Umbilical Cord Blood Transplantation

Current Results

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Donor Choices

Unrelated Marrow/PBSC

Unrelated UCB

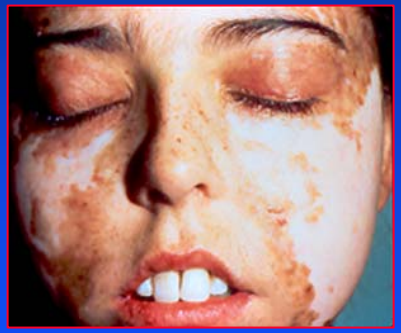
Haploidentical Relative

Results in SCID

- 50-77% survival
- complete immune reconstitution
- limited by donor availability
- potential for late effects (CGVHD, infertility, growth)

Unrelated Donor Bone Marrow Transplantation
Limitations

- Adverse effect of HLA mismatch restricting access
- Prolonged interval between search initiation and donor acquisition
- High risk of acute and chronic GVHD
- High risk of opportunistic infection



Haploidentical Related Donor Bone Marrow Transplantation
Limitations

- Prolonged immune reconstitution
- High risk of opportunistic infection
- KIR mismatching requirement?
- Impact of TCD on relapse?

UCB as an alternative stem cell source

Immune Properties

- ↓ cytotoxicity
- ↑ suppressor cell activity
- altered T cell cytokine production profile
- tolerance to NIMA

HSC Properties

- ↑ repopulating capacity
- high frequency of LTC-IC, ML-IC and SRC
- amenable to ex vivo expansion? transduction?

Less HLA restriction

No requirement for TCD

Reduced GVHD

Engraftment despite low cell dose

Hypothesis

UCB will extend the donor pool allowing greater access to HSCT.

- **Target collections**
- **Tolerability of HLA disparity**

Question

Will transplantation of UCB reduce TRM and improve survival?

- **General overview**
- **Registry data on outcomes in SCID/WAS**

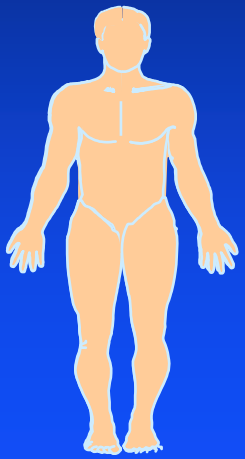
Patient Eligibility

- Age 0-55
- No available 5-6/6 HLA matched related donor

Donor Eligibility

UCB Unit

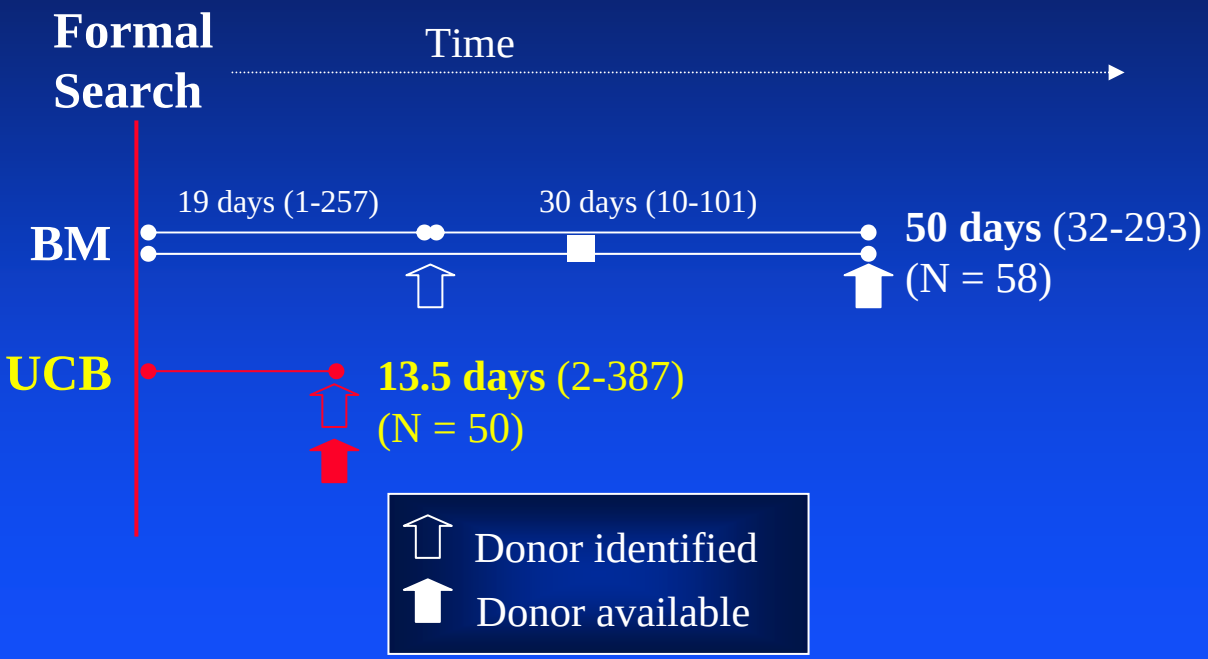
≤2 HLA ag mm



HLA typing

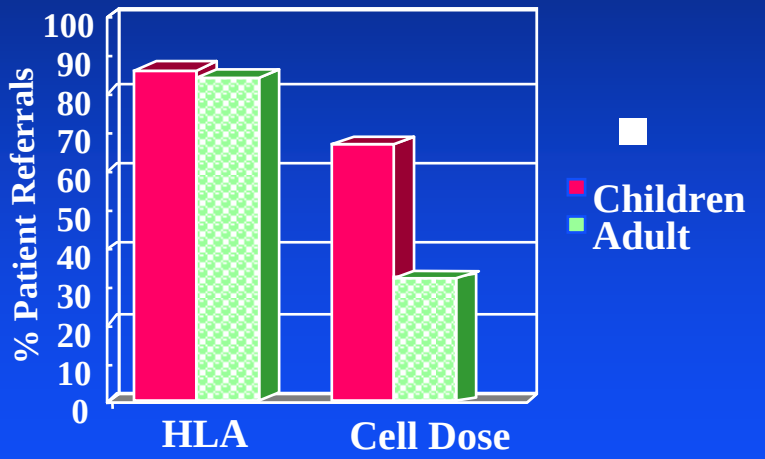
- **HLA A and B (serological level)**
- **HLA DRB1 (high resolution)**

Rapid Availability



Unrelated Donor UCB Transplantation

Cell dose rather than HLA restricts UCB Use



1999-2001

2003-2004

- 122 UCB searches
- UCB donors identified for 120 patients

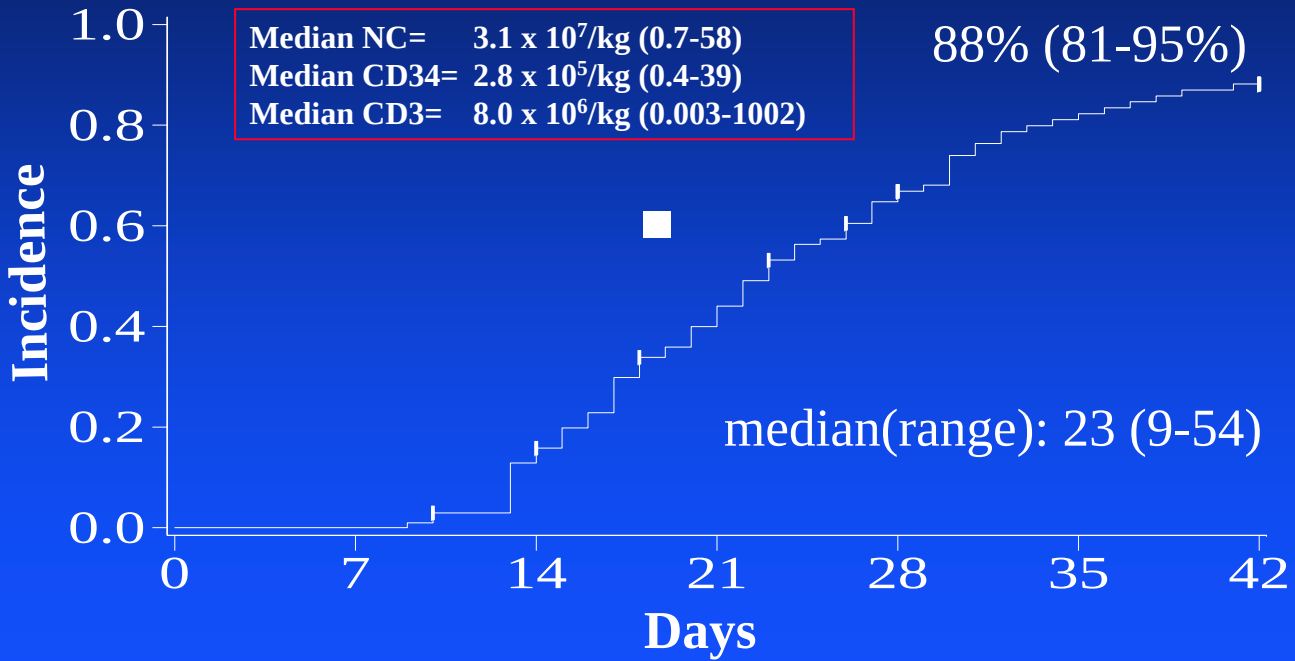
Search Outcome

UCB donors can be identified for nearly all patients

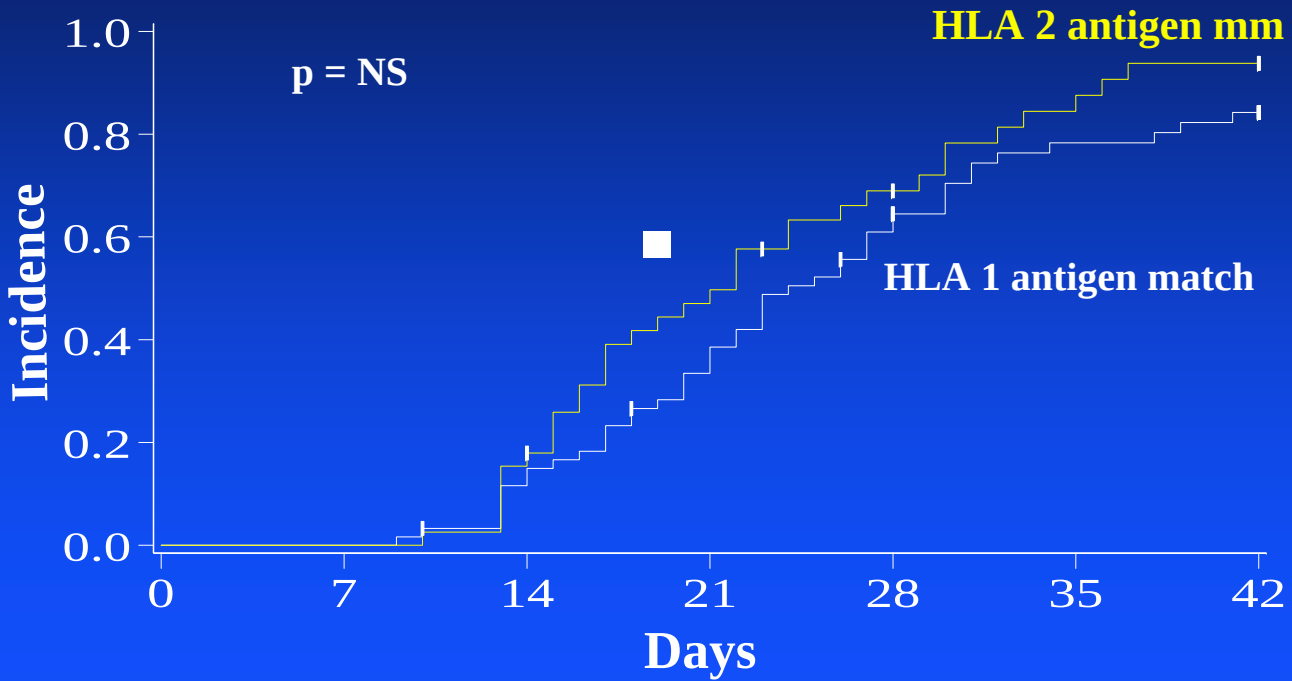
HLA match and cell dose are not limiting

Donor identification is rapid

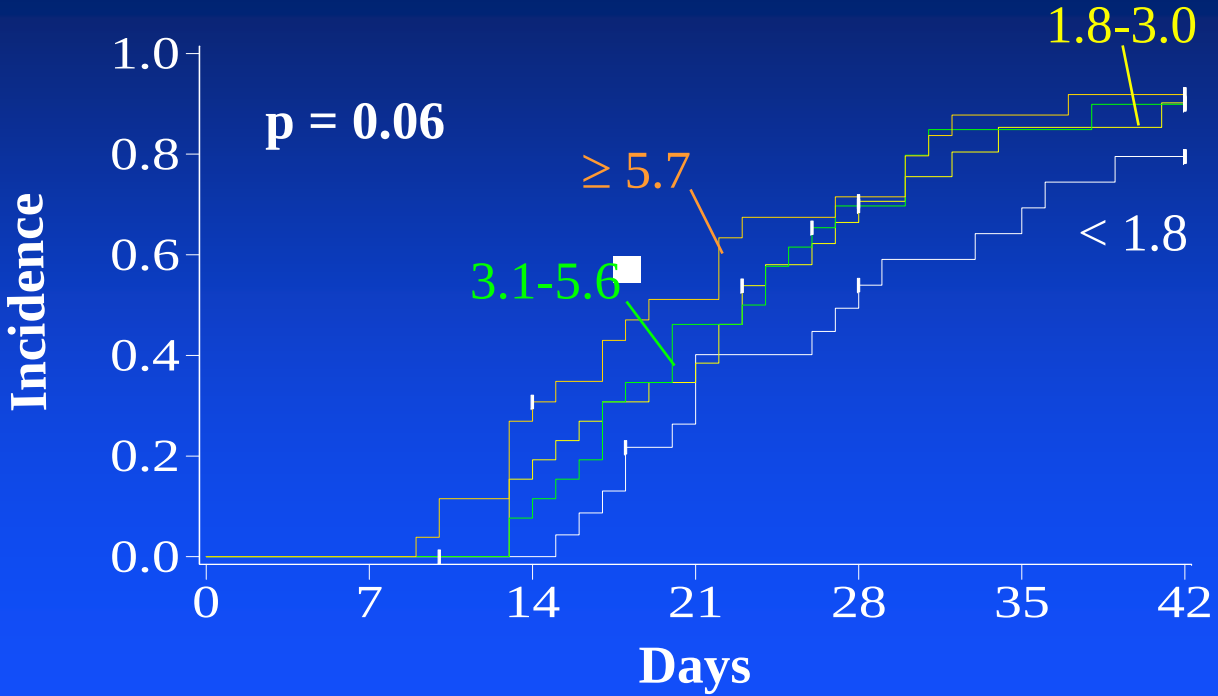
Neutrophil Recovery



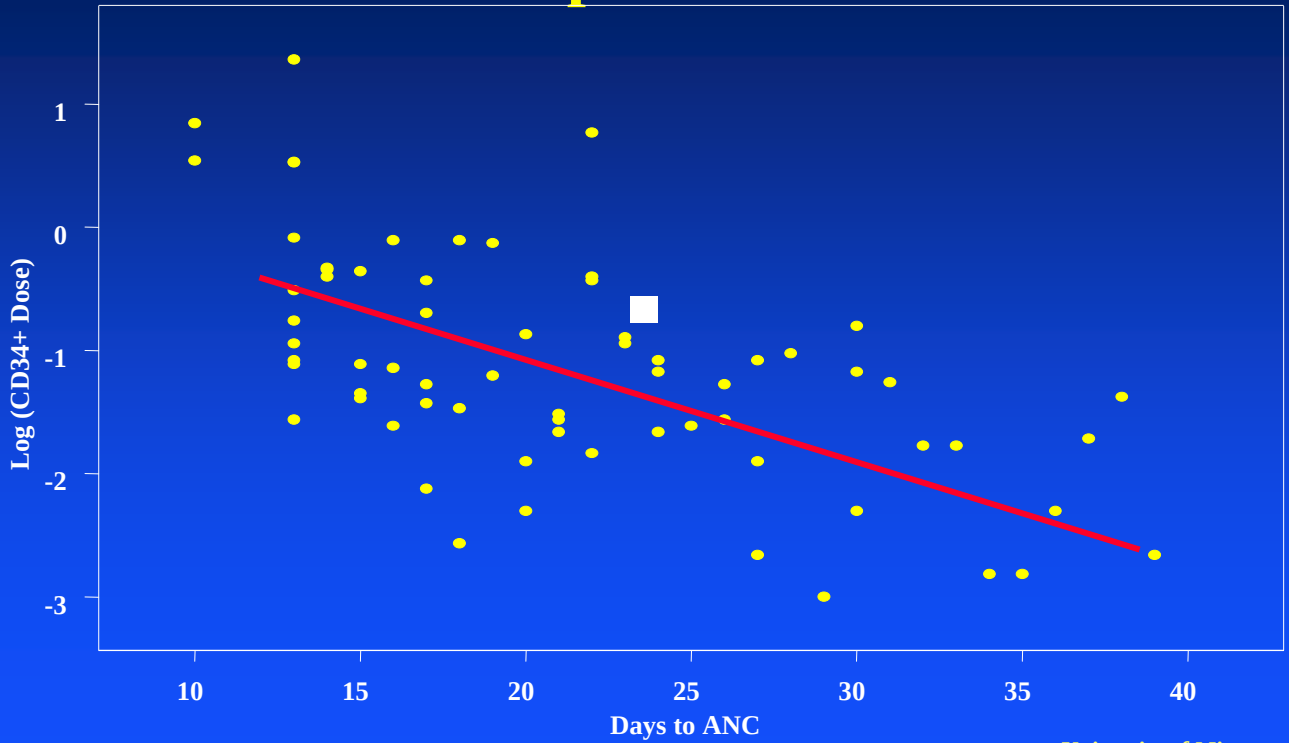
Neutrophil Recovery by HLA Disparity



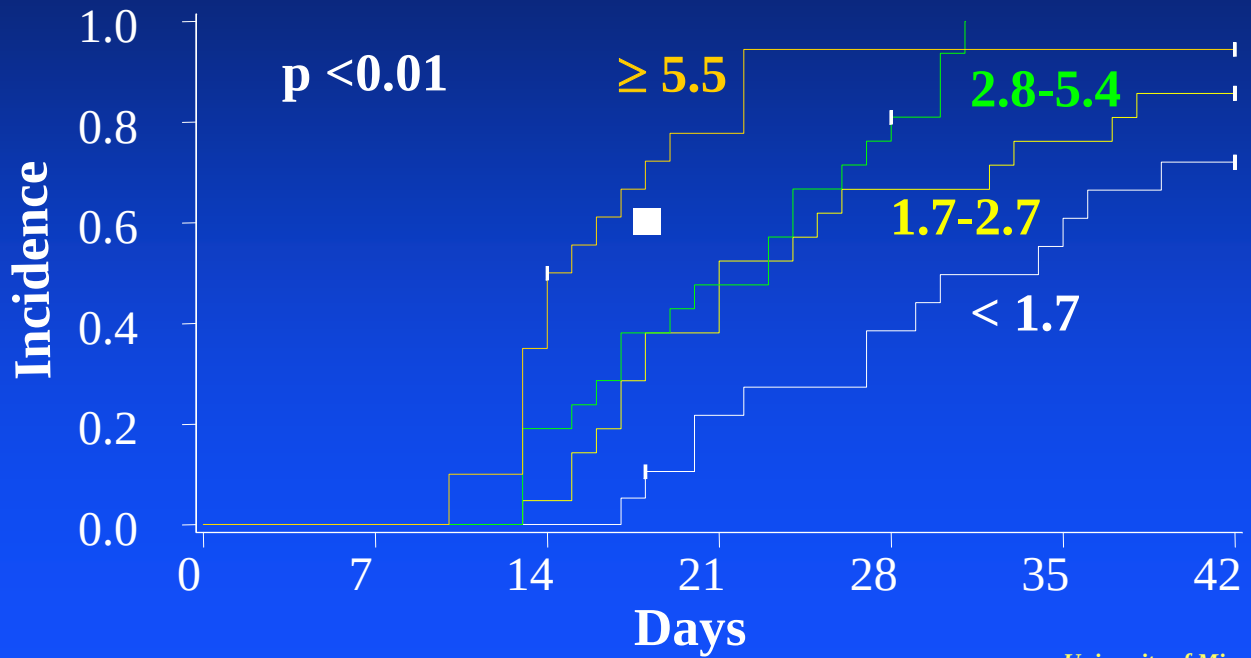
Neutrophil Recovery by Nucleated Cell Dose (x10^7/kg)



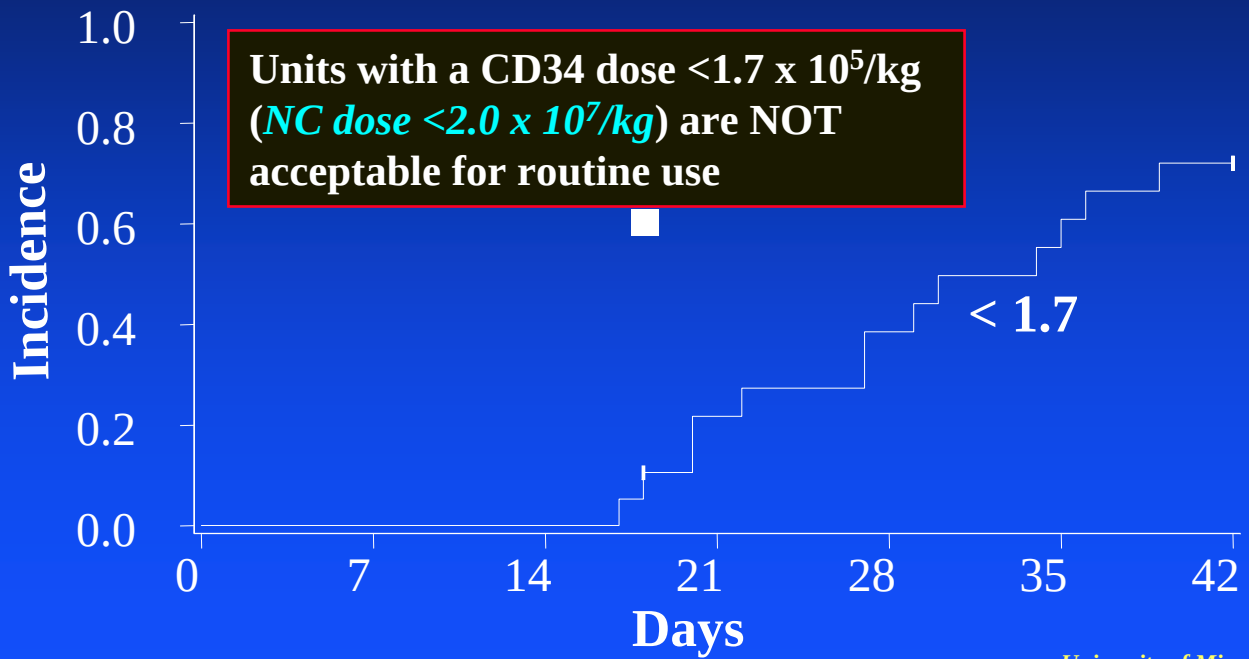
Rate of neutrophil recovery is cell dose dependent



Engraftment is cell dose dependent



CD34+ Cell Dose (x10^5/kg) defines the critical threshold



Neutrophil Recovery
Multiple Regression Analysis

HLA Match (graft vector)	Relative Risk	P-Value
6/6 and 5/6*	1.0	
4/6	0.9 (0.6-1.6)	NS
CD34 Dose ($x10^5$/kg)		
<1.7	1.0	
1.7-2.7	1.7 (0.8-3.6)	0.14
2.8-5.4	2.6 (1.3-5.4)	<0.01
>5.5	4.7 (2.2-9.8)	<0.01

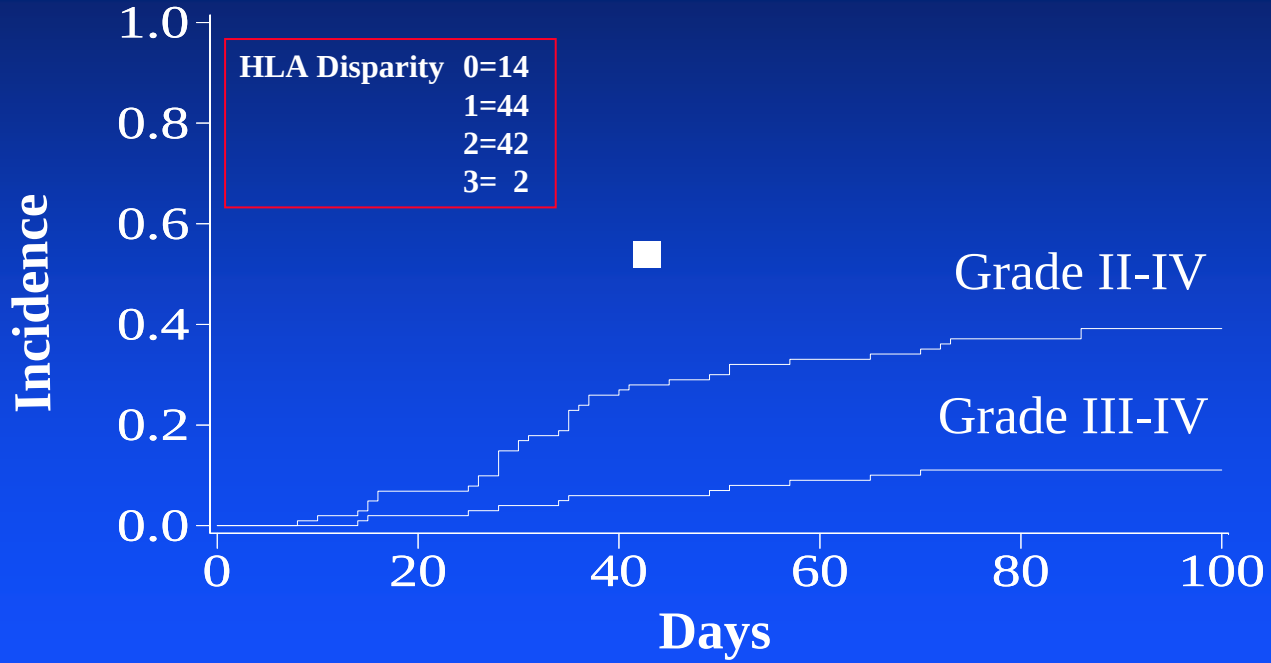
Engraftment Outcome

Engraftment is high in patients with malignancy

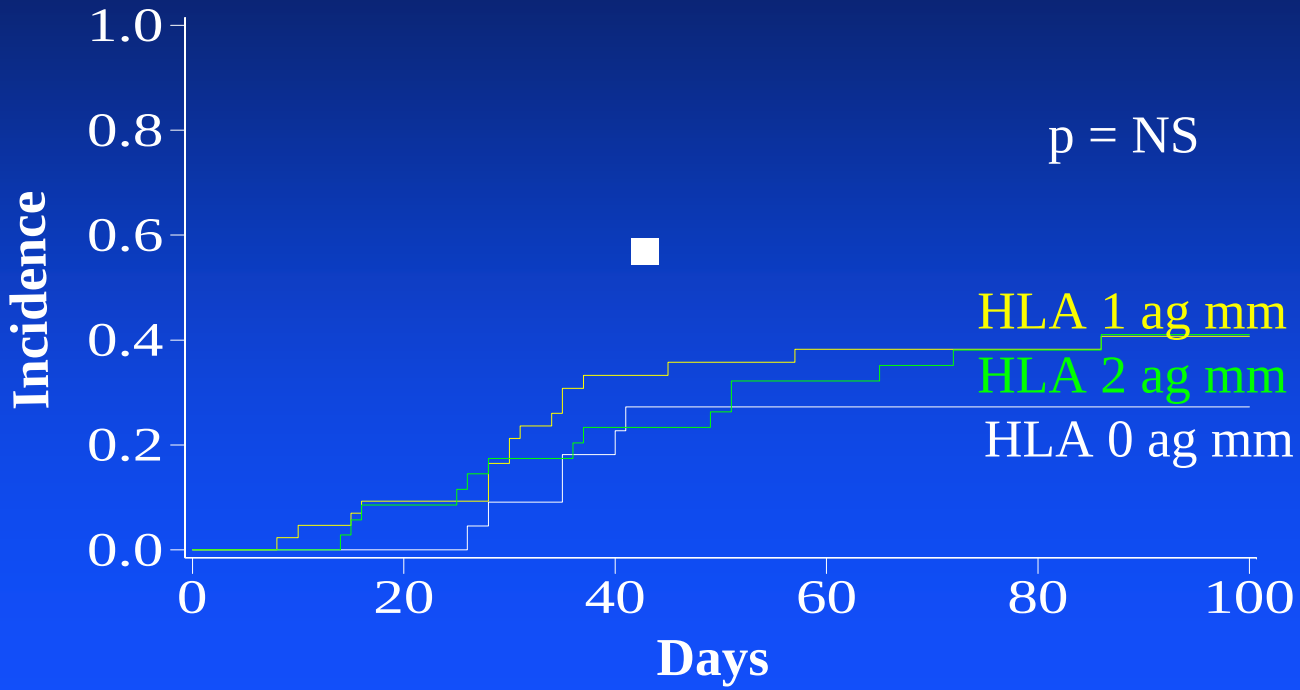
- **Rate of recovery is cell dose dependent**

Cell dose <1.7 x 10^5 CD34/kg is unacceptable

Acute GvHD


HLA Disparity 0=14
1=44
2=42
3= 2
Grade II-IV
Grade III-IV
Incidence
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
Days

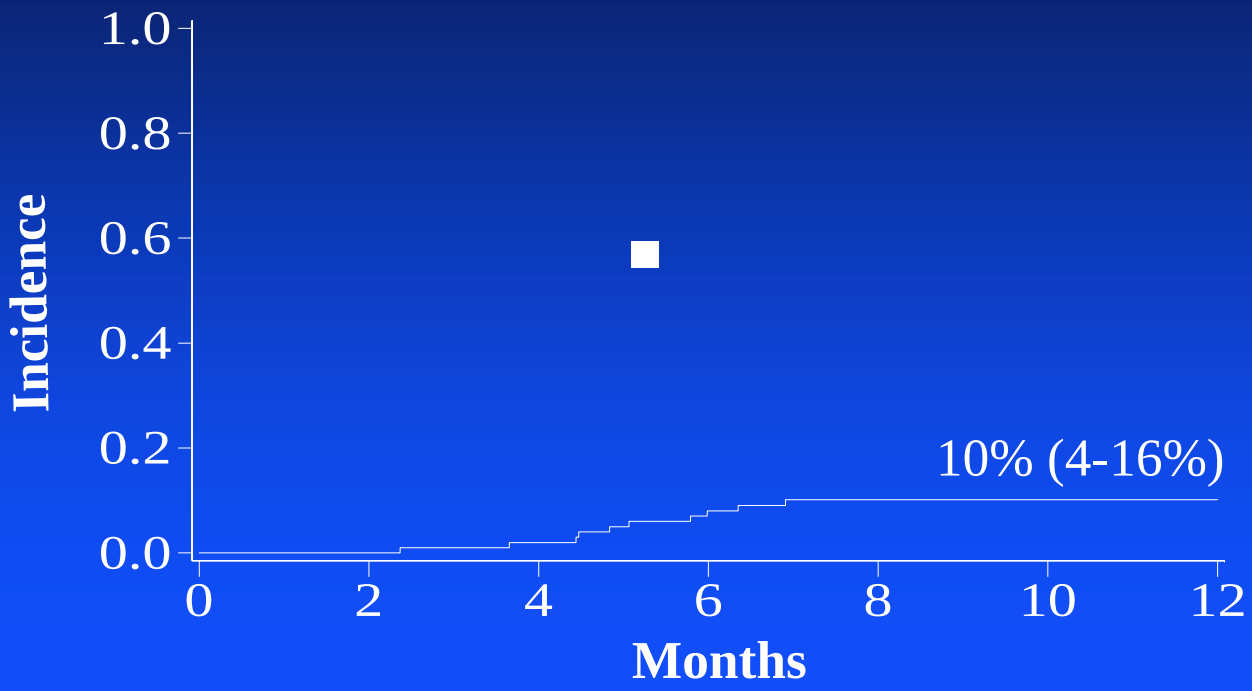
Grade II-IV Acute GvHD by HLA Disparity



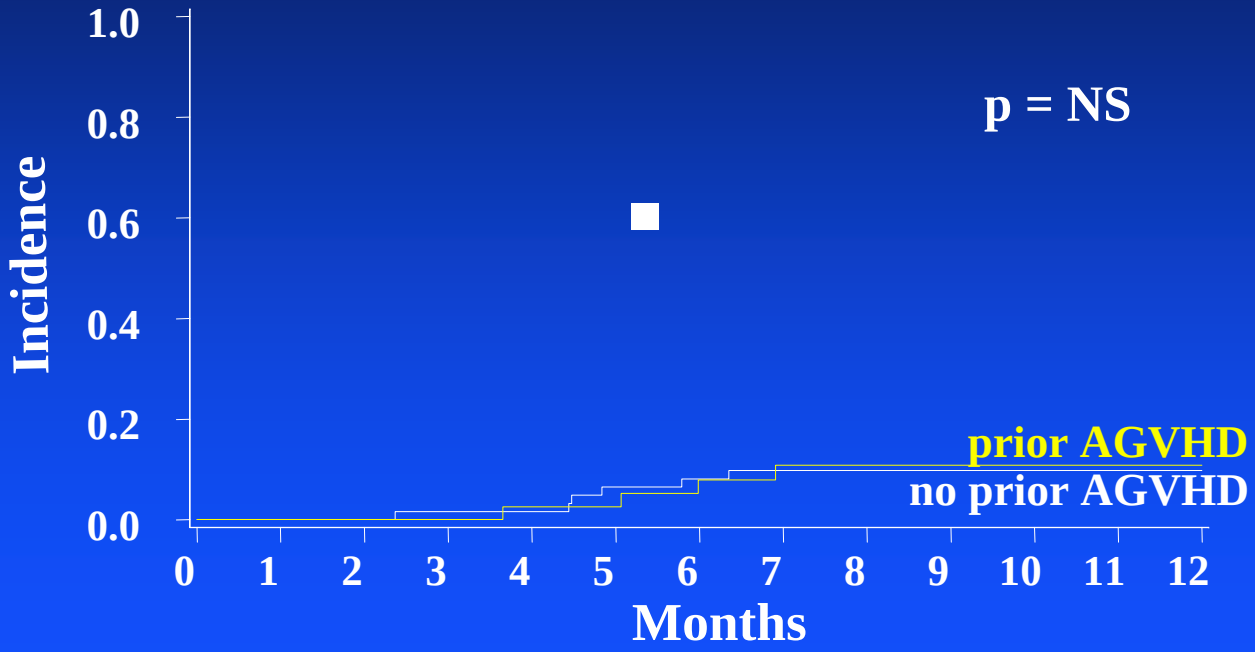
Acute GVHD
Multiple Regression Analysis

HLA Match (graft vector)	Relative Risk	P-Value
6/6 and 5/6*	1.0	
4/6	1.2 (0.5-2.7)	NS
CD3 Dose ($x10^6$/kg)		
<8	1.0	
≥8	0.7 (0.2-1.9)	NS
Age (decade)	1.0 (0.98-1.03)	NS

Chronic GvHD



Chronic GVHD by Prior AGVHD



GVHD Outcome

GVHD risk is low despite HLA mismatch

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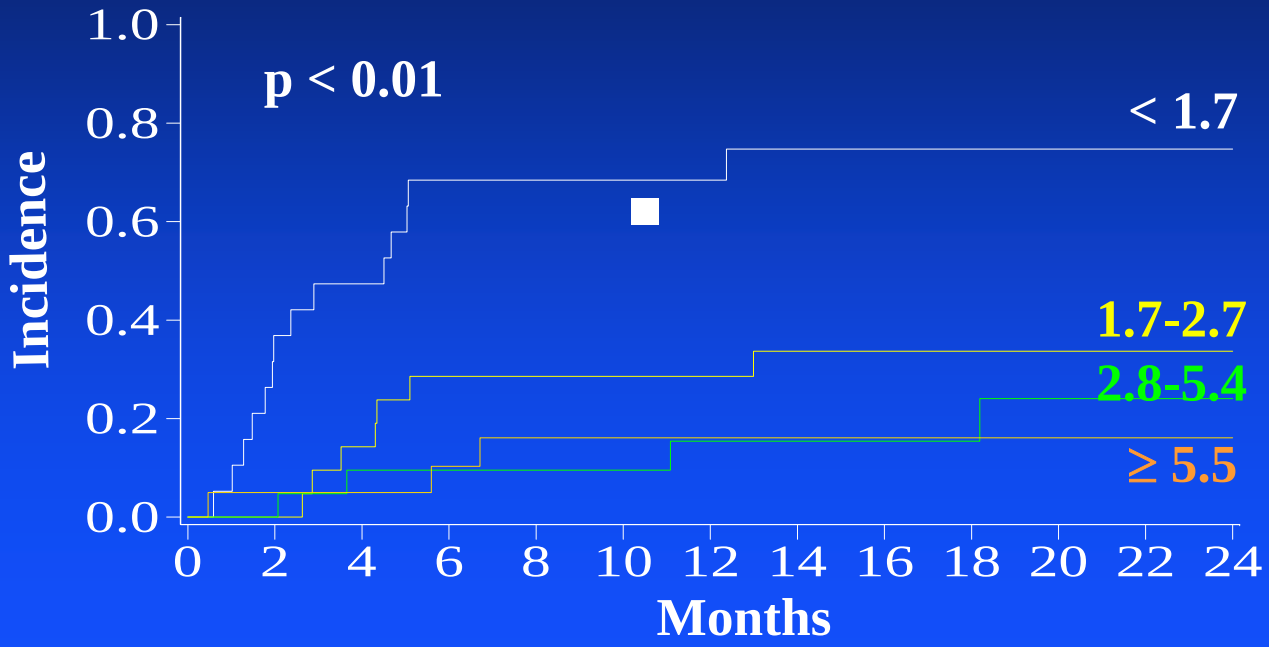
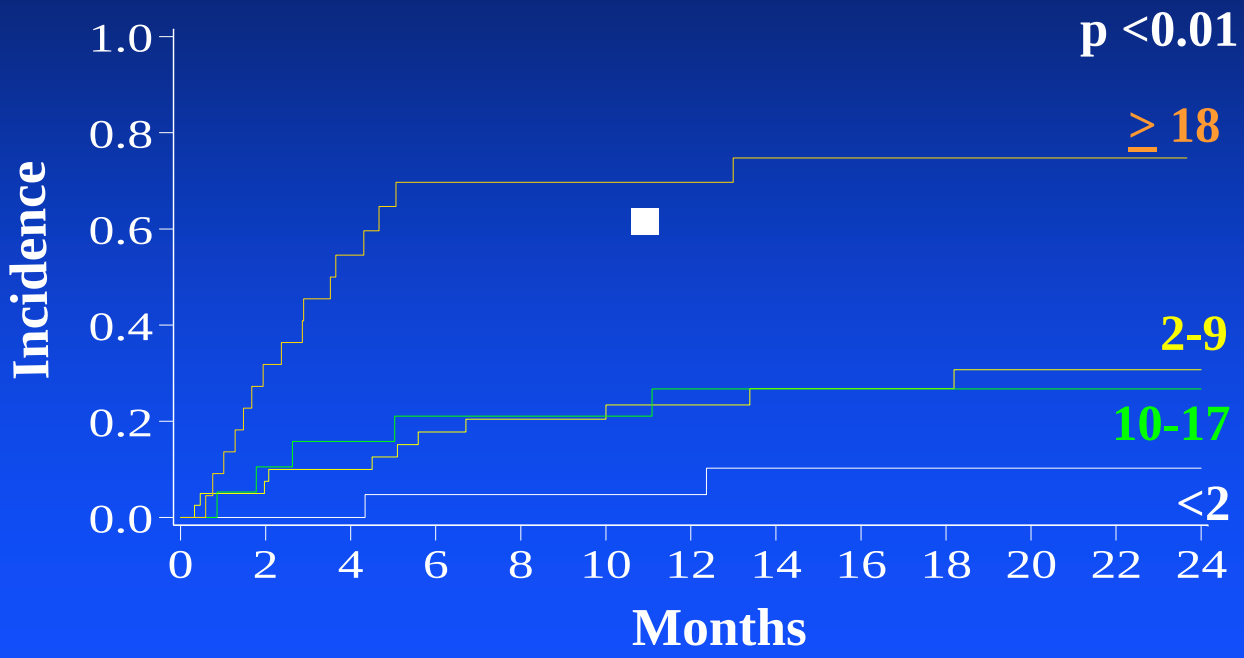
Transplant Related Mortality by CD34+ Cell Dose (x10^5/kg)



Treatment Related Mortality by Age



TRM Outcome

Incidence of TRM is low if the cell dose is >1.7 x 10^5 CD34/kg

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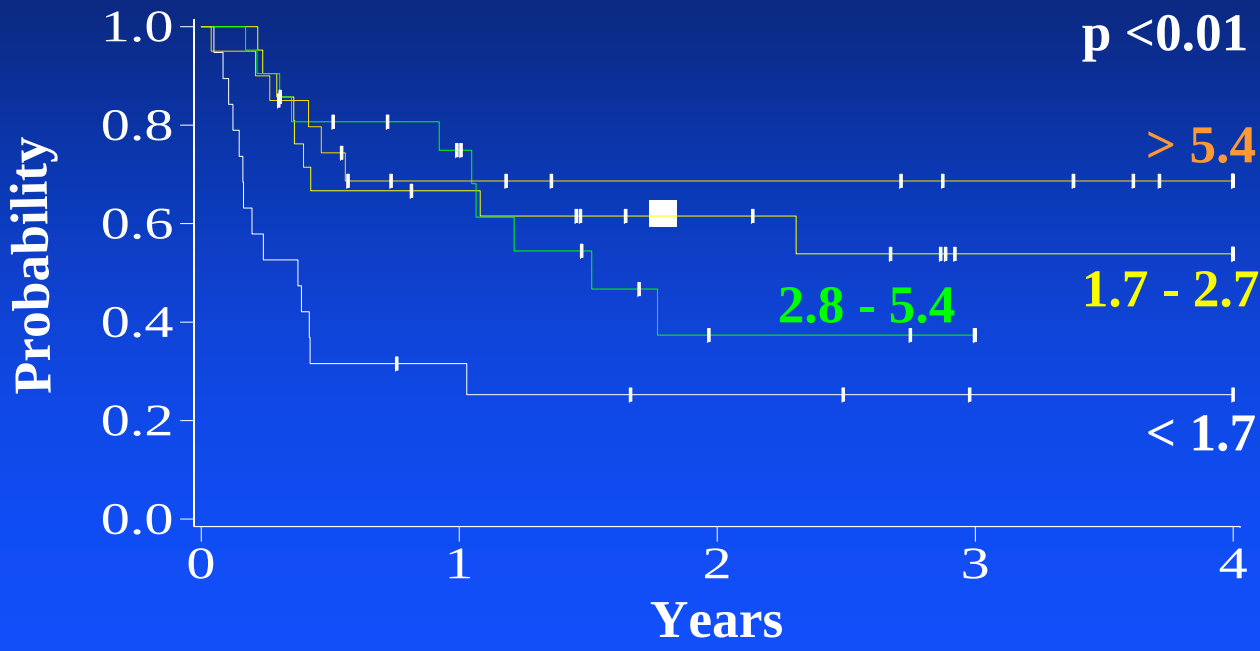
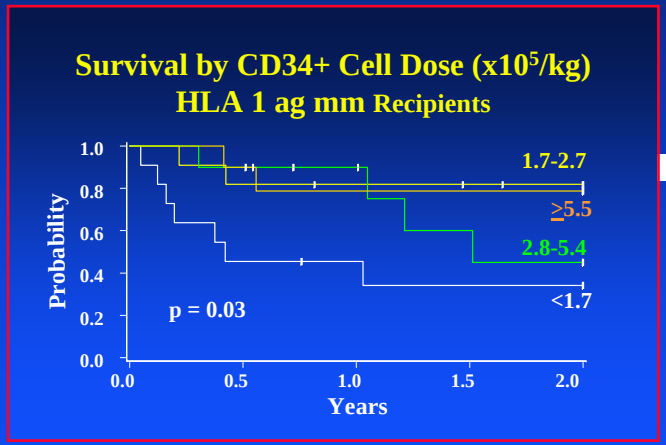
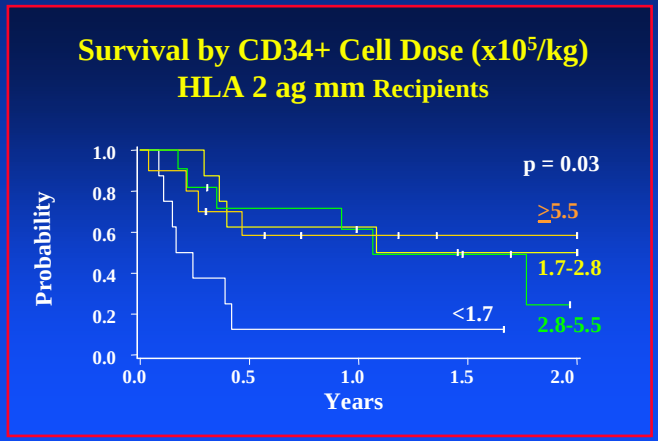
Survival by CD34+ Cell Dose (x10^5/kg)



Survival is cell dose and HLA match dependent

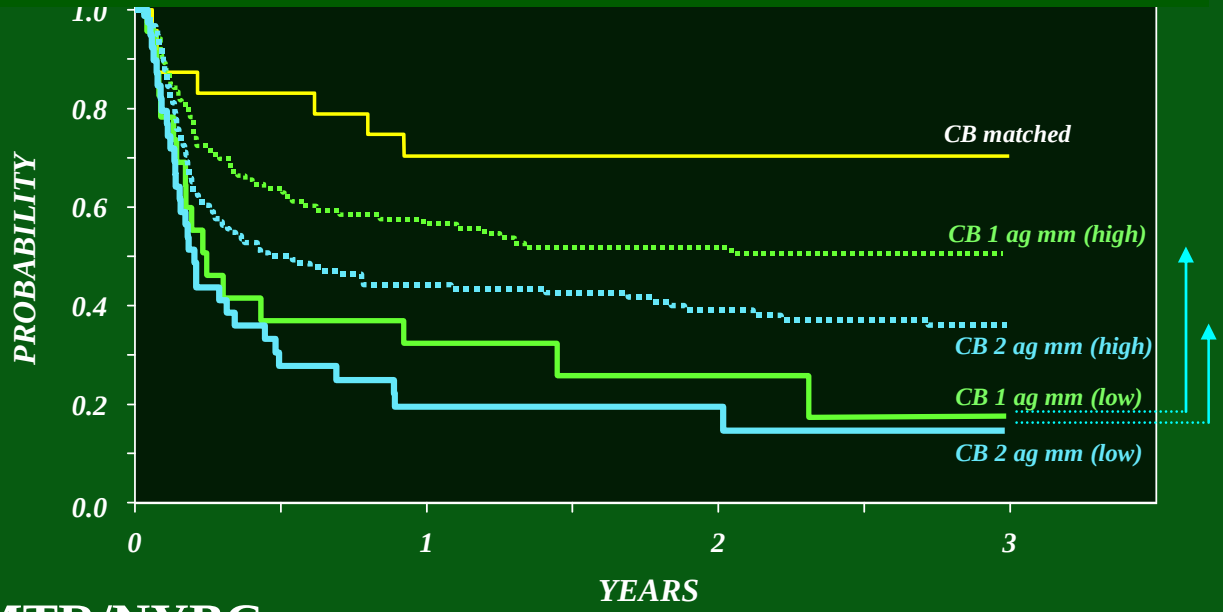




Survival
Multiple Regression Analysis

HLA Match	Relative Risk	P-Value
6/6 and 5/6*	1.0	
4/6	2.4 (1.2-4.7)	0.01
CD34 Dose ($x10^5$/kg) ■		
<1.7*	1.0	
>1.7	0.3 (0.1-0.5)	<0.01
Grade II-IV Acute GVHD (time-dependent)		
No*	1.0	
Yes	3.5 (1.5-7.9)	<0.01

Negative effect of HLA mismatch can be partially overcome by increasing cell dose



IBMTR/NYBC

Survival Outcome

Survival is impacted by cell dose and HLA match

Impact of HLA mismatch is partially overcome by higher cell dose

UCBT in the Treatment of Immunodeficiency Disorders

Critical issues:

- **Most patients are young**
- **Many patients come into transplant with infections**
- **Most do not have HLA identical sibling donors**

UCBT for Severe Immune Combined Immunodeficiency

- 57 transplanted February 1995-November 2004
- 52 with outcome data reported.

Patient Characteristics (n=52)

Age: Range: 1 month - 4 years 11 months
Median: 11 months

Sex: 60% male

Ethnicity: 59% Non-Caucasian

Transplant Center: 23% non-US

Prior Transplant: n=5

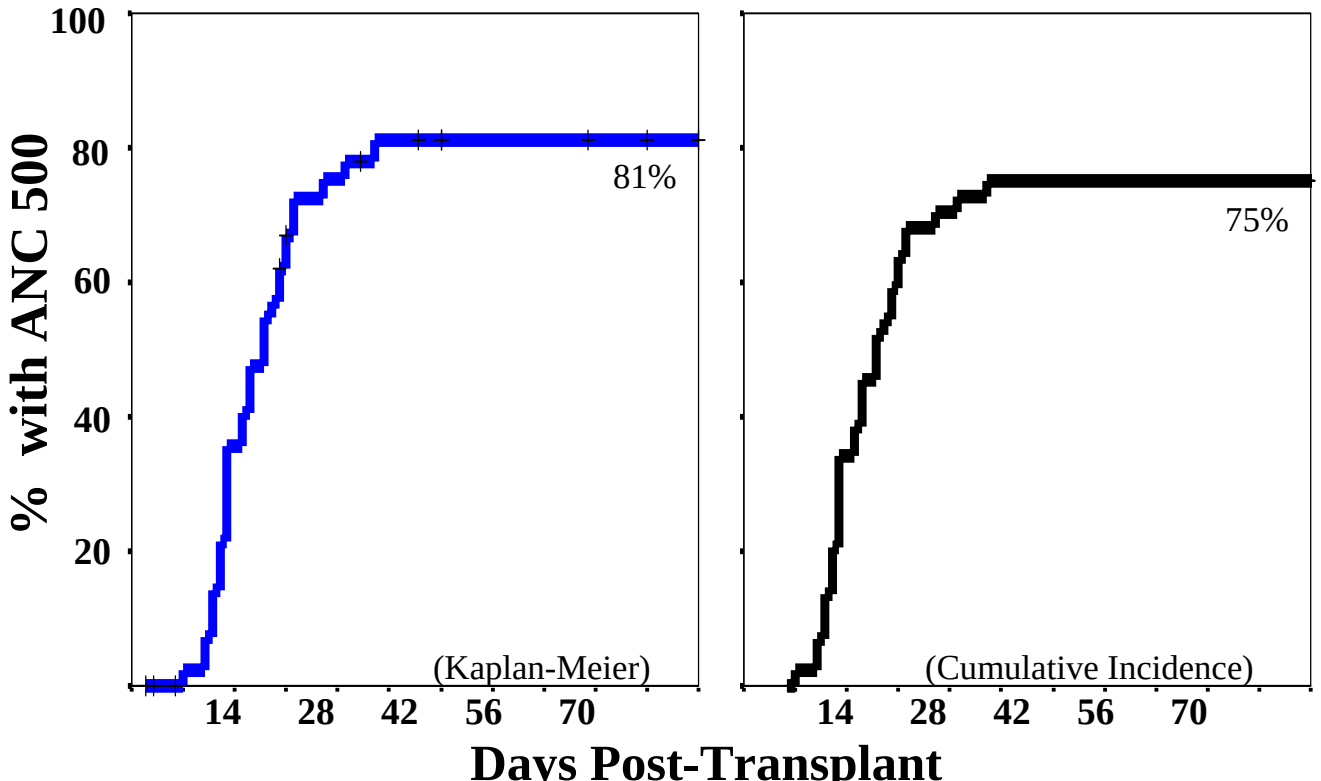
HLA Match: 6/6 n= 6
5/6 n=18
4/6 n=24
3/6 n= 4

TNC Dose (x10^7/kg): ≥ 10 (n=30)
5.0-9.9 (n=19)
2.5-4.9 (n= 3)
Median 11.3 x 10^7/kg

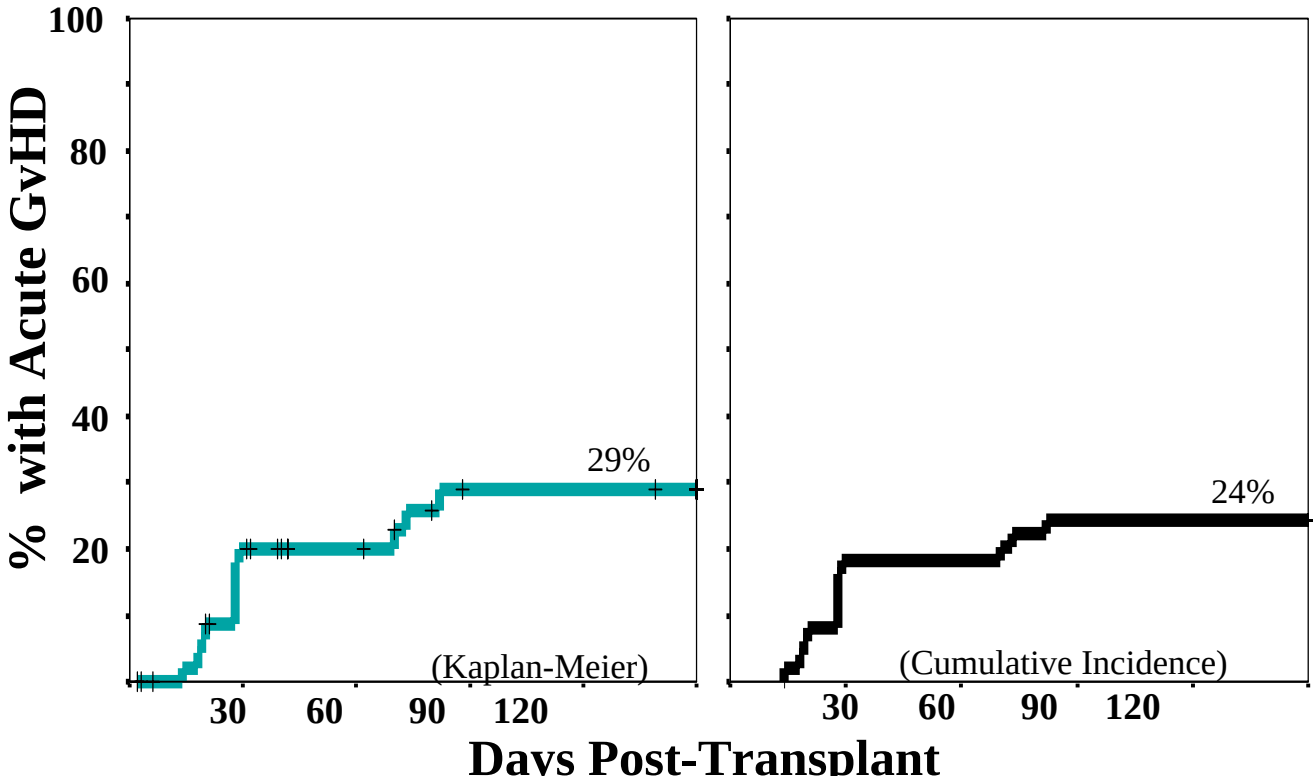
Conditioning Regimen

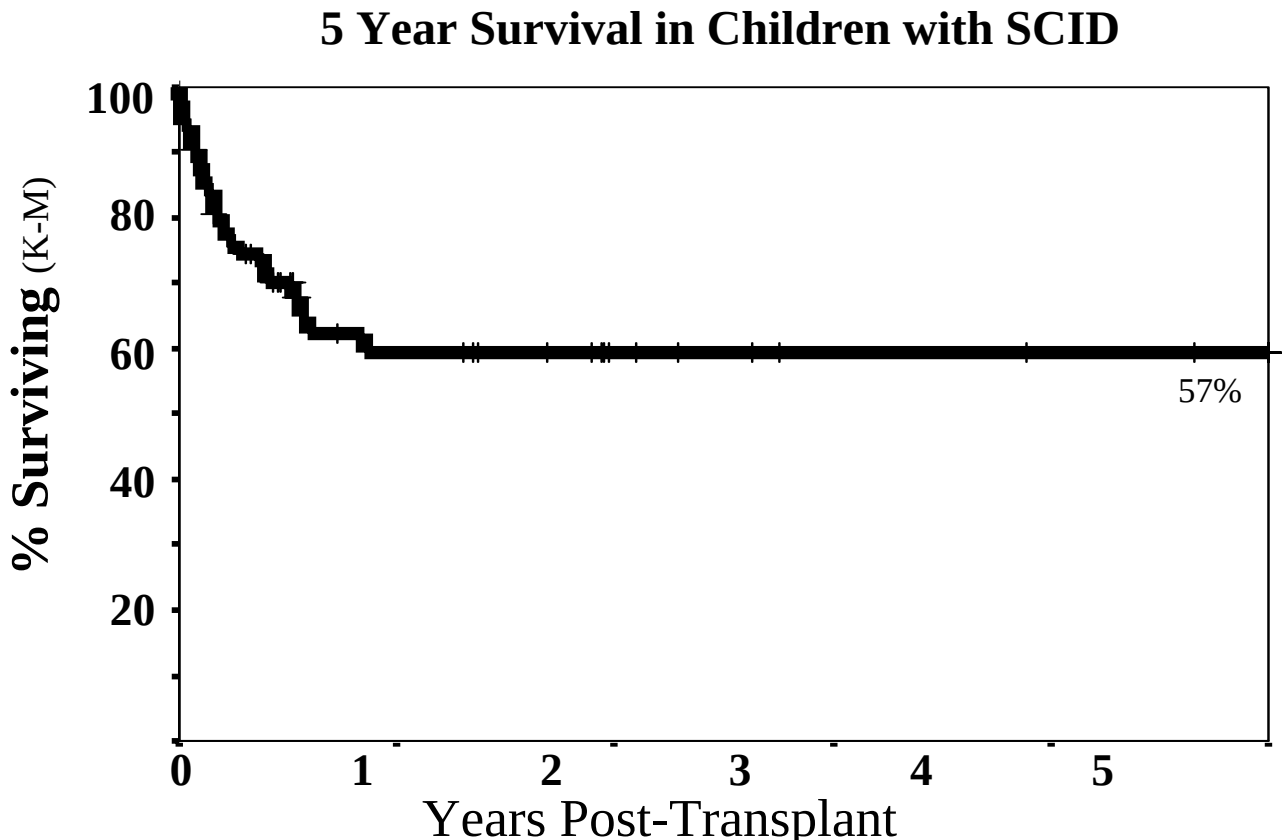
ATG, Busulfan, Cyclophosphamide:	23 patients
ATG ± Other:	15 patients
Other:	5 patients
Unknown:	9 patients

Myeloid Engraftment



Grade II-IV Acute GvHD




5 Year Survival in Children with SCID
100
80
60
40
20
% Surviving (K-M)
57%
0
1
2
3
4
5
Years Post-Transplant

NYBC *NCBP*

UCBT for the Treatment of Wiskott-Aldrich Syndrome

- 38 transplanted March 1996-December 2004
- 33 with outcome data reported

WAS Patient Characteristics (n=33)

Age: Range: 2 month - 7 years 10 months
Median: 19 months

Sex: 100% male

Ethnicity: 59% Non-Caucasian

Transplant Center: 30% non-US

Prior Transplant: n=0

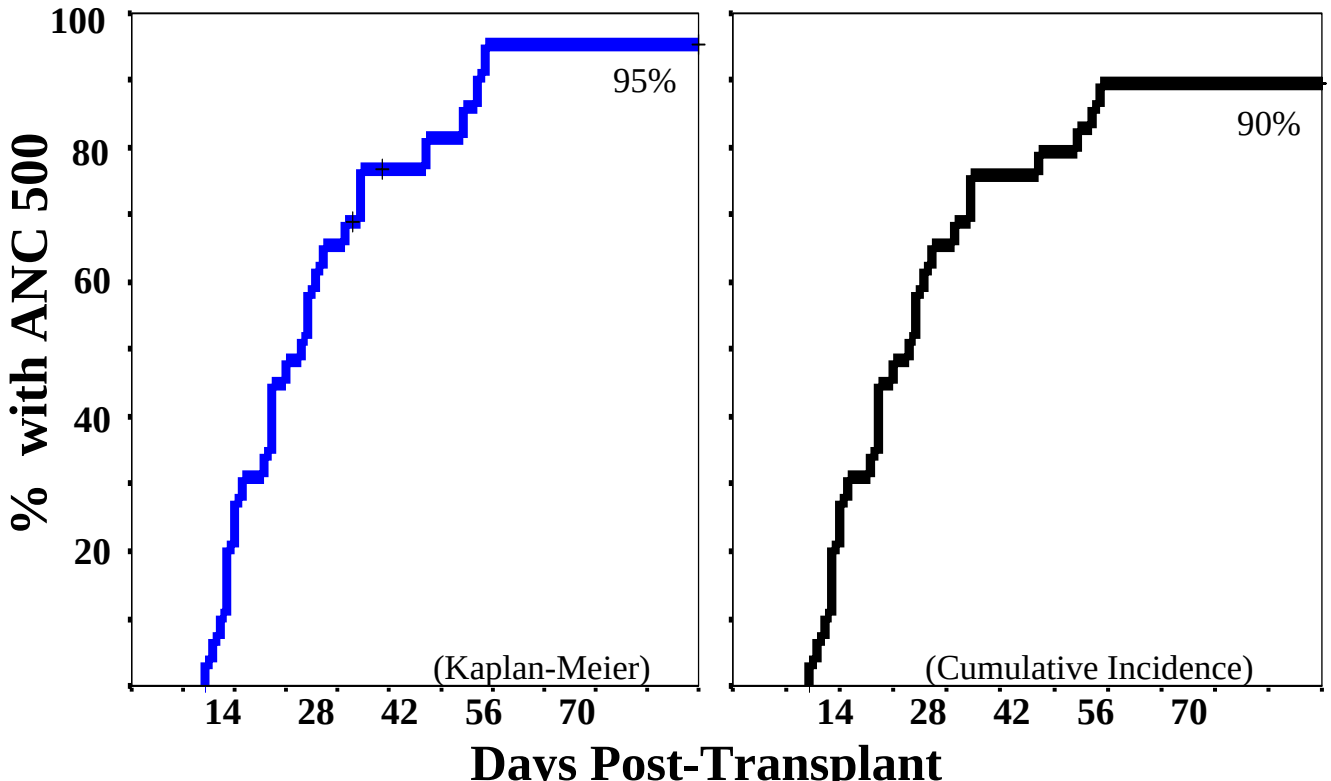
HLA Match: 6/6 n= 3
5/6 n=15
4/6 n=12
3/6 n= 3

TNC Dose ($x10^7$/kg): ≥ 10 n=10
5.0-9.9 n=19
2.5-4.9 n= 4
Median 8.0 x 10^7/kg

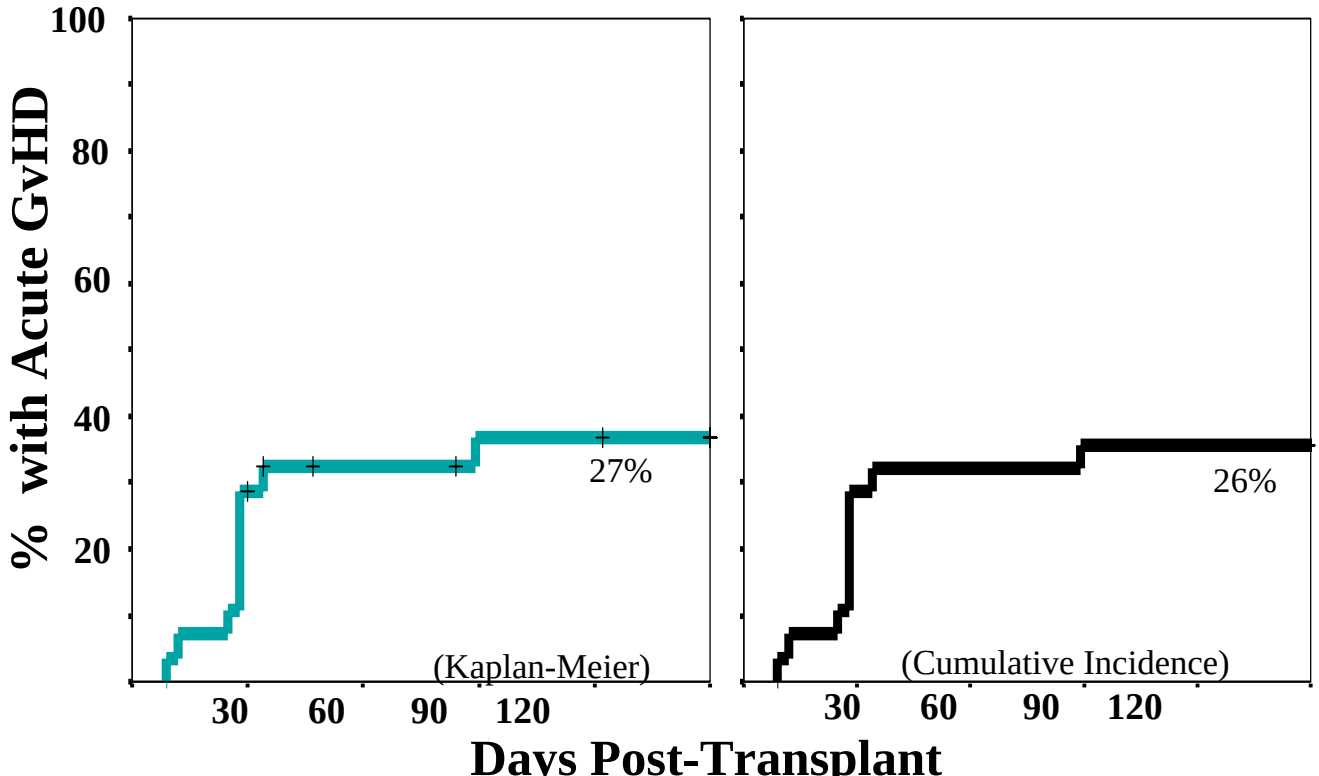
Conditioning Regimen

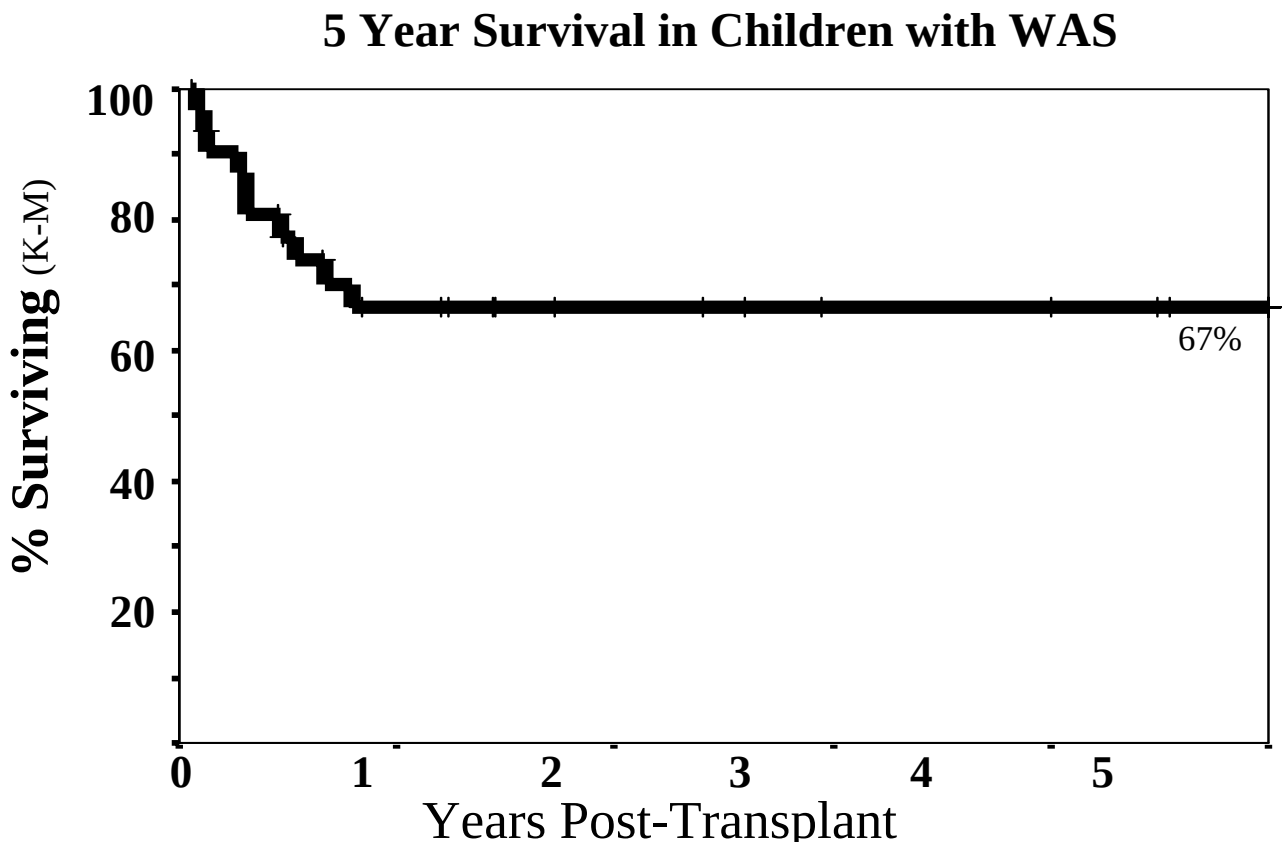
ATG, Busulfan, Cyclophosphamide:	22 patients
ATG ± Other:	6 patients
Other:	1 patients
Unknown:	4 patients

Myeloid Engraftment



Grade II-IV Acute GvHD




5 Year Survival in Children with WAS
% Surviving (K-M)
100
80
60
40
20
67%
0
1
2
3
4
5
Years Post-Transplant

NYBC *NCBP*

UCBT in the Treatment of Immunodeficiency Disorders

Conclusions:

- **Engraftment has been suboptimal for patients with SCID despite high cell dose**
- **No data on immune reconstitution**
- **Survival is comparable to results with HLA matched unrelated donor marrow**

Unrelated Donor UCB Transplantation

Next Generation

Improve Engraftment

Reduce TRM

Reduce Late Effects

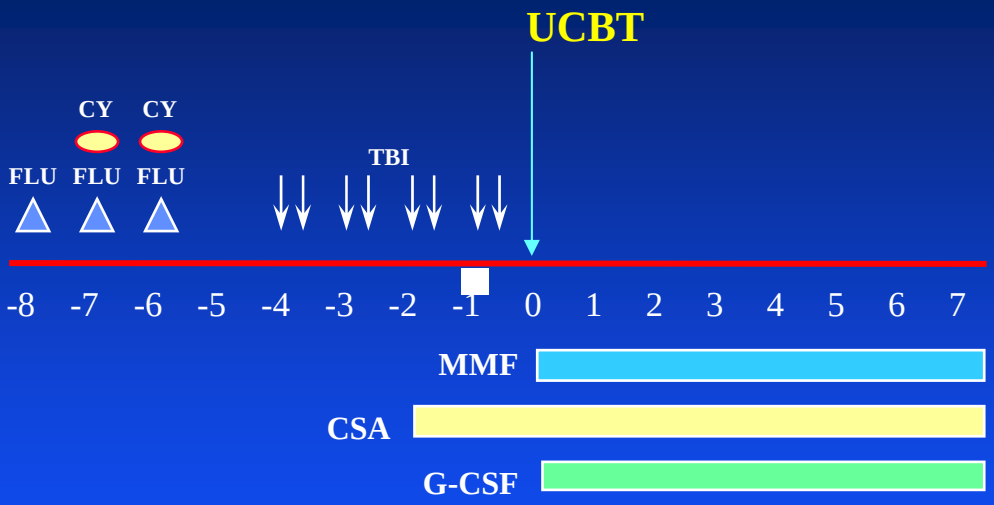
Improve Survival

Enhance Host Immune Suppression

Augment the Number of Hematopoietic Stem and Progenitor Cells

Eliminate Pre and Post Transplant Myelotoxic Drugs

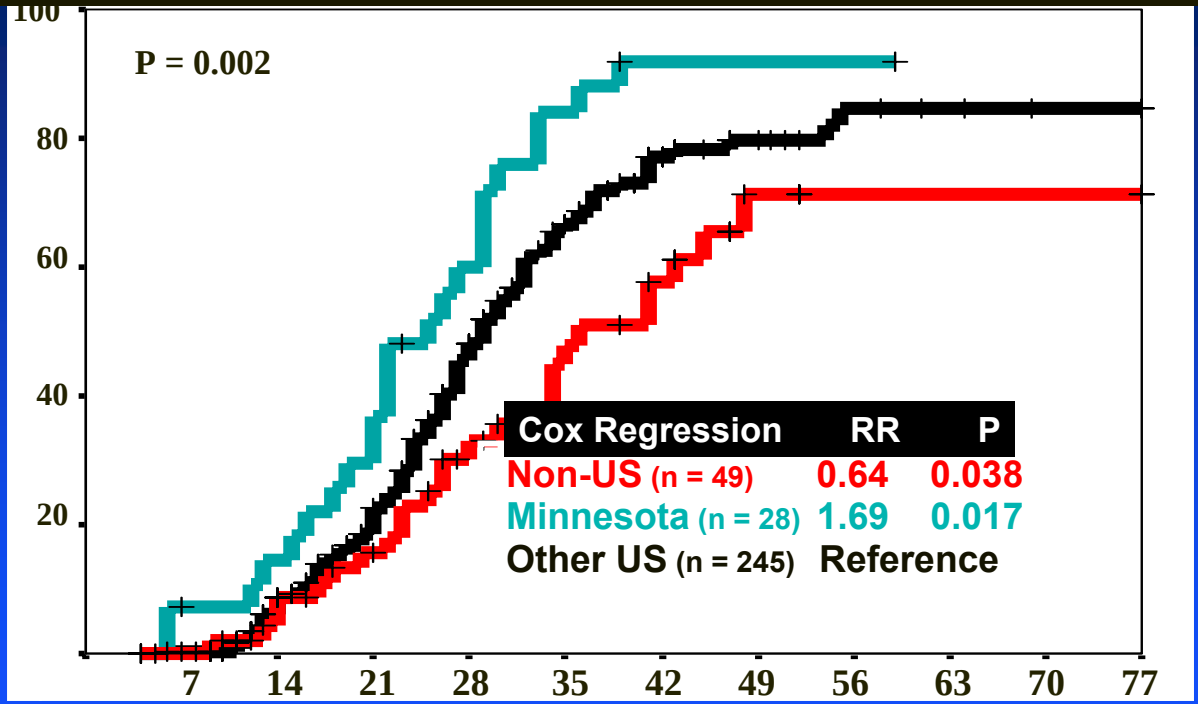
Effect of Enhanced Immune Suppression



TBI	165 cGy/fraction
CY	60 mg/kg/dose
FLU	25 mg/kg/dose

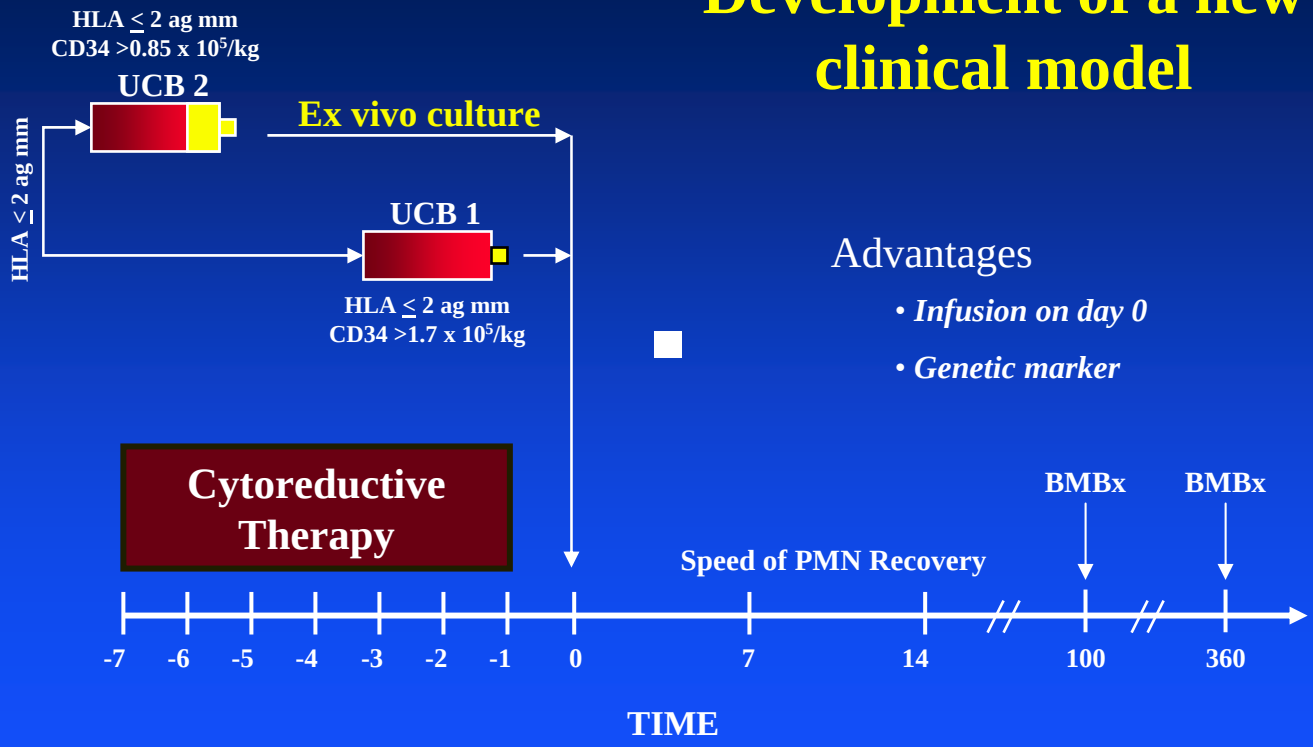
G-CSF	5 mg/kg/day
CSA	(maintain level 200-400)
MMF	1 g q12 hr d0-30

Improved Engraftment in Patients Aged ≥ 16 Years: due to addition of Fludarabine to the Preparative Regimen



NYBC *NCBP*

Development of a new clinical model



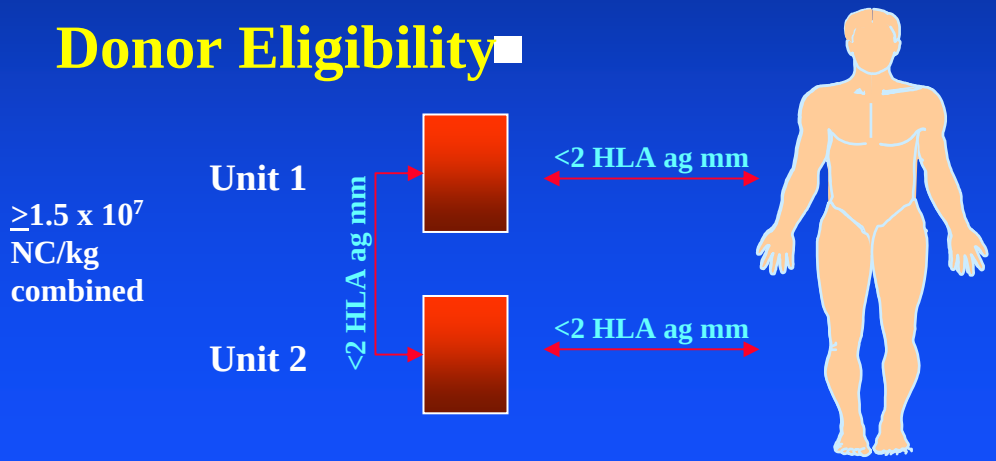
Advantages

- *Infusion on day 0*
- *Genetic marker*

Patient Eligibility

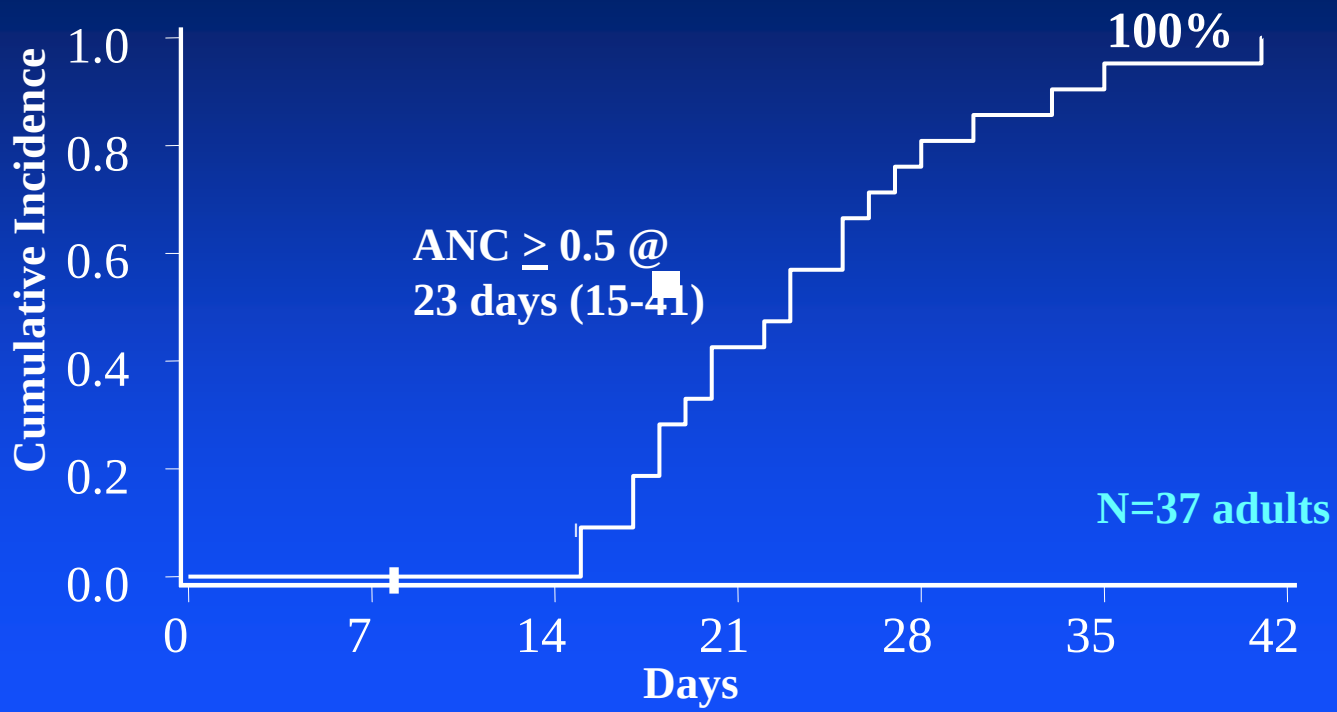
- Age 18-55 years (myeloablative therapy)
- High risk and/or advanced hematological malignancy
- No available 5-6/6 HLA matched related donor

Donor Eligibility

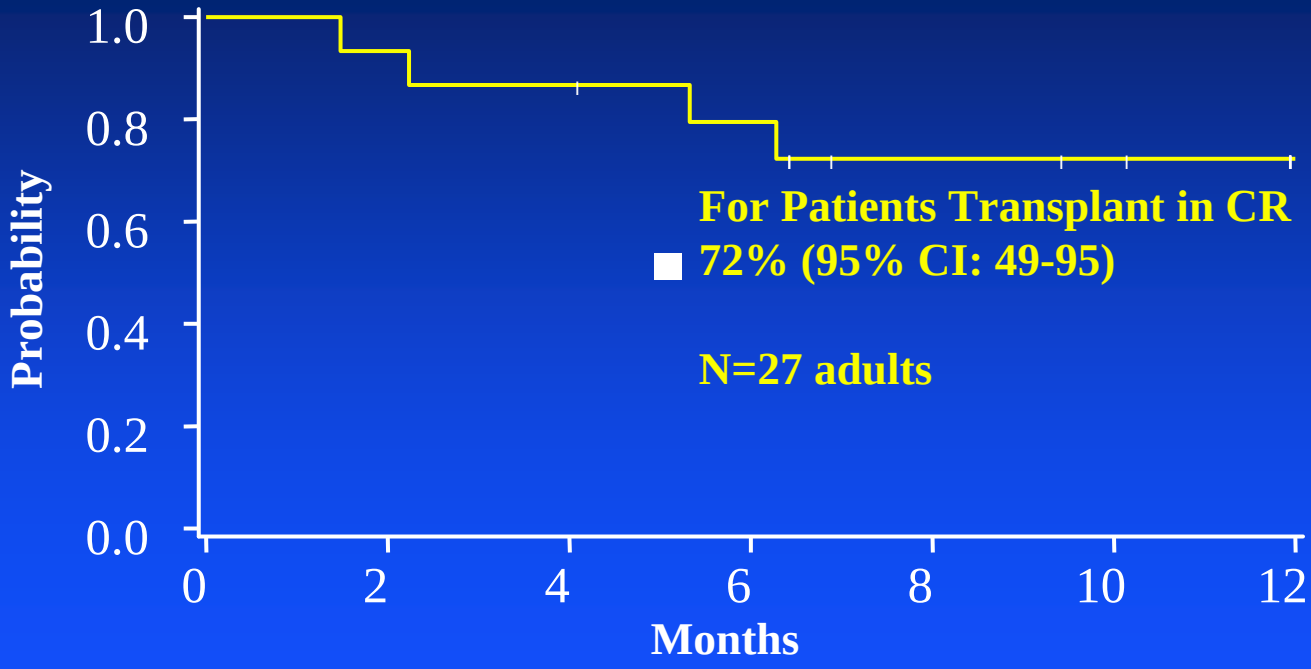


Neutrophil Recovery

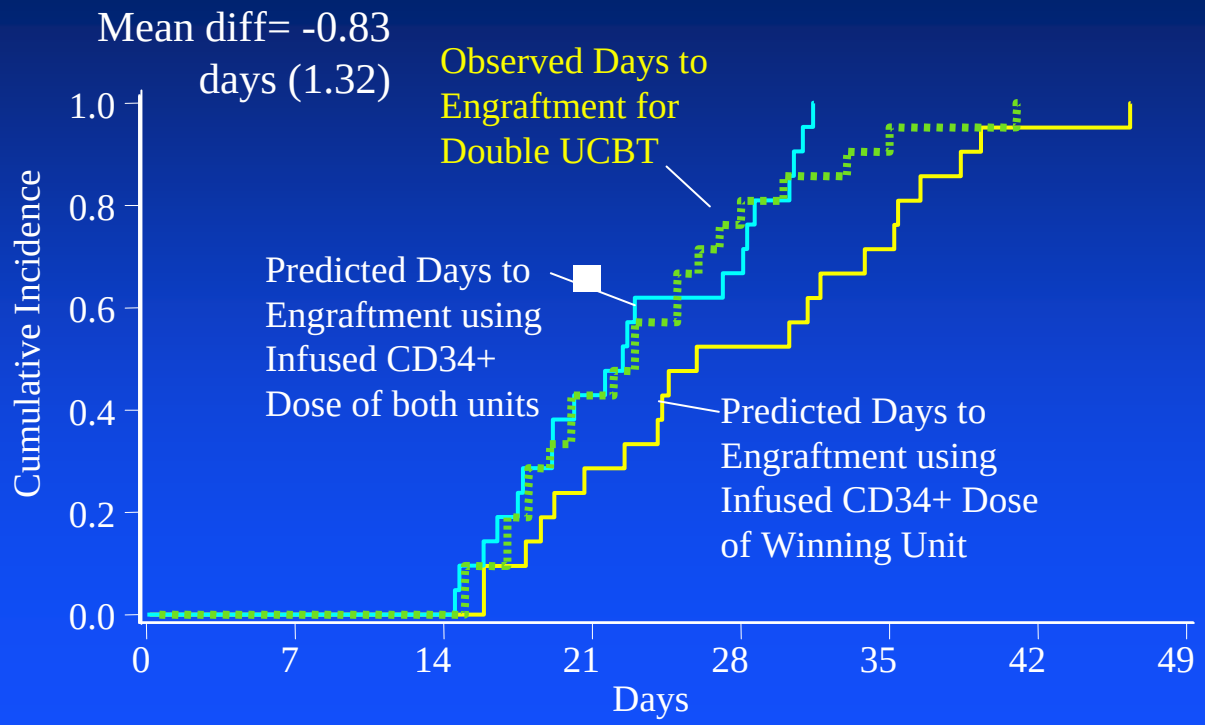
CY-FLU-TBI 1320



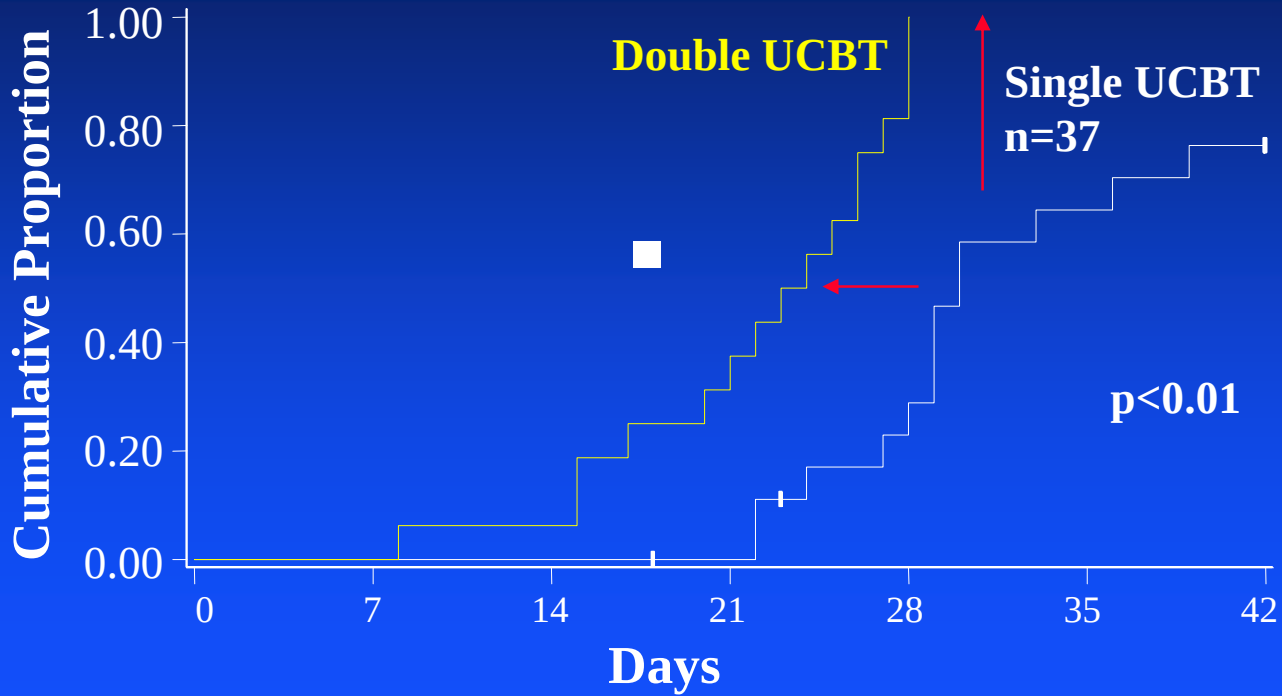
Disease-Free Survival



The Second Unit is Additive Based on Mathematical Model

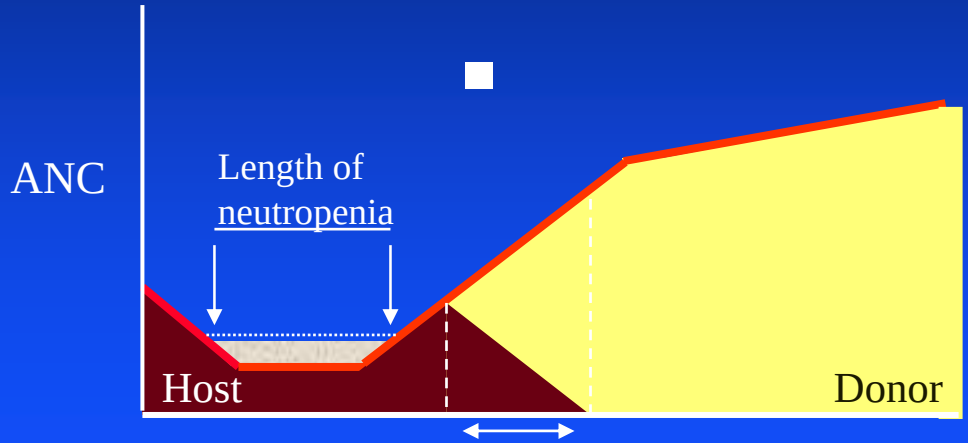


Is engraftment after double UCBT superior to single UCBT?

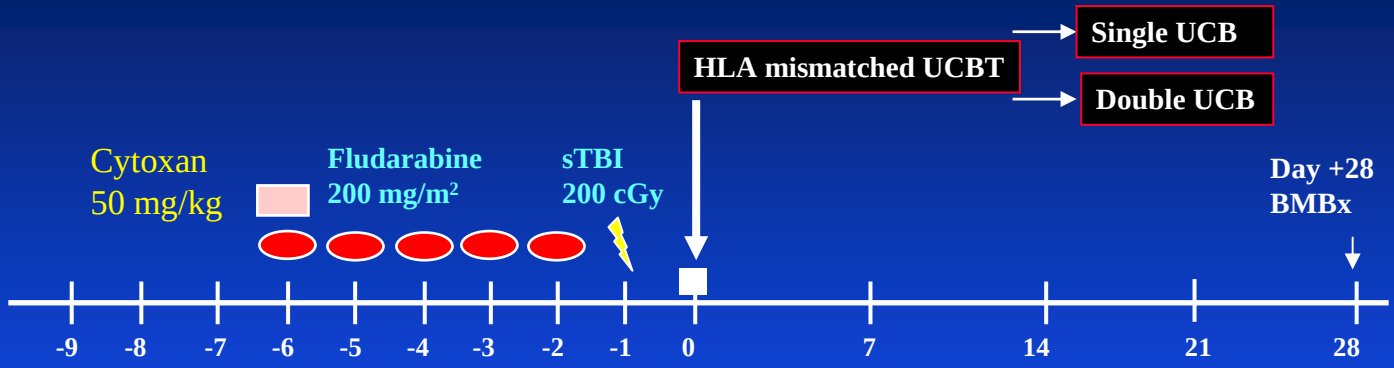


Hypothesis

A non myelablative therapy will reduce the period of neutropenia by allowing host hematopoiesis to continue until donor HSC recovery *and reduce TRM and potentially late effects (sterility)*



Non-Myeloablative Regimen



Eligibility:
- **< 70 yrs**
- **Heme malignancy**
- **High risk for TRM**
  - **age ≥ 45**
  - **extensive prior Rx**
  - **poor fitness**

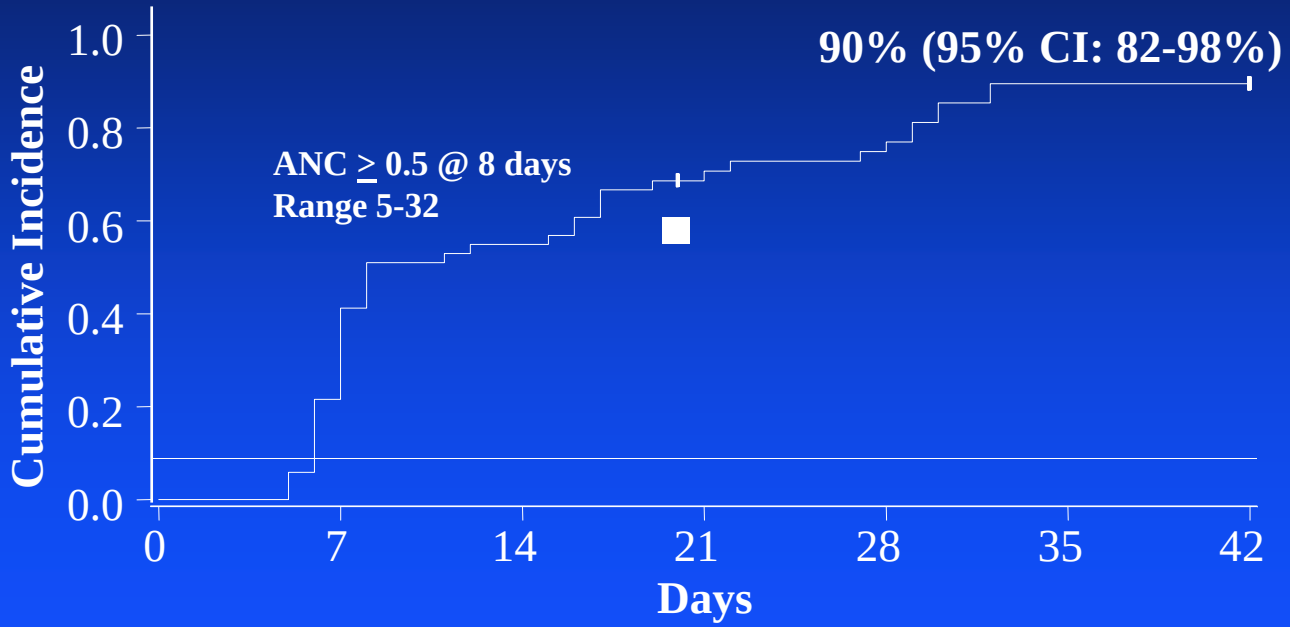
CSA - 3 to + 100

Mycophenolate - 3 to + 30

G-CSF until ANC >2500/uL

N=97 (30 single; 67 double)

High Incidence of Neutrophil Recover and Sustained Chimerism



Unrelated Donor UCB Transplantation

Measures of success

- **uUCBT surpasses uBMT/PBSC in children in U.S., Europe and Japan!**
- **uUCBT > uBMT in children and adults in Japan as reported at the JSH December 19, 2003. (*18 UCBT in 1997 to 562 UCBT in 2003; total 1750*)**

The Next Generation-Research

Cells to facilitate engraftment

- MSC
- Allogeneic NK cells
- $CD4^+/CD25^+$ T regulatory cells

IBMI

Ex vivo expansion culture

Up regulation of homing receptors

Assisted Reproduction in patients with Genetic Disorders

Ovarian Hyperstimulation

Goal 10-20 Oocytes

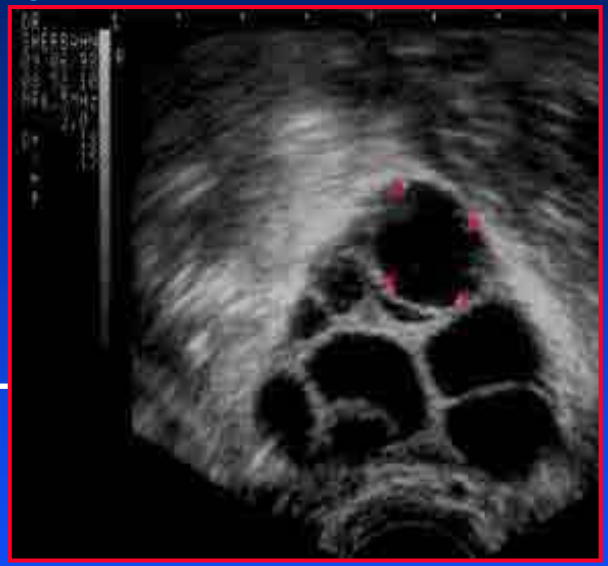
Daily estradiol monitoring

Daily transvaginal U/S

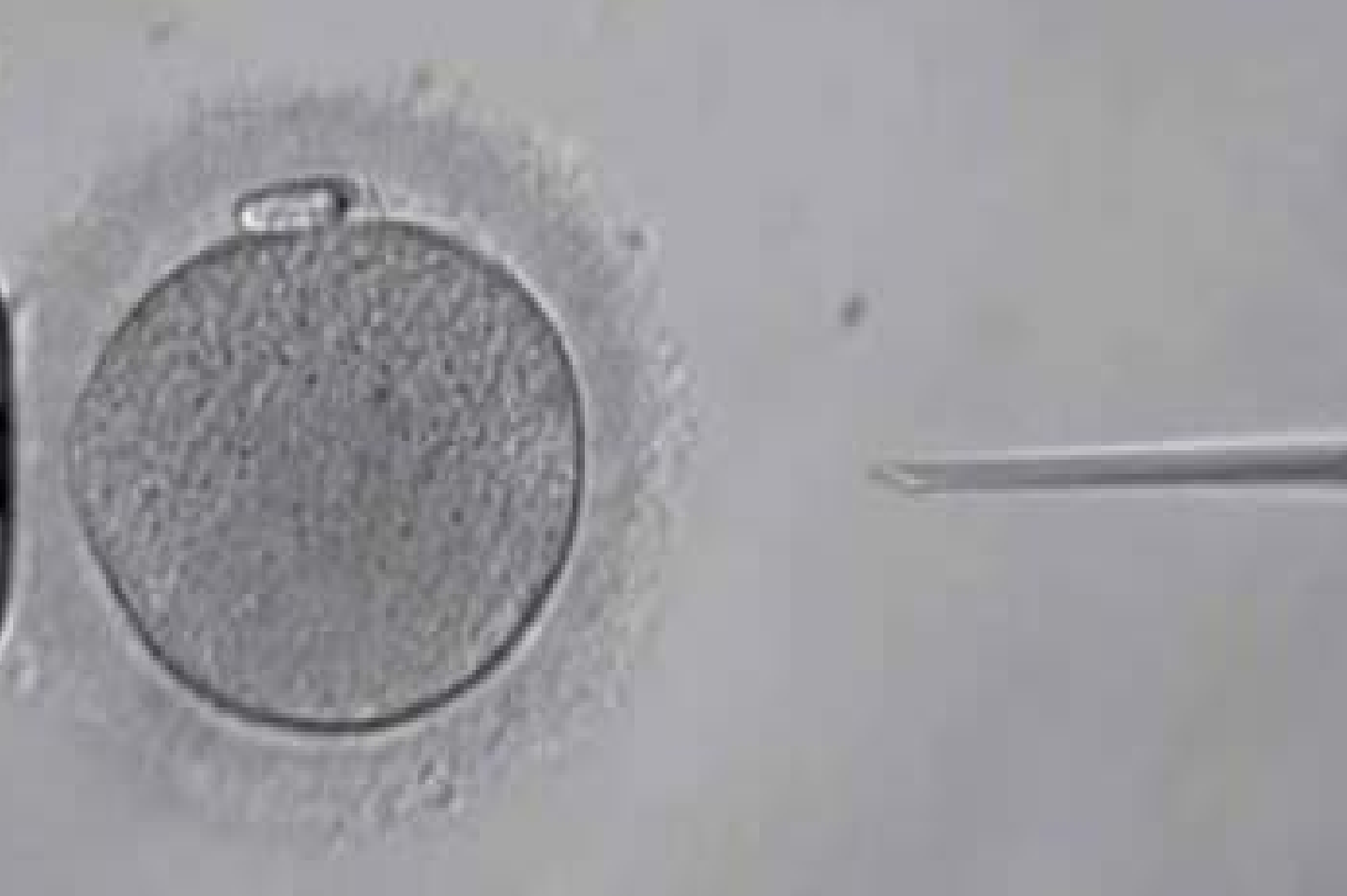
Gonadotropin stimulation

0 **7** **12**

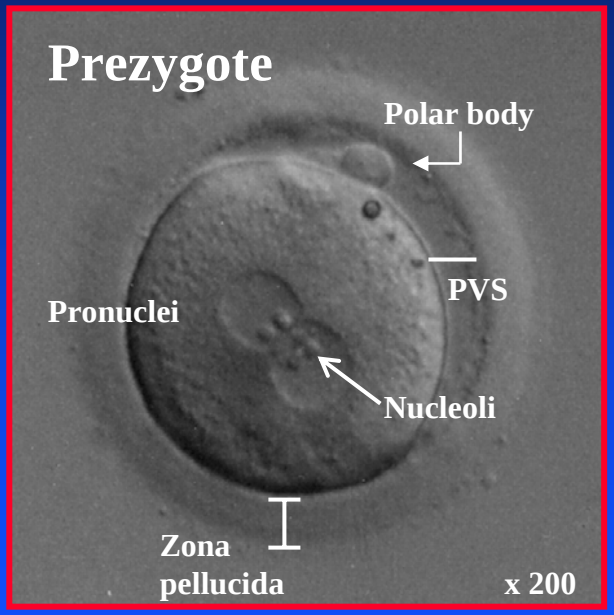
HCG induced follicular maturation

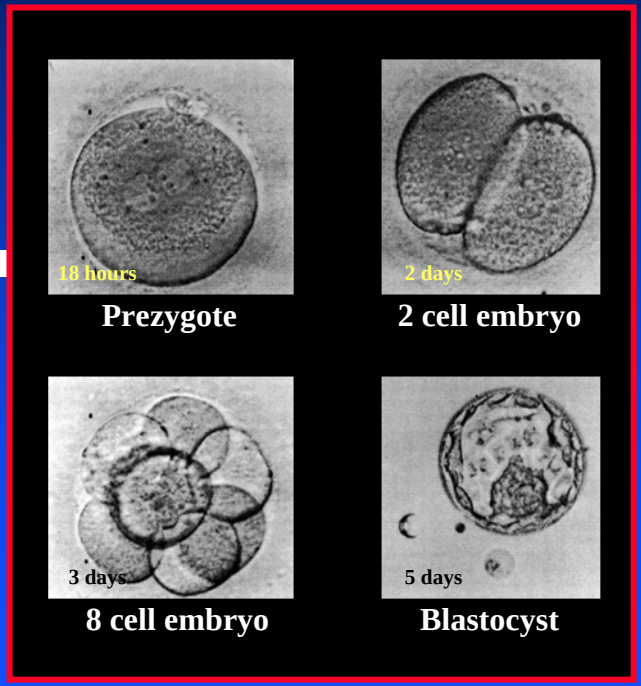


Oocyte retrieval occurs when follicular size is 18-22 mm; estradiol levels are >3000 pg/dL



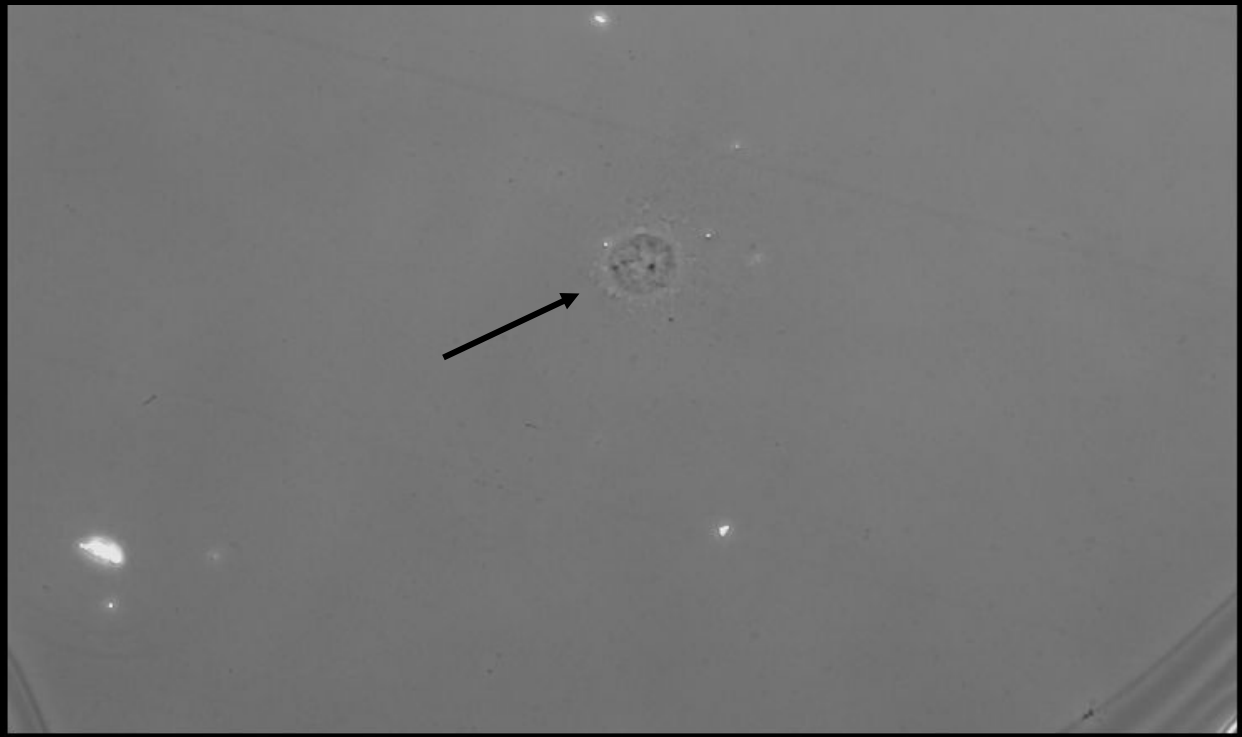
Embryonic Development



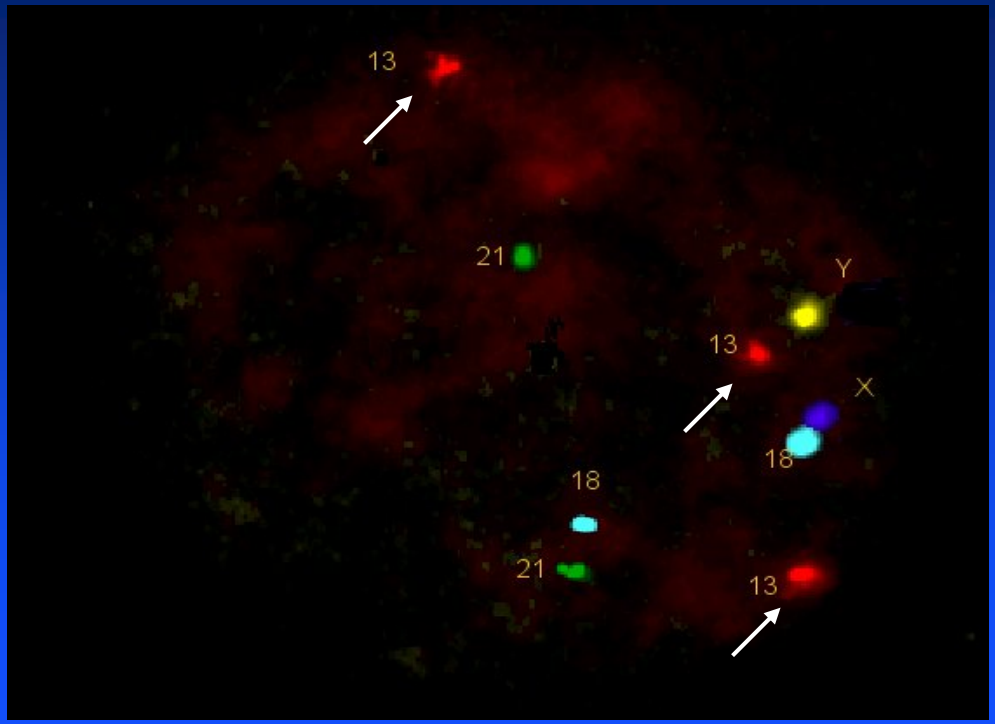



Embryo Biopsy
Reproductive Biology Associates, Atlanta, Georgia

FIXED BLASTOMERES



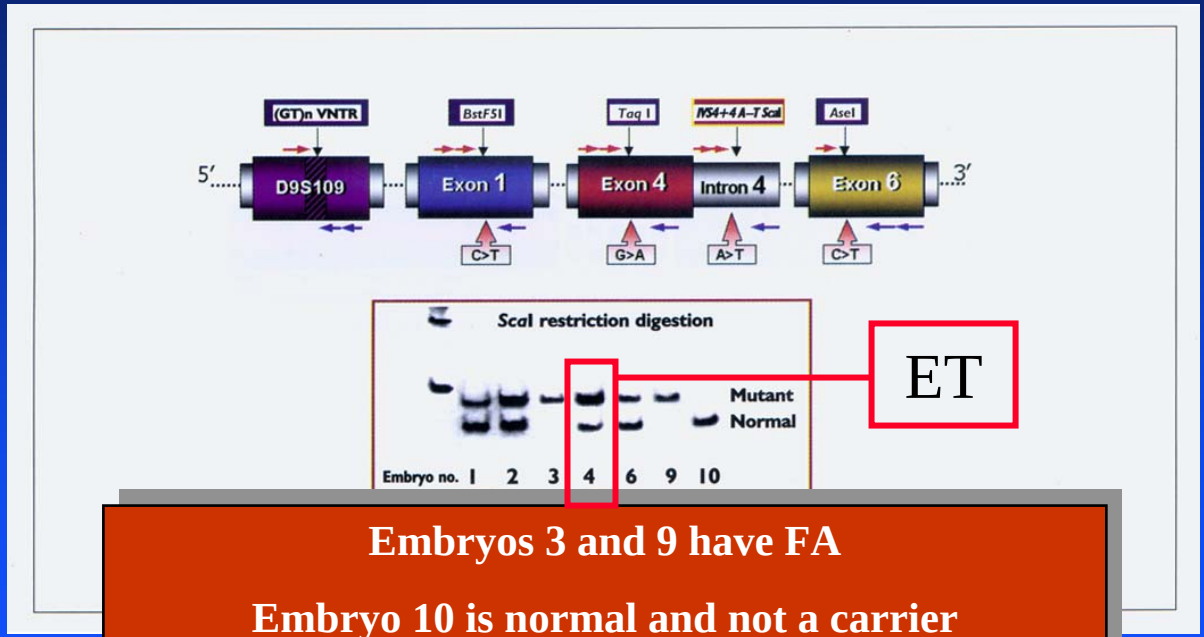
Trisomy 13



Identification of HLA Matched Embryo Using Allele Specific Amplification of HLA-DQβ and HLA-A

Embryos 2 and 4 are HLA-A and DQ matched with patient

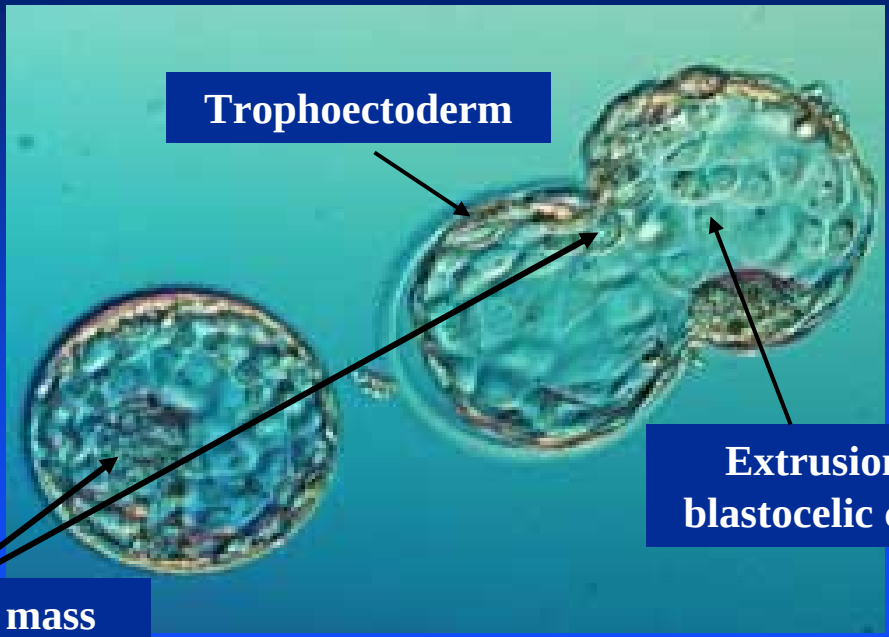
Identification of IVS4+4A→T mutation



Embryos 3 and 9 have FA

Embryo 10 is normal and not a carrier
Embryos 1, 2, 4 and 6 are normal but are carriers

Hatched Blastocyst



U/S Guided Embryo Transfer

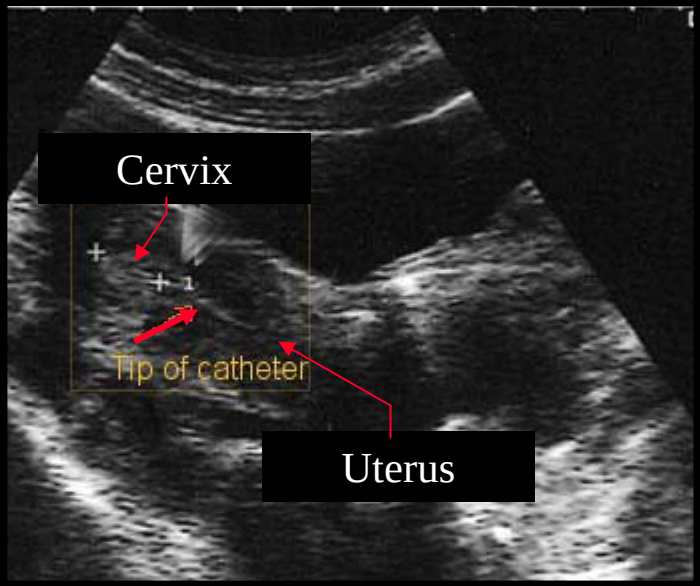
PGD Center

- Diagnosis
- Identification of embryos to tranfer

IVF Center

- Embryo transfer
- Verification of pregnancy thru day 35
- Transfer of care

Limited survival ex vivo



Logistics

PGD Center

Referring Physician

Transplant Center

IVF Center

Shipment of UCB unit

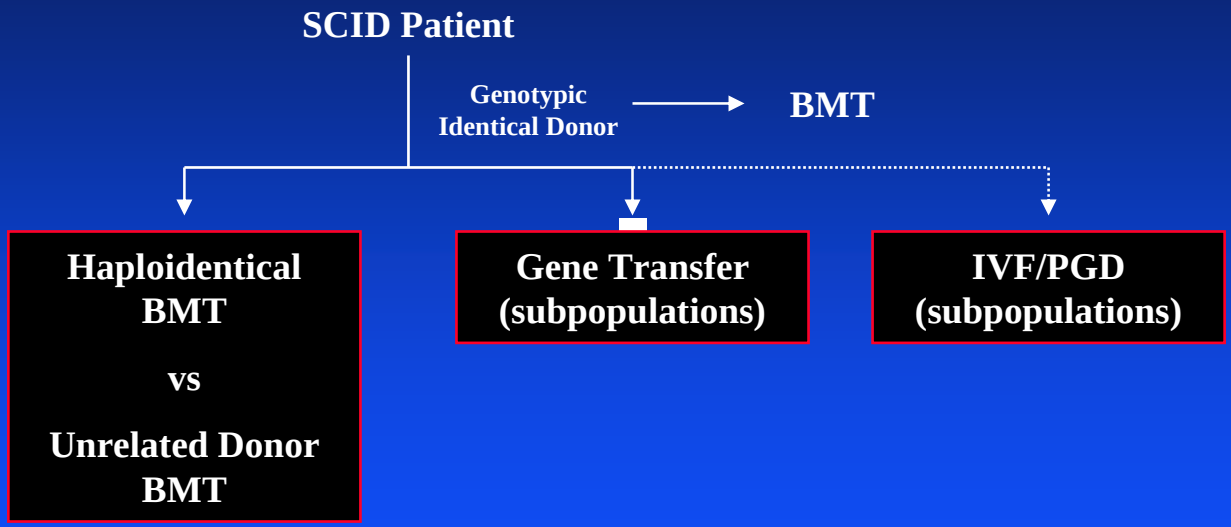
Obstetrical Unit

HLA matched UCB

Assisted Reproduction for Patients with Immunodeficiency Disorders

- High risk couples need to be informed of the technology ■
- May be an option for patients with WAS and some with SCID

Decision Algorithm



The Second Generation

The first generation demonstrated the 'proof of principal' that UCB is an acceptable alternative source of HSC.

The second generation will define the full potential of UCB in the treatment of children and adults with malignant and non malignant disorders

Stem Cells

Effector Cells