University of Wisconsin Newborn Screening for SCID Experience: Spanning the Spectrum

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Initial Presentation SCID infant #1

- Birth History: male infant born at 40 wks, via NSVD to parents without consanguinity.
- Newborn screen drawn on DOL 1
- DOL 2- Discharged home
- DOL 8- PCP contacted by Wisconsin State Lab of Hygiene with abnormal result for SCID screen

Drs. Mei Baker and Chuck Brokopp, Wisconsin State Lab of Hygiene

Identified SCID Infant #1: Initial Flow Cytometry

FLOW CYTOMETRY

- abs T cells: 111 (2500-5600)
- abs CD4 T cells: 56 (1800-4000)
- abs CD8 T cells: 56 (590-1600)
- abs B cells : 28 (430-3000)
- abs NK cells: 1112 (170-830)
- %CD45RO (memory T cells): 21 (3-16)
- %CD45RA (naïve T cells): 12 (77-94)
- Newborn screen repeated- absent TREC

Initial Management

- Admitted to AFCH in protective isolation
- Initiated antimicrobial prophylaxis
- Initiated intravenous gamma globulin
- Suspended breastfeeding
- Continued diagnostic testing for SCID

Diagnostic Testing Utilized

- Commercial genetic sequencing
- Research-based genetic sequencing with Dr. Jennifer Puck UCSF
- Commercial and research-based radiosensitivity testing (Dr. Gatti at UCLA, Drs. Cowan and Yannone UCSF and Lawrence Berkeley National Laboratory)
- T cell functional studies and FISH for maternal engraftment.
- ADA testing to Duke University, Dr. Michael Hirschfield

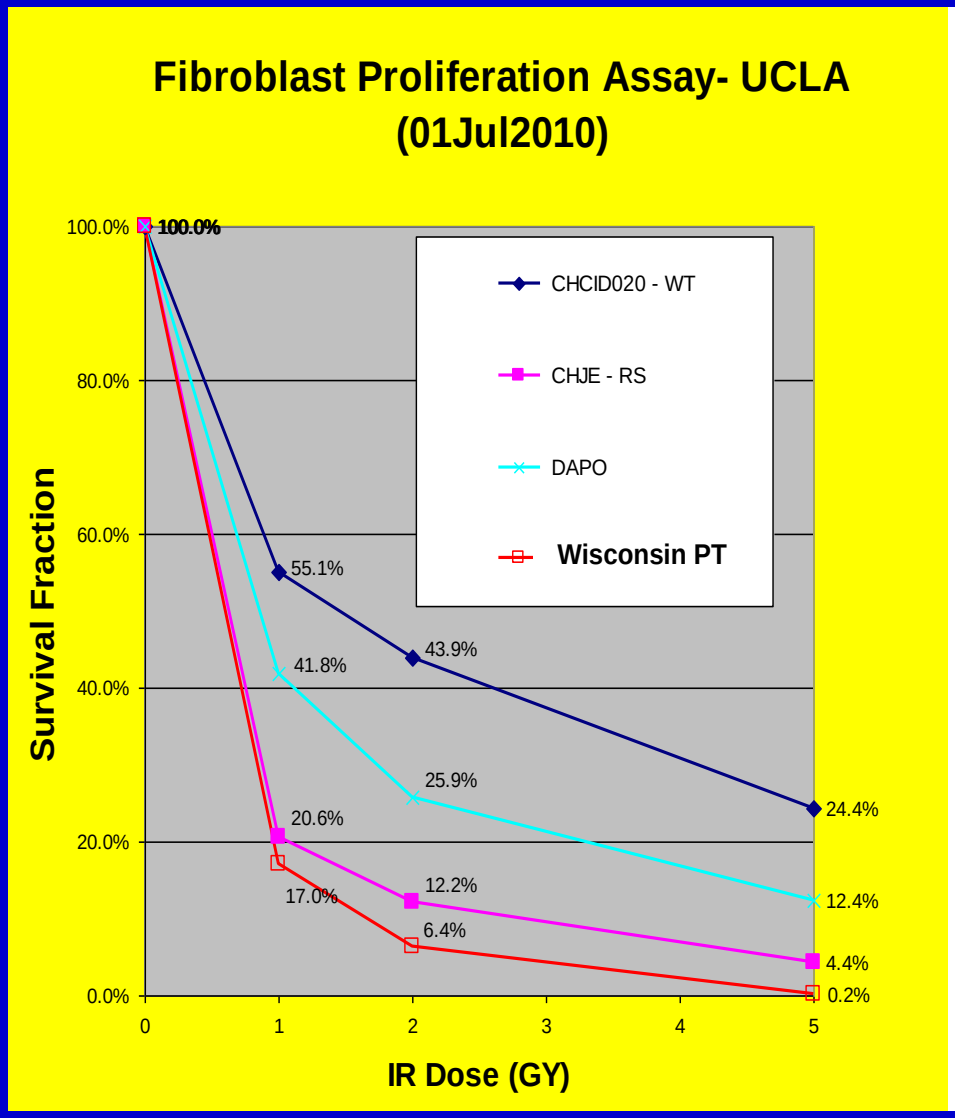
Gene sequencing

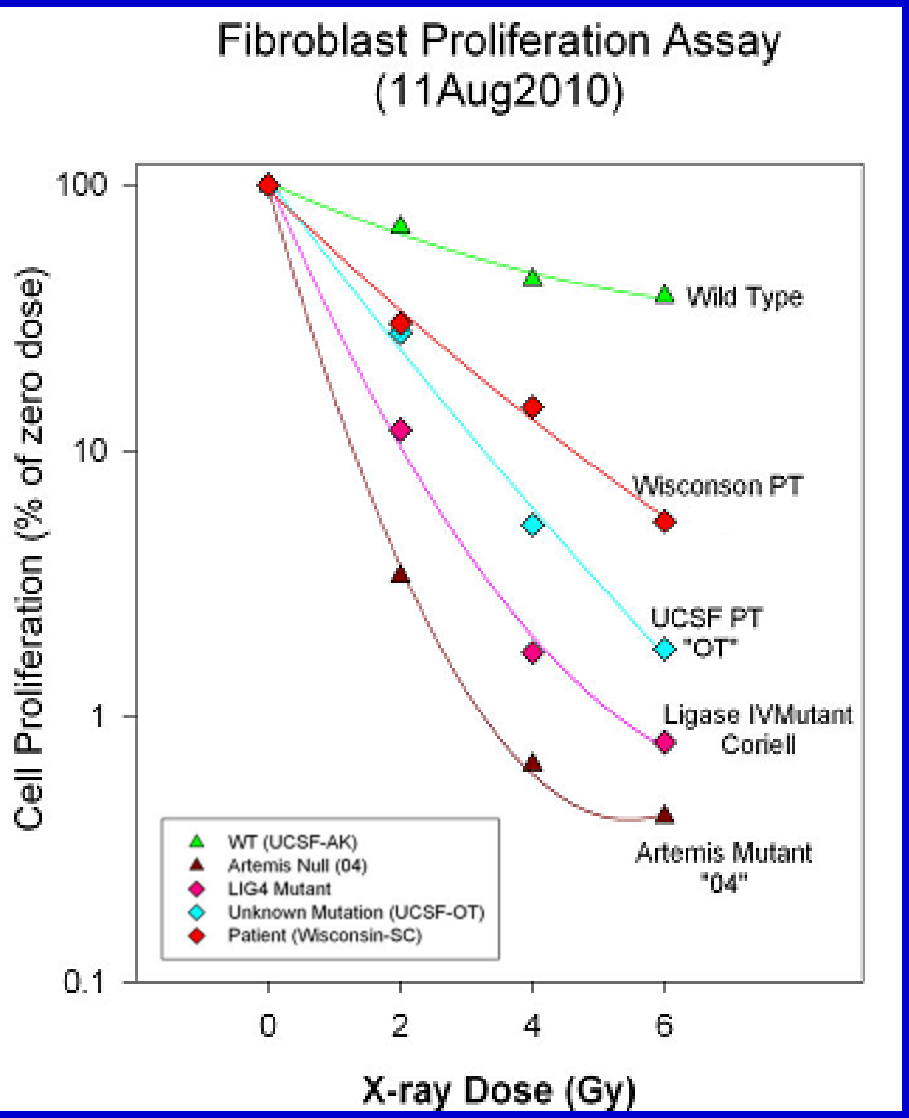
No deleterious mutations detected in:

- IL2γR, IL7Rα
- JAK3, CORONIN1A, AK2
- CD3δ, CD3ζ
- ADA
- DCLRE1C(Artemis)
- LIGIV
- RAG1/ RAG 2

Data generated by Dr. Jennifer Puck's laboratory and GeneDx

Fibroblast analysis





Data from the following laboratories: Drs. Richard Gatti, Mort Cowan and Steve Yannone

Identified SCID Infant #1: Persistent T-B-NK+ SCID Phenotype

	Patient 8 days	Patient 30 days	Patient 45 days	Normal range
Percent CD3+	8	18	11	51-77
Absolute CD3+	111	115	35	2500-5600
% CD3+CD4+	4	13	8	35-56
Abs. CD3+CD4+	56	83	26	1800-4000
%CD3+CD8+	4	6	4	12-23
Abs. CD3+CD8+	56	38	13	590-1600
% CD3-/CD16+	80	66	80	3-14
Abs. CD3-/CD16+	1112	421	256	170-830
%CD19+	2	3	5	11-41
Abs. CD19+	28	19	16	430-3000
media only	217			
PHA	4235			>100,000

Challenges in Decision-making for Curative Approach For SCID

- Timing of transplant—outcome better without pre-existing condition
- Donor source
- Conditioning

Transplant Decision

- High resolution HLA-A,B, C and DRβ1 matched cord blood identified.
- Patient received the following conditioning:

  Busulfan (maintain css 600 ng/ml): Days -9 to -6

  Fludaribine: Days -5 to -2

  rATG: Days -4 to -1
- GVHD prophylaxis: MMF and CsA

Dr. Ken DeSantes, Transplant physician University of Wisconsin

SCID infant #1 has increasing immune cell numbers after HLA-matched umbilical cord blood transplant

	Patient 45 days	Patient 113 days (D+36)	Patient 169 days (D+92)	Normal range
Percent CD3+	11	1	12	51-77
Absolute CD3+	35	6	420	2500-5600
% CD3+CD4+	8	0	8	35-56
Abs. CD3+CD4+	26	0	280	1800-4000
%CD3+CD8+	4	0	1	12, 23
Abs. CD3+CD8+	13	0	35	590-1600
% CD3-/CD16+	80	67	7	3, 14
Abs. CD3-/CD16+	256	375	245	170-830
%CD19+	5	13	77	11, 41
Abs. CD19+	16	73	2695	430-3000

Summary of SCID Infant #1

- Transplanted on DOL 77, tolerated procedure well.
- Discharged on DOL 107 and remains clinically stable.
- Molecular diagnosis is currently unknown. This may represent a novel mutation or a previously unknown presentation of a SCID-associated gene.
- This case provides evidence that implementation of TREC analysis on newborn screen could identify SCID patients early in order to successfully transplant patients while minimizing morbidity and mortality.

Identified SCID Infant #2: Initial Labs

CBC
WBC 4.2 HGB 18.1 HCT 54.5 PLT 211
ANC 3108 (1500-10000)
ALC 126 (2000-17000)

Flow Cytometry
Absolute T cells: 3
Absolute B cells: 4
Absolute NK cells: 1

Repeat TREC from peripheral blood: 0
Biochemical testing for ADA confirmed form of SCID

Initial Management

- Discharged to home with protective isolation
- Initiated PEG-ADA at 30U/kg twice weekly
- Initiated antimicrobial prophylaxis
- Initiated intravenous gamma globulin
- Continued breastfeeding

Monitoring Therapeutic Effects of PEG-ADA

st PADA: 2/22/10		Nominal	Plasma	Erythrocyte Nucleotides		
	Weeks of	weekly dose PEG-ADA	ADA µmol/h/ml	AXP µmol/ml RBC	dAXP µmol/ml RBC	% dAXP
Date	Therapy	U/kg/inj	*<0.5**	*1.465 ± 0.38**	*<0.002**	*<0.2**
6/21/10	0.0	-	-	0.437	0.394	47.4
7/6/10	2.1	30/30	47.00	1.272	0.149	10.5
7/20/10	4	30/30	56.87	1.831	0.116	5.9
8/16/10	8	30/30	63.83	1.523	0.019	1.2
8/30/10	10	30/30	62.58	1.384	0.018	1.3

Identified SCID Infant #2: Improving profound lymphopenia on PEG-ADA

	Patient cord blood	Patient 30 days	Patient 60 days	Normal range
ALC	147	945	850	2000-17000
Percent CD3+	2	16	53	51-77
Absolute CD3+	3	151	451	2500-5600
% CD3+CD4+		10	26	35-56
Abs. CD3+CD4+		95	221	1800-4000
%CD3+CD8+		4	24	12-23
Abs. CD3+CD8+		38	204	590-1600
% CD3-/CD16+	<1%	16	15	3-14
Abs. CD3-/CD16+	1	151	128	170-830
%CD19+	3%	68	32	11-41
Abs. CD19+	4	643	272	430-3000

Summary of SCID Infant #2

- Infant continues to grow and thrive.
- Infant remains infection-free.
- Plan is to proceed to gene therapy at the NIH once infant reaches 10kg.

UW NBS SCID cases: Span the Spectrum

SCID #1

- Molecularly undefinable SCID
- T-B-NK+ SCID
- Isolation in hospital

SCID #2

- Rapid metabolic test for screening
- Isolation at home
- Recombinant enzyme replacement
- Hematopoietic stem cell transplantation outcome fair
- Open protocols for gene therapy

Present Challenges

- Duration to follow genetically undefinable forms of SCID to ensure phenotype and move to curative approaches
- Rapid radiosensitivity test
- Donor selection and approach to transplant