

# SCIDX: Hematopoietic Cell Transplant and Gene Therapy Options

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I have no financial relationships to disclose that are relevant to this presentation

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCID*

- **Rationale:** replace defective with normal lymphocytes
- **Method:**
  - Find donor: sibling, haplo related, unrelated (adult, newborn)
  - Donor source: marrow, peripheral blood, cord blood
  - IV infusion  $\pm$  conditioning
- **Preventing rejection/"making space"**
  - **Immunosuppressive:** cytoxan, fludarabine, ATG, Campath
  - **Ablative:** busulfan
  - **Both:** thiotepa, melphalan, TBI
- **"Cure":** T cell reconstitution
  - Durable engraftment
  - Clear viral infections

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCID*

- Unique issues of treating SCID
  - Early diagnosis is difficult if no family history
    - Typically, normal term babies
    - Usually present with life threatening infections
      - PCP, RSV, CMV, Parainfluenza, Candida, adeno, etc
    - Chronic diarrhea: failure to thrive
    - Skin rashes (mat-fet GvHD, other)
  - Less tolerant of aggressive chemotherapy regimens, surgical procedures
    - Some have a DNA repair defect
  - Time to immune reconstitution is critical if pt infected

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCIDX*

- Unique features of SCIDX
  - Most common type of SCID – 40-50%
  - Relatively easy diagnostic tools
    - ILcγ protein expression
    - Genotyping, STAT5 activation
  - High incidence of prenatal maternal engraftment
  - Absent NK cell mediated graft resistance in majority
    - Immunosuppression not needed (T<sup>-</sup>, NK<sup>-</sup>)

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCIDX*

- Issues of Immune Reconstitution post HCT for SCIDX
  - Is ablation needed (all about stem cells)?
    - Without ablative therapy → T cell & ≤30% B cell
    - With ablative therapy → T & B cell
      - short/long term toxicity
  - Without ablation
    - Quality of T cell reconstitution?
    - Durability of T cell reconstitution?
    - Is HLA match a factor? vs haplocompatible donor

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCIDX*

- Types of Donors for SCIDX

- HLA matched sibling

- Genotypic match
- Donor immediately available
- ~100% engraftment without conditioning
- At least T cell reconstitution (30% B cell)
- 90-100% Survival

- Unrelated adult volunteer donor (MUD)

- 7/8 (9/10) or 8/8 (10/10) allele match
- Time for search (2-3 months) + 3 weeks to transplant
- ?>95% engraftment without conditioning (most are conditioned)
- T and B cell reconstitution (if conditioning used)
- Increased TRM from GVHD, pre-BMT infections, conditioning
- 63-81% Survival (all SCID); better with SCIDX

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCIDX*

- Types of Donors for SCIDX (continued)
  - Unrelated umbilical cord blood (UCB)
    - 4/6 – 8/8 match (A, B, C antigen & DRB1 allele)
    - Time for search (~1month for search, 72 hours to transplant)
    - ?>90% engraftment; unless 8/8 allele match most centers use conditioning (not been tested for SCIDX)
    - T & B cell reconstitution with conditioning
    - Increased TRM from GvHD, pre-BMT infections, conditioning, prolonged neutropenia/thrombocytopenia
    - Risk of autoimmune hemolytic anemia
    - 66-88% Survival (all SCID, *very limited numbers*)

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCIDX*

- Types of Donors for SCIDX (continued)
  - Haplocompatible relative
    - 4/8 matched parent (sibling, aunt, uncle, etc)
    - Donor immediately available so no waiting
    - ~100% engraftment without conditioning
    - At least T cell reconstitution (<30% B cell)
    - Early experience showed delayed T cell reconstitution and survival of 50-60% (T-B+ vs T-B-);
      - probably better for SCIDX but NK phenotype not delineated
    - More recent experience shows “normal” T cell reconstitution and survival of 61-98% (all SCID).

# *Severe Combined Immunodeficiency Diseases*

## *HCT for SCIDX*

- UCSF recent experience
  - 2000-2007 (BBMT 2008)
  - Prospective study of megadose CD34 and fixed CD3 haplocompatible HCT
    - No conditioning
    - PBSC
    - Isolex 300i + CD3 depletion (if necessary)
  - 15 pts with SCID entered who had no matched related donor
  - N=7 with SCIDX

# UCSF SCIDX Haplo Experience 2000-07

## Pre HCT Characteristics

UPN	CD3	CD4	CD19	CD16/56	PHA(%)	Maternal Engraft(%)	Pre-Tx Infections	Age @ Tx(mo)
401	121	16	3065	13	0	11	PCP	6.1
455	3	2	828	18	0	1	None	2.2
1056	314	0	4086	0	0	5	PCP	5.7
1057	1773	886	3656	111	1	24	PCP	5.7
1091	16	16	462	5	3	0	RSV PNA, Rota	5.7
1142	0	0	808	52	0	1	None	0.5
1148	30	20	0	1	0	87 (GvHD)	Rhinovirus, <i>Enterobacter</i> spp.	2.6

# UCSF SCIDX Haplo Experience 2000-07

## Transplant Characteristics

<b>UPN</b>	<b>Donor</b>	<b>Ag Mat</b>	<b>Condition</b>	<b>Source</b>	<b>CD34 (10<sup>6</sup>/kg)</b>	<b>CD3 (10<sup>4</sup>/kg)</b>	<b>DLI (10<sup>4</sup>/kg)</b>
401	M	4/6	NONE	PBSC	19	1	0
455	M	4/6	NONE	PBSC	23.4	1	0
1056	M	3/6	NONE	PBSC	28.2	3	0
1057	M	3/6	NONE	PBSC	28.3	3	0
1091	M	4/6	NONE	PBSC	20	1	3
1142	F	4/6	NONE	PBSC	18.4	6	0
1148	M	4/6	FLU90	PBSC	30.1	1	0

# UCSF SCIDX Haplo Experience 2000-07

## Engraftment and Survival

<b>UPN</b>	<b>%Donor CD3</b>	<b>%Donor CD19</b>	<b>%Donor CD14/15</b>	<b>aGVHD</b>	<b>cGVHD</b>	<b>Alive(mo)</b>
401	98	3	2	0	0	Y (95)
455	97	3	1	2	0	Y (74)
1056	96	0	0	2	Skin	Y (39)
1057	98	0	0	2	0	Y (39)
1091	79	0	0	0	0	Y (33)
1142	97	3	3	2	Skin	Y (24)
1148	100	100	100	2	0	Y (22)

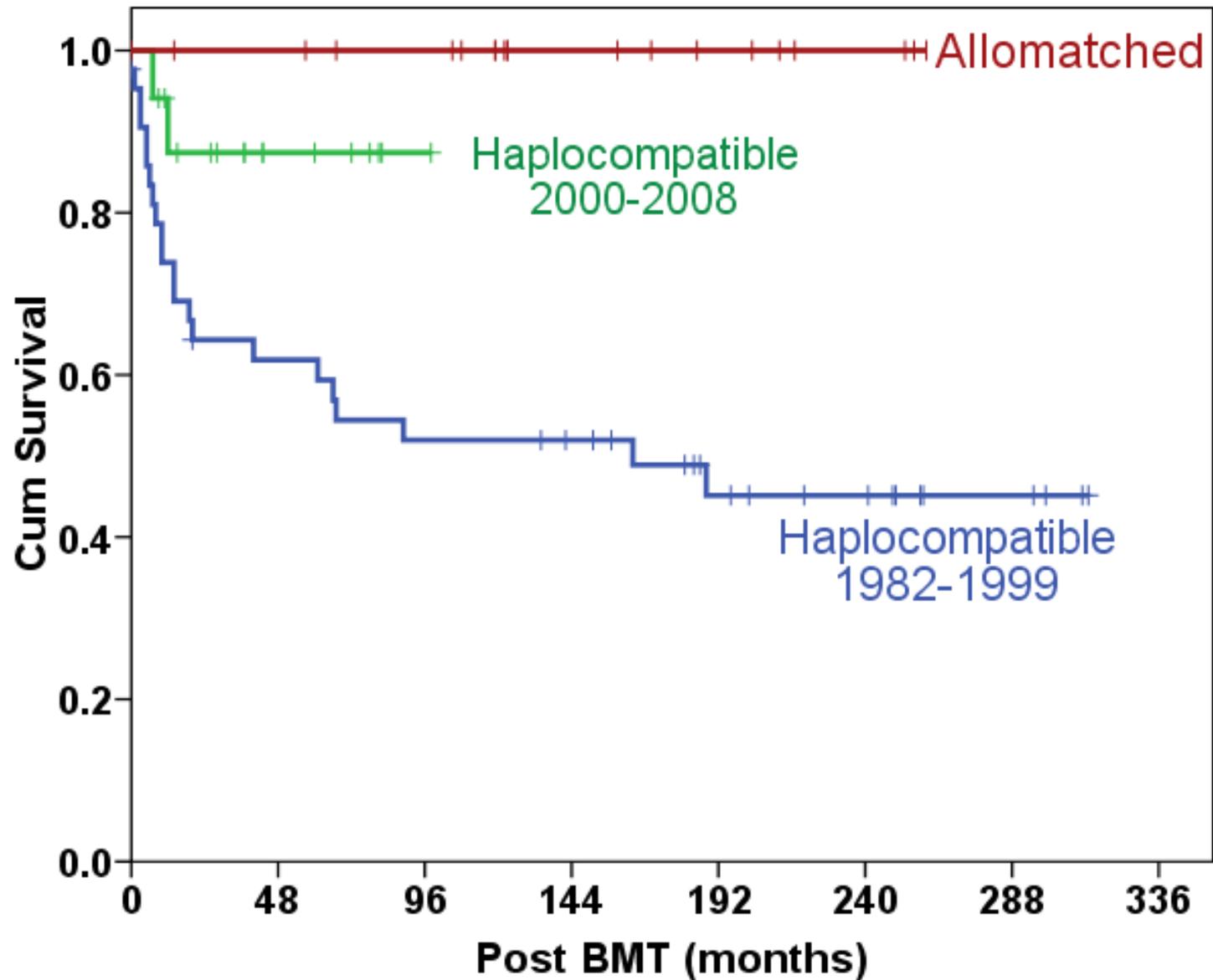
# UCSF SCIDX Haplo Experience 2000-07

## Time (mo) to Immune Reconstitution

<b>UPN</b>	<b>CD4 &gt;200</b>	<b>CD4 &gt;400</b>	<b>PHA &gt;50%</b>	<b>PHA &gt;90%</b>	<b>IgM &gt;50</b>	<b>ISH</b>	<b>Tet Ab</b>	<b>IV IG</b>
401	1.2	1.2	6.2	6.2	34	NR	ND	Y
455	1.1	1.1	3.4	12	46	46	***	N
1056	0.6	12	10.3	10.3	NR	NR	ND	Y
1057	1.1	3.5	3.5	5.5	NR	NR	ND	Y
1091	0.9	0.9	10.5	NR	NR	NR	ND	Y
1142	2.2	3.8	12.6	18.5	NR	NR	ND	Y
1148	0.8	9.2	6.1	9.2	5	13	16	N

# BMT for Children - Advances

## *SCID HSCT @ UCSF : Donor Match & Date*



# SCIDX: **Risks** of HCT with Alternative Donors

## – **MUD**

- Time to find a donor
- GvHD: 50% grade 2-4
- Organ toxicity: dependent on conditioning
- TRM especially in pts with viral infection, FTT: 10-20%

## – **UCB (unrelated)**

- Time to find a donor
- GvHD: 25% grade 2-4??
- Organ toxicity if conditioning used
- Delayed engraftment
- TRM especially in pts with viral infection, FTT: 10-20%

# SCIDX: Risks of Therapy Alternative Donors (continued)

## – **Haplocompatible TCD related**

- GvHD: 25-50% ≤grade 2
- Organ toxicity: none (no conditioning)
- Delayed kinetics of immune reconstitution; if megadose → equivalent to matched sib
- Autoimmune hemolytic anemia: 20% (we haven't seen it in SCIDX)
- Quality and durability of T cell reconstitution: ??

# Contraindications to **HCT** for SCIDX

- HLA matched relative
  - No contraindication
- MUD/UCB
  - Viral pneumonia (RSV, parainflu)
    - Time for search
    - Conditioning & GvHD will increase TRM
- Haplocompatible relative
  - Infections not a contraindication
    - Only issue would be speed of reconstitution
  - *Not every center has capability of doing TCD*
  - Severe maternal-fetal GvHD could be a relative contraindication



# SCIDX: Risks of Alternative Therapy

## – Gene therapy

- Risk of marrow harvest in an ill patient
- Risk of inadequate immune reconstitution
  - Especially in patient with untreatable viral infection
- Risk of insertional mutagenesis

# Contraindications to Gene Rx for SCIDX

- HLA matched donor available
  - Sibling
  - 8/8 allele matched adult unrelated donor
  - 8/8 matched umbilical cord blood (allele matched at DRB1)
- Untreatable pneumonia (RSV, parainfluenza)
  - Efficacy of novel transduction protocol/vector?
  - If there is delayed immune reconstitution pt won't last 6 months for haplo transplant
  - ?1<sup>st</sup> 5 patients until immune reconstitution defined
- Maternal-fetal GvHD??
  - Could be an indication

# Indications for Gene Therapy for SCIDX

- No HLA matched sibling
- No 8/8 allele matched MUD or 8/8 matched UCB
- Treatable viral infection (PCP, adenovirus, CMV)
- Able to tolerate marrow harvest