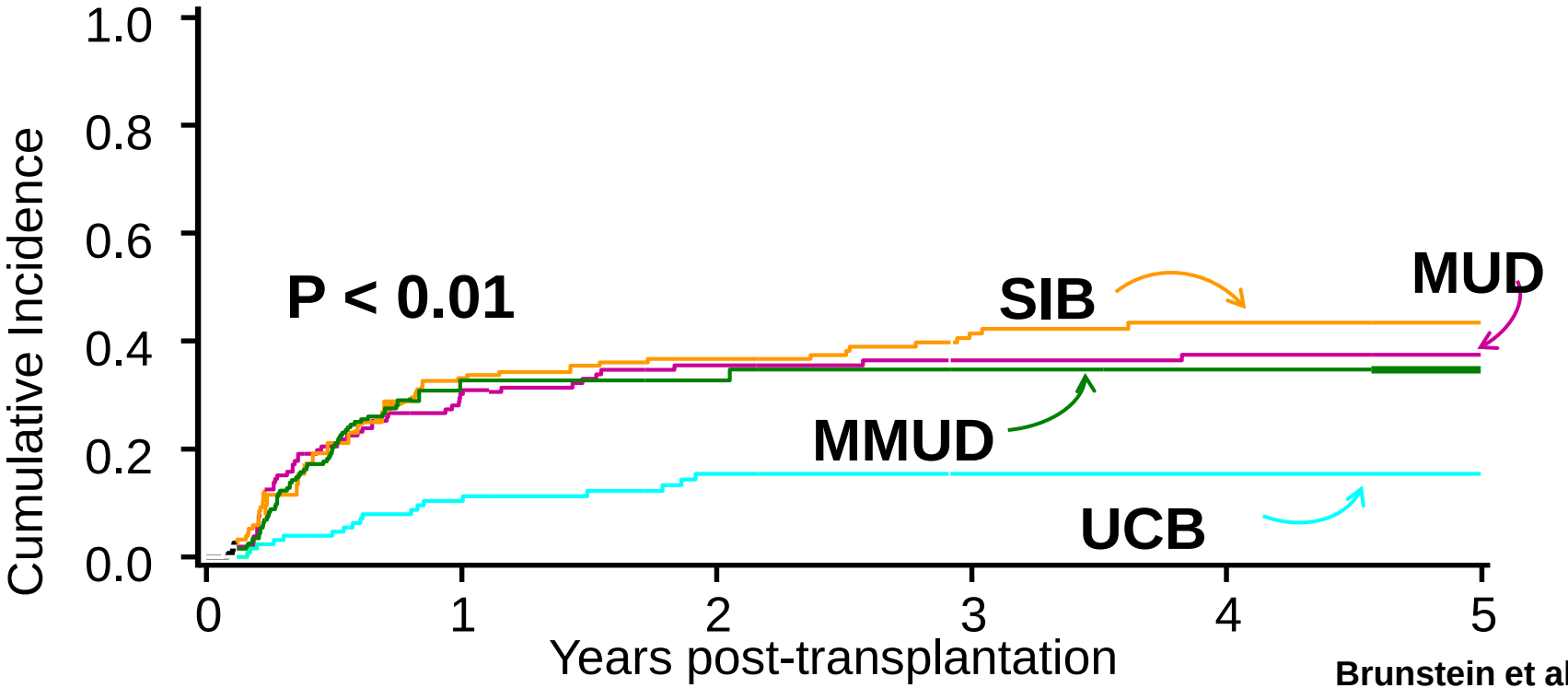
Randy Pausch

Overall Survival with UCB can be Comparable to Other Graft Sources



Brunstein et al.
Blood 2010; 116: 4693-4699

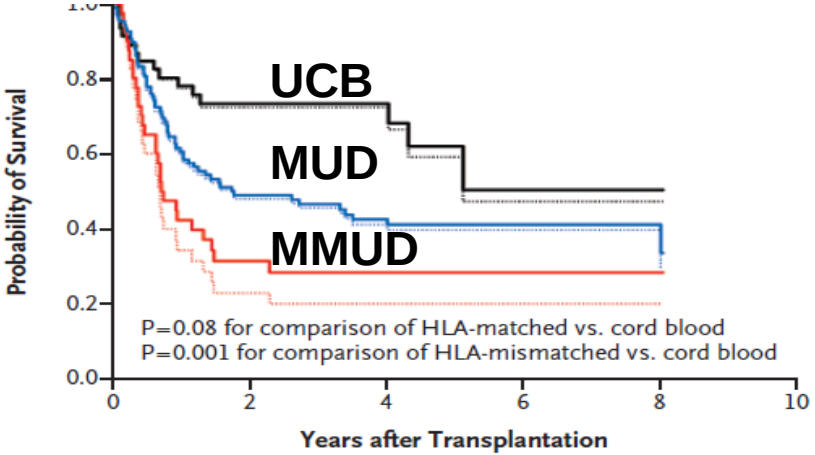
Relapse Risk with UCB is Relatively Low



Brunstein et al.
Blood 2010; 116: 4693-4699

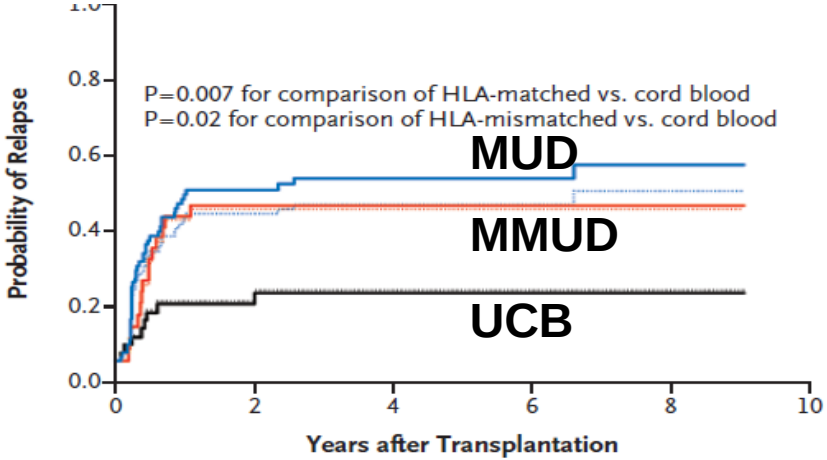
Enhanced GVL particularly in the state of MRD

Survival



No. at Risk					
Cord blood	45	22	9	2	1
HLA-matched	104	35	25	12	3
HLA-mismatched	35	7	6	3	1

Relapse



No. at Risk					
Cord blood	45	23	11	2	1
HLA-matched	104	31	23	11	4
HLA-mismatched	35	7	6	3	1

Milano and Delaney

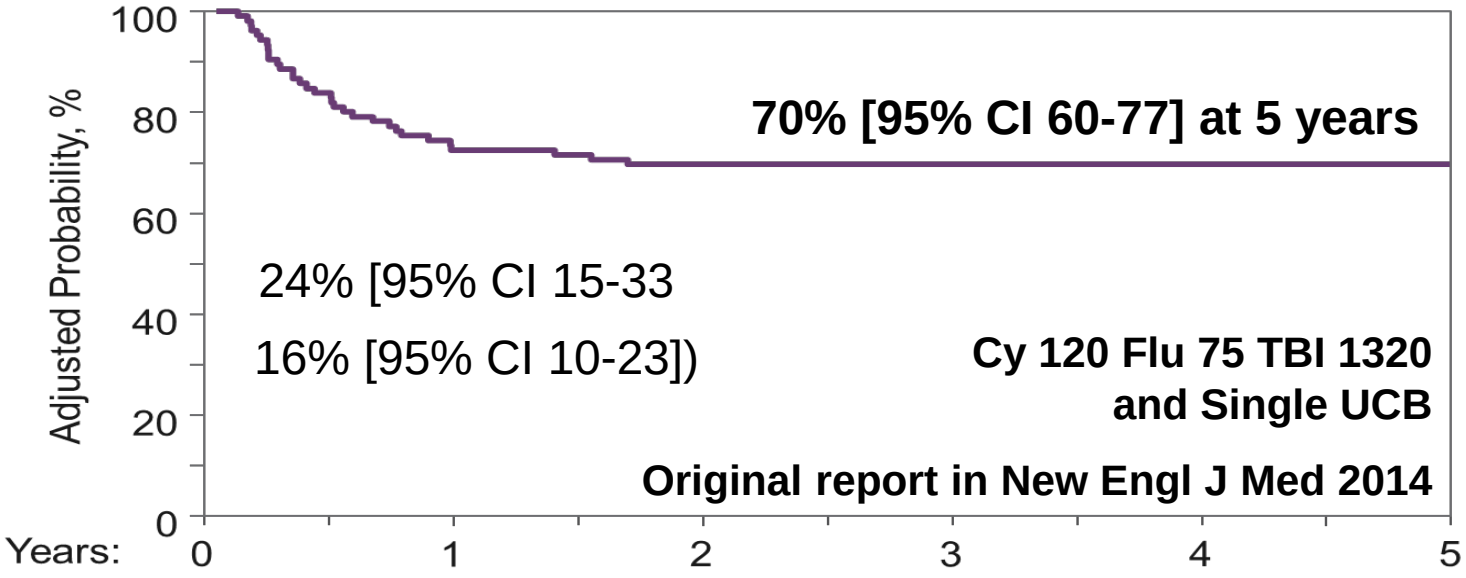
N Engl J Med 2016;375:944-53.

Advantages of UCB
High Survival and Low Relapse Risk

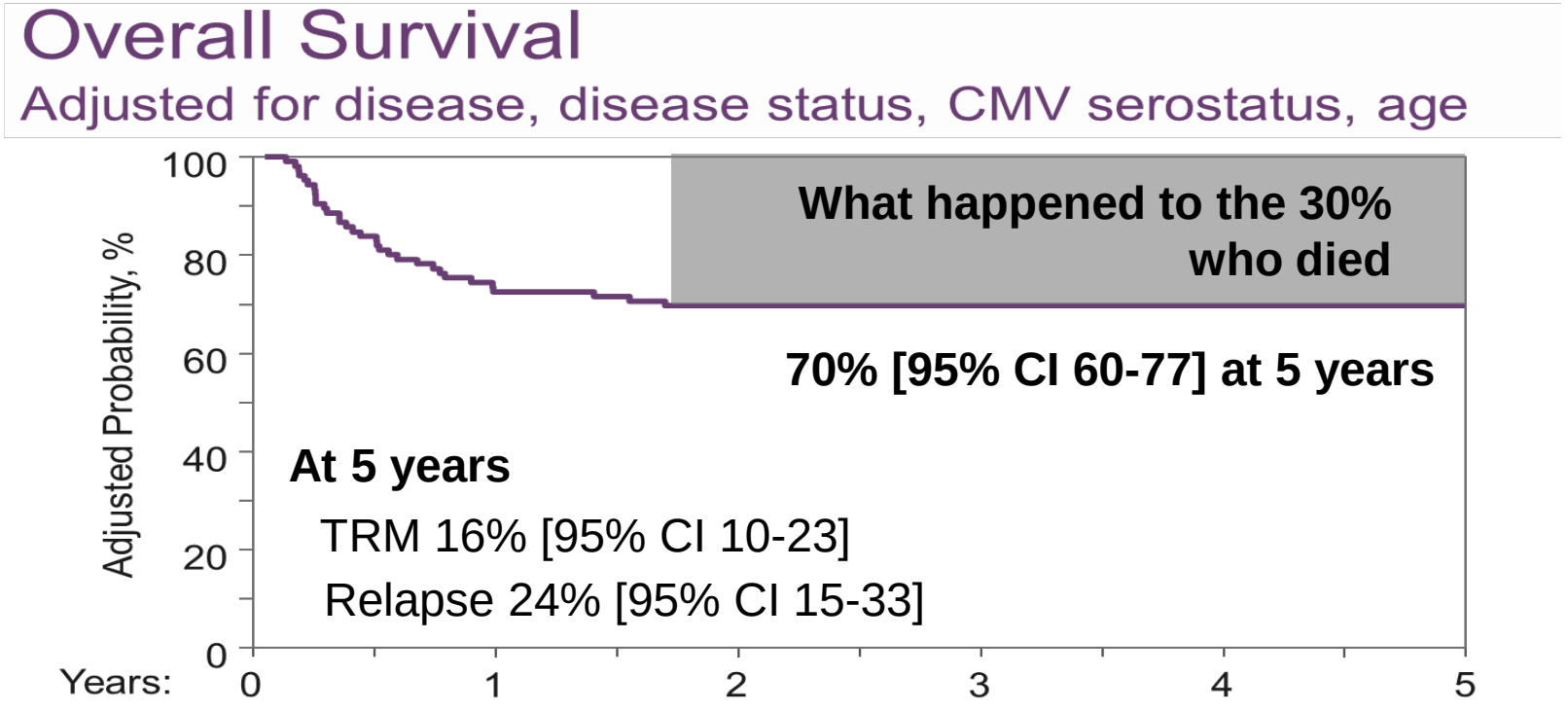
BMT CTN 0501 Children with Acute Leukemia

Overall Survival

Adjusted for disease, disease status, CMV serostatus, age

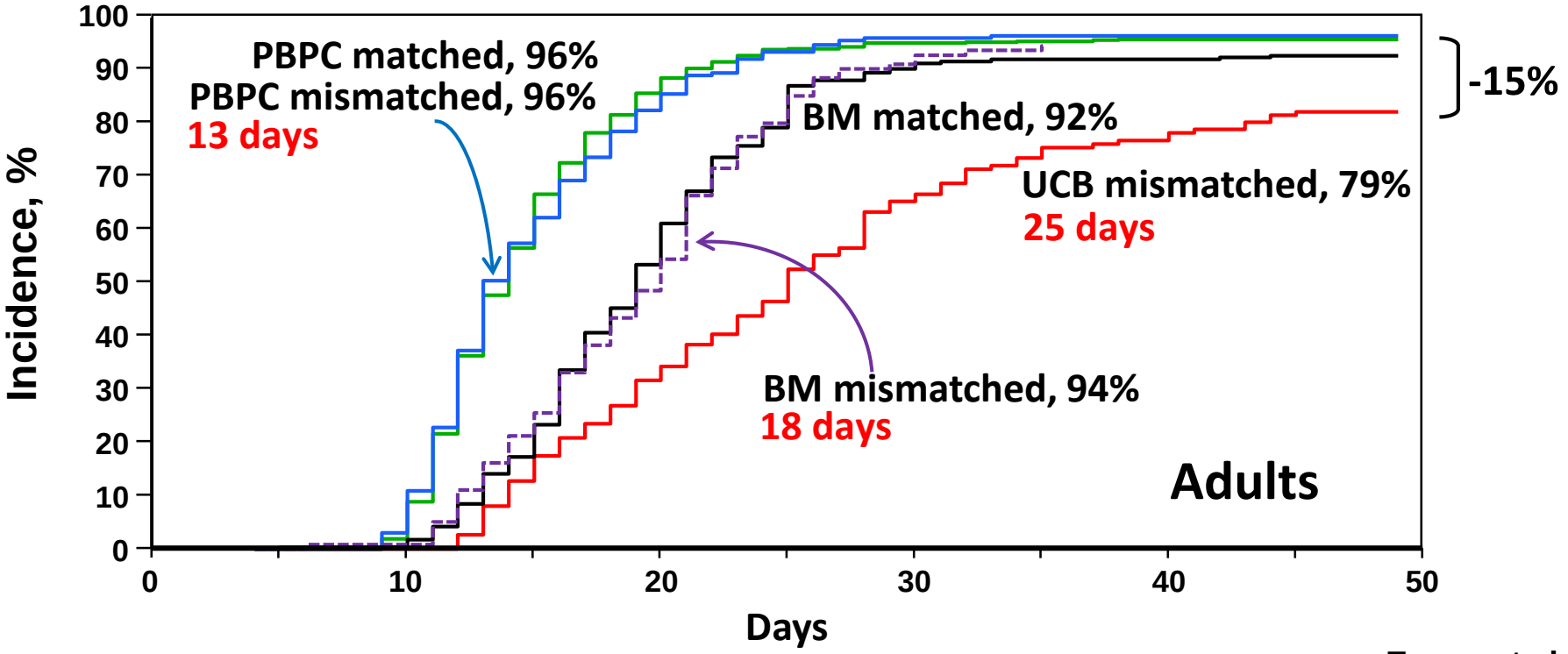


Conditioning Impacts High Survival and Low Relapse Risk after UCBT



Biol Blood Marrow Transplant 23 (2017) 1714–1721

Neutrophil recovery by HSC source
PBSC > BM > UCB (Disadvantage for UCB)

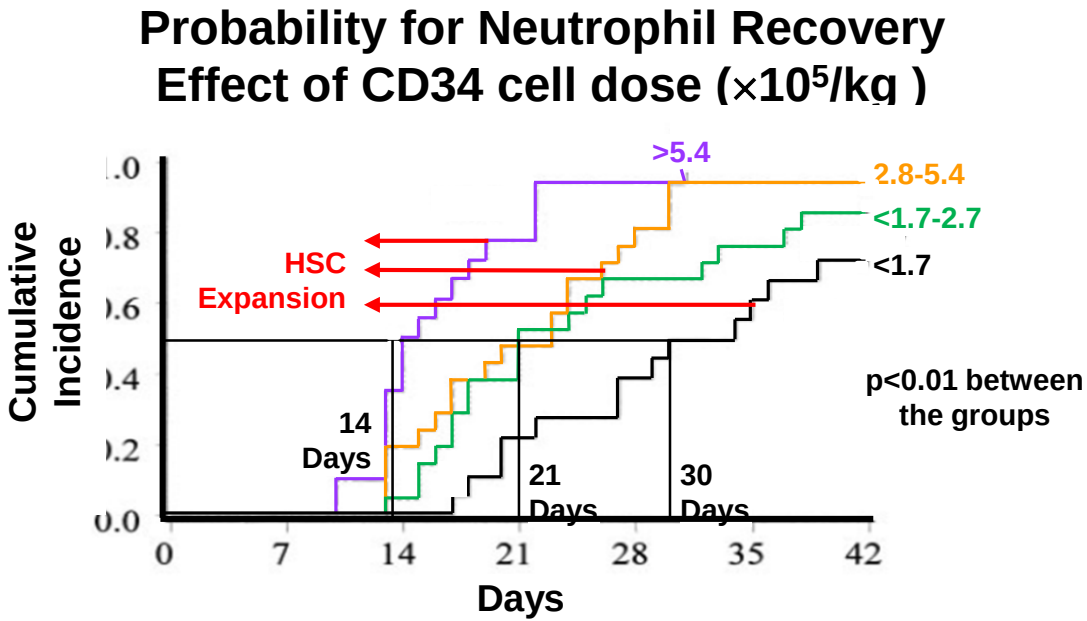


Eapen et al.
Lancet Oncol 2010; 11: 653-660

Lesson

‘When they go low, we go high!’

Higher UCB CD34+ cell dose is associated with faster recovery



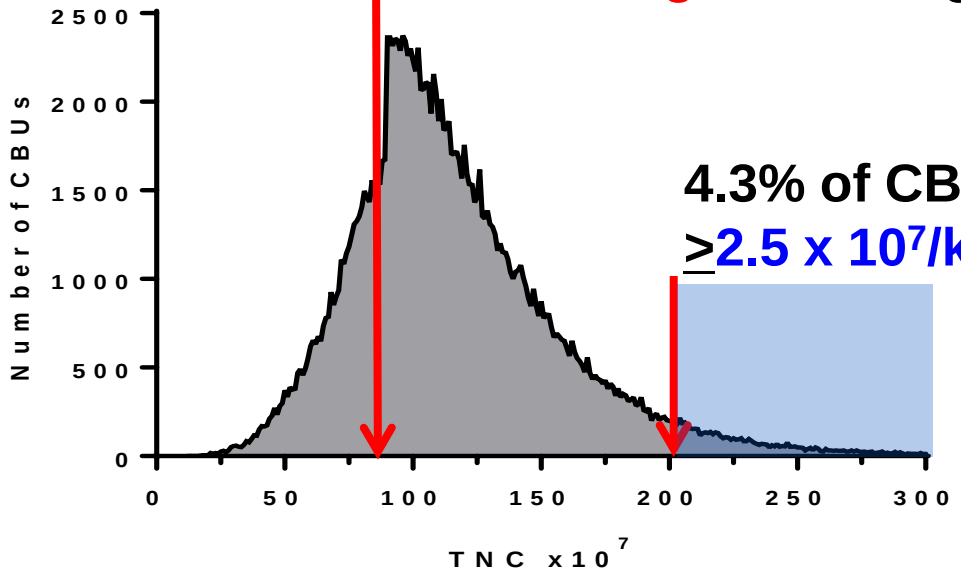
Interpretation:

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 x 10^7 TNC/kg
Greater Number of Availability of Useable UCB Units

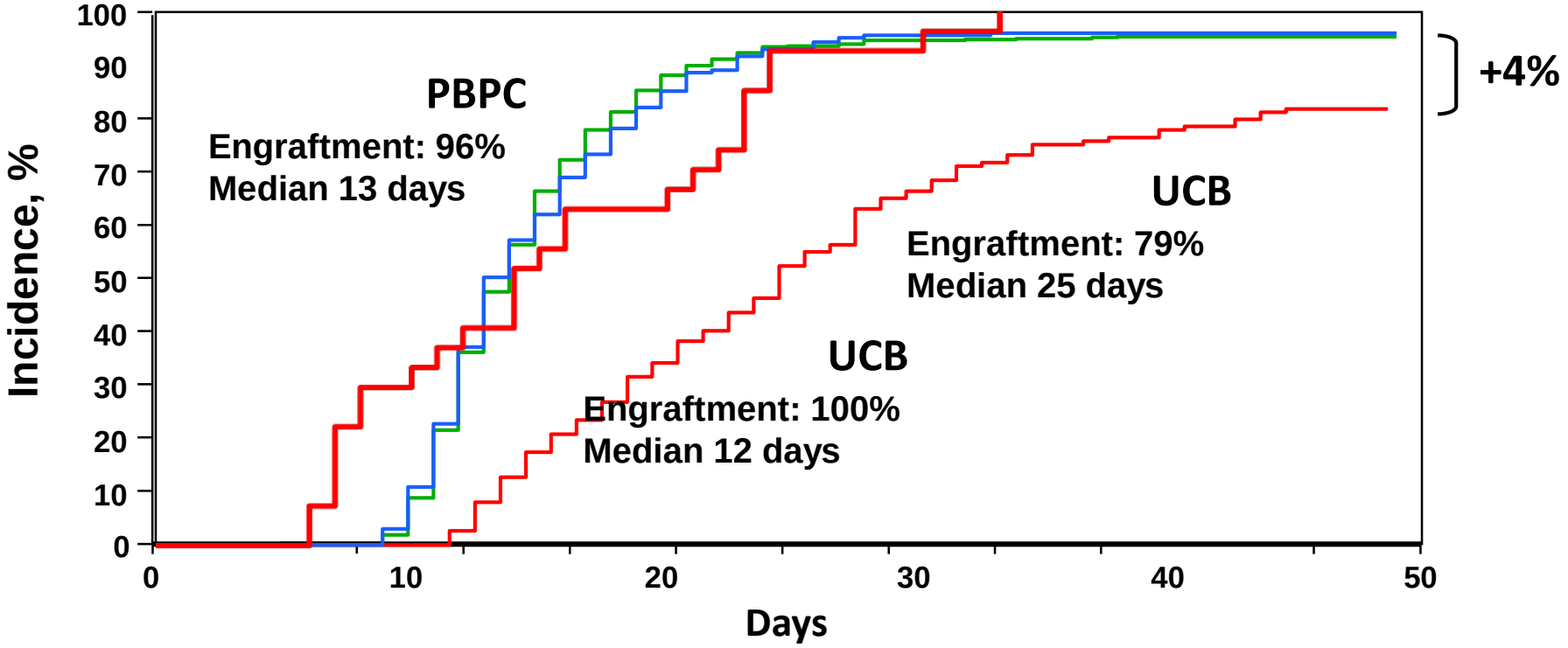
75% of CBUs have a TNC dose ≥1.0 x 10^7/kg for a 80 kg adult



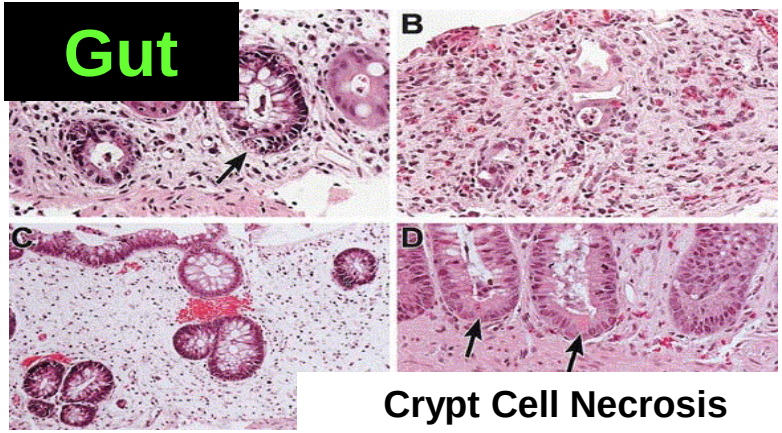
4.3% of CBUs have a TNC dose ≥2.5 x 10^7/kg for a 80 kg adult

NMDP Cord Blood Searchable Inventory

MGTA-456 – Provides neutrophil recovery and engraftment rates comparable to GCSF mobilized PBPC

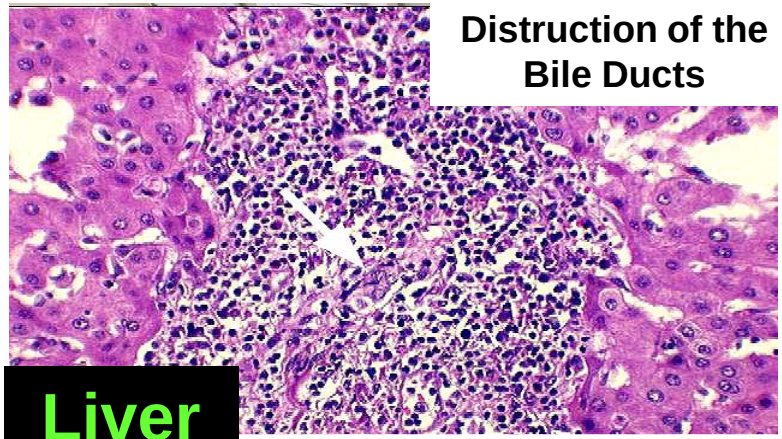


Gut



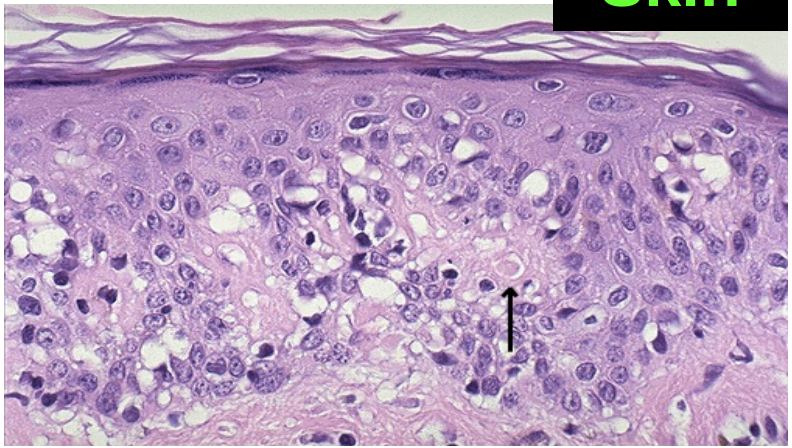
Crypt Cell Necrosis

Skin



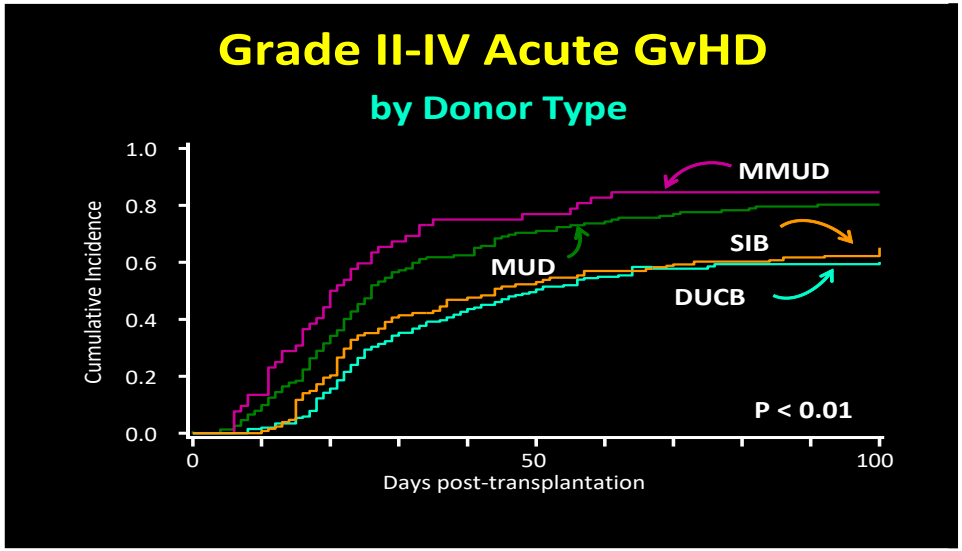
Distruction of the Bile Ducts

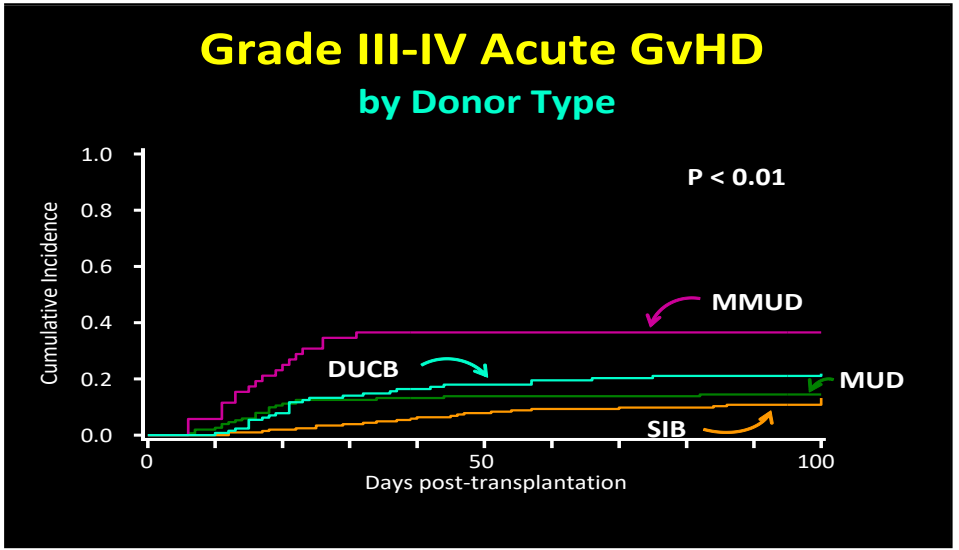
Liver



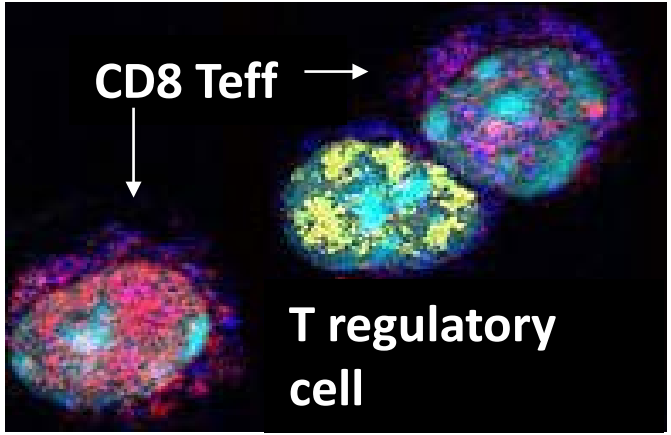
Strategies to Enhance Immune reconstitution after Allogeneic HSCT

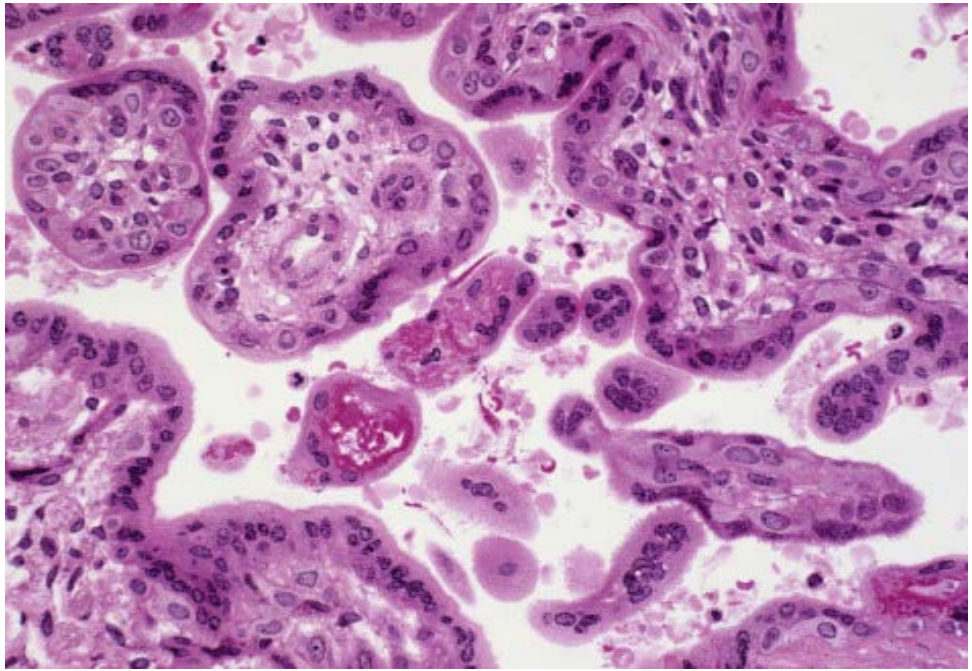
High Risk of GVHD Regardless of HSC Source





Maternal-Fetal Tolerance
Modulating the Immune Response



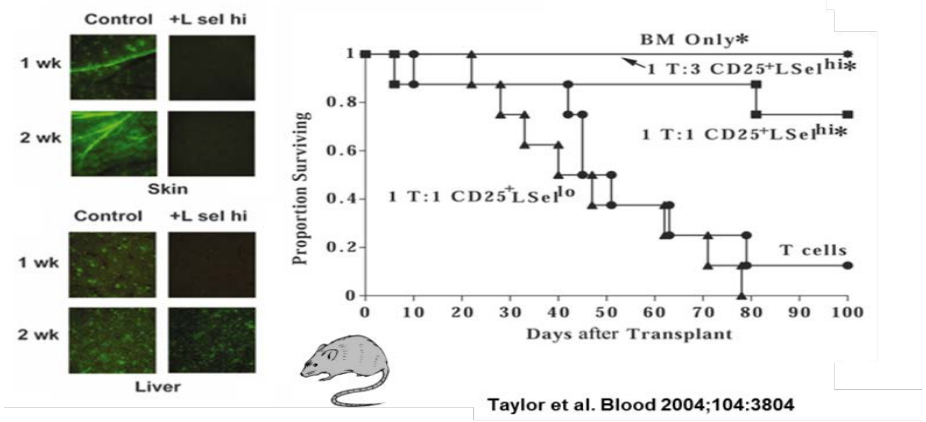


Placenta

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

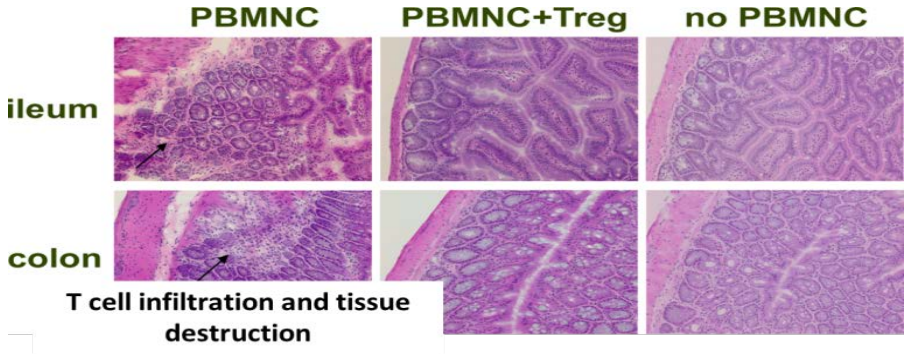
tTreg Proof of Concept
Dose Target



Taylor et al. Blood 2004;104:3804

Experiment 1

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



T cell infiltration and tissue destruction

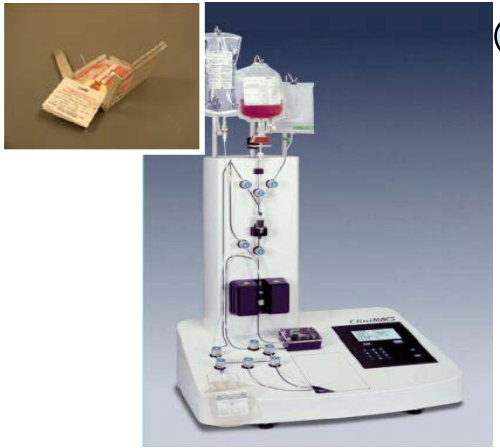
Target

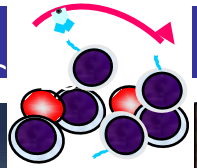
1 Treg : 1 Teff

>15 million/kg
(6-8 x 10^6 CD3 per kg per UCB unit in adults)

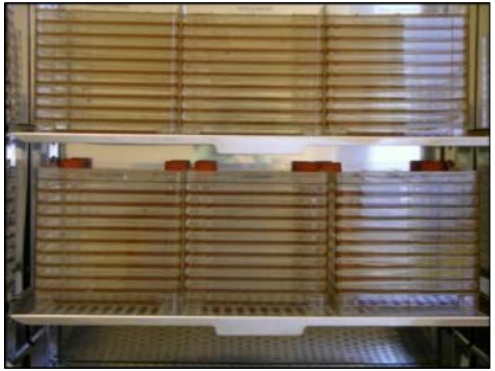
Optimization of UCB CD25 Selection and Expansion Culture

CD25+ selection





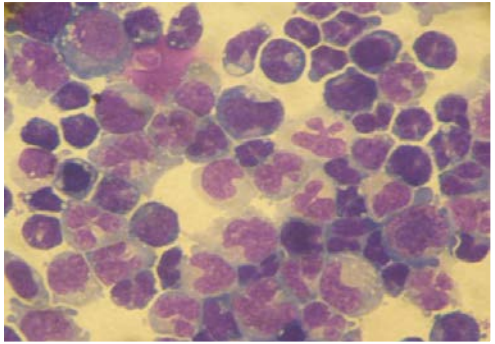
Flask culture



- Culture in X-VIVO 15
- Human AB serum 10% ,
- Anti-CD3/antiCD28-coated beads.
- Supplemented with IL-2 300 IU/mL

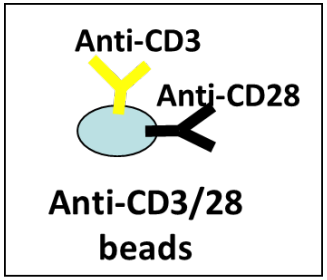
18+/-1 days in culture

Lot Release

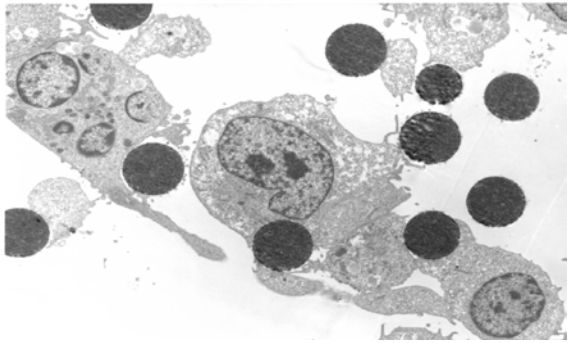


- Gram stain negative
- Endotoxin <5 EU/kg
- Viability ≥70%
- CD4+/CD25+ ≥70%
- CD3+/CD8+ ≤10%
- Sterility negative
- Mycoplasma negative
- Bead count <100/3x10^6cells

Strategy 1
CD3/28 bead based expansion



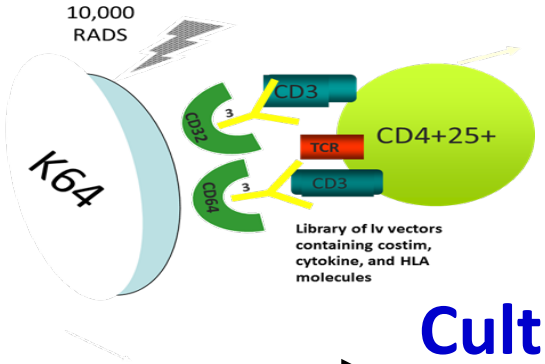
$CD25^{++}$ → **Culture**
18-21 days



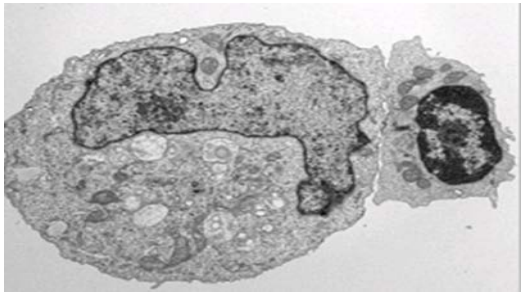
Rationale

- Track record in humans
- Available GMP reagents
- Standardized protocols

Strategy 2
Artificial APC based expansion



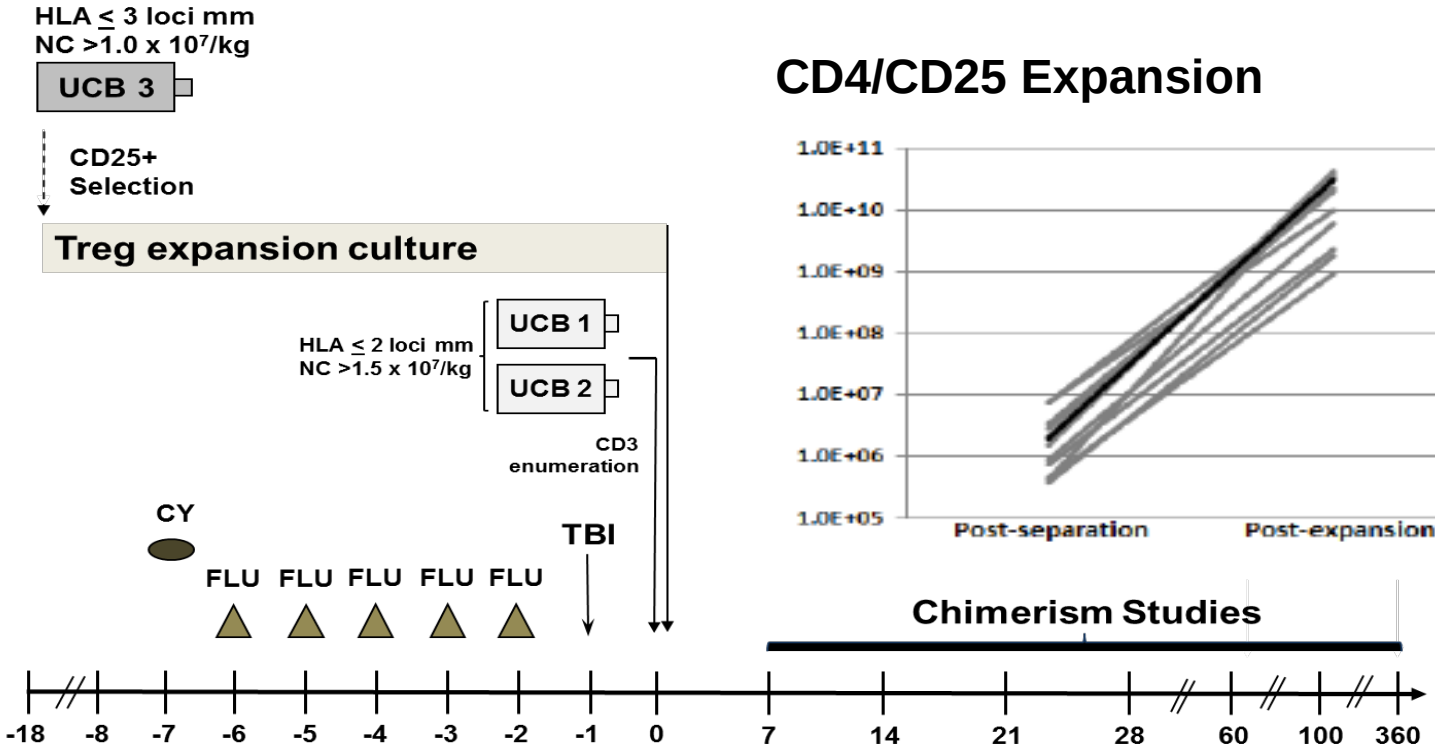
$CD25^{++}$ → **Culture 18-21 days**



Considerations

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

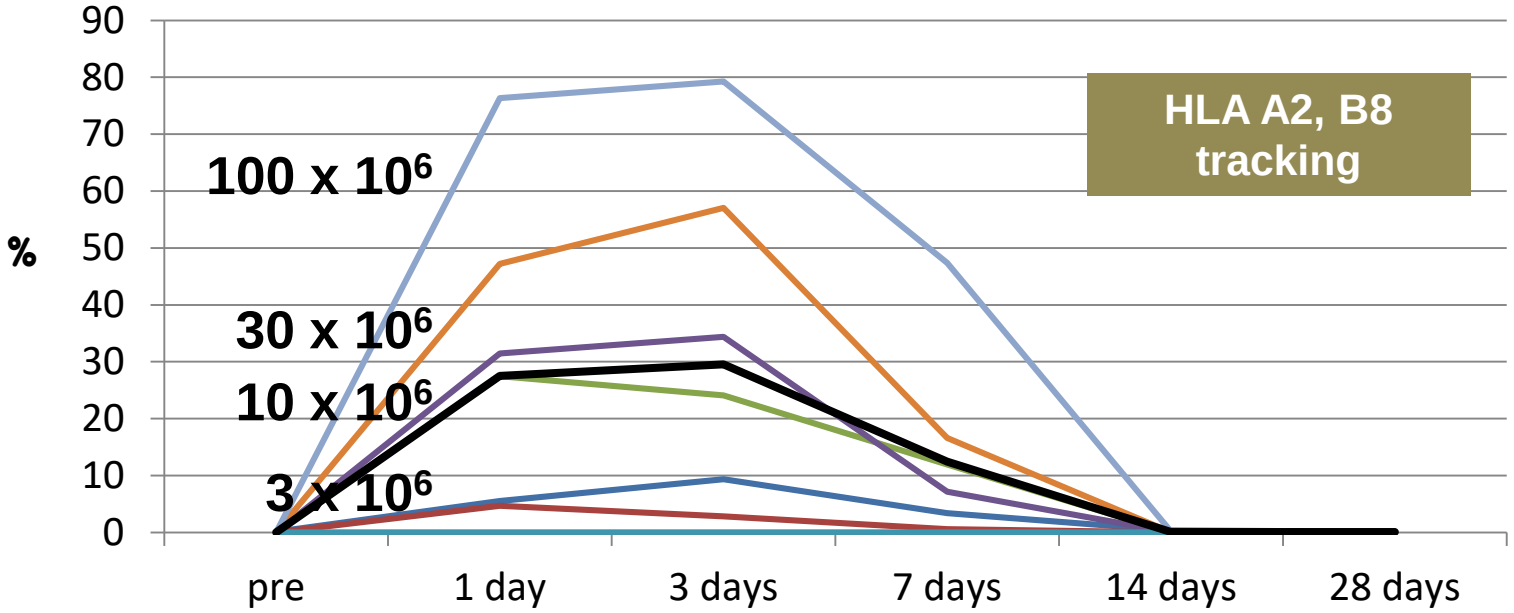
Safety and Efficacy of UCB Treg Phase I/II Clinical Trial



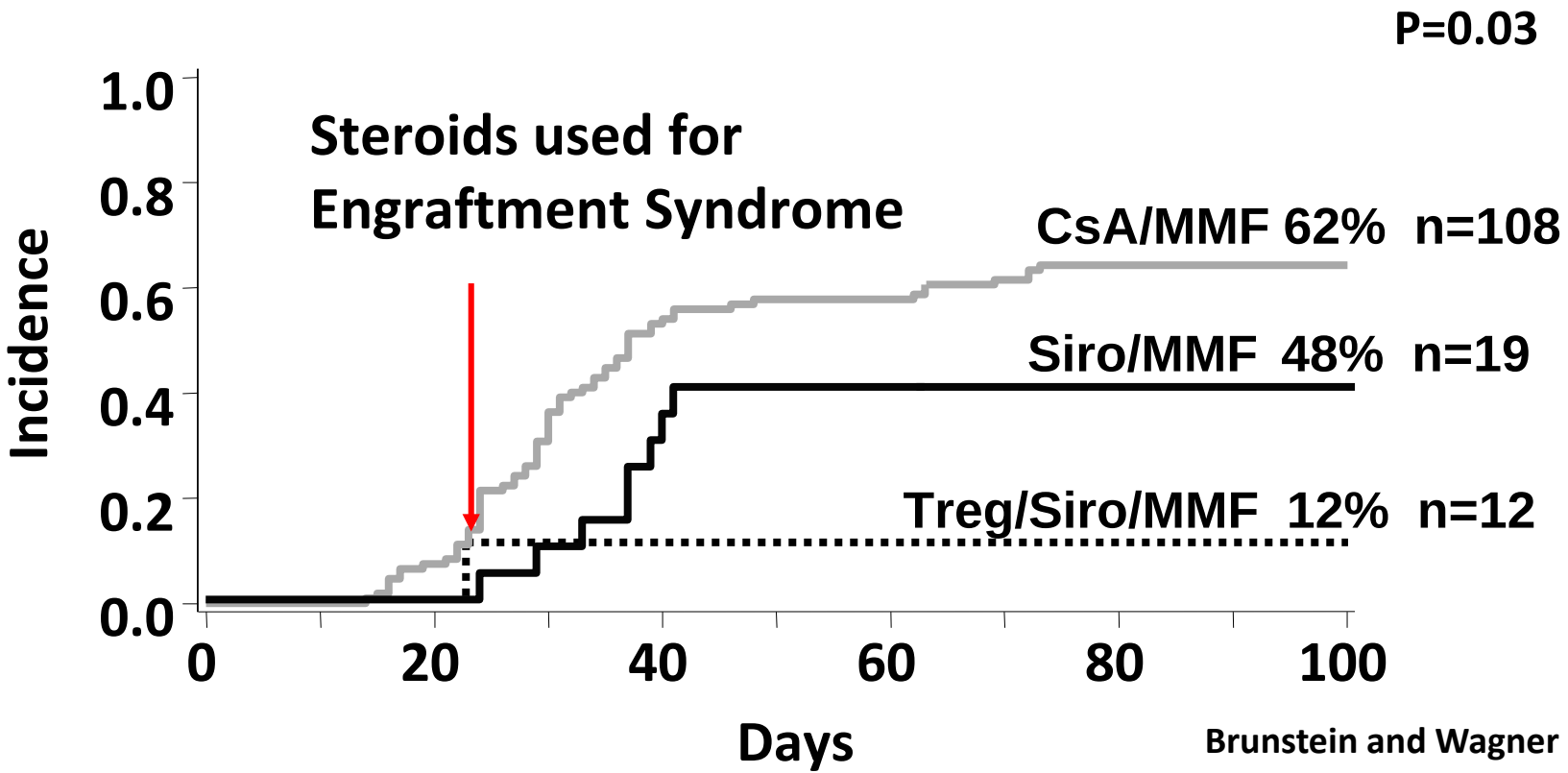
CD4/CD25 Expansion

Brunstein, Blazar and Wagner et al. Blood 2016

tTreg Pharmacokinetics
Dose Effect

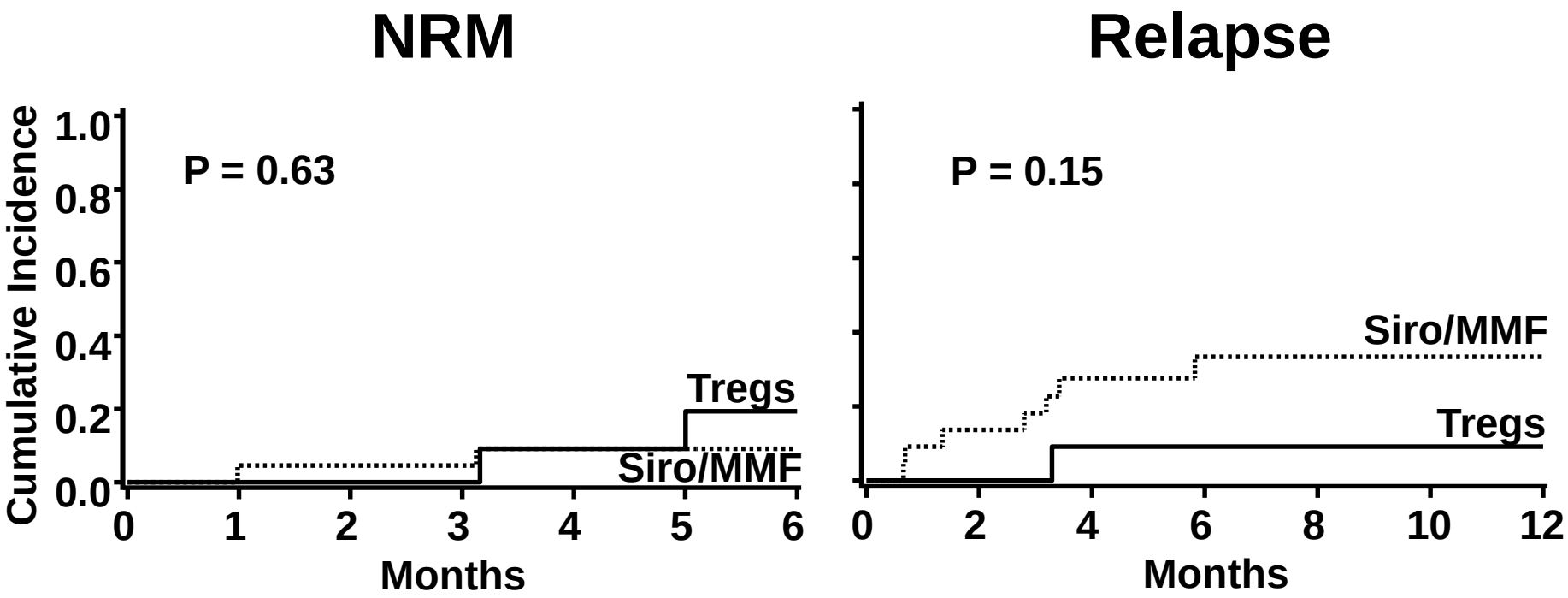


UCB tTreg
Impact on Acute GVHD

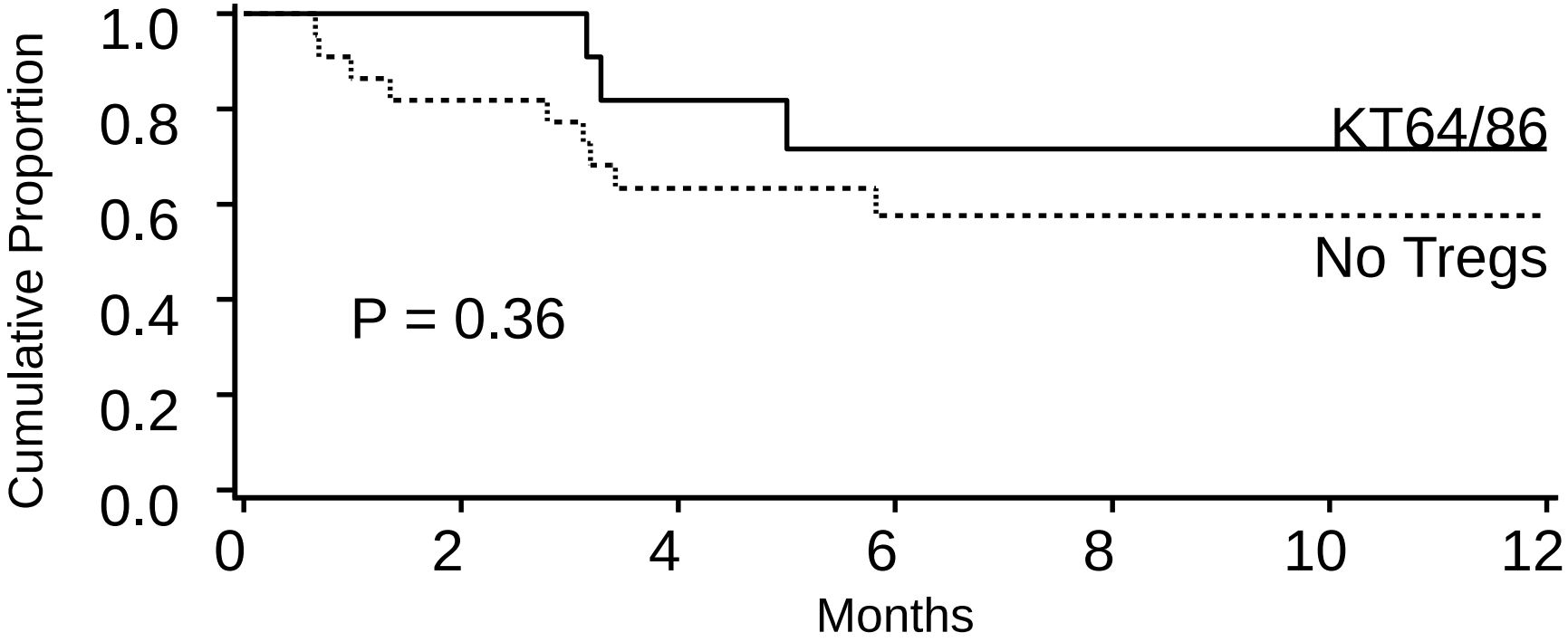


Brunstein and Wagner et al.
Blood 2015

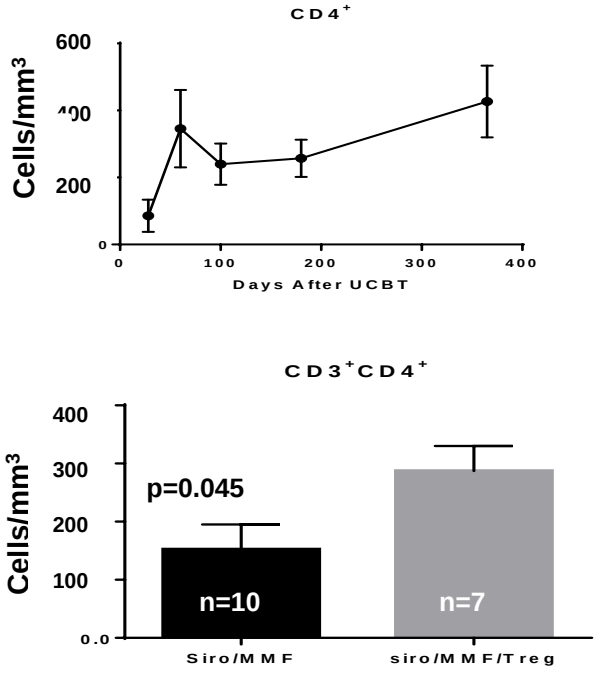
UCB tTreg
Impact on NRM and Relapse

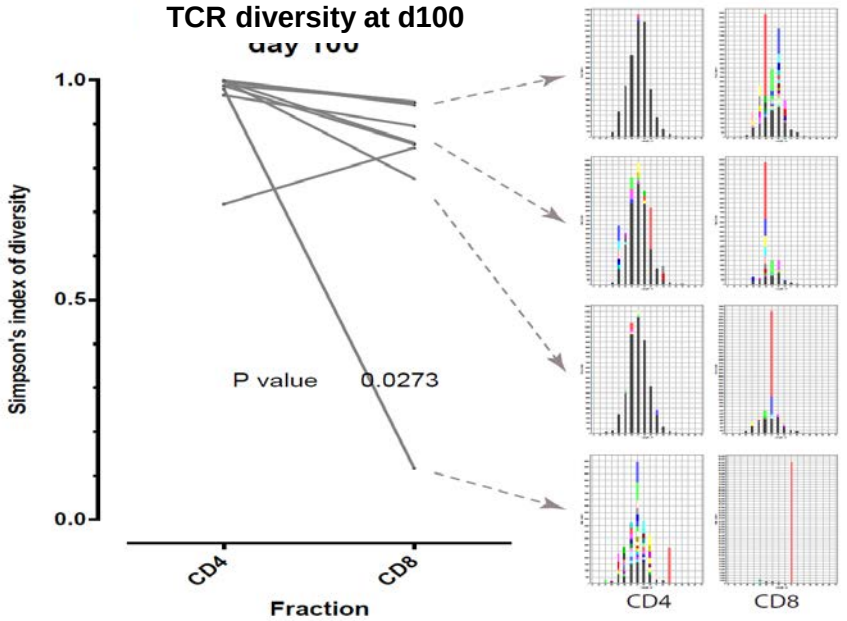


UCB tTreg
Impact on DFS

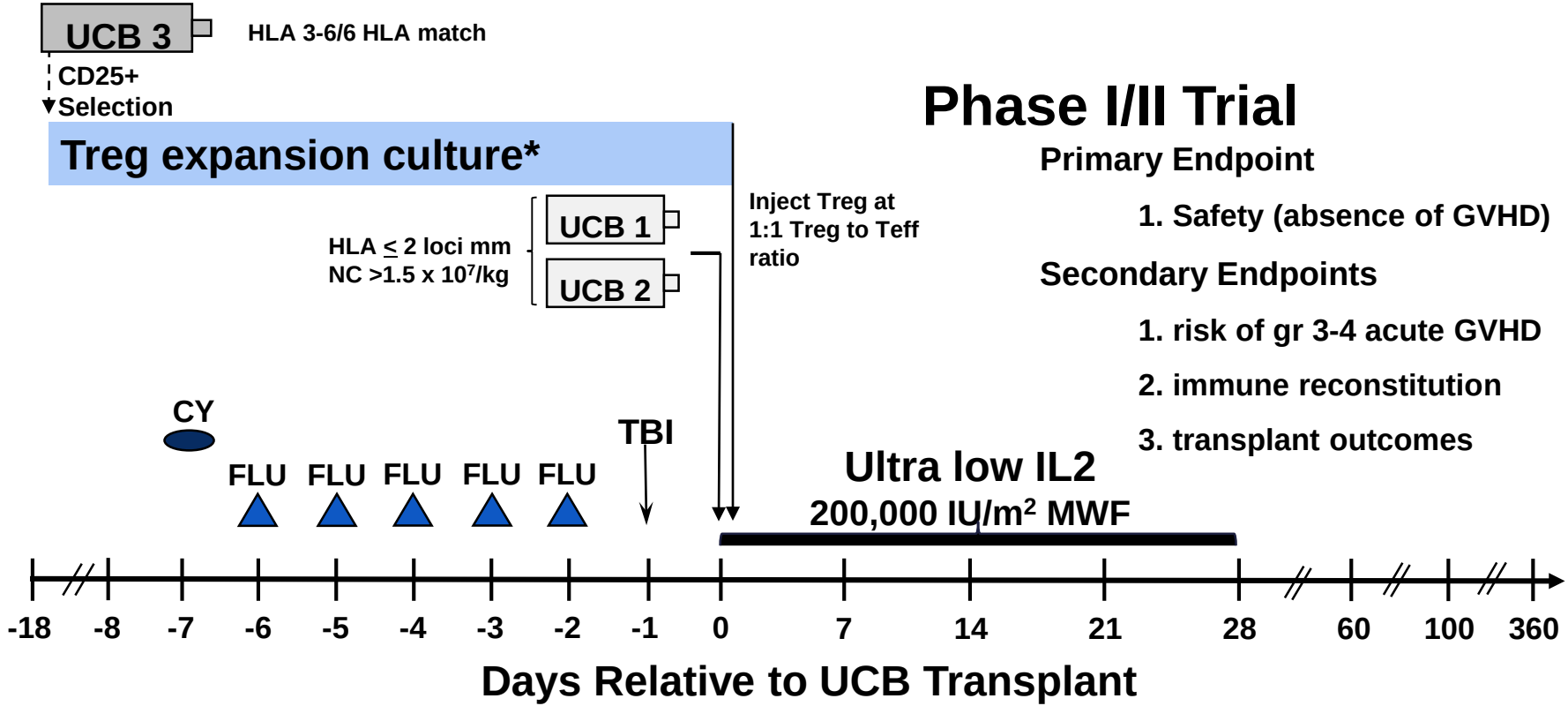


UCB tTreg
Potentially Faster Immune Recovery





UCB tTreg + Ultra Low Dose rh-IL2 Pilot Study (10 patients)



Phase I/II Trial

Primary Endpoint

1. Safety (absence of GVHD)

Secondary Endpoints

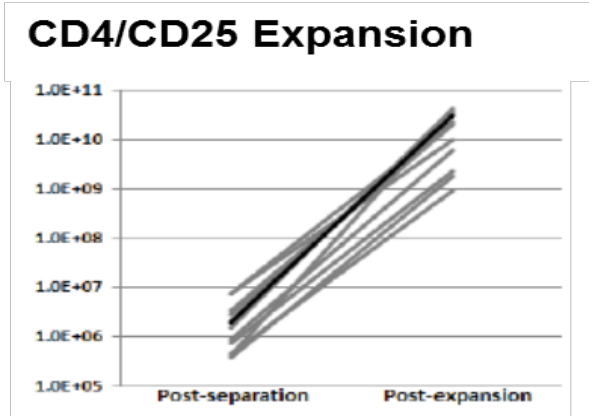
1. risk of gr 3-4 acute GVHD
2. immune reconstitution
3. transplant outcomes

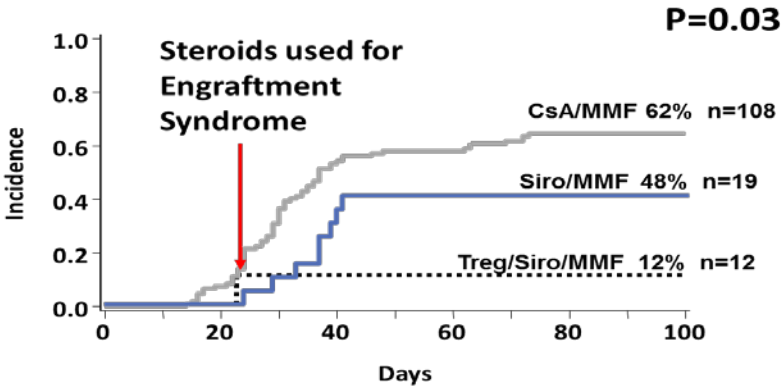
Next Steps

- 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

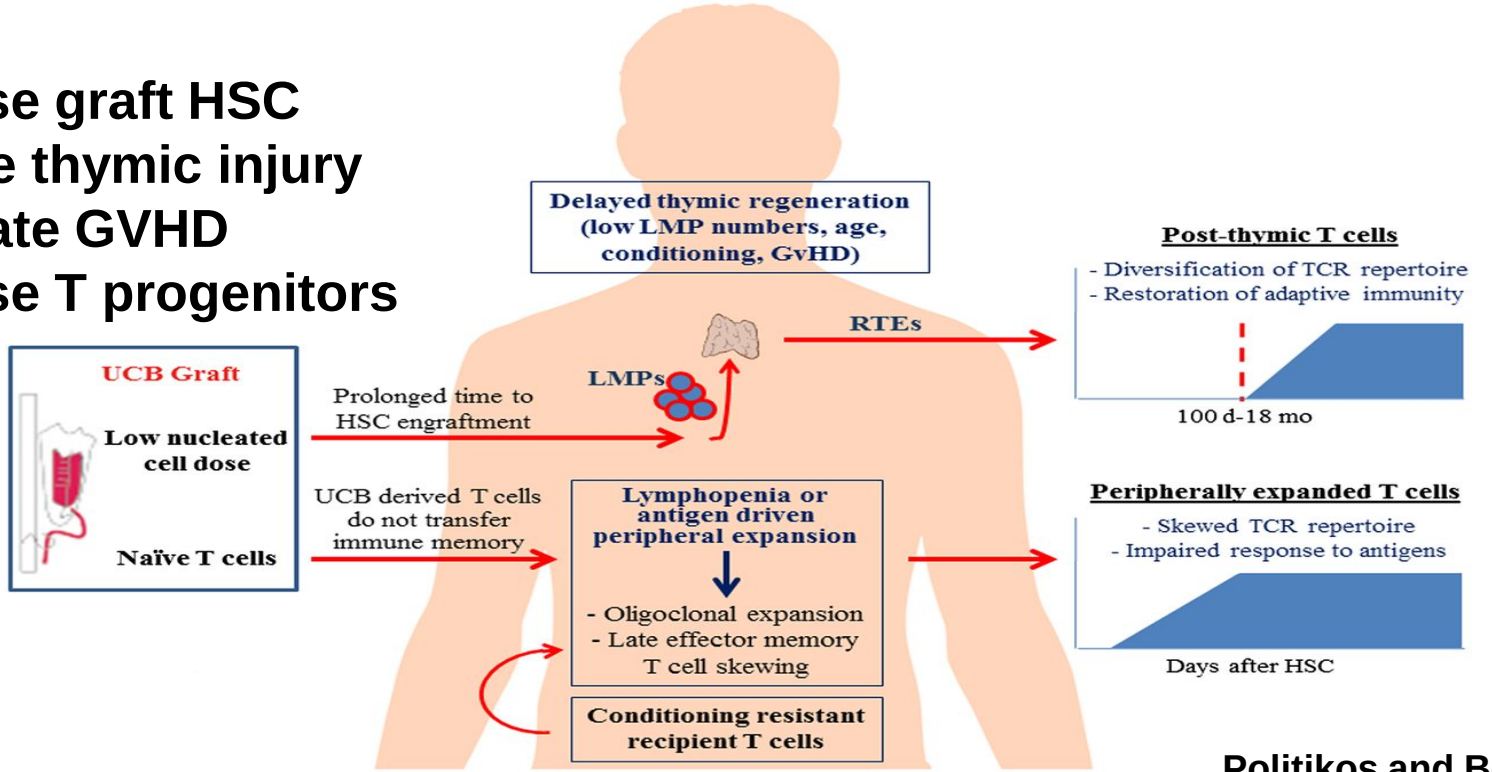
- UCB tTreg are potent modulators of the alloreactive response
- UCB tTreg at high doses are safe and have not increased the risk of opportunistic infection or relapse
- Safety and effectiveness of ultra-low dose rh-IL2 + UCB tTreg are under evaluation; if results are positive, it will markedly reduce 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



Politikos and Boussiotis
Blood 2014;124:3201-3211

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’

BMT CTN 0501 Children with Acute Leukemia