

# Curing Sickle Cell Disease

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Jane Sande, MD

Medical Director, Blood and Marrow  
Transplant

Children's National Medical Center

# Sickle Cell Disease

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- ❑ One of the most common genetic diseases worldwide
  - ❑ Up to 500,000 affected infants born per year
  - ❑ High morbidity and mortality
    - Varies with geographic region
  - ❑ Poor access to comprehensive health care
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# Economic Impact

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- U of Miami, Blood, 2000
    - Chronic transfusion, \$400,000 per patient decade (FY 2000 dollars)
  - U of Florida, 2009
    - For 4,294 patients, health care costs rose with age
      - \$892 per patient-month, 0-9 years
      - \$2,562 per patient-month, 50- 64 years
  - Uncomplicated MRD BMT, 2009 estimate
    - \$600,000 lifetime
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# Sickle Cell Disease

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- Variable phenotype
    - 5- 20% have severe manifestations
  - Acute manifestations
    - ACS, CNS stroke, infection
    - Recurrent VOC, aplastic and sequestration crises
  - Chronic manifestations
    - CV, renal, AVN, visual, pulmonary hypertension
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# Sickle Cell Disease

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- Supportive Care
    - Penicillin prophylaxis
    - Aggressive management of fevers, VOC
    - TCD/ MRI/ MRA
  - Hydroxyurea
    - Reduces VOC, ACS
    - No effect on stroke incidence
  - Chronic transfusion
    - Decreases primary and recurrent stroke
    - May reduced risk of renal failure and chronic lung disease
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# Sickle Cell Disease

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- Hydroxyurea
    - Marrow suppression
    - Rash, nausea, vomiting
    - ?Leukemogenic
  - Chronic Transfusion
    - Iron overload
    - Allo-immunization
    - Risk of infection
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# BMT

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- Accepted treatment for PID, SAA, some hematologic malignancies
  - Goal: “ablate” defective marrow and replace it with healthy marrow
    - Immune suppression
    - Chemotherapy +/- Total Body Irradiation
  - Matched related donors preferred
    - “alternative” donors: matched unrelated and umbilical cord blood
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# BMT and Sickle Cell Disease

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- Allows replacement of sickle hemoglobin-making red cell precursors with donor marrow, restoring normal hematopoiesis
  - "Cure"
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# BMT and SCD

## International Collaborative Trial

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- Indications for transplant
    - <16 years
    - HLA-identical related donor
    - Stroke
    - Recurrent ACS
    - Recurrent VOC/priapism
    - Alloimmunization
    - Other end-organ dysfunction
      - Lung, renal, visual, bone
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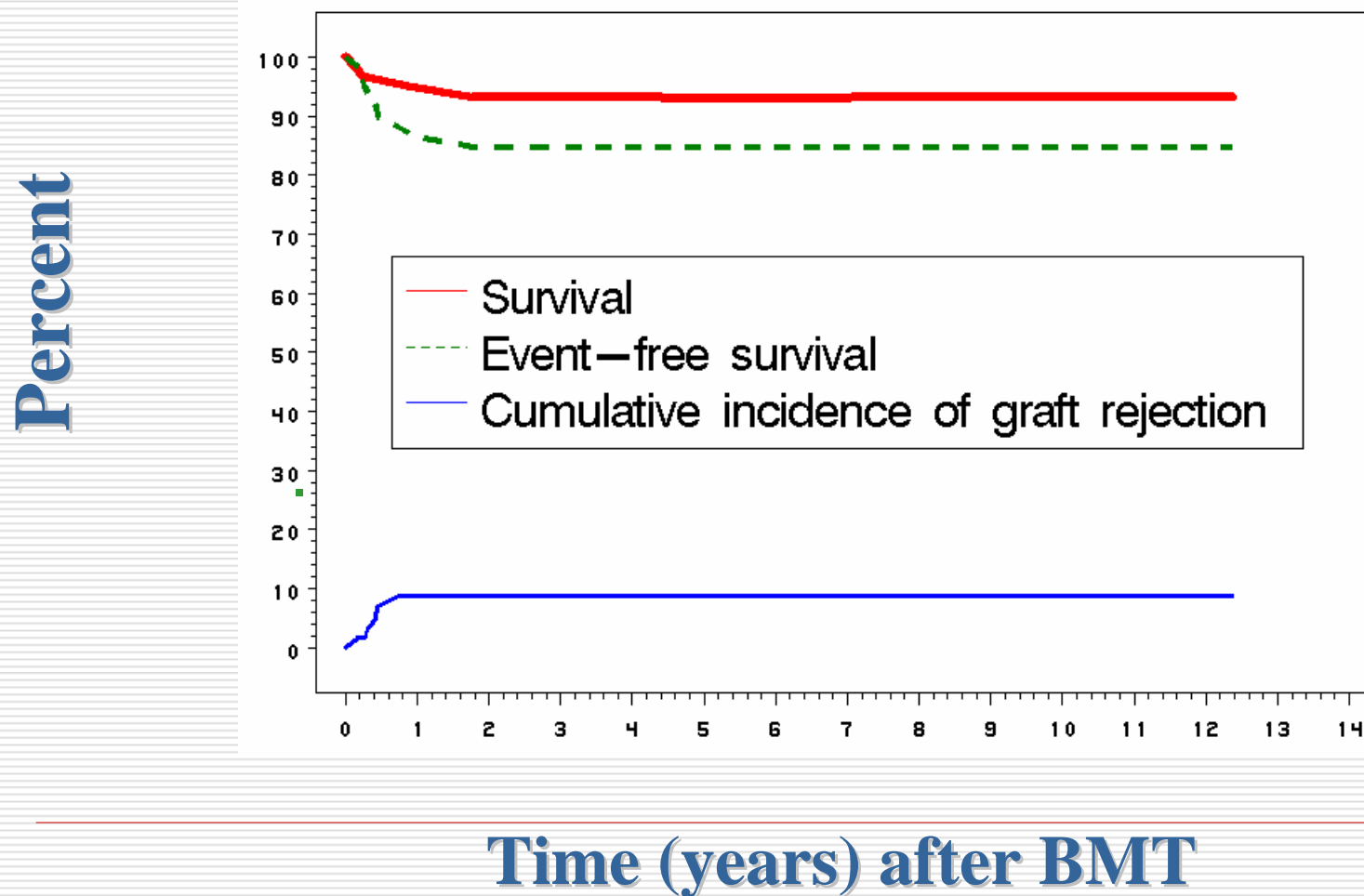
# International Collaborative Trial

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- 59 patients
  - Myeloablative regimen
    - Busulfan 14 mg /kg
    - Cyclophosphamide 200 mg /kg
    - ATG 90 mg /kg
  - GvHD prophylaxis
    - CSA and MTX
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# BMT for SCD (N=59)

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# International Collaborative Trial

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- Mixed chimerism in 13 patients
    - 8/50: 90- 99% donor
    - 5/50: 11- 74% donor
    - HgbAA donors: Highest Hgb S 7%
    - HgbSA donors: 34- 40% hgb S
  
  - Graft versus host disease
    - 11/59
    - COD in 3 patients
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# BMT in SCD – world experience

	USA 1991-1999 Walters et al	Belgium 1986-1997 Vermylen et al	France 1996-2000 Bernaudin et al	France 2001-2004 Bernaudin et al
# Patients	59	50	43	44
Median age	9.4 y(3.3-14)	7.5 y(0.9-23)	8.3 y(3.2-20)	9.3 y(3.2-22)
Graft rejection %	9	10	12	5
Overall survival %	93	93	86	100
Event-free survival %	85	82	75	95

# BMT- Worldwide experience

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- Recovery of splenic function
  - Stabilization of or improvement in cerebrovascular flow
  - Some stabilization of chronic lung disease
  - No further complications of SCD in those who engrafted
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# BMT- Conclusion

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- Results of matched related donor transplant for sickle cell disease using a myeloablative regimen are very good
  - BUT.....
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# BMT- the down side

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## □ Collaborative Trial

- 5 patients rejected
  - 4 patients died (GvHD, ICH)
  - Some had progressive lung disease
  - Many had gonadal toxicity
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# BMT- the down side

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## □ Belgium

- 3 patients rejected
  - 2 died
    - cGvHD + CMV and aspergillus
    - 1 sudden death 6 years post-BMT
  - 18 patients had seizures
  - 20 patients had aGvHD; 10 had cGvHD (2 with chronic lung disease)
  - 1 with cGvHD developed AML
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# BMT- the down side

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- France- 87 patients total
    - 7 rejected (all but 1 initially engrafted)
    - 6 died (sepsis, ICH, GvHD)
    - 17 aGvHD
    - 11 cGvHD
    - 16 patients had seizures
    - Most females had ovarian failure
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# Does myeloablative MRD BMT confer a survival advantage?

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- Quinn, et al
    - SCD population in Dallas
    - Patients received recommended preventive and supportive therapy
    - Cumulative survival 85.6%; SCD related survival 93.6%, stroke-free survival 88.5% (0.59/100 patient years)
  - Survival appears to be equivalent in ablative MRD BMT and modern preventive and supportive therapy
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# Can we make BMT safer in SCD?

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## □ Problems:

- TRM
- Lack of MRD
- Late Effects

## □ Solutions:

- Reduced Intensity Conditioning
  - Use of alternative donors
  - Reduced Intensity Conditioning
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Unrelated Donor Hematopoietic Cell  
Transplantation for children with severe  
SCD using a reduced intensity regimen  
SCURT (BMT-CTN 0601)

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Co-Chairs:           Shalini Shenoy, MD  
                              Naynesh Kamani, MD

# BMT-CTN 0601

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- 45 children with severe SCD (Hgb SS or Hgb S- $\beta^0$  thal) over 4 yrs
  - 1<sup>o</sup> end-points:
    - EFS at 1 yr after URD HCT (death, disease recurrence or graft rejection)
  - 2<sup>o</sup> end-points:
    - Effect on clinical/lab manifestations of SCD
    - Incidence of HCT-related outcomes: OS, count recovery, aGVHD, cGVHD, VOD, IPS, infection, donor chimerism, health related QOL etc
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# Eligibility criteria

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- ❑ 3 – 16 yr old with Hgb SS or S-β<sup>0</sup> thal
  - ❑ ≥ ONE of the following:
    - Stroke or neurologic deficit lasting > 24 hrs + infarct on cerebral MRI
    - ≥ 2 episodes of ACS in past 2 yrs
    - ≥ 3 VOC/yr in past 2 yrs
  - ❑ Lansky score ≥ 40
  - ❑ Absence of matched related donor
  - ❑ Donors: 8/8 allele matched unrelated donor bone marrow OR ≥ 5/6 unrelated cord blood unit
  - ❑ Approval by External Review Panel
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# Preparative regimen

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- Alemtuzumab Days -21 to -19
- Fludarabine 30 mg/m<sup>2</sup> Days -8 to -4
- Melphalan 140 mg/m<sup>2</sup> Day -3
- Stem cell infusion Day 0
- G-CSF 5 ug/kg/day Day +7 until ANC > 500

\* Hbs S < 45% within 7 days prior to Alemtuzumab

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# Additional study measures

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- Health related QOL assessment at pre-BMT, days 100, +6, +12, +24 mos
  - Cerebral MRI/MRA, Neurocognitive assessment and pitted red blood cell count pre-BMT and +2 yrs
  - Hgb electrophoresis at pre-BMT, days 100, +6, +12, +24 mos
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# SCURT Trial

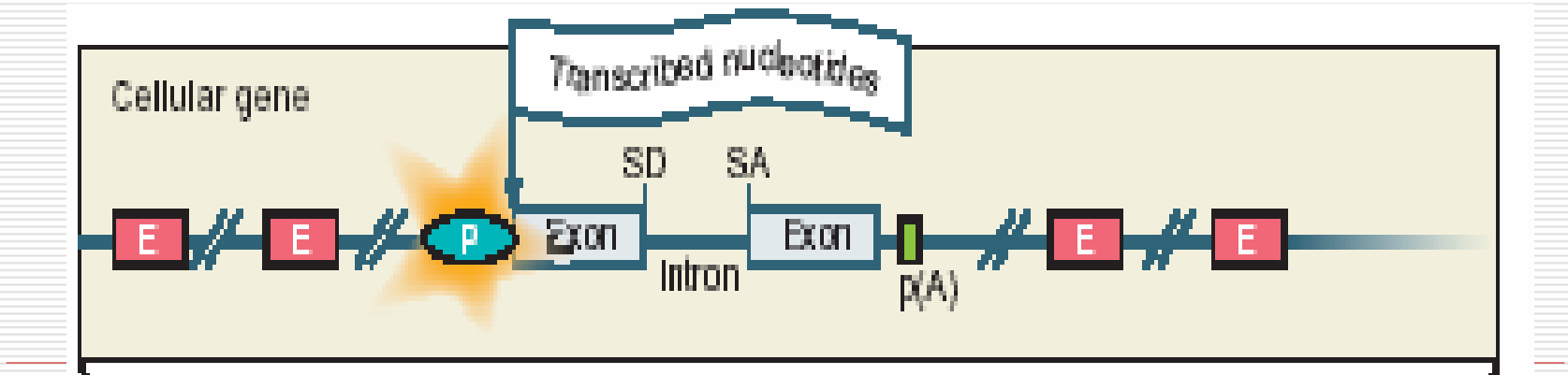
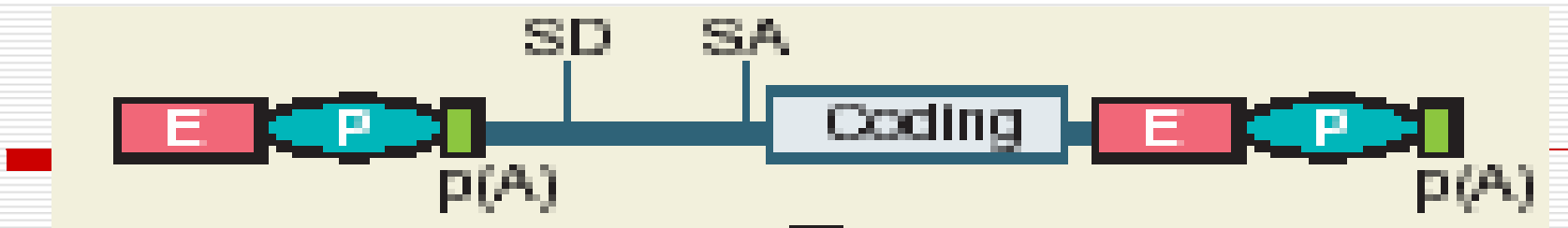
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- ❑ Initiated in July 2008
  - ❑ Study now activated at 10 centers
  - ❑ 15 subjects enrolled,
  - ❑ 14 have undergone BMT
    - 7: unrelated cord blood
    - 7: unrelated marrow
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# Gene Therapy

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- Ideal Candidate Disease
    - Single gene defect localized to hematopoietic system
  
  - Gene Insertion vs Gene Replacement
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# Gene Therapy

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## □ Gene Insertion/Addition

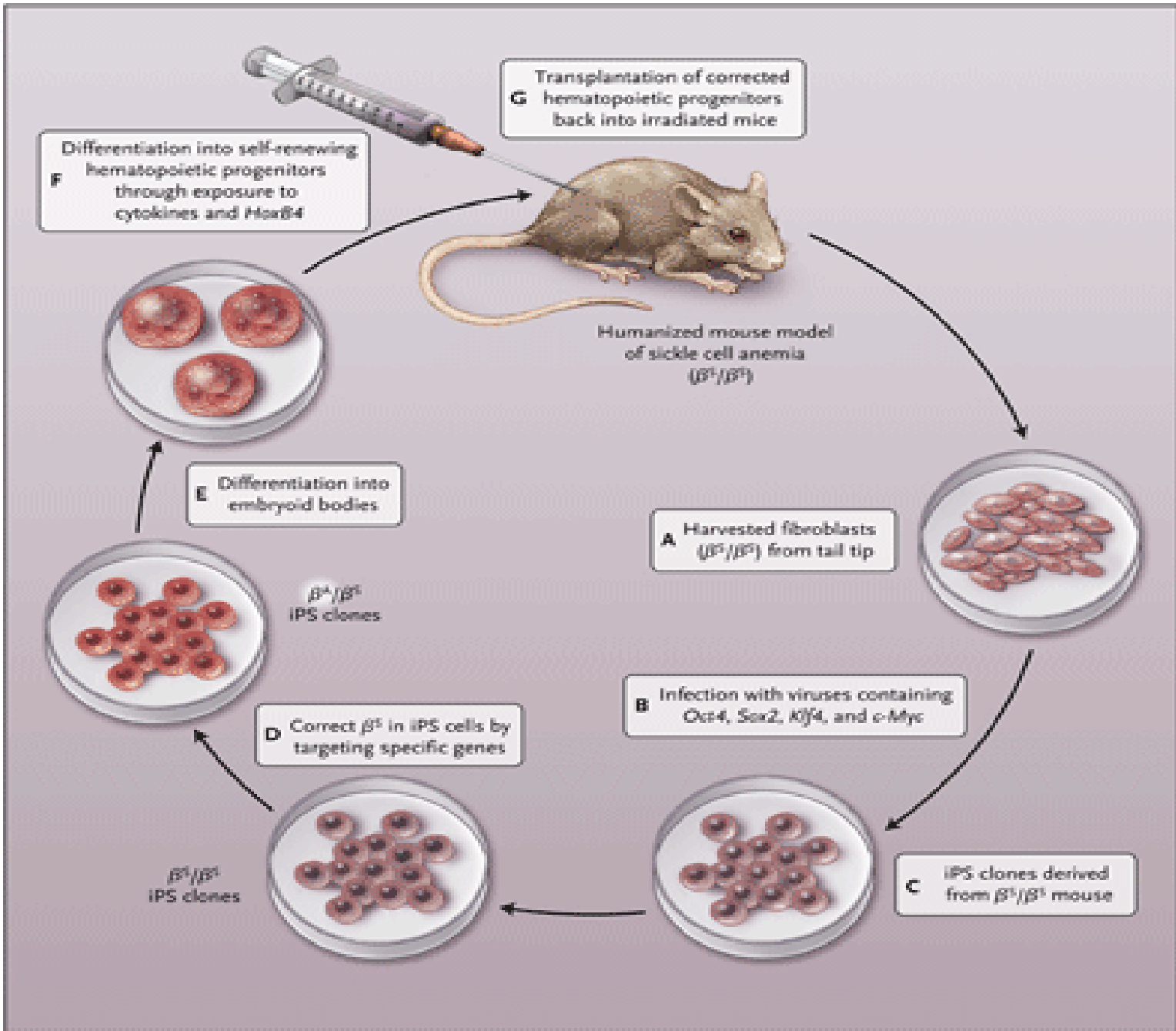
- Insertional mutagenesis a risk
  - Very slow transduction rates
  - Need for sustained, high-level  $\beta$ -globin gene production
  
  - Involve autologous harvest, transduction, irradiation (mice), re-infusion
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# Gene Therapy

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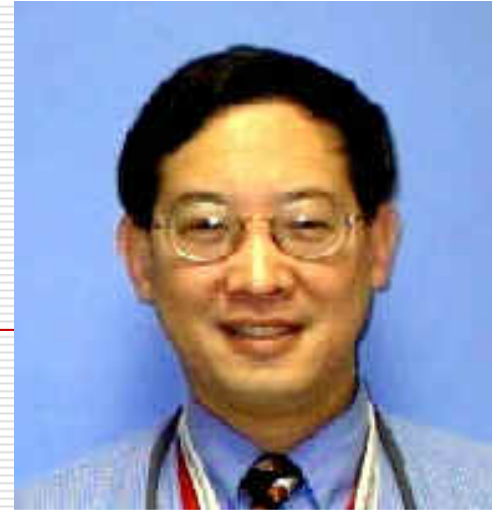
## □ Gene Replacement

- De-differentiation of fibroblasts
  - Use homologous recombination to correct defective sickle cell gene
  - Transduced cells are differentiated in culture into HSC
  - Differentiated cells are transplanted into recipient
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# Sickle Cell Disease at Children's National Medical Center

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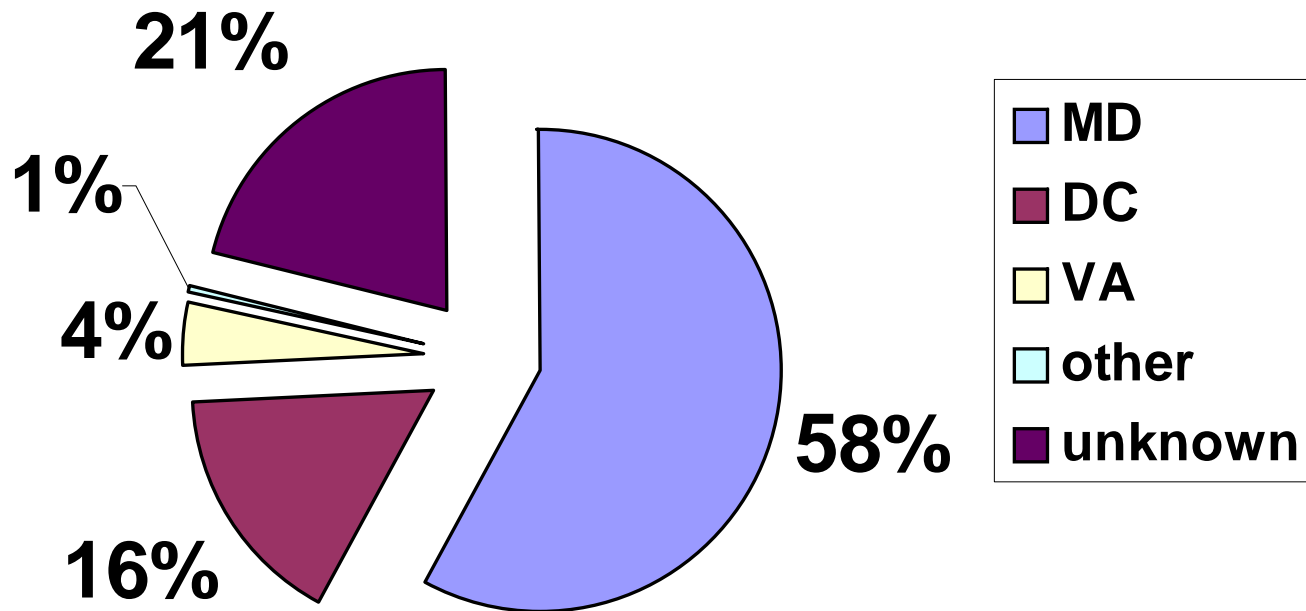
- I wish I could have been here in person, but I am giving a talk at the 5<sup>th</sup> Brazilian Symposium for Sickle Cell Disease today.
- I am a big proponent of transplantation to cure sickle cell disease.
- We share a vision that Children's National Medical Center will be a global leader in successful BMT for hemoglobinopathies.
  - Lewis Hsu, MD, PhD  
Director, Sickle Cell Disease Program

# The Sickle Cell Disease Program at Children's National Medical Center is one of the largest in the country.

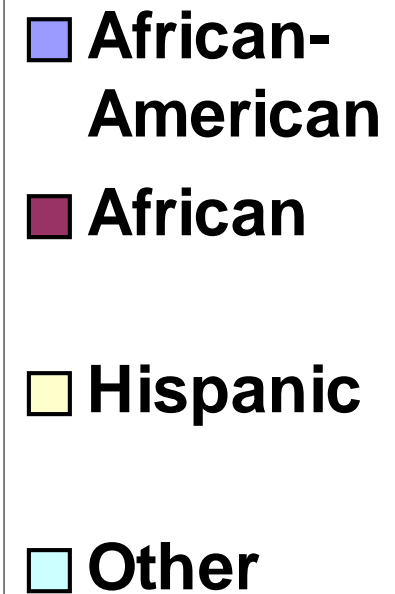
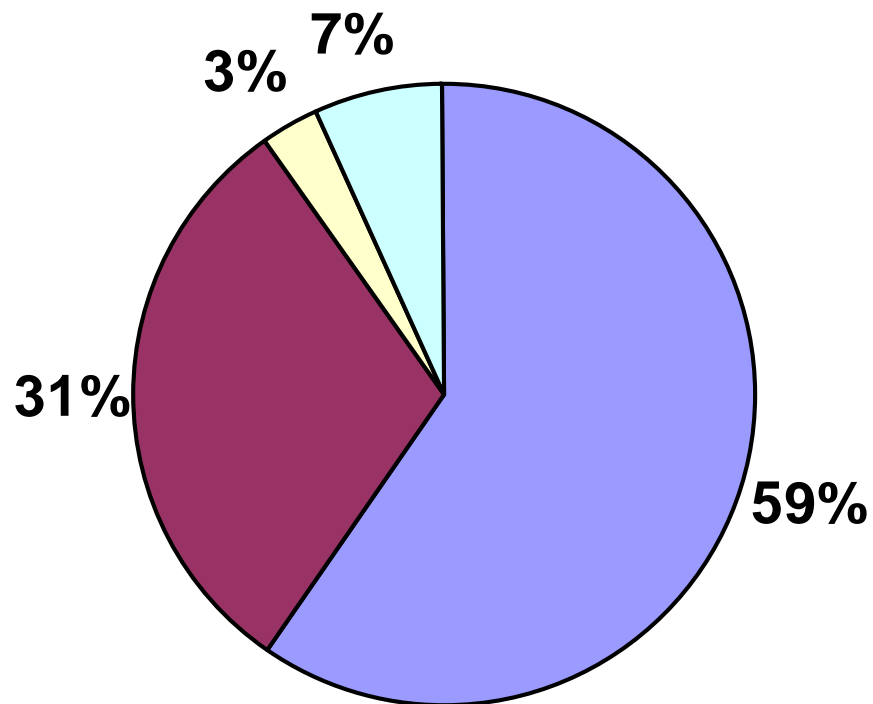
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- ~ 1,300 children with sickle cell disease
    - 1000 at CNMC
    - 350 at CNMC-Northern Virginia
  - Avg 1 admission per day for sickle cell vaso-occlusive pain (365 in FY09)
  - Ethnic & socioeconomic diversity
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**Geographic distribution of  
sickle cell patients at CNMC  
(1225 patients seen in the past 5 years)**



**Multicultural distribution of  
sickle cell patients at CNMC  
(seen in the past 5 yrs)**



# SCD at CNMC

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- BMT for SCD
  - 15 transplants in 14 patients
    - 6 busulfan/cyclophosphamide/ATG
      - MRD
      - 5 alive and well
      - 1 died suddenly 22 months post-BMT
    - 1 fludarabine/TBI (MRD)
      - Rejected; retransplanted with bu/cy/atg
      - Alive and well
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# SCD at CNMC

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- Alemtuzumab/fludarabine/melphalan
    - 7 patients
      - 3 MUD, 2 unrelated cord, 1 MRD cord, 1 MRD cord + marrow
    - 2 rejected their donors (both cords)
    - 1 died suddenly 11 months post-BMT (MUD)
    - 1 developed skin GvHD (cord)
    - All have had viral reactivation, treated without sequelae
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# SCD at CNMC

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- Establishment of an intradisciplinary team
    - Hematologists
    - Transplant physicians
    - Social Work/Psychology
    - Pulmonary
    - Neurology (BIG-SS: Brain Interest Group in Sickle Cell Disease)
    - Blood Bank
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# Summary

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- ❑ BMT should be considered an option for persons with severe manifestations of Sickle Cell Disease
  - ❑ Current mortality with RIC regimens and MRD donors ~3%
  - ❑ Alternative donors possible but needs further study
  - ❑ Gene therapy, although promising, is also problematic and 5 to 10 years away
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