Severe Combined Immunodeficiency (SCID) Data Collection

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Presented to the Advisory Committee on Heritable Disorders in Newborns and Children
April 24, 2019
The **Primary Immune Deficiency Treatment Consortium** is part of the Rare Diseases Clinical Research Network (RDCRN), a group of consortia and a Data Management and Coordinating Center, united by the NIH Office of Rare Diseases Research, National Center for Advancing Translational Sciences (NCATS).

Major support for PIDTC is from NIH NIAID.
- First U54 6-year Award 9/1/2009, Competitive renewal 9/1/2014
- Upcoming renewal for 3rd cycle, if funded, to start 9/1/2019

PIDTC goals are to conduct natural history studies in SCID, Wiskott-Aldrich syndrome and Chronic Granulomatous Disease.

Sites apply for membership, which is based on experience and commitment.

Patient Advocacy Groups have been critical collaborators, from the start, including Jeffrey Modell Foundation, Immune Deficiency Foundation, SCID Angels for Life Foundation.
PIDTC Organization

• 44 Centers in US and Canada [1749 subjects enrolled]

• PIDTC Protocols
  6901 SCID Prospective, Longitudinal [293 enrolled]
  6901 SCID Retrospective, Cross-sectional [743 enrolled]
  6903 CGD Prospective and retrospective [406]
  6904 WAS Prospective and retrospective [307]
SCID Paradigm Shift with Newborn Screening

TREC: T Cell Receptor Excision Circle

TCRA locus

SCID Diagnosis by TREC Screening vs. Infection, Family History in PIDTC Cases
Central IRB

- Single IRB is now mandated by NIH for multicenter clinical studies (non-U.S. sites exempt).
- UCSF IRB is the IRB of record for PIDTC, thanks to Tara Bani, UCSF PIDTC, and Laurie Herraiz, UCSF IRB.
- Reliance agreements are in place for nearly all U.S. Sites (not the 5 Canadian sites).

**SCID Definitions**

**Typical SCID**
- <300 (autologous) CD3 T cells/uL
- <10% of normal proliferation to PHA
- Supported by detectable maternal T cells in peripheral blood
- Proven deleterious defect(s) in a known SCID gene.

**Leaky (Atypical) SCID**
- 300-1500 or more CD3 T cells, but few naive T cells
- Reduced (10%-50% of normal) proliferation to PHA
- No maternal T cells detectable
- Supported by incomplete defect(s) in a known SCID gene

**Omenn syndrome**
- Oligoclonal T cells
- Reduced proliferation to PHA (10%-50% of normal)
- Erythoderma, hepatosplenomegaly, eosinophilia, and elevated serum IgE antibody
Prospective SCID Data Collected

CIBMTR (legal requirement to report all USA transplants)
SCID Research Form has extensive transplant details
- SCID Genotype
- Phenotype
- Donor/recipient HLA
- Conditioning (agents, dose/exposure)
- Cell dose
- GVHD

PIDTC Case report forms
- Eligibility (voting panel, genotype, mutation police)
- Demographics, study withdrawal or death
- Early life features (NBS, dx trigger, nursing, infections)
- Hematopoietic cell transplant
- Enzyme replacement therapy (ADA)
- Gene therapy (XSCID, ADA)
- Subsequent treatment (HCT, boost, ERT)
- Follow up at 100 d; 6 m; 1, 2, 3, 4, 5 and 8 y

PIDTC
NBSTRN DMCC
Database
Prospective SCID Samples Collected

**All SCID enrollees**
- DBS for TREC
- RNA (PaxGene tube) for spectratyping to measure T cell diversity
- Baseline, 100 d, 6 m, 1 and 2 y

**Special studies through Pilot Program**
- B cell development
- T cell exhaustion
- Host and donor HLA restriction for patients with EBV, CMV infection

PIDTC NBSTRN DMCC Database
Sample of Case Report Form

This Day 100 Assessment form captures history within ±2 weeks of the scheduled visit date.

**DATE OF CONTACT WITH PATIENT**
Date of actual contact with the recipient to determine the medical status for this visit date’s follow-up report.

**HEALTH ASSESSMENT**

1. **Current Treatment**
   a. Is the patient on enzyme replacement therapy at the present time?
      - Yes, if yes, what date was the treatment initiated? __/__/____ (dd/mm/yyyy)
      - No
   b. If patient was previously on enzyme replacement therapy, what was the date of the final treatment? __/__/____ (dd/mm/yyyy)
   c. Has the patient received gene therapy?
      - Yes, if yes, what was the date? __/__/____ (dd/mm/yyyy)
      - No

2. **Additional Health Assessment**
   - Height: ___ cm ___ to ___ cm ___ for age or Not done
   - Weight: ___ kg ___ to ___ kg ___ for age or Not done

   Nutritional source (select all that apply):
   - Enteral supplementation (NG, G-tube, oral)
   - Parenteral nutritional support
   - PO

   Does the patient have lymphadenopathy?
   - Yes

3. **Infectious Disease Assessment**
   Did the patient have any infection(s) prior to initiation of conditioning for HCT therapy?
   - Yes, if yes, have all infections resolved?
     - Yes
     - No (Please enter any unresolved infection on CBMRTR Form 2131)

4. **Autoimmune Disease Assessment**
   Was the patient diagnosed with any of the following autoimmune diseases? (check all that apply)
   - None
   - Hypothyroidism
   - Thrombocytopenia
   - Neutropenia (ANC<500)
   - Arthritis
   - Myositis
   - Nephritis
   - Bronchial obliterans or other pulmonary autoimmune disease
   - Villigo
   - Apeopia
   - Inflammatory bowel disease
   - Neurodegeneration
   - Vasculitis
   - Other: ____________________________

5. **Brain**


1. Genetic/pathogenic evaluation of newly-diagnosed SCID patients.

- ~50 SCID infants/year at PIDTC Centers
- Clinical SCID gene panel; some with clinical WES

- Enroll ~3-5/year with unknown/unproven genotype with parents/siblings;
  Collect patient pre-treatment PBMC and/or fibroblasts for genomics and iPS

- Genomics: WGS for trios (patient, parents)

- Gene expression: RNA seq in T cells from parents (and patient if possible)

- In vitro function testing:
  - T-cell intrinsic: primary PB CD34 cell differentiation
  - Thymic: iPS thymic epithelial cell model

- Candidate variants (exome and regulatory) for genes expressed in developing HSC, thymocytes, thymus stroma. Validation through various functional testing.

- Edit variants into iPS cells for in vitro T cell differentiation and thymic epithelial cell differentiation.
**Selected Goals for Future**

2. Quality of life assessments with validated PROMIS Pediatric self- and proxy-reported health measurements.

<table>
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<th>Age 5-7 y</th>
<th>Age 8-17 y</th>
<th>Age 18 y +</th>
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<tr>
<td>Current 6901+6902 patients</td>
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</tr>
<tr>
<td>Aged 5-7 y at start of 6907</td>
<td>Aged 8-17 y at start of 6907</td>
<td>Aged 18+ y at start of 6907</td>
</tr>
<tr>
<td>≥5 years post-HCT</td>
<td>≥5 years post-HCT</td>
<td>≥5 years post-HCT</td>
</tr>
<tr>
<td>Complete Parent Proxy PROMIS Measures Only</td>
<td>Ages 8-10 y + 10-17 y (if unable to self-complete): Complete both Pediatric &amp; Parent Proxy PROMIS Measures</td>
<td>Complete Adult PROMIS Measures Only</td>
</tr>
<tr>
<td>a. General Profile 37</td>
<td>Ages 10-17 (if able to self-complete): Complete Pediatric PROMIS Measures</td>
<td>a. General Profile 37</td>
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<tr>
<td>b. Global Health 7+2</td>
<td>a. General Profile 37</td>
<td>b. v1.2 Global Health</td>
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<tr>
<td>c. Cognitive Function-Short Form 7a</td>
<td>b. Global Health 7+2</td>
<td>c. PROMIS-29 v2.1</td>
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<tr>
<td>d. Fatigue-Short form 10a</td>
<td>c. Cognitive Function-Short Form 7a</td>
<td>d. 2.0 Cognitive Fatigue 7a short form</td>
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</table>
3. CMV evaluation and natural history sub-study.

SCID diagnosed via Newborn Screening

Infant managed according to local protocol with isolation (either in hospital or at home). Breastfeeding held or not per local site. Infant age will be about 5-21 d, at consent, study d 0.

Baseline CMV Samples:

**Mother**
- Serum CMV IgG, IgM; CMV PCR.
- Breastmilk CMV PCR.
- Saliva CMV PCR.

**Infant**
- Blood, Urine, & Saliva for CMV PCR.
- Liver function tests, bilirubin.
- Request newborn screen DBS for CMV PCR.

Mother CMV IgG, IgM neg:
- Infant not CMV exposed.
- Allow nursing; continue surveillance.
  - Maternal milk & saliva CMV PCR at 1 wk; if neg stop.
  - Infant serum CMV PCR at 1, 3 wk, then per local SOC until engrafted >50 CD4 T cells/μL.
- If (+) move to CMV positive

Mother CMV IgG pos:
- Infant CMV exposed.
- Local protocol for nursing; continue surveillance.
  - Maternal milk, saliva CMV.
  - Infant serum CMV PCR & LFTs; if neg then per local protocol until engrafted with >50 CD4 T cells/μL.
- If (+) move to CMV positive

Infant CMV PCR positive: Infected
- Most sites stop nursing.
  - Maternal studies as with exposed infant.
  - Infant serum CMV PCR, LFTs, CBC/diff q wk.
- Infant ophtho, neuro, & audio exams.
  - Treatment per local SOC with anti-virals +/- CTLs.
- If (+) move to CMV positive

Goals for Future
• The Primary Immune Deficiency Treatment Consortium (U54-AI082973) is part of Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS)

• The PIDTC is funded through collaboration between NCATS-ORDR, and the National Institute of Allergy and Infectious Diseases (NIAID)
Mort Cowan, first PI of the PIDTC, is dedicated to raising a new generation of leaders in Primary Immune Deficiencies.