2024 Master Pediatrician

Lolie C. Yu, MD

Eugenie and Joseph Professor of Pediatric Oncology

Vice-Chair, Clinical Research

LSUHSC, New Orleans. LA

August 16-18, 2024

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Speaker Disclosure

I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this CME activity.

Educational Background

- Medical School: University of Santo Tomas
  School of Medicine and Surgery
  Manila, Philippines

- Post- Graduate: Master in Public Health
  University of Texas
  Houston, TX

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Medical Training

- Pediatric Residency: UMC (LSU Affiliate)
  Lafayette, LA
  1982-85
- Pediatric Hematology-Oncology Fellowship
  LSUHSC, New Orleans, LA
  1985-87
- BMT fellowship: Fred Hutchinson Cancer Research Center
  Seattle. WA
  1988

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Dr. Donall Thomas visited LSU, New Orleans

BMT---Blood & Cellular Therapy Program

- BMT program at CHNOLA/LSUHSC was established & developed in 1989
  - 1 Bed unit (HEPA-Filtered room)
  - 3 Bed unit in 1992
  - 18-Bed HEPA-Filtered unit in 2003
- Types of Stem Cells:
  - BM
  - Cord blood
  - Mobilized Peripheral blood SC
  - CAR T-cells

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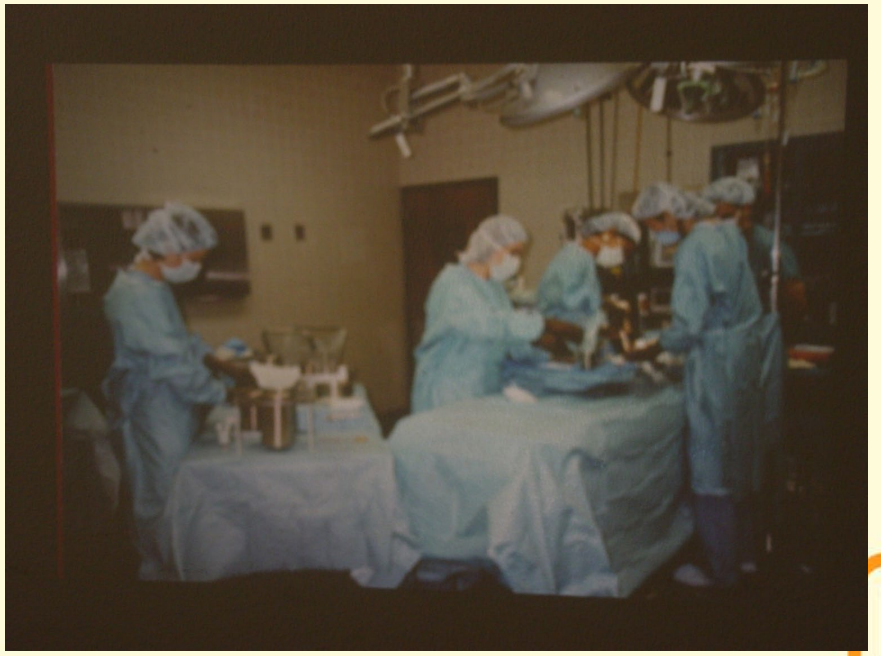
Bone Marrow Transplantation

- Goals:
  - Reconstitution of Hematopoietic system
  - Reconstitution of Immune system
  - “Beneficial” Antitumor Effect



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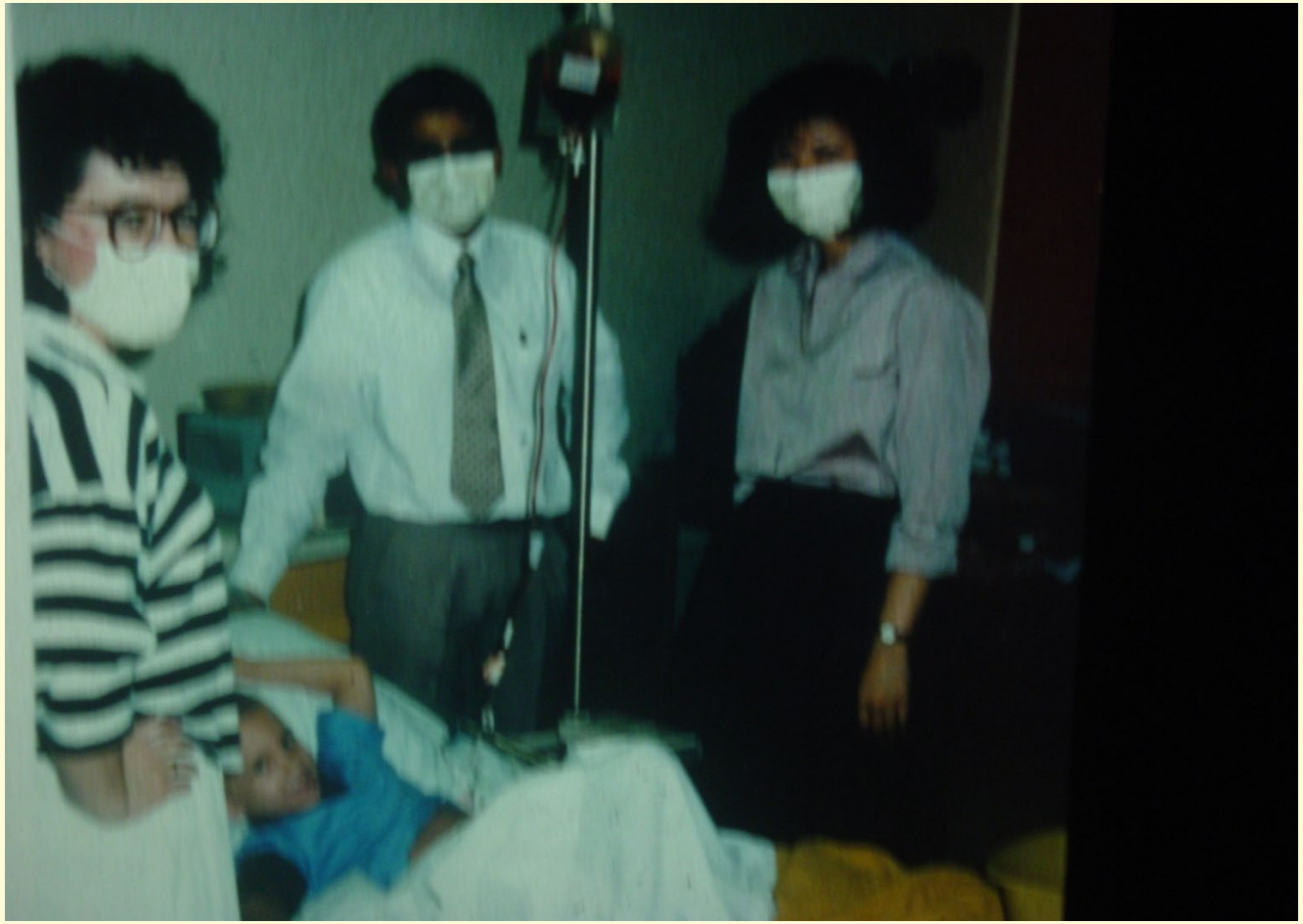
BM Infusion



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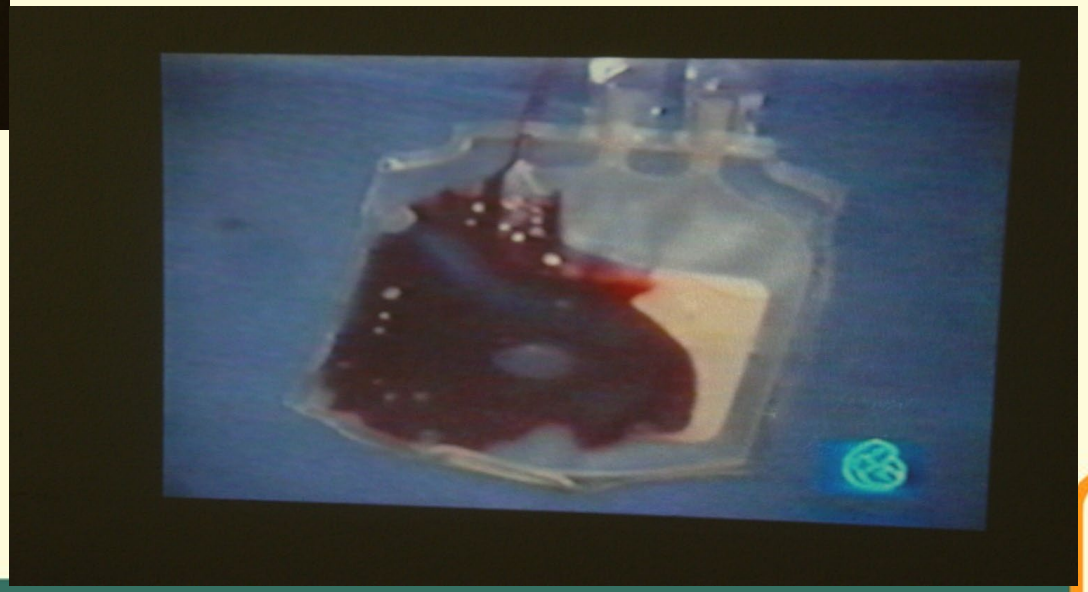
Cord Blood Stem Cells



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Cord Blood Stem cells

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Cord Blood Transplantation

- ANOTHER SOURCE OF STEM CELLS
- DURABLE BUT SLOWER RATE OF ENGRAFTMENT
- LOW INCIDENCE OF SEVERE GVHD DESPITE HLA DISPARITY
- BENEFICIAL EFFECT OF GVL IS MAINTAINED

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Cord Blood Transplantation

- UNLIMITED SOURCE OF STEM CELLS
- ETHNIC BALANCE CAN BE MAINTAINED
- LOW VIRAL CONTAMINATION
- IMMEDIATELY AVAILABLE
- LESS GVHD BUT WITH GRAFT VS LEUKEMIA EFFECT

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Cord Blood Transplantation

- MINIMUM CELL DOSE: 2.5 X 10^7 CELLS/ KG
- NO EVIDENCE OF HEMOGLOBINOPATHY
- NEGATIVE INFECTIOUS MARKERS:
  - HIV 1/2, HTLV 1/2, HEP C, HB surf Ag, STS, ETC
  - BACTERIAL AND FUNGAL CULTURES
- RED CELL DEPLETION
- MINIMUM VOL 60 ML

Mobilized PBSC

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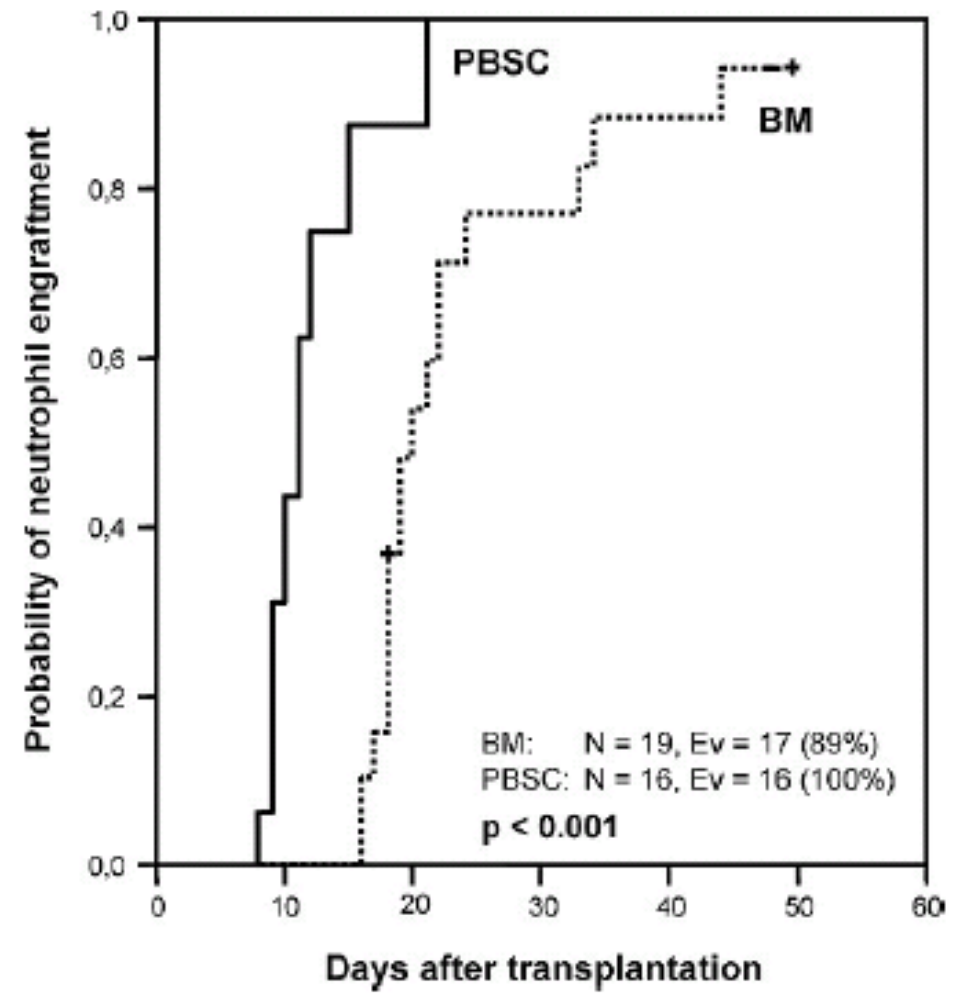
Mobilized PBSC

- Alternative source of Stem cells
- Myeloid Growth Factor SQ injections x 5 days
- Faster recovery of Hematopoiesis
- Avoids Gen Anesthesia
- Less Painful
- Less tumor contamination

PBSCT



HLA-sibling Transplants In Children

Meisel R et al; Klin Pediatr 2005; 217

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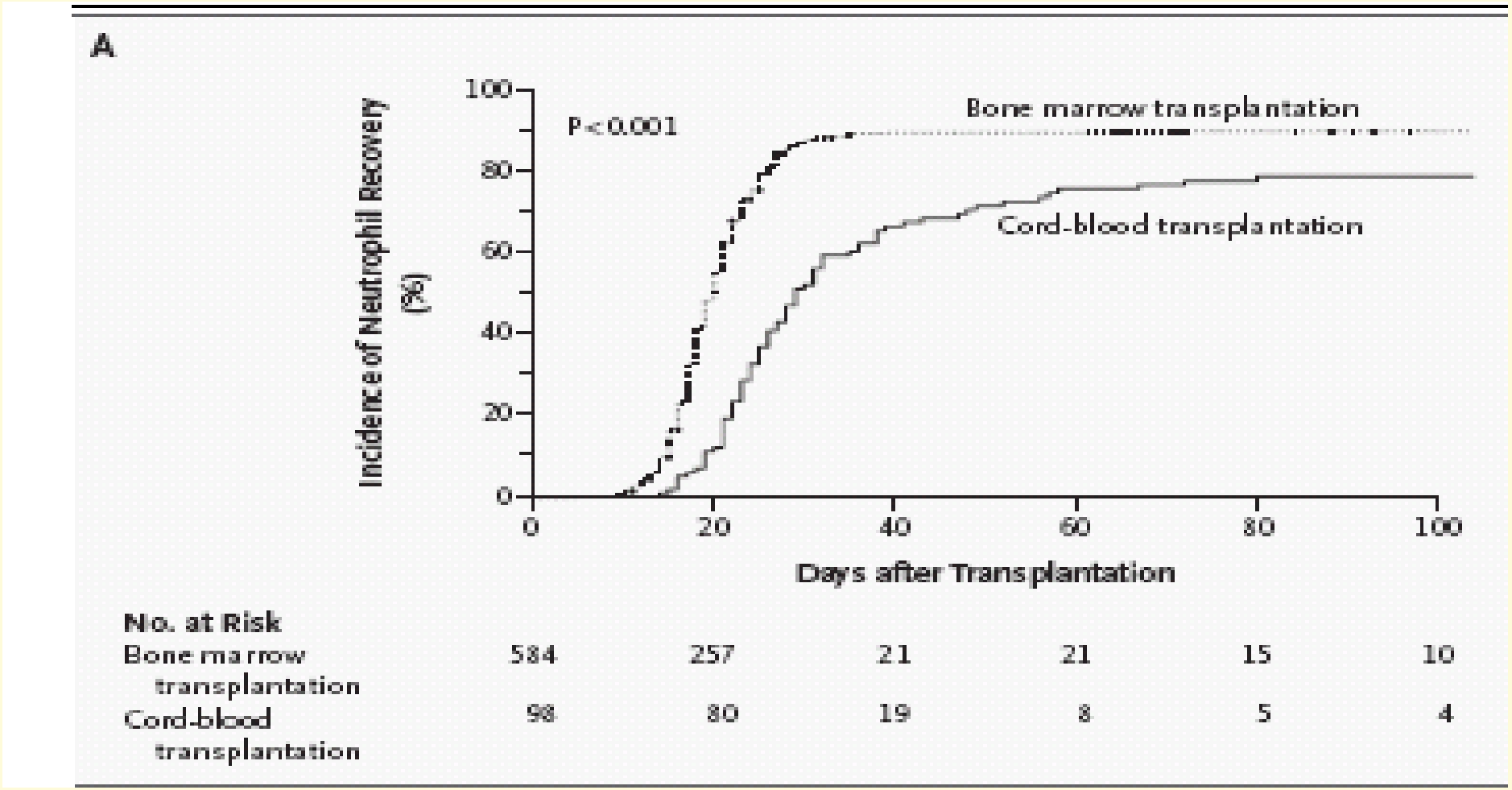
CBT vs BMT



Rocha V et al; NEJM 2004; 351 (22)

COMPARISON OF RATE OF MYELOID ENGRAFTMENT

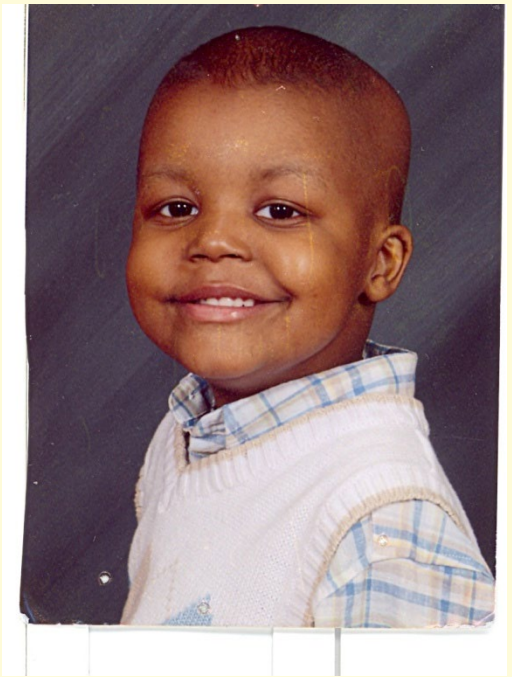
- BM
  - 14-21 DAYS
- PBSC
  - 7-10 DAYS
- CB
  - 21-36 DAYS

Human Placenta derived Stem cells (HPDSC)

- Celgene proprietary process
- Perfusion of full term human placenta
- HPDSC is harvested & processed to remove RBC, non viable cells, and tissue debris
- TNCC ≥ 50 x 10^6
- CD 34+ ~ 4%

Study Subject #001

- 5 year old Boy who presented with low blood counts
  WBC = 4K; ANC = 120
  Hgb = 6gm
  Pl ct = 10K
- Disease History
  Dx with ALL precursor B-cell
  07/13/07
  Cytogenetics revealed
  marked hypodiploid marrow 08/16/07
- DNA index was 0.584=VVHR ALL



Treatment

- Induction chemo 7/16/07
  3 drug regimen x 4 weeks
- Patient achieved remission but due to VVHR features, pt was considered for transplant in the presence of HLA-ID sibling.
- Overall DFS for VVHR pts ~ 3o%

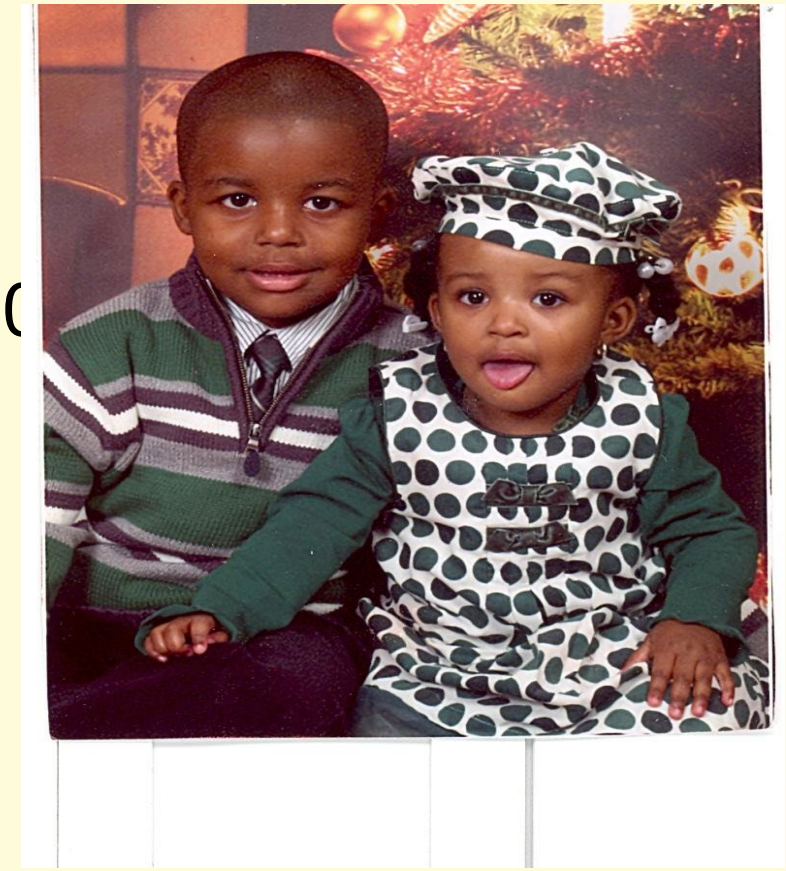
- Mother was pregnant when pt was diagnosed with leukemia.

Transplant of HUCB plus HPDSC on 3/28/08

- HUCB and HPDSC collected from sibling born 12/22/07
- 6/6 HLA match
- HUCB unit: (596.20 x 10^6 TNC, 73% post-thaw viability, 0.26% CD34+)
- HPDSC unit (294 x 10^6 TNC, 63% post thaw viability, 0.85% CD34+)
- Standard full ablative conditioning and TBI
- GVHD prophylaxis (steroids and cyclosporine)

Results

- No clinically significant infusion reactions
- No HPDSC-related serious adverse events to date
- Myeloid engraftment by Day +17
- Platelet engraftment- pl ct >20 by Day +40 pl ct >50 Day+70
- No serious infection or acute GVHD
- Complete donor chimerism by Day +30 and continued to be 100% donor
- Discharged from the hospital on Day +17
- PT is CR post 16 years transplant

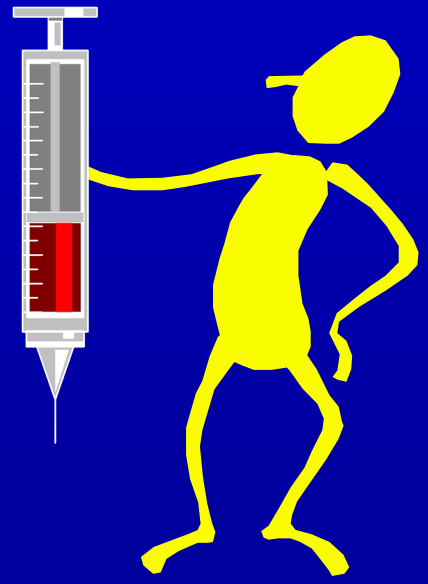


First CBT at CHNOLA/LSUHSC

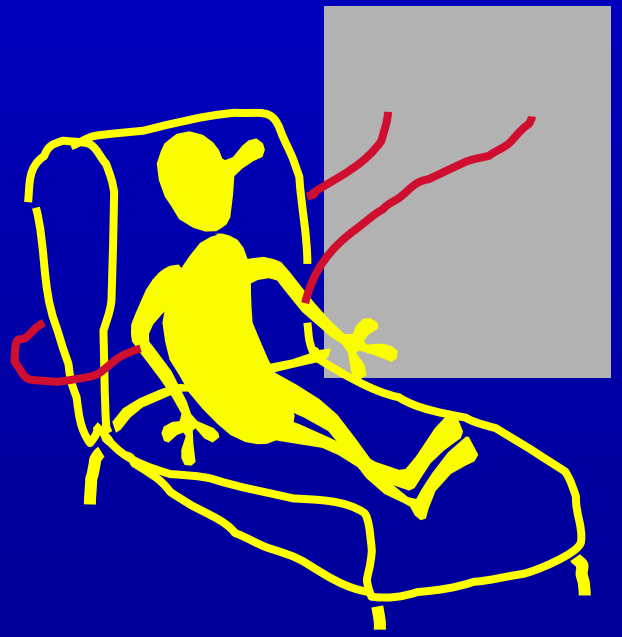
Stem Cells Sources

Sources of Stem Cells

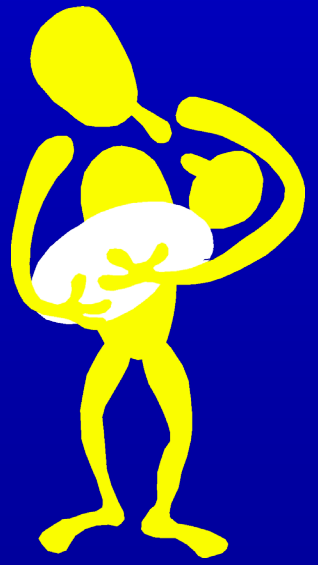
Bone Marrow



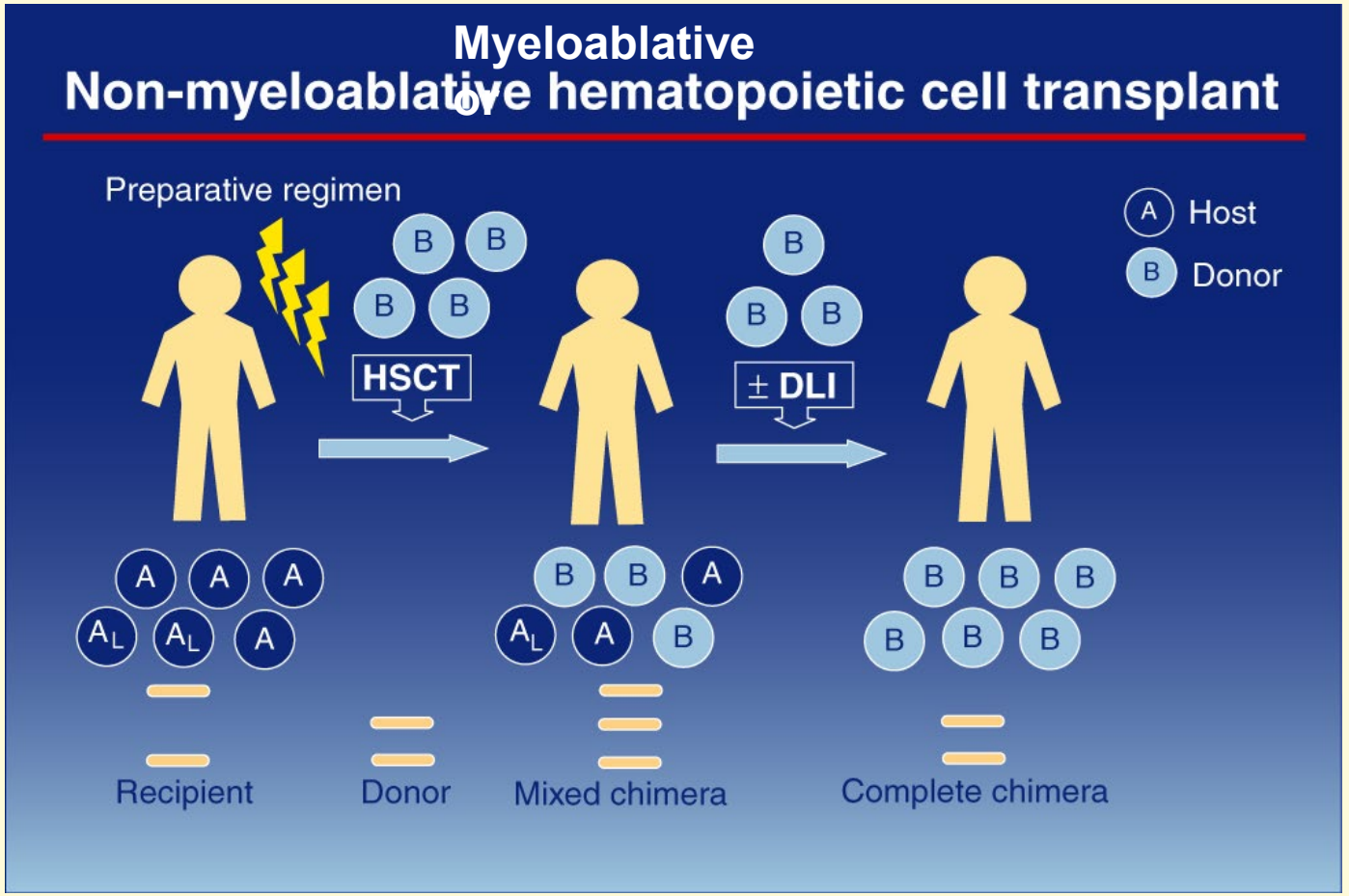
Peripheral Blood Stem Cells (PBSC)



Cord Blood



Types of Prep Regimens



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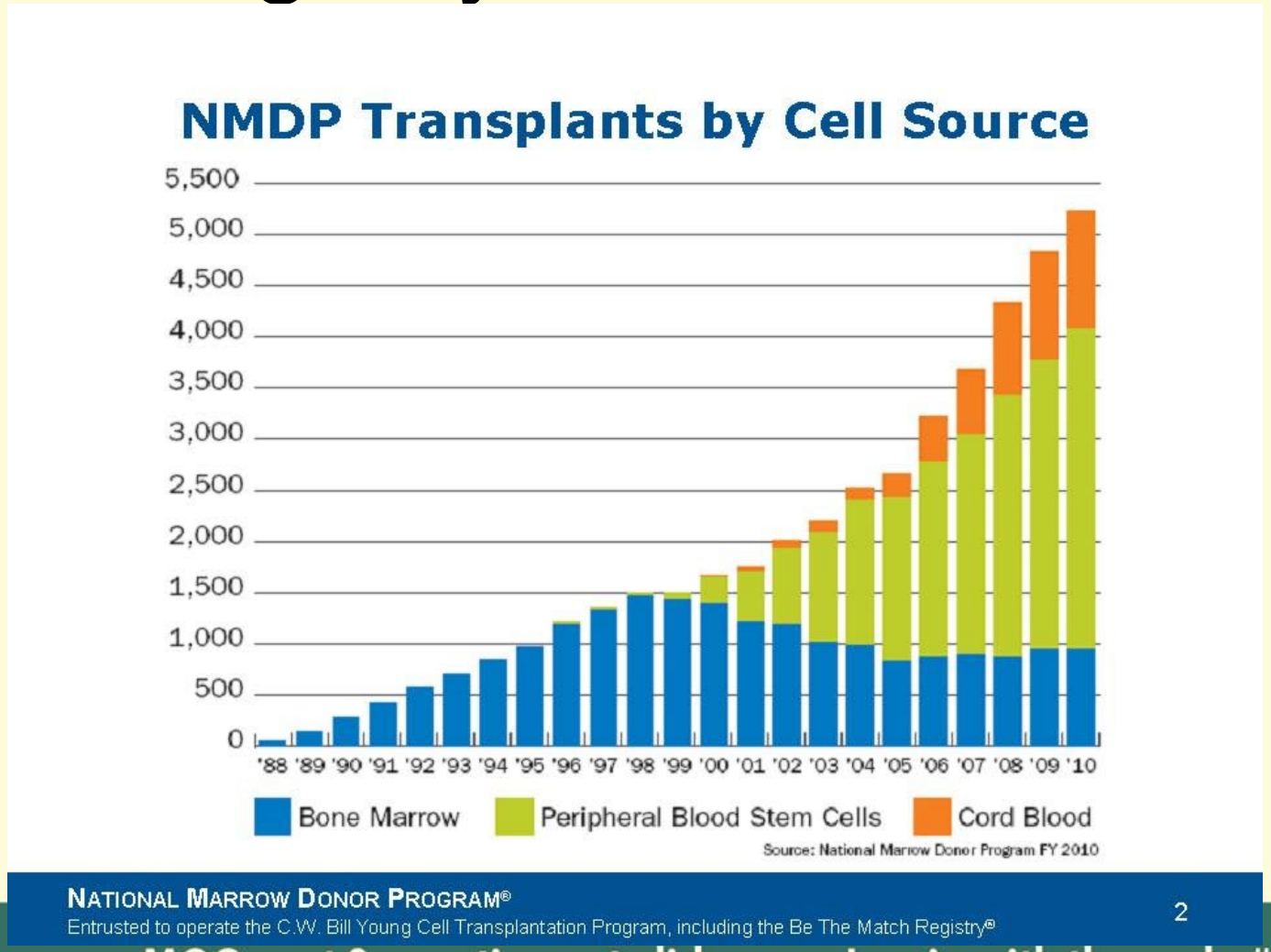
NMDP Registry



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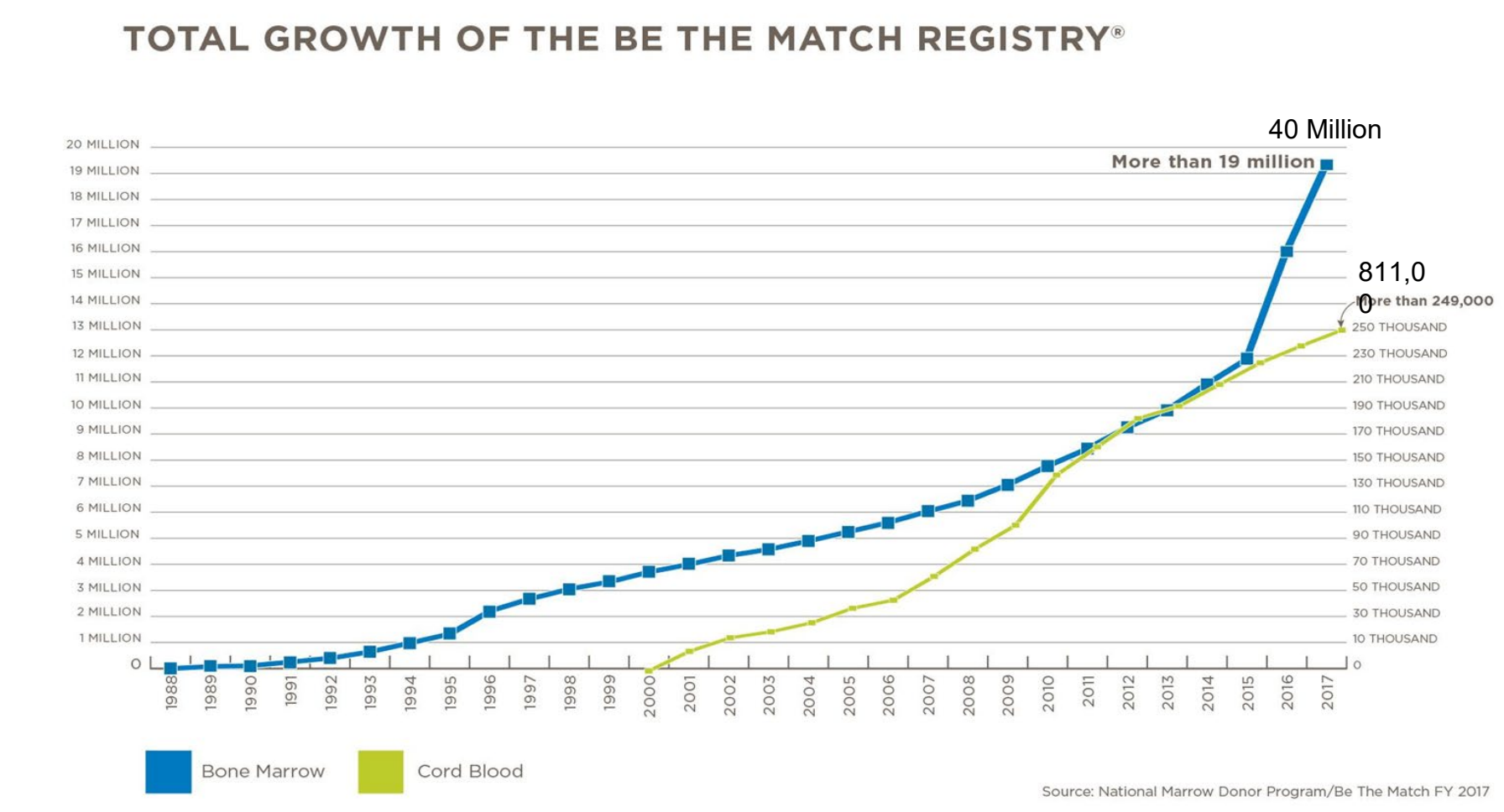
Be the Match Registry

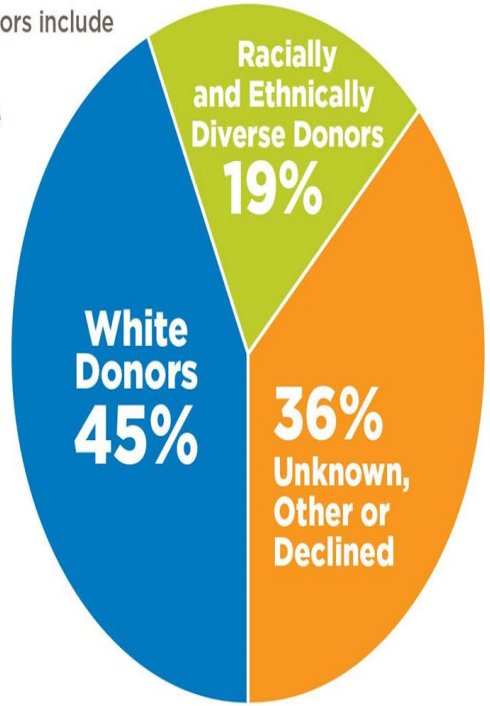


Diversity of Adult & Cord Blood Donors on the Be The Match Registry ® 2017

DIVERSITY OF ADULT DONORS ON THE BE THE MATCH REGISTRY® 2017

Racially and ethnically diverse donors include those who identify as:

- American Indian or Alaska Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander

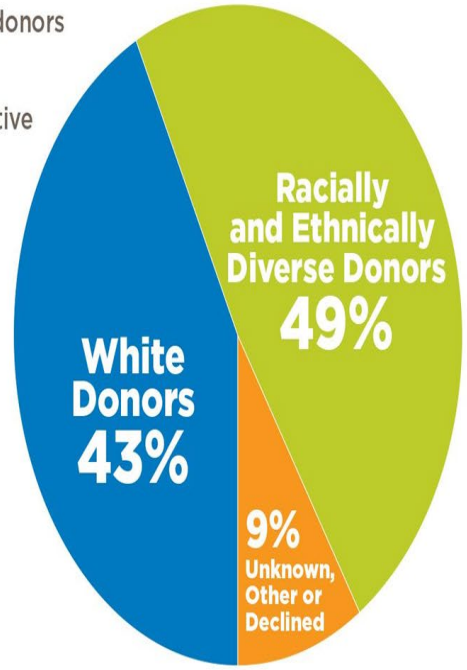


Source: National Marrow Donor Program/Be The Match FY 2017

DIVERSITY OF CORD BLOOD UNITS ON THE BE THE MATCH REGISTRY® 2017

Racially and ethnically diverse donors include those who identify as:

- American Indian or Alaska Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander



Source: National Marrow Donor Program/Be The Match FY 2017

Indications for HSCT

- MALIGNANT CONDITIONS
  - LEUKEMIAS AND LYMPHOMAS
  - SOLID TUMORS
    - NEUROBLASTOMA
    - BRAIN TUMORS
    - HIGH RISK SARCOMAS

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Indications of HSCT

- INHERITED DISEASES
  - IMMUNODECIFICIENCIES
  - HEMOGLOBINOPATHIES
    - SICKLE CELL*****
    - *THALASSEMIA*
- STORAGE DISEASES
  - HURLERS
- ADRENOLEUKODYSTROPHY
- OSTEOPETROSIS

- BONE MARROW FAILURE
  - SAA
  - FANCONI'S ANEMIA
  - KOSTMAN SYNDROME
  - DBA
  - GRANULOCYTE AND MACROPHAGE DISORDER
  - CGD
  - CHEDIAK HIGASHI
  - HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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MAJOR COMPLICATIONS

- INFECTIONS
  - CMV
  - Fungal
  - ADV
- ORGAN DAMAGE
  - RIC
- GVHD
  - New Agents – Jakafi (Ruxolitinib); Abatacept
  - Post Cytoxan Regimen
- RELAPSE
  - CAR T-Cell Therapy

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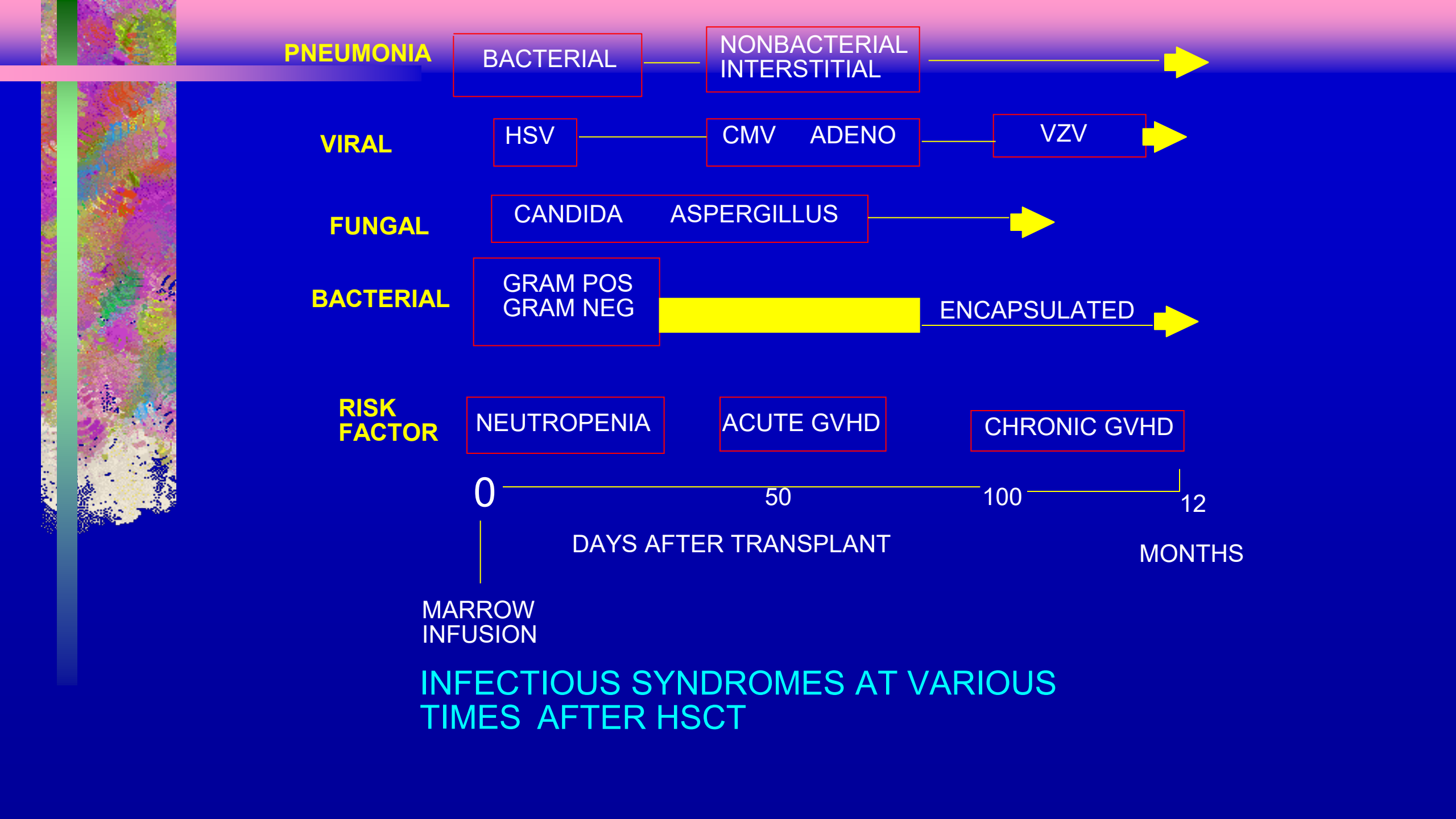
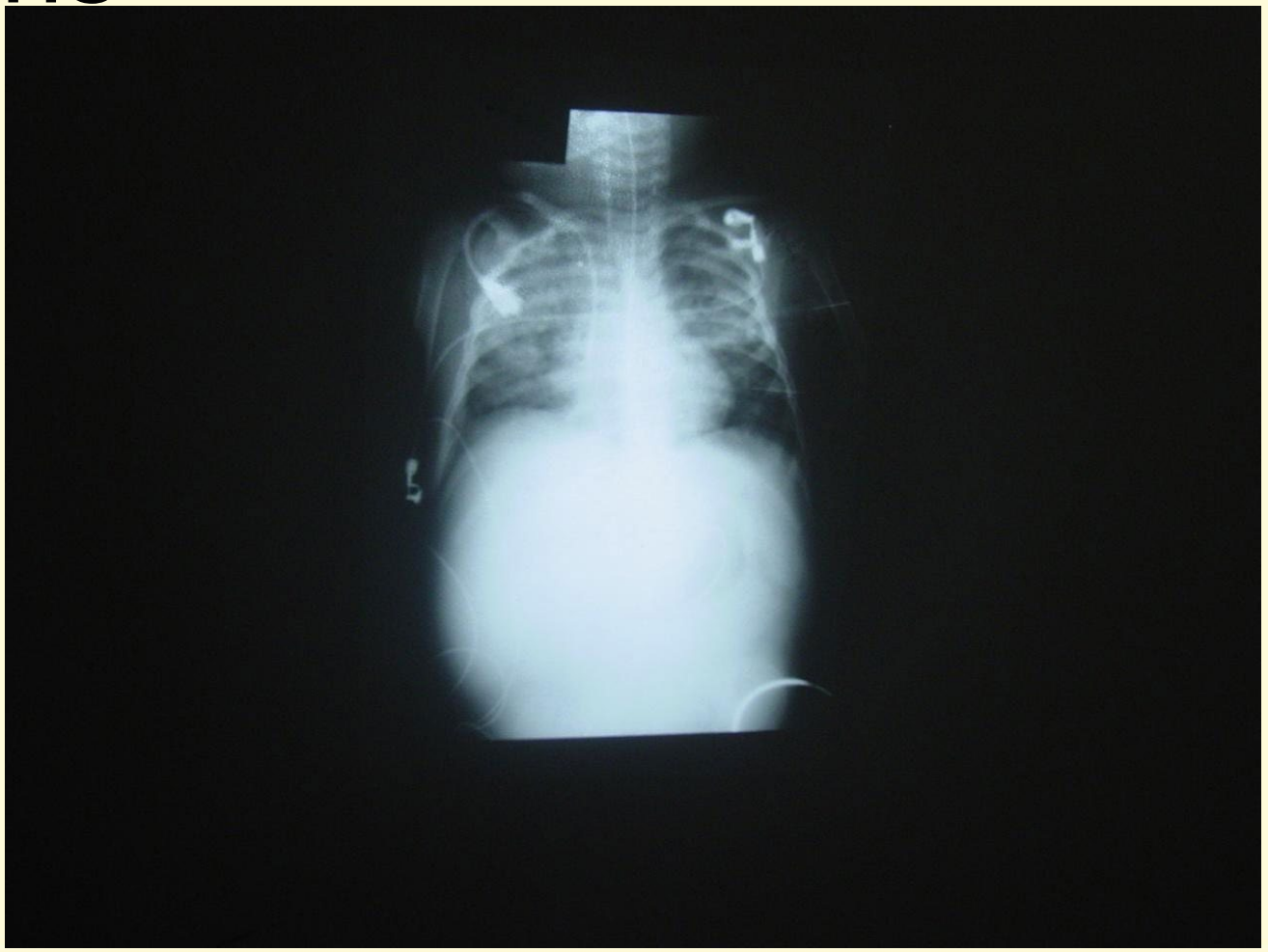


INFECTIOUS SYNDROMES AT VARIOUS TIMES AFTER HSCT

Infections



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MAJOR INFECTIONS AFTER HSCT

	CMV	FUNGAL
INCIDENCE	20-40%	15-30%
MORTALITY	50-70%	75-100%

CMV Infections—Pre-Emptive TX

- PCR for CMV weekly
- INDUCTION TX

  GCV 5 MG/KG X2 DAILY FOR 2-3 WEEK

  FORSCARNET 60-90 MG/KG/DAY
- MAINTENANCE TX

  5 MG/KG DAILY X 2-3 WKS
- Weekly IVIgG
- Antiviral resistance test (AVR) to CMV
- CMV disease 43% to 3% ($p<0.00001$)

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MAJOR INFECTIONS AFTER HSCT
LATE 90'S TO PRES

	CMV	ADV	FUNGAL
INCIDENCE	3.3%-10.5%	5-21%	15-20%
MORTALITY	<25%	>50%	50-90% (IA)

ADV Infections

- METHODS
  - CULTURE
  - SEROLOGY
  - FA OR EIA
  - PCR*****
- FREQUENCY
  - WEEKLY UNTIL DAY +100 OR LONGER IF ALC< 400

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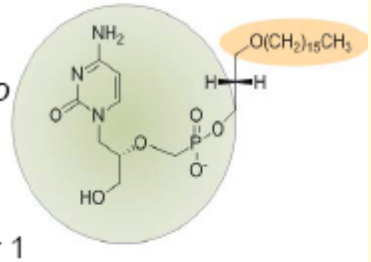
Treatment for ADV Infections

- CIDOFOVIR AT 2.5-5 MG/KG WEEKLY
- IV IgG ONCE WEEKLY
- DECREASE IMMUNOSUPPRESSANTS IF POSSIBLE
- CONTINUE TREATMENT UNTIL PCR NEGATIVE
- SUCCESS RATE 25-60%

ADV Infections

CMX001 (Brincidofovir)

- Orally bioavailable lipid-conjugate of the nucleotide analog cidofovir (CDV)
- High intracellular antiviral concentration of the active antiviral cidofovir-diphosphate (CDV-PP) with a long $t_{1/2}$ up to 6.5 days
- Broad spectrum activity against dsDNA viruses
- 65-fold more potent against AdV than CDV *in vitro*
  - EC_{50} < 0.02 uM against AdV
- No evidence of nephrotoxicity
  - Not a substrate of human organic anion transporter 1
  - No renal dysfunction in > 800 patients who have received CMX001 to date
- Announced dosing in the Phase 3 SUPPRESS trial for the prevention of CMV in HCT recipients in September 2013 (ClinicalTrials.gov: NCT01769170)



Cincinnati Children's

Source: Beadle et al. AAC 2002; 46:2381-6.

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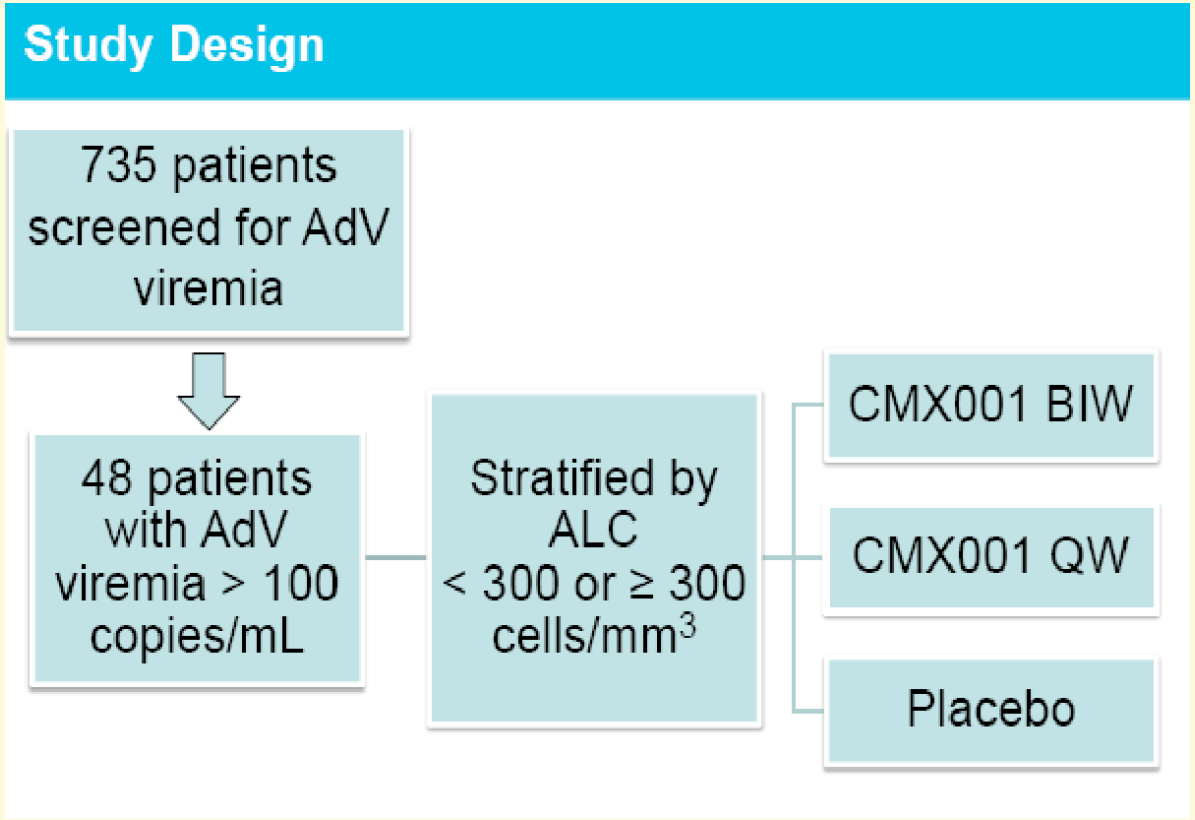
CMX001 Study



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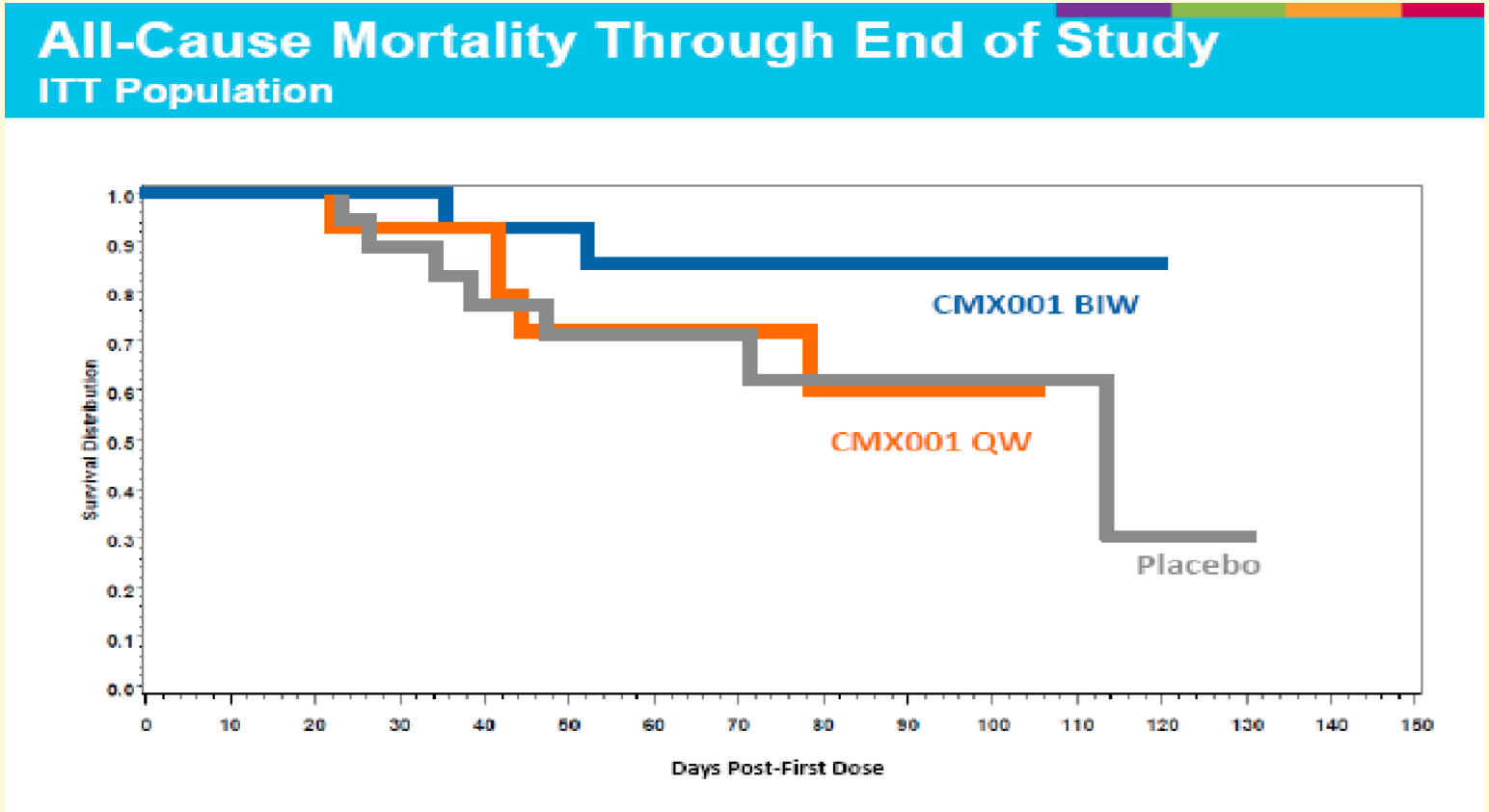
CMX001 study



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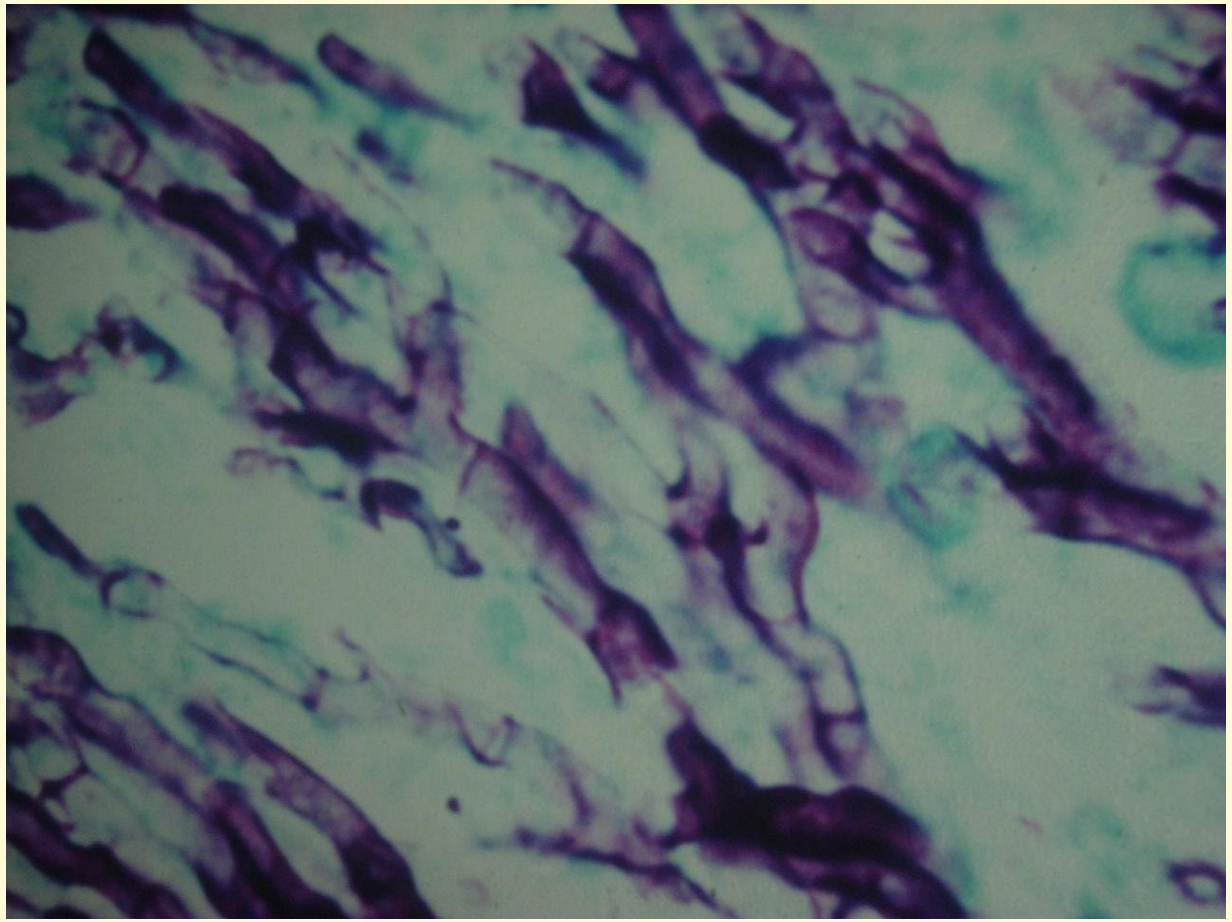
Fungal Infections



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Fungal Infections for HSCT Pts

- PERSISTENT FEVER
- CL INFECTION
- PNEUMONIA
- DISSEMINATED- VISCERAL ORGANS

“EMPIRIC TX WITH HD ANTIFUNGALS

REMOVAL OF CL IMMEDIATELY

INVESTIGATE HOW EXTENSIVE THE INVOLVEMENT

Fungal Infections

- AMPHOTERICIN B
- LIPOSOMAL AMPHOTERICIN
- AMPHOTERICIN B LIPID COMPLEX
- FLUCONAZOLE
- MICAFUNGIN; CASPOFUNGIN
- VORICONAZOLE/POSACONAZOLE
- CRESEMBA

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Prophylaxis for HSCT Pts

- ORAL CANDIDA - FLUCONAZOLE/VORI
- ASPERGILLUS/ FUNGAL - HEPA FILTER/ CASPOFUNGIN***
- BACTERIAL – CEFTA/ZOSYN/LEVO***
- HSV I/II - ACYCLOVIR
- CMV - ACYCLOVIR + HD IV IGG
  - Letermovir **** (480 mg or 240 mg)
- PCP - BACTRIM/SEPTRA DAPSONE/PENTAMIDINE

Advances in Supportice care for HSCT Pts

- ANTIBACTERIALS
  CARBAPENAMS
  FLUOROQUINOLONES
  3RD GEN CEPHALSPORIN
  CEFTAZIDIME/ETC
- ANTIVIRALS
  GANCICLOVIR
  FOSCARNET
  Brincidofovir-?
- ANTIFUNGALS
  AZOLES- FLUCONAZOLE, ETC
  LIPOSOMAL AMPHO; ECHINOCANDINS; Cresemba

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Advances in HSCT

- Supportive Care
  - Infection
  - GI microbione
- GVHD
  - Prophylaxis
    - In vivo or Ex vivo
    - Pharmaceutical agents
    - Post transplant Cytoxan
    - Haplo-ID donors
- Timing of SCT

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Multidiciplinary team

TRANSPLANT MDs • 2 FTE BMT MDs • Other H-O MDs & fellows	**NURSES & Nurse Navigator**	**BMT NP & other APPs**	**CHILD PSYCHOLOGIST**	**SOCIAL WORKERS**
CRA- 1 dedicated BMT	**Pharm D**	**HPC LAB**	**Apheresis Program**	**OT**
PT	**DIETICIAN**	**BLOOD BANK**	**RADIATION TX**	**QA COMMITTEE**
		HLA Lab		

Translational/clinical Research

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Hematology-Oncology Division
Receives

Clinical Research

- Children's Oncology Group (COG)
  - 1990 as a POG member
  - 2000 merged into COG
  - NCI supported group to conduct clinical oncology trials devoted to children and adolescent cancer research
  - >200 member institutions in US (incl Australia & New Zealand)
  - >90% of children with cancer are treated in one of these institutions
  - 5 year survival rate > 80%


HOGWARTS EXPRESS


These Are
The Reasons We Walk
The CureSearch Walk
Jennifer Zdon, Twirl Photography

CHNOLA

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4 West – Inpatient unit

Clinical Facility

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