A multicenter trial of BMT for patients with Fanconi Anemia

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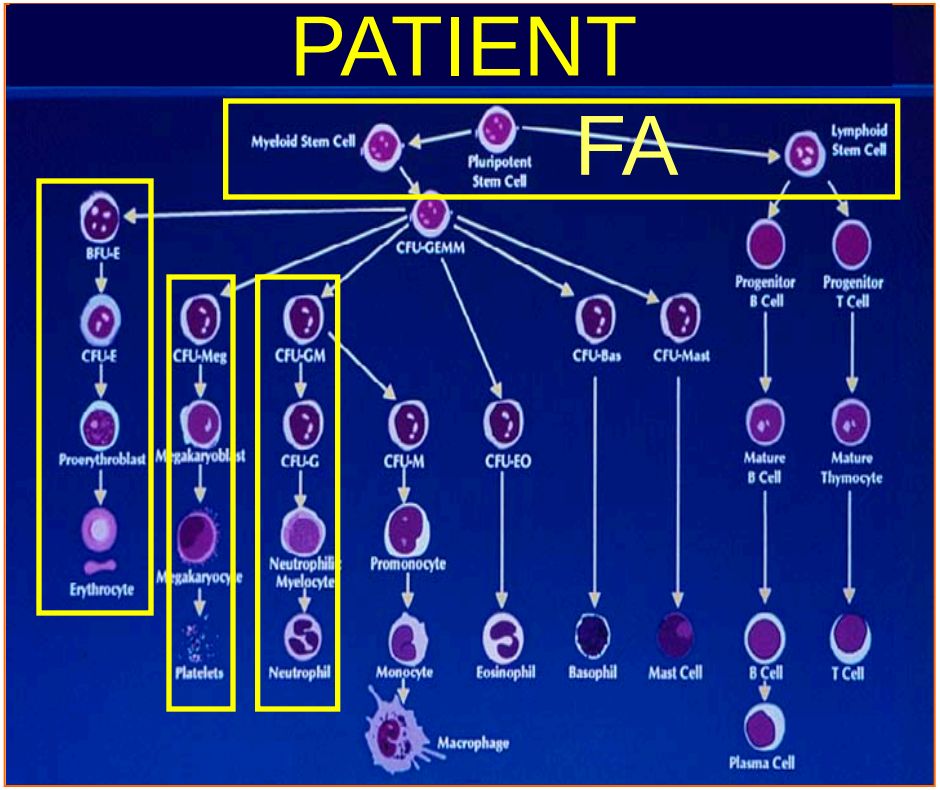
Cincinnati Children's Hospital Medical Center

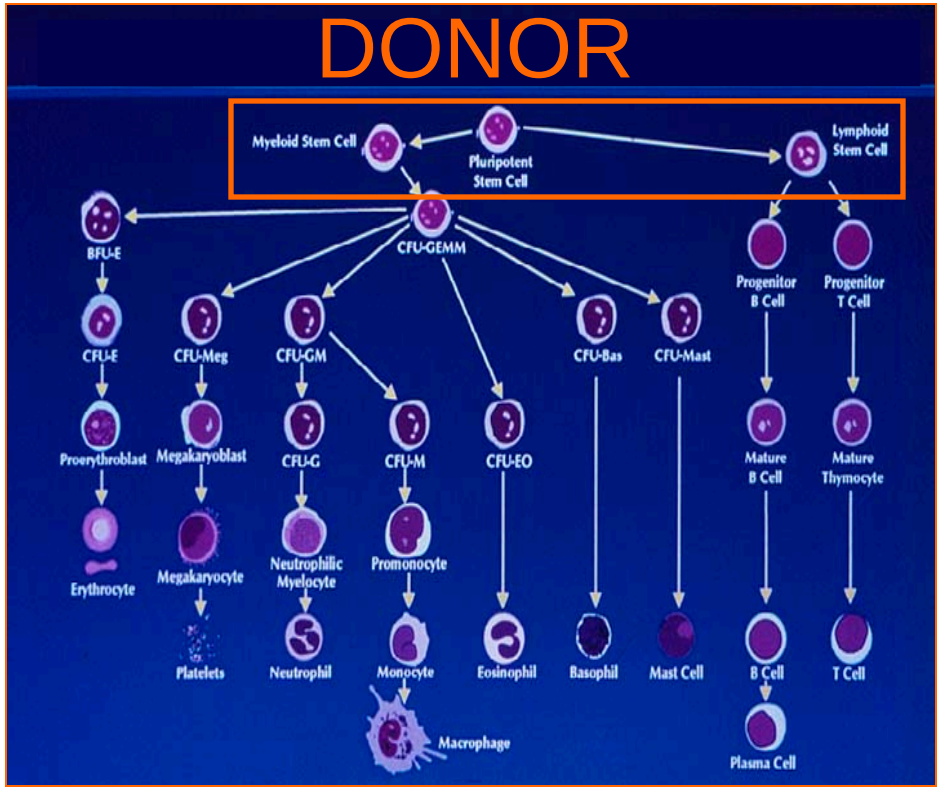
Seattle Children's HOSPITAL • RESEARCH • FOUNDATION

Boston Children's Hospital Until every child is well

Children's Hospital of Wisconsin

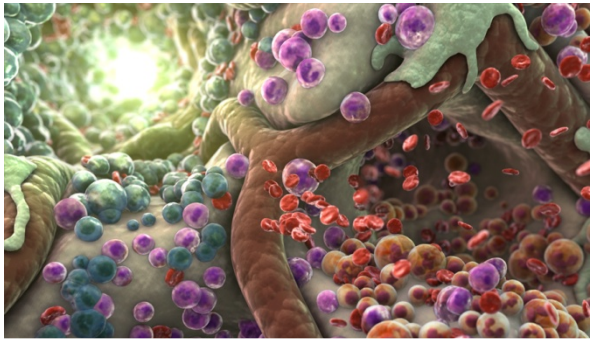
ALLOGENEIC
HEMATOPOIETIC STEM CELL TRANSPLANTATION



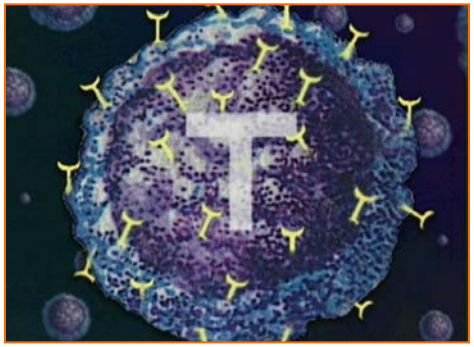


Patient

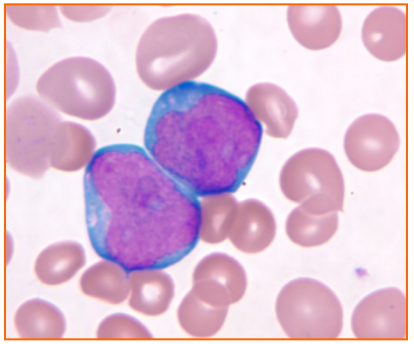
Bone Marrow Cells



T –cells



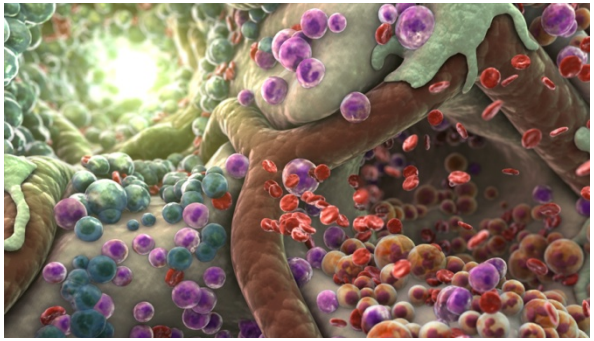
AML clone/cells



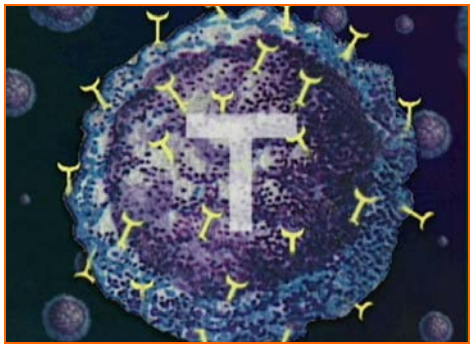
In order to do a transplant successfully, we need to get rid of all 3 elements.

That is the **Conditioning Regimen** or **Cytoreduction**

Bone Marrow Cells



T –cells



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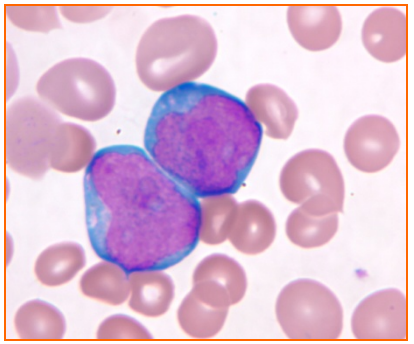


EFFECTS: Different agents have different properties:

FA

Radiation (TBI)	can attack all 3
Busulfan	attacks primarily BM cells and AML cells
Cyclophosphamide	attacks primarily the T-cells
Fludarabine	attacks primarily the T-cells (+/- AML cells)
ATG	attacks only the T-cells

OTHER

Melphalan	attacks primarily BM cells and AML cells
Thiotepa	can attack all 3
Clofarabine	attacks primarily BM and AML cells

But …

These agents also have **SIDE EFFECTS**:
Side effects can be acute-early or late

Some of the acute effects:
- Mouth sores
- Stomach problems
- Low counts
- Hemorrhagic cystitis

Some of the late effects 

LATE EFFECTS POST HSCT

Boulad F, Bromley M, et al. Thyroid Dysfunction following bone marrow transplantation using hyperfractionated radiation. *BMT 1995*

Huma Z, **Boulad F**, et al. Growth in Children after bone marrow transplantation for acute leukemia. *Blood 1995*

Sarafoglou K, **Boulad F**, et al. Gonadal function following bone marrow transplantation during childhood for acute leukemia. *J Peds 1996*

Sklar C, **Boulad F**, et al. Endocrine complications of pediatric stem cell transplantation. *Frontiers in Bioscience 2001*

Chemaitilly W, **Boulad F**, et al. Endocrine Complications of Childhood Hematopoietic Stem Cell Transplantation. Ped HSCT 2006

Chemaitilly W, **Boulad F**, et al. Final height in pediatric patients after hyperfractionated total body irradiation and stem cell transplantation. *BMT 2007*

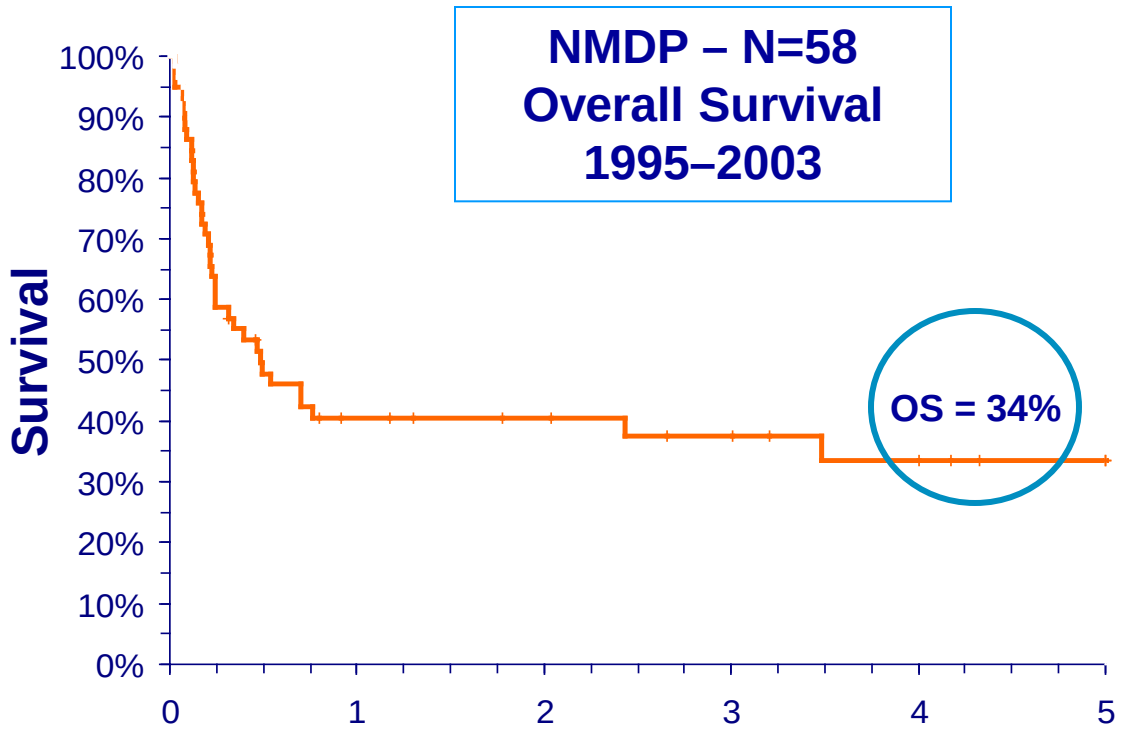
Chemaitilly W, **Boulad F**, et al. Disorders of glucose homeostasis in young adults treated with total body irradiation during childhood: a pilot study. *BMT 2009*

So what is the deal with transplant for FA

Why is it so hard?

FA and allogeneic HSCT

1990's



- Graft rejection / failure
- Acute and chronic GvHD
- Transplant related organ toxicity
- Infections

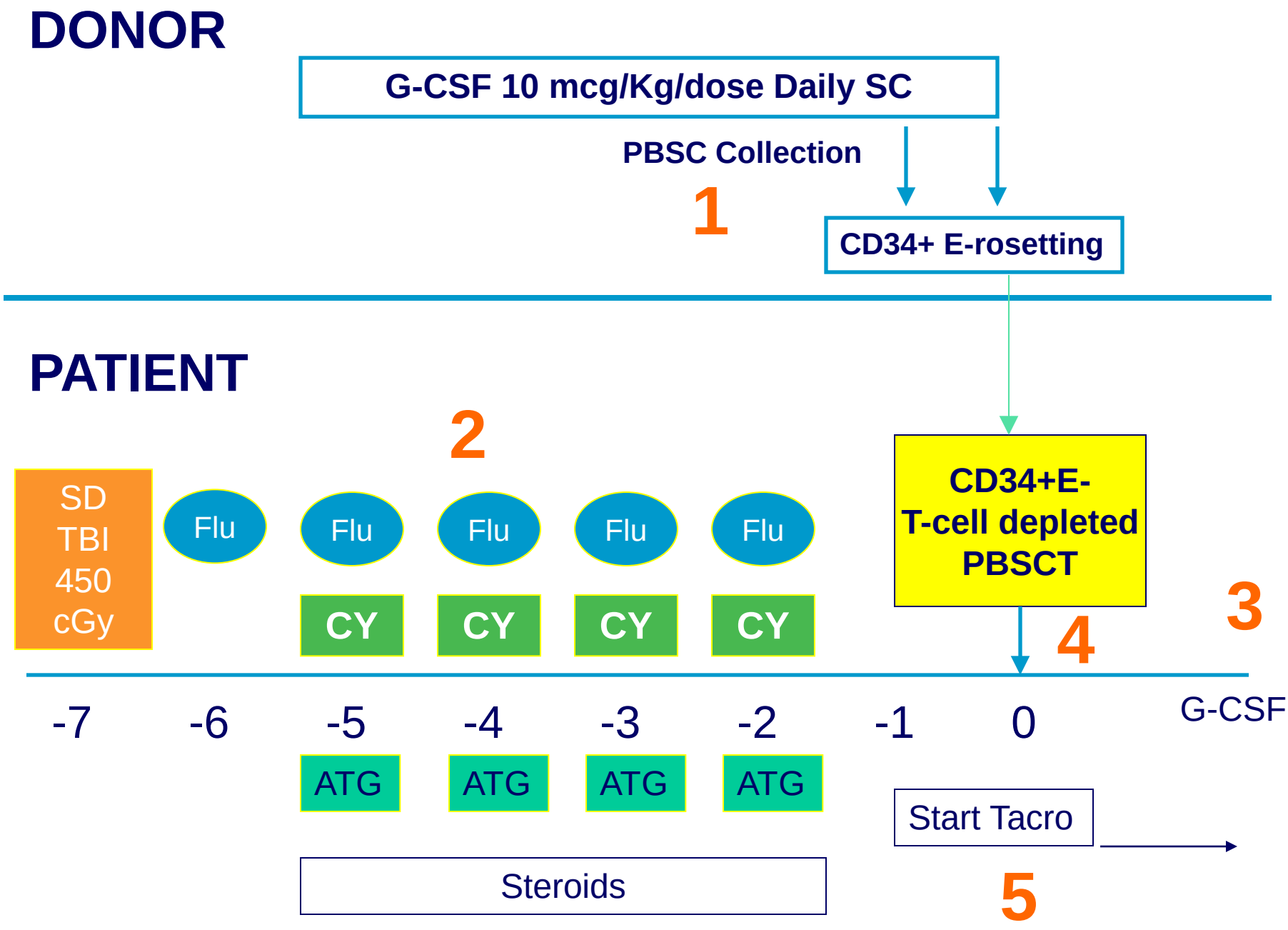
- DFS: ~ 30%

Late 1990's - 2000's

Can we improve on these results?

Trial(s) #1 – Single center studies

New York - Cincinnati - Minnesota


DONOR
G-CSF 10 mcg/Kg/dose Daily SC
PBSC Collection
1
CD34+ E-rosetting
PATIENT
2
SD TBI 450 cGy
Flu
Flu
Flu
Flu
Flu
CY
CY
CY
CY
CD34+E- T-cell depleted PBSCT
3
4
-7
-6
-5
-4
-3
-2
-1
0
G-CSF
ATG
ATG
ATG
ATG
Start Tacro
Steroids
5

TBI FLU CY – ATGTacro – CD34+ PBSCT
OVERALL OUTCOME
(MSKCC - N = 26)

5 year overall success: 60-75%

Depending on disease, age, infections, donors, …

But also

Risk of GvHD: 9.6%

Risk of Rejection: 3.8%

Despite 21 of 26 patients with mismatched donors

FA and allogeneic HSCT
Trial #2 – Multi-Center

Can we perform allogeneic HSCT in patients with FA without the use of TBI?

Hypothesis 1:

Rejection and GvHD problems significantly better
Can we perform these transplants
with comparable outcome results
while decreasing the acute TBI-related **acute toxicity**?

Hypothesis 2:

Can we reduce the **late effects** of TBI
including **secondary malignancies**

Why is this relevant in the FA host?

SECONDARY NEOPLASMS POST HSCT

NON FA

The risks of secondary neoplasms post HSCT is significantly higher in the patients who have received TBI-based cytoreductive regimens

Socie et al. 1993 – New England Journal of medicine
Lowsky et al. 1994 – Journal of Clinical Oncology
Deeg et al. 1996 – Blood
Kolb et al. 1999 – Annals of internal medicine

FA

Survival in patients with FA after HSCT with the use of T-cell depleted transplants and Fludarabine-containing cytoreductive regimens has significantly improved

HOWEVER, patients with FA continue to succumb to a high rate of **secondary malignancies**.

The prevention of these secondary malignancies must be a priority for us physicians caring for patients with FA:
(1) **HPV – (2) Chronic GvHD – (3) Radiation**

TRIAL DESIGN

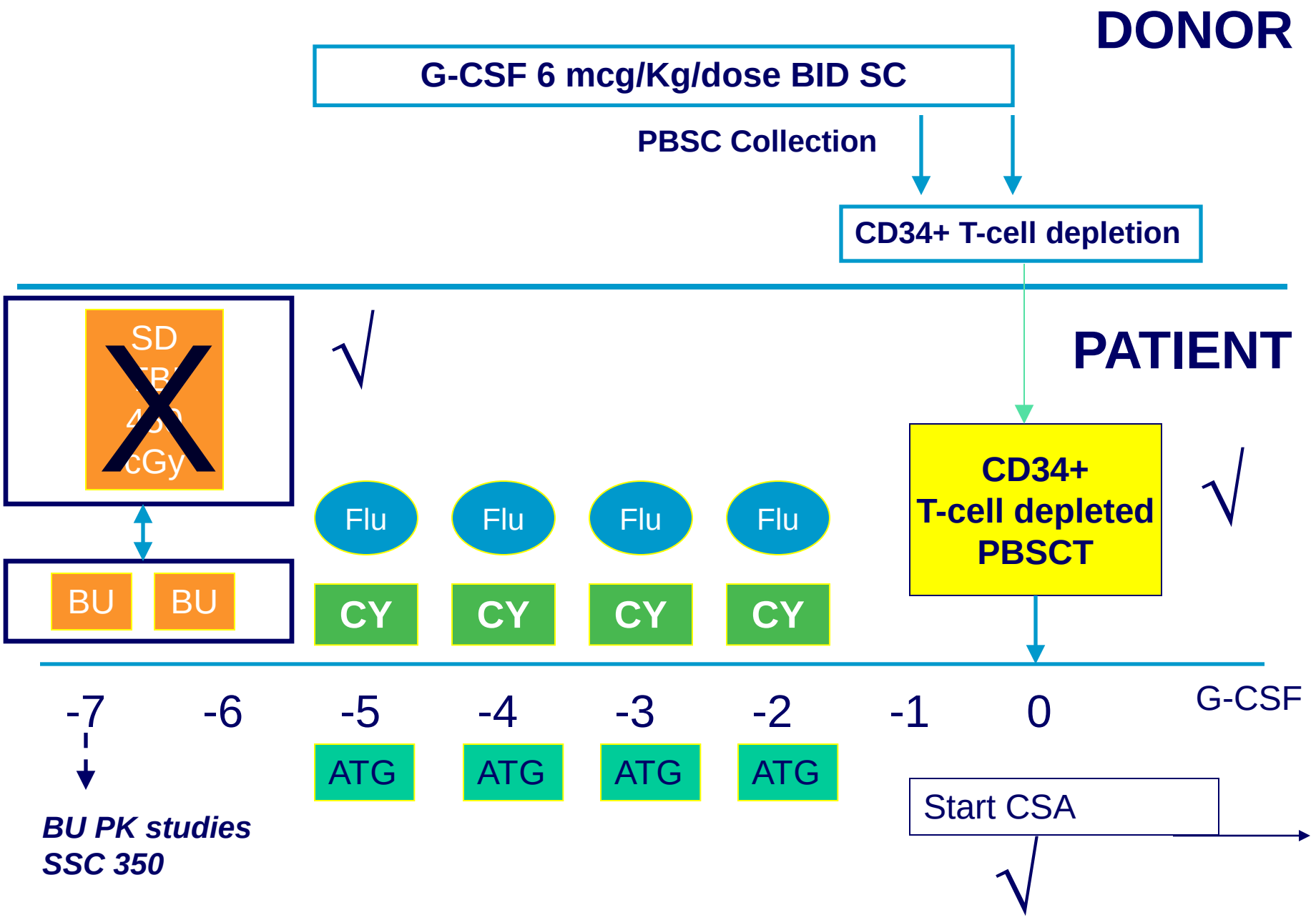
FA and allogeneic HSCT

- Centers involved in multicenter protocol
- **2004**
  - **USA**
    - Memorial Sloan-Kettering
    - Cincinnati Children's Hospital
    - University of Minnesota
    - Boston Children's Hospital
    - Children's Hospital Wisconsin
    - Hackensack Medical Center
  - **OTHER**
    - Hopital Saint Louis - France
    - Ospedale Pediatrico Gaslini – Genova - Italy
    - Hadassah Hospital - Israel

9 CENTERS

- **2008**
  - **USA**
    - Memorial Sloan-Kettering
    - Cincinnati Children's Hospital
    - Boston Children's Hospital
    - Children's Hospital Wisconsin
    - + 2013 Fred Hutchinson Cancer Research Center

4 + 1 CENTERS


DONOR
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CD34+ T-cell depletion
PATIENT
SD
cGy
BU
BU
Flu
Flu
Flu
Flu
CY
CY
CY
CY
CD34+
T-cell depleted
PBSCT
-7
-6
-5
-4
-3
-2
-1
0
G-CSF
ATG
ATG
ATG
ATG
Start CSA
BU PK studies
SSC 350

OBJECTIVES

The **primary objectives** of this trial are to establish:

1. E**ngraftment** and **hematopoietic reconstitution**.
2. Organ Toxicity
3. A**cute GvHD and chronic GVHD.**

Secondary objectives of this study are to establish initial estimates of:

4. the incidence of **overall survival and disease-free survival** over time

5. The incidence of **late effects** post transplant
6. The incidence of **secondary malignancies**

Design – Patient Numbers

- This phase II trial is designed to investigate the safety and efficacy of hematopoietic stem cell transplantation for the treatment of patients with Fanconi Anemia lacking a genetically identical donor. A maximum of **25 patients** will be accrued onto the study. It is anticipated that the accrual will last 3 years, and will include patients from 5 different centers.

- As of April 2012, patient accrual is nearly complete in the HSCT Fanconi Anemia study. As a result, after the completion of the planned 25 patient study, we have amended the protocol to accrue at most an **additional 20 patients** in order to gain clinical experience using alternative levels of Busulfan.

- Initial cohort: **Busulfan doses 0.8 – 1.0 mg/Kg**
  Subsequent cohort: **Busulfan doses 0.6 – 0.8 mg/Kg**

- **Stopping rules for (1) rejection, (2) GvHD, (3) TRM**

- **Trial patient number reached - Stopping rules NOT achieved -**

BU CY FLU - CD34+ T-cell depleted HSCT

N= 45

- **Age** Median 8.2 (range 0.4 – 44)

< 10 years:	27
10-18 years	13
> 18 years:	5

- **Diagnosis**

SAA	29
MDS	11
Severe Single Lineage Cytopenia	5

- **Donor**

Matched Unrelated	25
Mismatched Unrelated	14
Mismatched Related	5
Phenotypically matched related	1

Centers: CCH 29 – MSKCC 10 – BCH 3 – FHCRC 2 – WCH 1

BU CY FLU - CD34+ T-cell depleted HSCT

N= 45

- **F/U** **10.4 months (range: 8.7 - 61)**

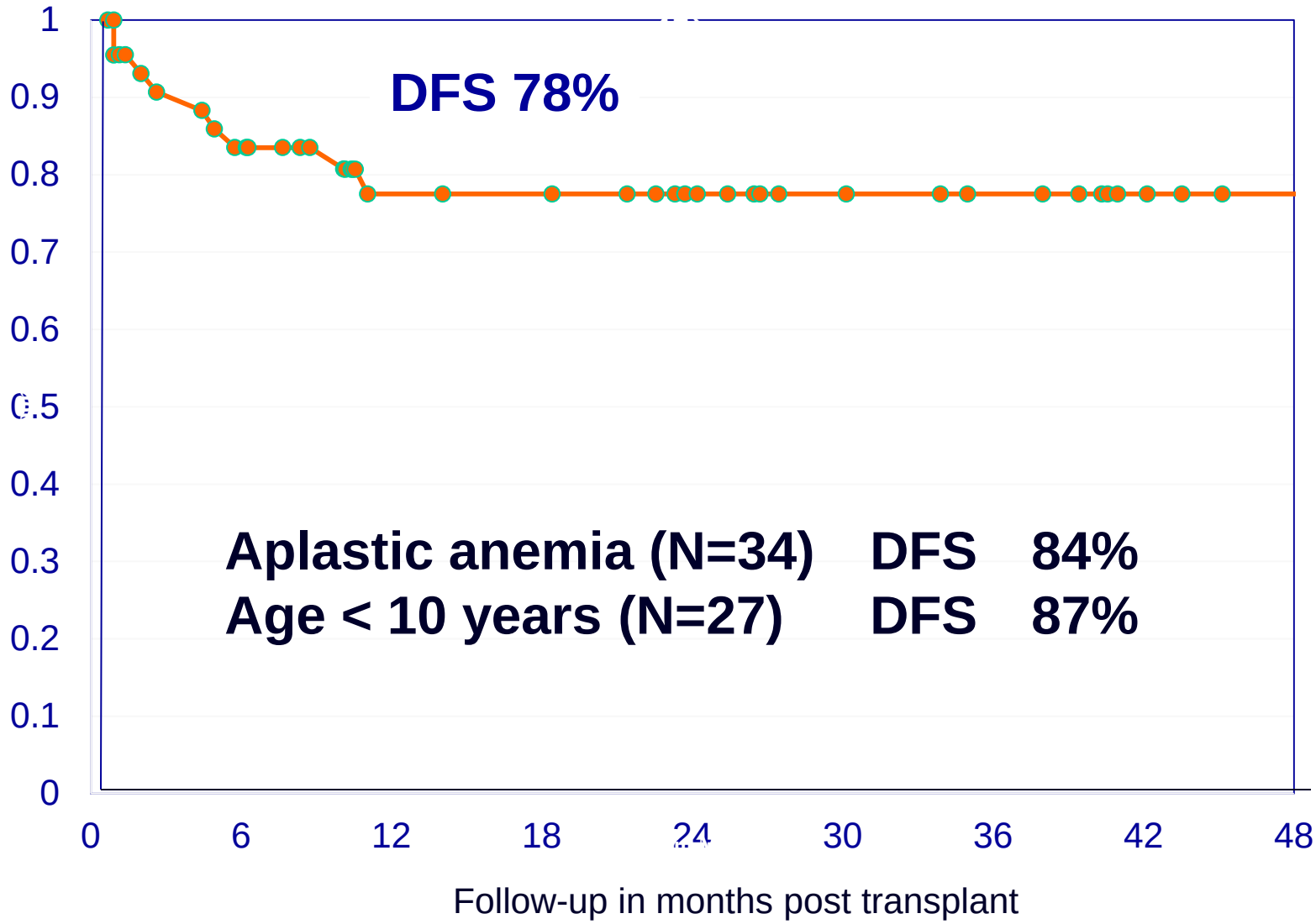
- **GvHD**
  Acute: Grade 1-2 FOUR – Grade 3-4: ZERO **0%**
  Chronic: Limited **3** **6.7%**

- **Outcome** Alive N=37 - Overall Survival: 81%

  8 people left us (incl. 4 of the 5 pts older than 18 years)
  Infection: 5 (inc. botulism)
  BMT related toxicity: 3

BU CY FLU - CD34+ T-cell depleted HSCT

N= 45



CONCLUSIONS (1)

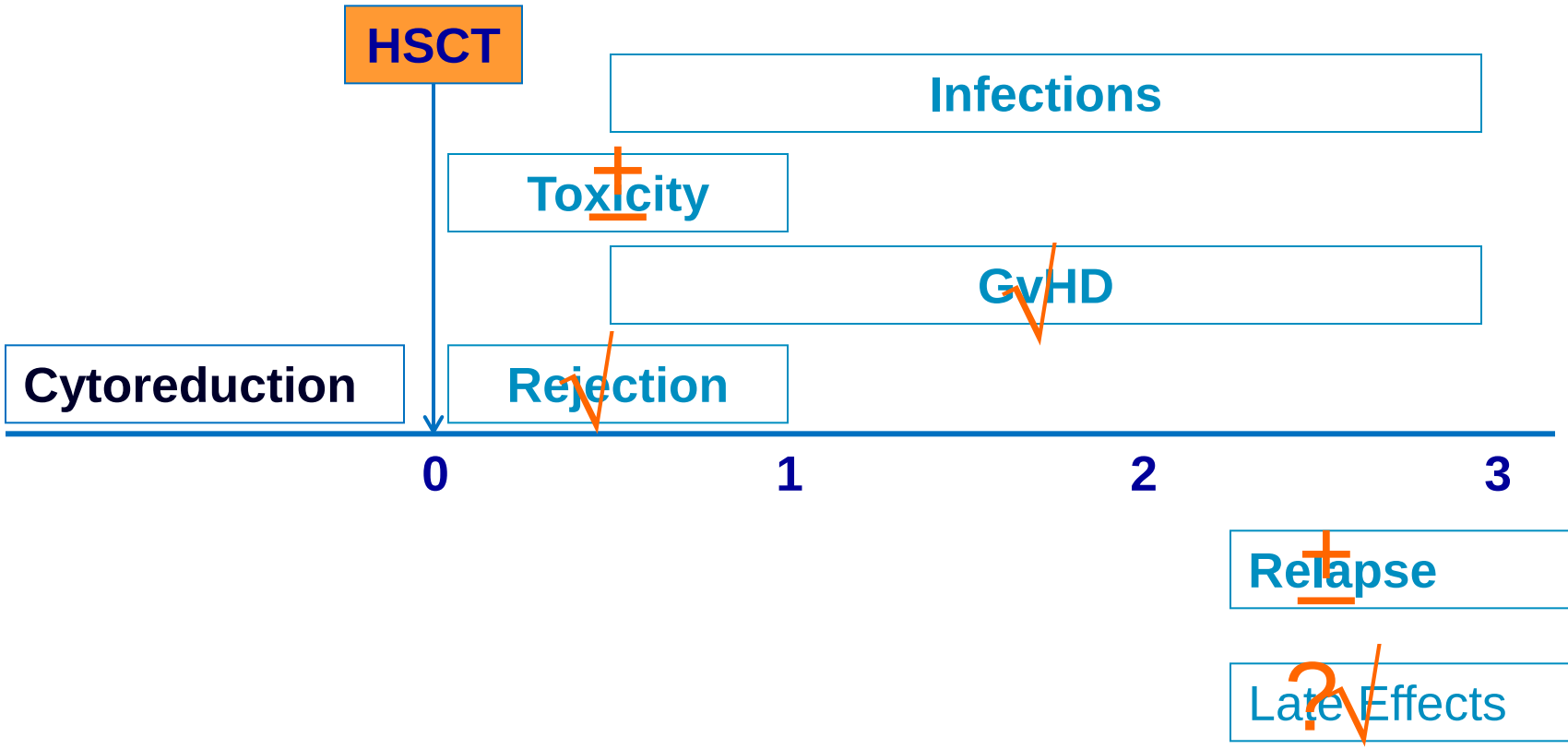
- The use of **T-cell depletion** has allowed to perform transplants successfully in patients with FA with no graft rejection and minimal risk of GvHD.

- The use of **FLU + low dose TBI and CY** followed by T-cell depleted transplants, has been associated with promising outcome in patients with FA and AA or MDS/AML.

- The use of **FLU + low dose BU and CY** followed by T-cell depleted transplants in patients with FA has been associated with no graft rejection and minimal GvHD as well. It is associated with comparable toxicity and comparable outcome

- Longer follow-up is needed to assess (1) late effects and (2) secondary neoplasms

HSCT CHECK – WISH LIST



FUTURE DIRECTIONS

Infections:

- We presently have the **Cell therapy** approach for CMV, EBV, Adeno
- Role for **Interleukin 7**?

Toxicity - Leukemia

- We need a better laboratory (animal?) model to to answer certain questions that are important for future HSTC trials.
  - The use of **Palifermin (KGF)** decrease **toxicity**
  - The use of other Cytoreductive agents for myeloablation and dosing determination with ?less **toxicity** than Busulfan including:
    - **Thiotepa - Melphalan - Clofarabine**
  - The use of **anti-leukemic** agents in patients with myeloid malignancies including
    - **5-Azacytidine or Decytabine - Clofarabine**

With the difference in results based on age and disease, we are proceeding with our Multi-Center Protocol #2 which is led, and will be presented by:

Thanks

- **Eva Guinan**

- **Stella Davies and Parinda Mehta**
- David Williams and Leslie Lehmann
- David Margolis
- Scott Baker and Akiko Shimamura

- **The Fanconi anemia Research Fund**

MSKCC

- All the Attending Physicians. Nurse Practitioners, Nurses at MSKCC
- Elizabeth Klein – Data management at MSKCC

The FAMILIES

The PATIENTS - the ones who are with us

Especially the ones who are no longer with us