

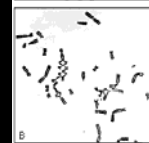
# Hematopoietic Stem Cell Transplantation for Fanconi Anemia

John E. Wagner, M.D.

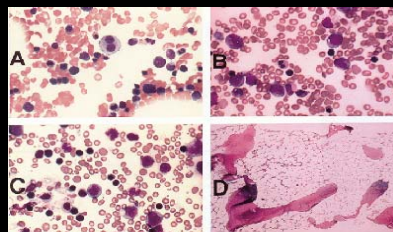
Blood and Marrow Transplant Program  
University of Minnesota

Cell Therapy for Pediatric Diseases  
NHLBI PACT Workshop  
14-15 September 2011

## Classic Manifestations of FA

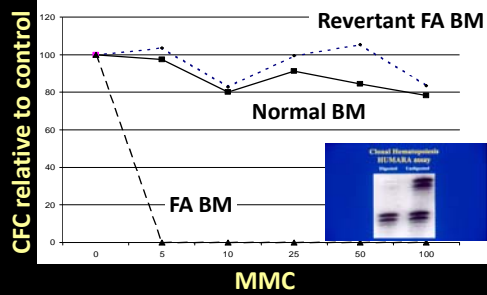
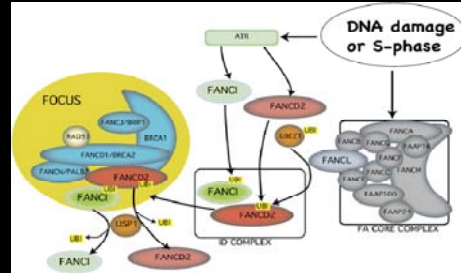


Short stature  
Renal agenesis  
Radial ray defects  
Marrow failure



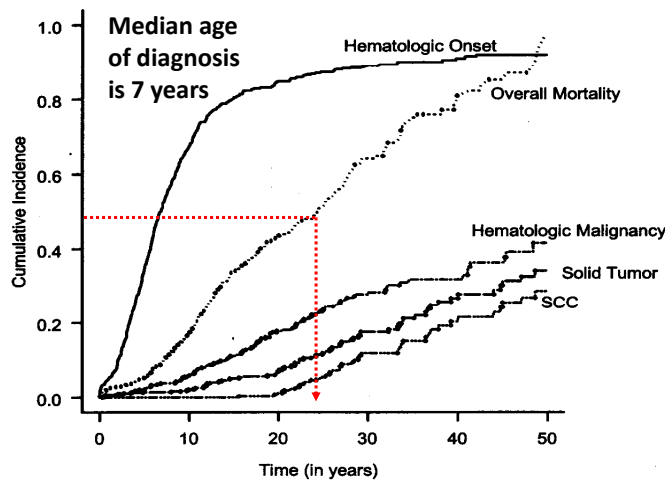
# Fanconi Anemia

- >14 genes identified
- Defect in DNA repair pathway
- Defined natural history (phenotype/genotype correlations but ethnic and racial variations)
- Broad impact (model for understanding DNA repair, cancer biology, stem cell survival, organogenesis)
- Selective growth advantage of normal HSC



## Fanconi Anemia

### Predisposition to Marrow Failure and Cancer

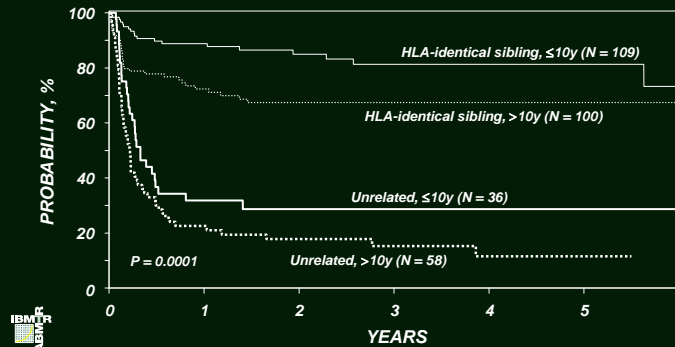


Most early deaths are due to BM failure or leukemia

Most late deaths are due to solid tumor

## State of BMT for FA in 1995

### PROBABILITY OF SURVIVAL AFTER ALLOGENEIC TRANSPLANTS FOR FANCONI ANEMIA IBMTR /ABMTR Newsletter 1 Feb 2002



## Reasons for Poor Outcomes in Patients with an Unrelated Donor

### Sibling Donor

HLA matched  
Earlier treatment  
Cy 20 TAI 500 cGy

Good  
Outcome

### Unrelated Donor

HLA mismatched  
Late treatment  
Cy 40 TBI  $\geq 450$  cGy

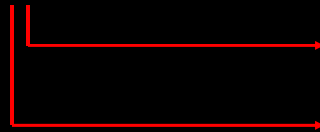
Poor  
Outcome

# Setting the Agenda

## Fanconi Anemia Research Fund

### Identify potential solutions

Have an HLA matched donor



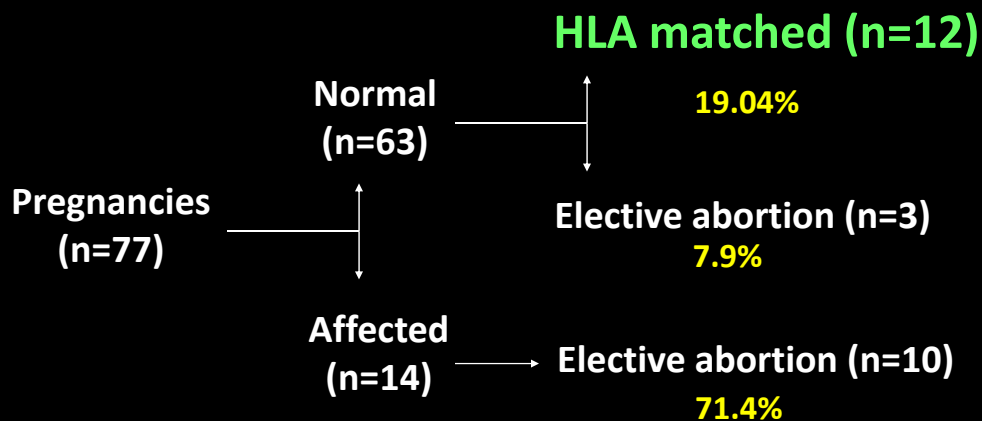
Development of Unrelated Donor Registry  
PGD/IVF  
'Savior Sibling'

### Fund the work

Identification of Genes  
Gene Therapy Trials  
BMT Trials

# Observations

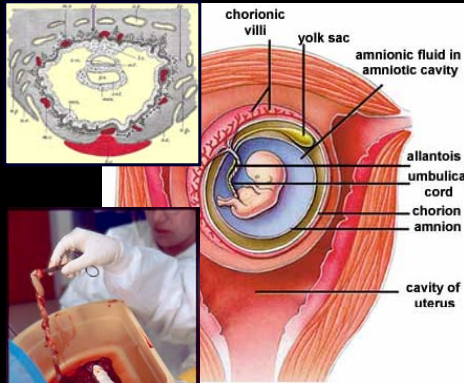
## Deliberate Conception 1985-1995



Auerbach AD, Blood Cells 1994

# Umbilical Cord Blood Transplant

## New Source of HSC



Broxmeyer et al.

UCB collected in North Carolina

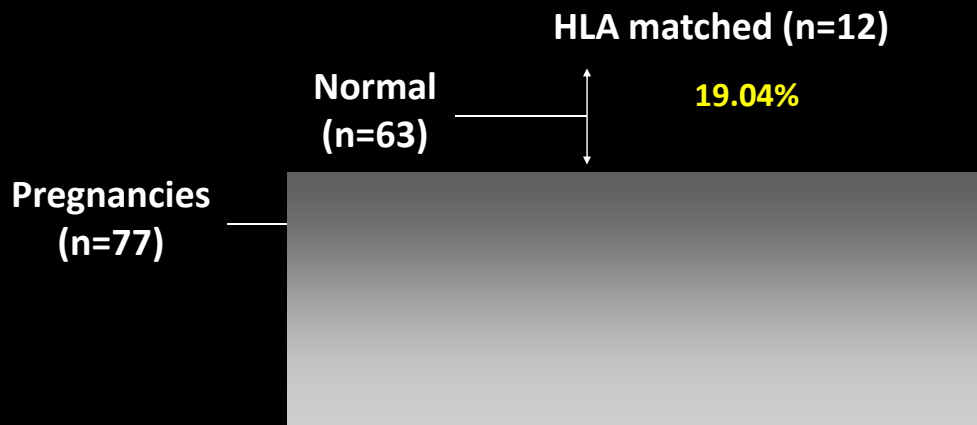
Tested at Rockefeller, Indiana University and Baylor

Shipped to Paris



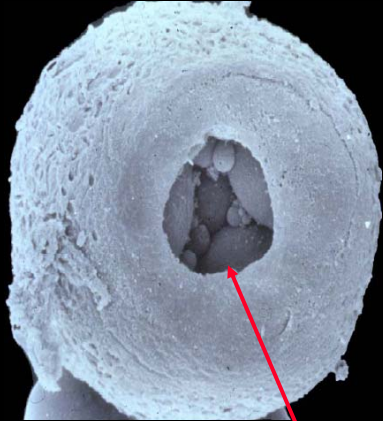
# Observations

## Deliberate Conception 1985-1995



# PGD to prevent disease and save the life of an existing child

zona pellucida



blastomeres

PGD for mutation

To eliminate risk of genetic disease

PGD for HLA

To create an HLA identical stem cell donor

HLA-DQB: I\*0201, I\*0602

HLA-A: A2, A26

Embryo no. 1 2 3 4 5 6 7 8 9  
ET ET

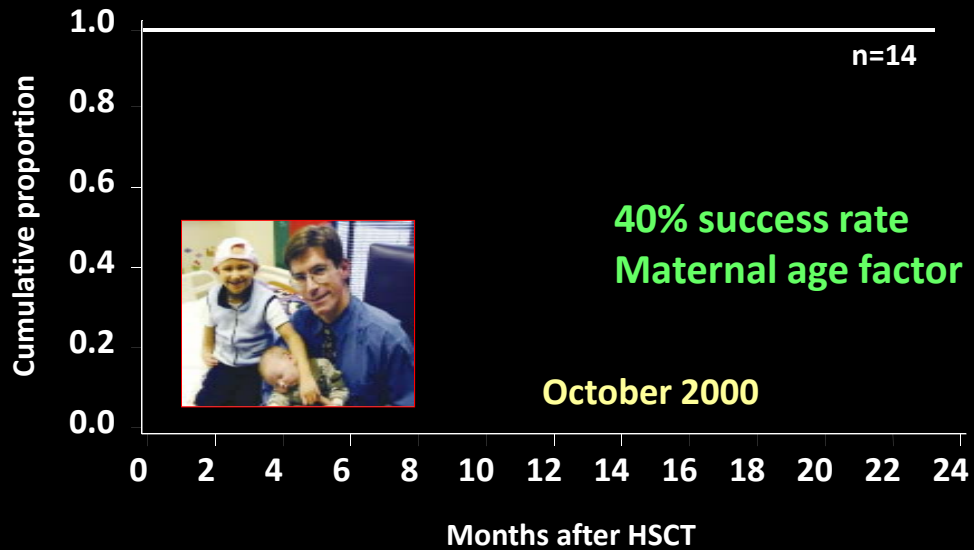
Scal restriction digestion

Embryo no. 1 2 3 4 6 9 10  
ET ET

**Embryo 4**

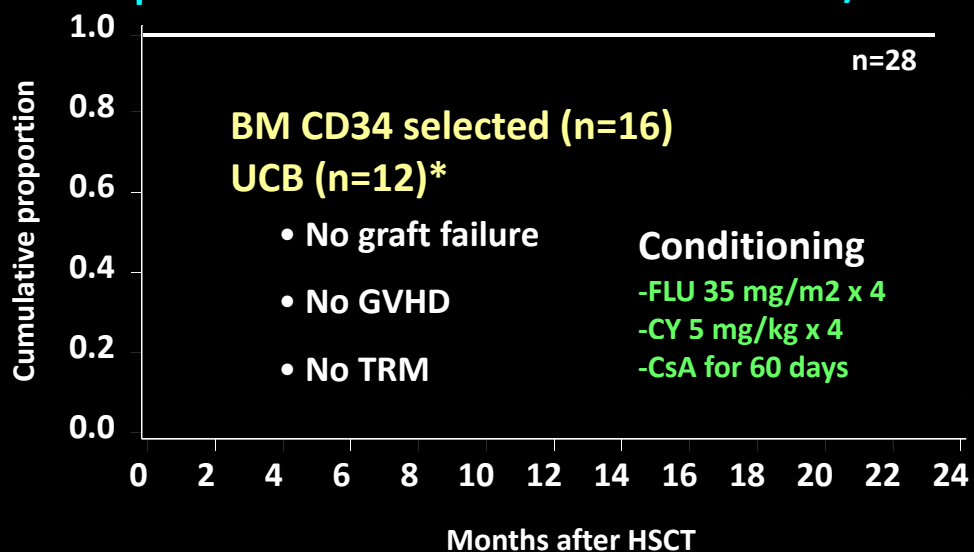
## Fanconi Anemia

### Survival after HLA matched UCBT



## Fanconi Anemia/Aplasia

### Transplant Outcomes after HLA matched BMT/UCBT

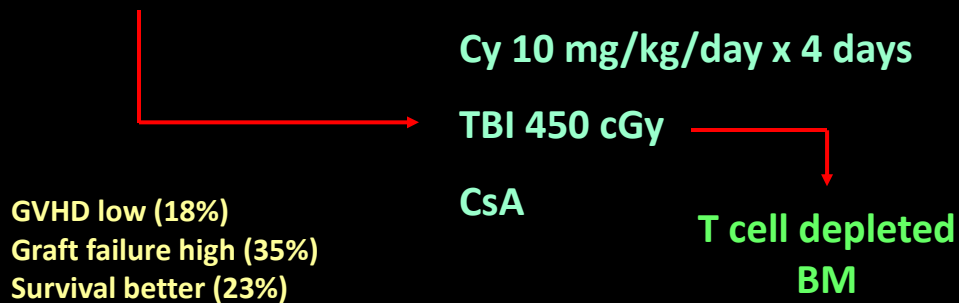


## Unrelated Donor HSCT for FA Tackling Problems

Poor engraftment

Intolerance to GVHD and/or its treatment

High risk of infection



## Unrelated Donor HSCT for FA Tackling Problems

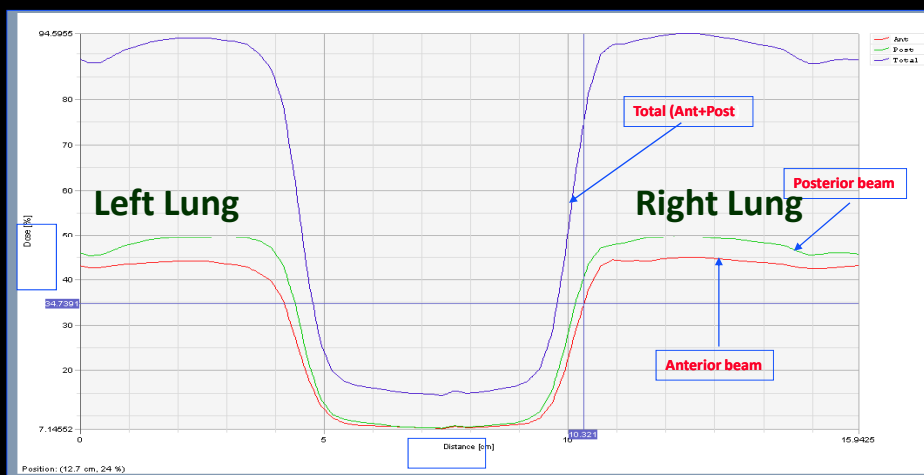
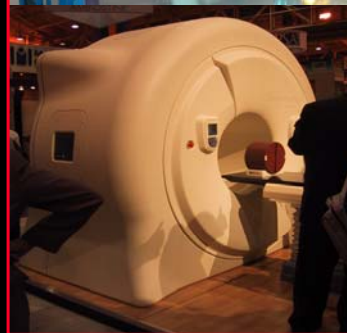
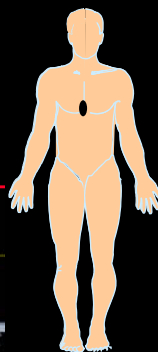
Series of 20-25 patient trials

Add TCD	→	GVHD solved
Add fludarabine	→	GF solved
Add thymic shielding	→	Reduced OI
TBI dose de escalation		? Too early



# Radiation Therapy

## Thymic Shielding



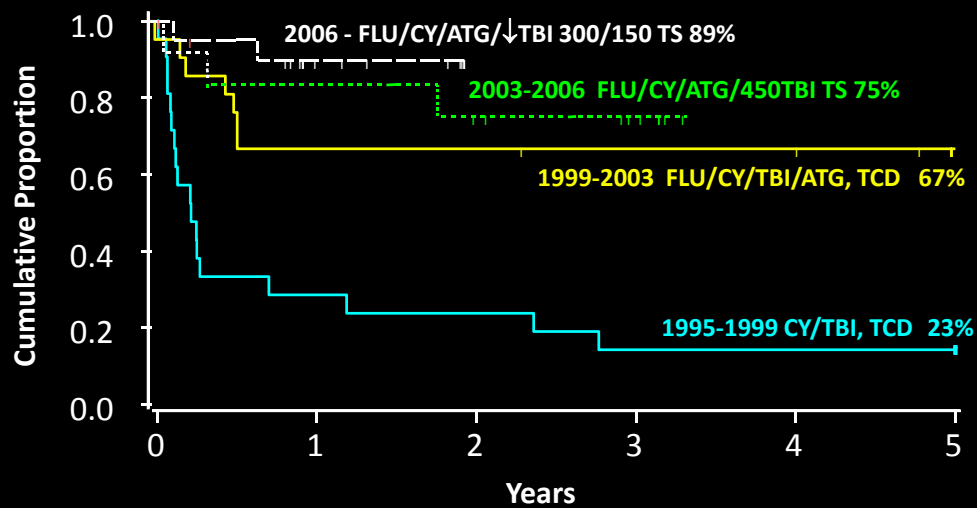
### Thymus

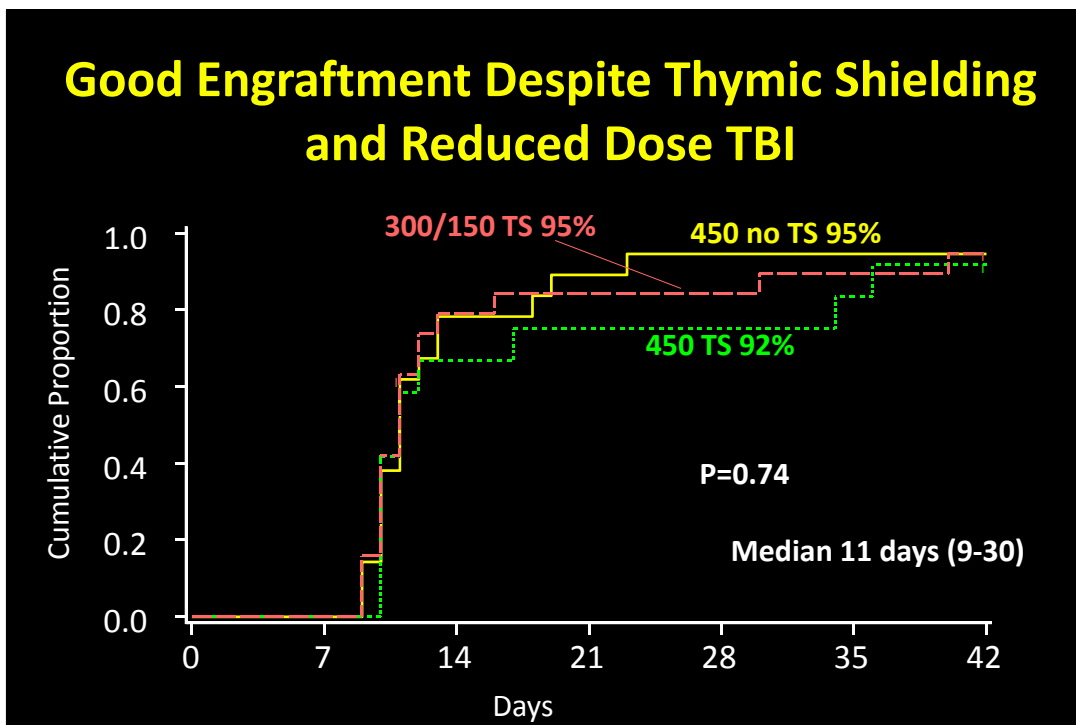
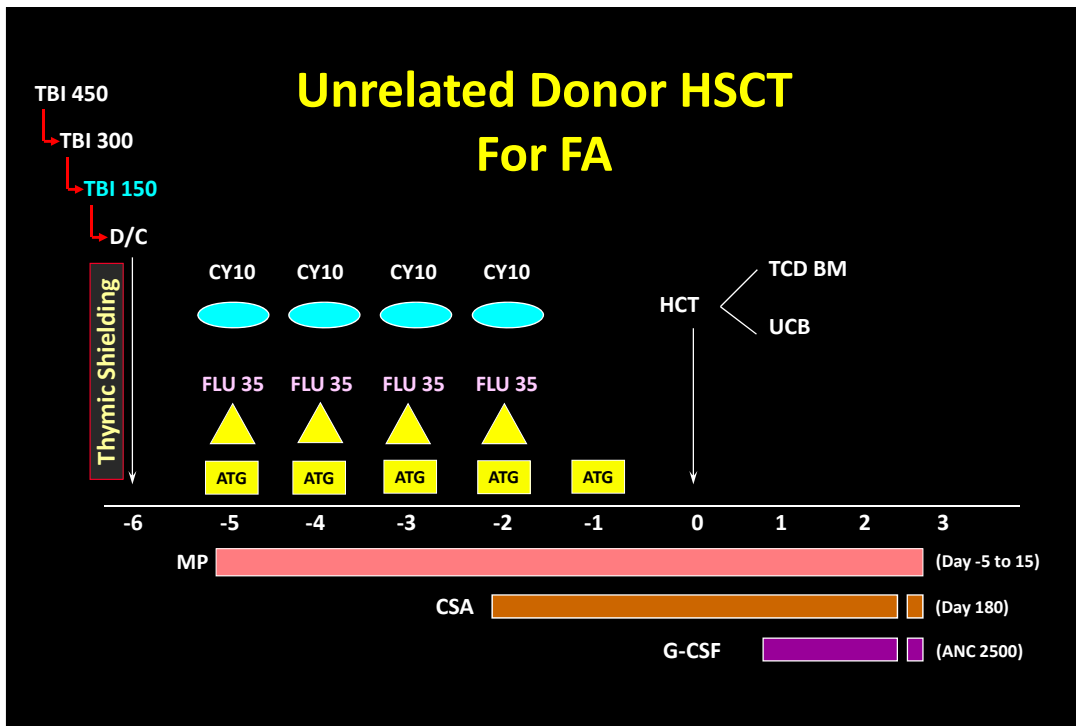
Mean dose 15% (45 cGy)  
 Maximum dose 17% (51 cGy)

## Thymic Shielding Reduces Risk of Infections

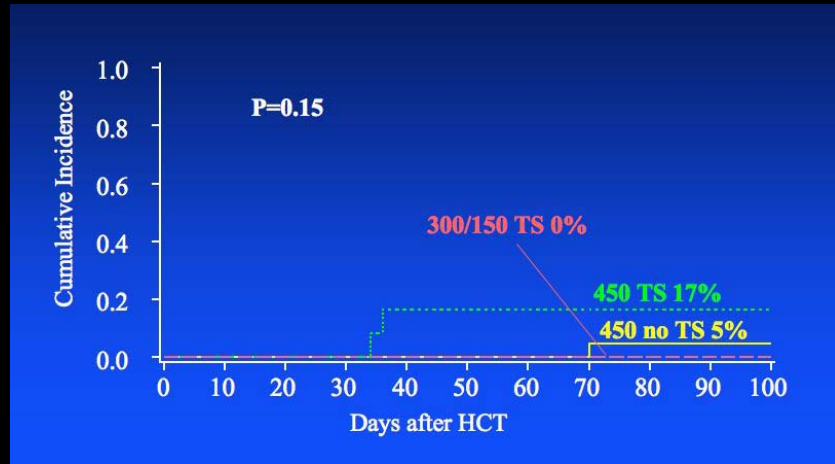
	Total # Infections per Patient	# Bacterial Infections per Patient	# Viral Infections per Patient	# Fungal Infections per Patient
<b>TBI 450 including Thymus</b>	2.93	1.58	0.86	0.49
<b>P value</b>	P < 0.01	P < 0.01	P < 0.01	P < 0.01

## Small Patient Trials Impact on Survival

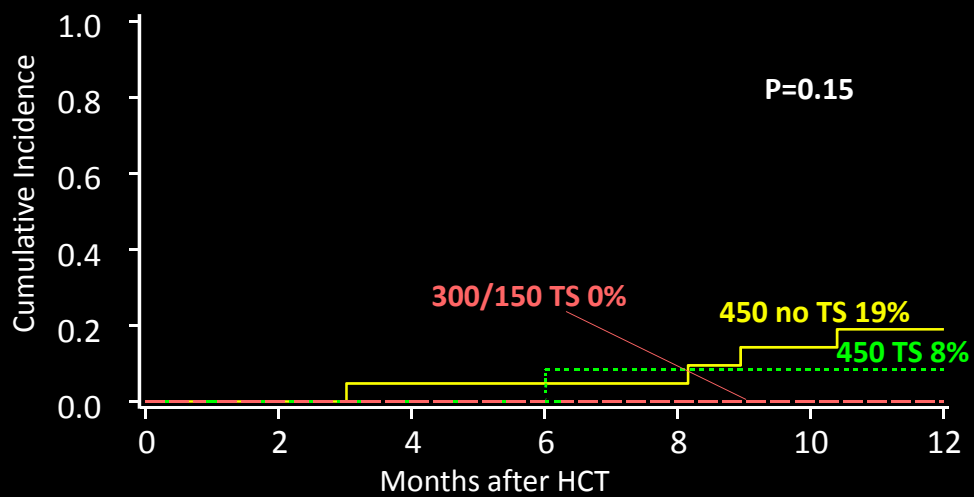


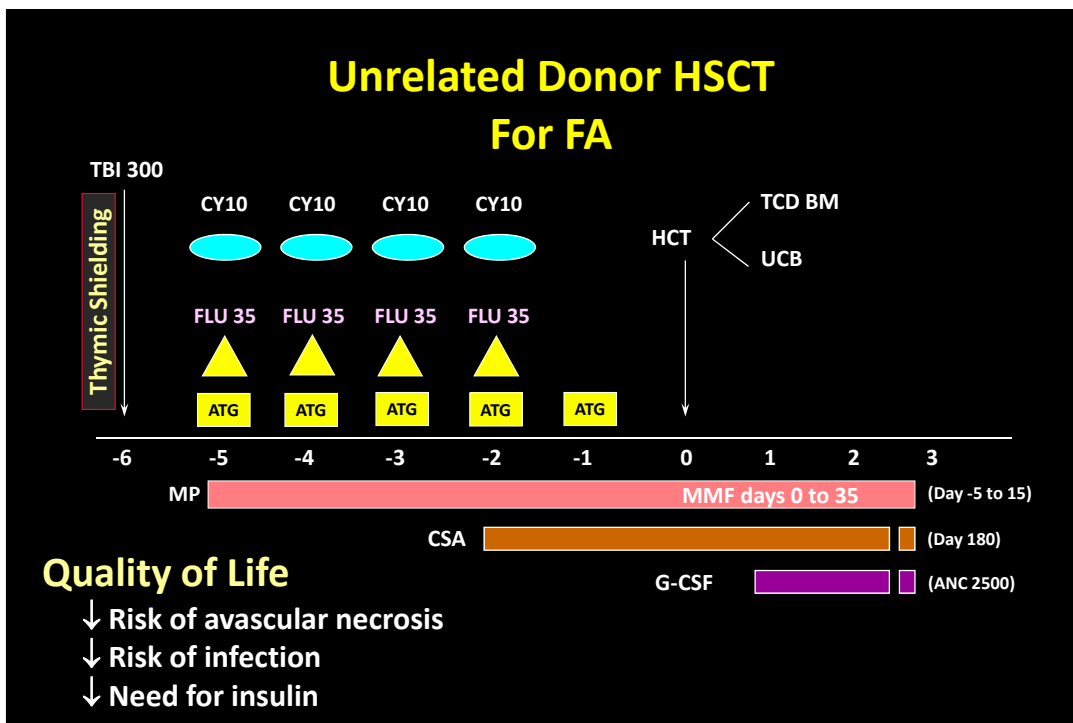
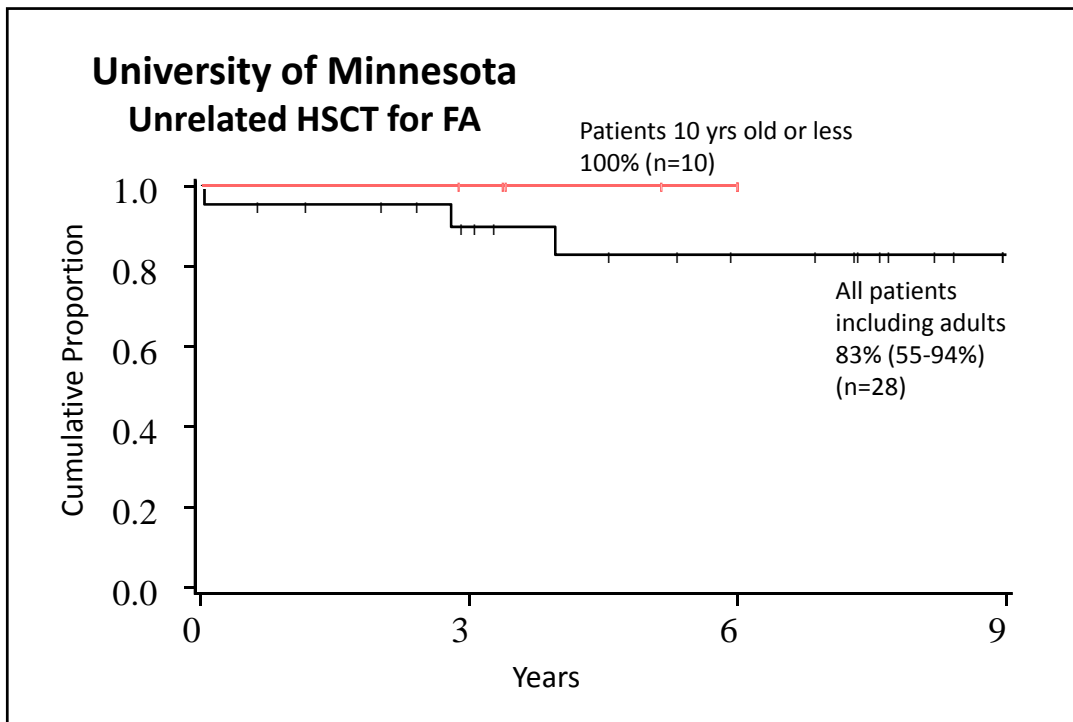


## Low Risk of Acute GVHD with TCD



## Low Risk Chronic GVHD





## Lessons Learned

### General

- Embed research and clinical care, clearly demarcating the two
- Educate the FDA reviewers about the disease and its severity
- Enlist outside consultants to insure objectivity about patient eligibility and responses to therapy
- Develop a roadmap, making one change at a time

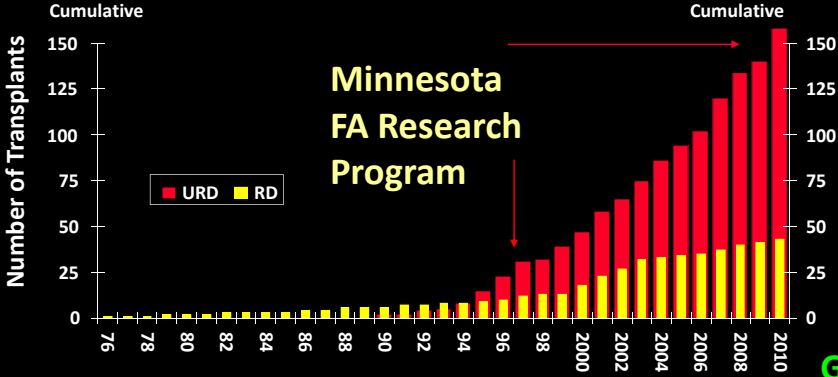
## Lessons Learned

### Disease specific

- Utilize patient advocacy groups
  - to help direct questions next questions
    - TCD even for those with HLA genotypic identical donors
    - Embryo selection
  - to generate seed funding

# Fanconi Anemia

## Pathway to Cure



Gene therapy?

High dose therapy

Dose reduced therapy

1<sup>st</sup> Umbilical cord blood transplant

1<sup>st</sup> T cell depletion for URD BMT

1<sup>st</sup> successful PGD/IVF

TBI dose escalation study

1<sup>st</sup> use of fludarabine