

Workshop summary

Primary Immune Deficiency Treatment Consortium (PIDTC) report

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The Primary Immune Deficiency Treatment Consortium (PIDTC) is a network of 33 centers in North America that study the treatment of rare and severe primary immunodeficiency diseases. Current protocols address the natural history of patients treated for severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and chronic granulomatous disease through retrospective, prospective, and cross-sectional studies. The PIDTC additionally seeks to encourage training of junior investigators, establish partnerships with European and other International colleagues, work with patient advocacy groups to promote community awareness, and conduct pilot demonstration projects. Future goals include the conduct of prospective treatment studies to determine optimal therapies for primary immunodeficiency diseases. To date, the PIDTC has funded 2 pilot projects: newborn screening for SCID in Navajo Native Americans and B-cell reconstitution in patients with SCID after hematopoietic stem cell transplantation. Ten junior investigators have received grant awards. The PIDTC Annual Scientific Workshop has brought together consortium members, outside speakers, patient advocacy groups, and young investigators and trainees to report progress of the protocols and discuss common interests and goals, including new scientific developments and future directions of clinical research. Here we report the progress of the PIDTC to date, highlights of the first 2 PIDTC workshops, and consideration of future consortium objectives. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Allogeneic hematopoietic cell transplantation, gene therapy, primary immunodeficiency, clinical trial

In 2008, North American experts in the diagnosis and treatment of primary immunodeficiency (PID) diseases met at the National Institutes of Health (NIH) in Bethesda, Maryland,

Abbreviations used

ADA:	Adenosine deaminase
CGD:	Chronic granulomatous disease
CIBMTR:	Center for International Blood and Marrow Transplant Research
EBMT:	European Group for Blood and Marrow Transplantation
ESID:	European Society for Immunodeficiencies
GT:	Gene therapy
GVHD:	Graft-versus-host disease
HCT:	Hematopoietic cell transplantation
IEWP:	Inborn Errors Working Party
MAC:	Myeloablative conditioning
MUD:	Matched unrelated donor
NBS:	Newborn screening for SCID
NIAID:	National Institute of Allergy and Infectious Diseases
NIH:	National Institutes of Health
NK:	Natural killer
PID:	Primary immunodeficiency
PIDTC:	Primary Immune Deficiency Treatment Consortium
RIC:	Reduced-intensity conditioning
SCETIDE:	Stem Cell Transplantation for Immunodeficiencies in Europe
SCID:	Severe combined immunodeficiency
USIDNET:	United States Immunodeficiency Network
WAS:	Wiskott-Aldrich syndrome

to discuss opportunities for collaboration, the feasibility and prioritization of clinical research questions, and the scope of expertise that would be needed to establish an effective multicenter consortium.¹ Historically, procedures for hematopoietic cell transplantation (HCT) have differed according to local practice, with relatively few patients treated at each center. Therefore multicenter longitudinal retrospective, prospective,

and cross-sectional protocols were designed to capture, for the first time in a common comprehensive database, survival and other outcomes after HCT, gene therapy (GT), or enzyme

replacement therapy for PIDs performed in North America. The results of these studies were envisioned to become a resource and foundation for the design of future prospective

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interventional studies. The group has worked together successfully to establish the Primary Immune Deficiency Treatment Consortium (PIDTC), which currently includes 33 centers in North America with expertise in HCT for PIDs and is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, NIH. PIDTC clinical studies in severe combined immunodeficiency (SCID) are now well underway, and protocols in Wiskott-Aldrich syndrome (WAS) and chronic granulomatous disease (CGD) are expected to open in 2013 (Table I).

To evaluate the progress of PIDTC protocols, review new advances, and consider the best directions for future clinical research, a PIDTC Annual Scientific Workshop has been held since 2011 to bring together the membership of the consortium; invited outside speakers, including European colleagues; young investigators and trainees; and patient advocacy groups.

The purpose of this interim report on the progress of the PIDTC is to revisit the priorities presented in the report of our consensus workshop at the NIH in 2008,¹ assess the work of this group and others in the immune deficiency community to meet those objectives, and provide an update on key questions that remain for future investigation. We will also briefly present the immediate next goals of the PIDTC.

PIDTC MISSION

Conduct of multicenter clinical studies

The initial focus of the consortium is on SCID, WAS, and CGD. Two PIDTC natural history studies for the prospective and retrospective analysis of outcomes of treatment for SCID are currently open (Table I). Cross-sectional evaluation, including current status and quality of life, is underway for surviving subjects in the retrospective study. Similar protocols are expected to open in 2013 for CGD and WAS.

Conduct of pilot/demonstration projects

The PIDTC also funds a pilot/demonstration project every 2 years. The initial project was a study of newborn screening for SCID (NBS) on the Navajo Reservation, where the incidence of Artemis-deficient SCID is high (discussed below). The second project is an examination of aspects of recovery of B-cell function after HCT for SCID.

Administrative and operations partnerships

Several partnerships are critical to the progress of the PIDTC. Administrative operations for the PIDTC are based at the University of California San Francisco and University of California San Francisco Benioff Children's Hospital and at the Data Management and Coordinating Center of the Rare Diseases Clinical Research Network, University of South Florida (<http://rarediseasesnetwork.epi.ucsf.edu/PIDTC>). The Center for International Blood and Marrow Transplant Research (CIBMTR; Table II)^{2,3} collects part of the prospective data for the PIDTC natural history studies. To refer patients to PIDTC participating centers, for PIDTC protocols, or both, see the ClinicalTrials.gov Web site for institutional review board–approved studies (Table I), the PIDTC Web site above, or both.

Communication with patient advocacy groups

The cooperation and support of representatives of patients with PIDs and their families are essential to the success of the PIDTC. Working partners include the Immune Deficiency Foundation, the Jeffrey Modell Foundation, the Chronic Granulomatous Disease Association, the Wiskott-Aldrich Foundation, the SCID Family Network, and the SCID Angels for Life Foundation. Contact information for the advocacy groups is provided in Table E1 in this article's Online Repository at www.jacionline.org; to register patients with PIDs in the United States Immunodeficiency Network (USIDNET), see Table II.

Mentoring and training young investigators

The PIDTC sponsors research awards to young investigators and invites the awardees to present their work at the PIDTC Annual Scientific Workshop. To date, 10 trainees and junior faculty have been funded with 1-year \$25,000 awards to support research in PIDs.

Scientific collaboration nationally and internationally

The PIDTC has worked consistently to strengthen scientific interaction between North America and international colleagues in the field. Members of the Inborn Errors Working Party (IEWP) of the European Group for Blood and Marrow Transplantation (EBMT)/European Society for Immunodeficiencies (ESID) are invited to the PIDTC workshops, and members of the PIDTC participate in IEWP annual meetings.

ALLOGENEIC HCT AS CURATIVE THERAPY FOR SCID: PIDTC CLINICAL STUDIES

In the initial consensus workshop at the NIH in 2008, the group recommended that capture of the cumulative experience of HCT for SCID in North America by means of natural history studies was essential.¹ Currently, the PIDTC is conducting both retrospective and prospective studies directed to this purpose (Table I). Outcomes that are being assessed include overall survival, lineage-specific engraftment and immunologic recovery, and current status and quality of life; analysis of the variables that affect these outcomes will include patient genotype and phenotype, donor type, donor source, HLA matching, and any conditioning received before HCT. Cross-sectional studies of subjects surviving at least 2 years after HCT will assess immune reconstitution, late effects, and quality of life. Common data points are collected across the multiple clinical sites, with outcomes analyzed for the group as a whole. The study design and databases of the PIDTC protocols were developed so that key questions, as identified in the consensus workshop at the NIH in 2008 (see Table E2 in this article's Online Repository at www.jacionline.org),¹ can be analyzed. The PIDTC collaborates actively with the CIBMTR to share prospective data collected by the CIBMTR that is relevant to PIDTC protocols, and this partnership is essential to the success of the PIDTC studies.

To date, the PIDTC has evaluated the presenting characteristics of the first 50 children given a diagnosis of SCID by consortium centers since 2010 (Protocol 6901).⁴ We are in the process of evaluating the collected outcome data for children with SCID treated with HCT in North America at PIDTC centers between January 1, 2000, and December 31, 2009 (Protocol 6902; manuscript in preparation).

TABLE I. PIDTC protocols

Protocol no., title, principal investigators,* and ClinicalTrials.gov identifier†	Therapy	Status	Target enrollment, estimated	Mechanistic studies
6901: A prospective natural history study of diagnosis, treatment, and outcomes of children with SCID disorders Principal investigators: Rebecca Buckley Morton Cowan ClinicalTrials.gov identifier: NCT01186913	HCT, gene transfer, or enzyme replacement	Recruiting	SCID: 58 per year; leaky SCID, Omenn syndrome, reticular dysgenesis: 14 per year	1) Radiation sensitivity: Pre-HCT testing of $T^+B^-NK^+$ SCID and/or Artemis, ligase IV, Cerunnos, or RAG genotypes 2) T cells: Post-HCT T-cell receptor excision circles; repertoire diversity by spectratyping or $V\beta$ use 3) B cells: Post-HCT reconstitution, function, and dysregulation; analysis of γc expression on $CD19^+$ cells and plasmablast differentiation (limited to X-linked SCID and JAK3 deficiency)
6902: A retrospective and cross-sectional analysis of patients treated for SCID (1968-2010) Principal investigators: Richard O'Reilly Morton Cowan ClinicalTrials.gov identifier: NCT01346150	HCT; gene transfer; or enzyme replacement	Recruiting	739; with about 150 currently alive at 5 y after HCT and >200 currently alive at 10 y after HCT	Cross-sectional analysis 1) T cells: T-cell receptor excision circles, repertoire diversity by spectratyping or $V\beta$ use 2) T-cell HLA restriction: Compare antigen-specific HLA restricted by engrafted donor-derived T cells and the donor's own T cells after unmodified or T cell-depleted transplantations (limited to selected subjects) 3) B cells: Analysis of γc expression on $CD19^+$ cells and plasmablast differentiation (limited to X-linked SCID and JAK3 deficiency) 4) NK cells: Functional and phenotypic attributions of NK tolerance in long-term SCID survivors after unmodified or T cell-depleted transplantations 5) CD34⁺ progenitor cells: Quantitate proportion of donor-derived clonogenic $CD34^+$ cells in peripheral blood 6) Molecular diagnosis: Genotyping; mutation (if not performed previously; separate research protocol and consent)
6903: Analysis of patients treated for chronic granulomatous disease (since 1995) Principal investigators: Elizabeth Kang Harry Malech Luigi Notarangelo	HCT or conventional therapy; those receiving conventional therapy will be matched for both age and oxidase activity of the subject undergoing HCT with whom they are paired and must have been alive at the age at which the subject undergoing HCT received transplantation.	In development; IRB submission anticipated in 2013	Sixty retrospective and 12 new transplant patients per year; 120 control nontransplant patients	Cross-sectional analysis 1) Definition of CGD subtype: Western blot gene testing and/or mother demonstrates X-linked carrier mosaicism based on results of nitroblue tetrazolium or DHR activity assays 2) Molecular diagnosis: Genotyping; mutation (if not performed previously; separate research protocol and consent) 3) DHR carrier study: Durability of DHR activity in carrier donors and recipients 4) Microbiome study: Gastrointestinal tract and skin (Steve Holland)

(Continued)

TABLE I. (Continued)

Protocol no., title, principal investigators,* and ClinicalTrials.gov identifier†	Therapy	Status	Target enrollment, estimated	Mechanistic studies
6904: Analysis of patients treated for Wiskott-Aldrich syndrome (since 1998) Principal investigators: David Rawlings Lauri Burroughs Alexandra Filipovich Luigi Notarangelo	HCT or gene transfer	In development; IRB submission anticipated in 2013	Two hundred fifty retrospective and 29 new patients/year; 58 currently alive at 5 y after HCT and >70 currently alive at 10 y after HCT	Prospective and/or cross-sectional analysis 1) T cells: Repertoire diversity by means of deep sequencing 2) B cells: KRECs; repertoire diversity by means of deep sequencing; BAFF/APRIL level in serum 3) NK cells: CD107a degranulation assay 4) Lineage-specific chimerism by means of flow cytometry (WAS protein expression) 5) Autoantibodies: Microarray analysis

BAFF/APRIL, B cell-activating factor of the TNF family/a proliferation-inducing ligand; DHR, dihydrorhodamine; KREC, κ -deleting recombination excision circle; JAK3, Janus kinase 3.

*Principal investigator and co-principal investigator(s).

†Additional information about studies that are IRB approved, including study locations and contact information, is available at the ClinicalTrials.gov Web site.

PILOT PROJECT FOR NEWBORN SCREENING OF SCID

Recognizing that the diagnosis of SCID early in life would allow life-saving anti-infective measures and optimal HCT,⁵ the PIDTC contributed to a pilot study to develop an NBS test in Athabascan-speaking Navajo Native Americans. A founder mutation in the *DCLRE1C* (Artemis) gene causes autosomal recessive SCID in an estimated 1 in 2000 births in this population,⁶ a 20-fold higher incidence of SCID than estimated in the general population. In May 2010, SCID was officially added to the recommended uniform panel of screening tests for all newborns in the United States.^{7,8}

GRAFT FAILURE AFTER HCT FOR SCID

Graft failure is a relatively frequent complication of HCT for SCID,⁹ especially when no conditioning or a reduced-intensity conditioning (RIC) regimen^{10,11} is used for HCT from donors other than HLA-matched siblings, although graft failure can also occur when myeloablative conditioning (MAC) is used. North American (n = 20) and European (n = 5) centers were surveyed as to their management of the need for retransplantation of patients with SCID. The group defined failure of T-cell engraftment as undetectable CD3⁺ T cells and absence of donor T-cell chimerism occurring at 3 months (90 days) after HCT for T cell-depleted grafts and at 2 months (60 days) after HCT for unmanipulated grafts, independent of the type of conditioning (none, RIC, or MAC; manuscript submitted).

KEY QUESTIONS IN HCT FOR SCID (SEE TABLE E2)

The effect of the transplantation regimen on the extent and durability of T-cell, B-cell, and natural killer (NK) cell lineage-specific reconstitution and concerns regarding the long-term toxic effects of any conditioning used are critical questions in allogeneic HCT for SCID.^{1,12,13} The consortium has reviewed the published experience of B-cell reconstitution after allogeneic HCT for SCID when using no

conditioning versus using a conditioning regimen by means of a debate during the PIDTC Second Annual Scientific Workshop in 2012.¹²

We now add the following questions:

1. Regarding T-cell, B-cell, and NK cell reconstitution after HCT for SCID, what determines the kinetics, level of reconstitution, durability, and quality of immune reconstitution? Can a preparative regimen be designed to facilitate the reconstitution of a particular lineage (or lineages) while minimizing patient toxicity? What is the role of the thymus in this process? What differences in outcomes are attributable to the patient's underlying genetic defects? What is the contribution of CD34⁺ stem cell versus common lymphoid progenitor engraftment in determining long-term T-cell reconstitution? Are there aspects of recovery of T-cell numbers, phenotype, and function that affect the recovery of B-cell function? What are the critical determinants of reconstitution of B-cell function, and are they distinct among SCID genotypes?
2. What is the role of autologous NK cells in transplantation outcome for SCID, particularly in patients with T⁺B⁺NK⁺ SCID, which includes the recombination-activating gene and Artemis genetic defects?¹⁴ What is the role of NK cells in graft rejection, can NK cells be suppressed/ablated by using nonchemotherapy approaches, and can the NK cell-specific receptors and ligands be manipulated to promote engraftment and reduce the risk of graft-versus-host disease (GVHD) after transplantation?

ALLOGENEIC HCT AS CURATIVE THERAPY FOR NON-SCID DISEASES: PIDTC CLINICAL STUDIES

In 2008, the PIDTC recommended a study of the cumulative North American experience of HCT for WAS and CGD by using natural history studies; these are expected to open in 2013 (Table I). Cross-sectional studies of subjects surviving at least 2 years after HCT will assess immune function, late effects, and

TABLE II. Clinical research database resources in PIDs

Database	"Owner" and primary financial resource(s)	Required or voluntary	Year started
United States Immunodeficiency Network (USIDNET) Contact: http://www.usidnet.org/ USIDNET PID registry Contact: http://www.usidnet.org/pub/Disease-Registry	Immune Deficiency Foundation (IDF), Towson, Md; NIH, NIAID U24 (research resource) grant award, PI: Charlotte Cunningham-Rundles, MD, PhD (Mount Sinai Medical Center) Nonprofit with US Government and corporate sponsorship	Voluntary	1997 (CGD started 1992)
CIBMTR Contact: http://www.cibmtr.org/pages/index.aspx CIBMTR Immune Deficiencies and Inborn Errors Working Committee Contact: http://www.cibmtr.org/About/WhoWeAre/ Committees/Working/pages/index.aspx	Medical College of Wisconsin, Milwaukee, Wis; NIH, NCI (NHLBI and NIAID co-fund) U24 (research resource) grant award, PI: Mary Horowitz, MD, MS; HRSA SCTOD Contract Awards, PI: Douglas Rizzo, MD, MS Nonprofit with US Government and corporate sponsorship	Registration is required for each allogeneic transplantation performed in the United States (for the SCTOD, as required by US law) Transplantation centers worldwide voluntarily submit allogeneic transplantation data	1972
ESID Contact: http://www.esid.org/ ESID registry Contact: http://www.esid.org/registry ESID Bone Marrow Transplantation and Gene Therapy Working Party Contact: http://www.esid.org/bone-marrow-transplantation	Nonprofit with corporate sponsorship	Voluntary	1994 (informal organization started 1983)
EBMT Contact: http://www.ebmt.org/Contents/Pages/Default.aspx EBMT IEWP Contact: http://www.ebmt.org/Contents/About-EBMT/ Who-We-Are/Workingparties/Pages/Working-parties. aspx	Nonprofit with corporate sponsorship	Voluntary	1974
SCETIDE; a Collaboration of EBMT and ESID	NA	Voluntary	1968
Resource of Asian Primary Immune Deficiency Diseases (RAPID) Contact: http://rapid.rcai.riken.jp/RAPID	RAPID is a joint collaboration between the Immunogenomics Research Group at RIKEN Research Center for Allergy and Immunology in Yokohama, Japan, and the Institute of Bioinformatics in Bangalore, India Funding: Special Coordination Funds for Promoting Science and Technology, from the Ministry of Education, Culture, Sports, and Science of Japan Funding for open access charge: RIKEN Research Center for Allergy and Immunology, Yokohama, Japan	NA	2009

HRSA, Health Resources and Services Administration; IRB, institutional review board; NA, not applicable; NCI, National Cancer Institute; PI, primary investigator; RAG, recombination-activating gene; SCTOD, Stem Cell Transplant Outcomes Database.

quality of life. PIDTC Protocols 6903 (CGD) and 6904 (WAS) will address most of the 2008 consensus workshop recommendations for these diseases.¹

KEY QUESTIONS IN HCT FOR NON-SCID DISEASES (SEE TABLE E2)

Important questions from the 2008 Consensus Workshop remain unresolved in allogeneic HCT for non-SCID conditions, including the intensity of the preparative regimen needed for each disease and whether mixed donor chimerism is sufficient and in which cellular compartments it should occur for resolution of the clinical symptoms¹ (see also Table E1 in Griffith et al¹⁵).

We now add the following questions:

1. What are the mechanisms of pretransplantation and post-transplantation autoimmune/inflammatory complications in patients with non-SCID PIDs? Is autoimmunity after HCT related to the extent of donor chimerism, and in particular, what is the contribution of mixed chimerism in the myeloid and B-cell lineages? What are the best approaches to transplantation of patients with WAS with autoimmune disease, and should full donor chimerism be the goal?
2. What is the importance of the CGD genotype or phenotype in the decision to move forward with HCT? New research indicates the level of oxidase activity in patients with CGD is directly related to overall survival¹⁶; is this the best indicator of the need for HCT? When is the best time to

TABLE II. (Continued)

Enrollment to date	Purpose or goal	Utilization process
3025 in PID registry, see note Note: Web site accessed April 2013	The purpose and scope of this project is to assemble and maintain a registry of residents of the United States with PID diseases. Objectives include providing a minimum estimate of the prevalence of each disorder in the United States; providing a comprehensive clinical picture of each disorder; and providing a resource for clinical and laboratory research.	Queries to the steering committee of the registry are accepted from patients, physicians in practice, clinical researchers, and members of the lay public.
>330,000 in CIBMTR database; 5245 with transplantation essential data in immune deficiencies; of these, 2876 with research data; see note Note: Data through November 2012, from the "Immune Deficiencies and Inborn Errors Working Committee Report 2013," as posted on the Web site	CIBMTR leads a worldwide collaboration of scientists and clinicians to advance understanding and outcomes of HCT. CIBMTR collects baseline and follow-up data on patients who have received HCT.	Members of the Immune Deficiencies Working Committee develop and submit concepts that are reviewed by the committee and CIBMTR leadership before writing a study protocol for outcomes research of the database.
16,547 in ESID database, see note Note: Enrollment from 96 ESID documenting centers as of December 31, 2012; Web site accessed April 2013	The registry of the ESID includes patients in Europe given a diagnosis of PID. ESID promotes collaboration among medical professionals, patient advocacy groups, industry, and governmental bodies to further education and research in PIDs. Together, the IEWP of the EBMT and the ESID Bone Marrow Transplantation and Gene Therapy Working Party develop and regularly update guidance for HCT in PIDs, which is posted to the EBMT IEWP and ESID Web sites: http://www.esid.org/downloads/BMT_Guidelines_2011.pdf	Membership of the Bone Marrow Transplantation and Gene Therapy Working Party includes physicians of the ESID interested in clinical research in PIDs. This working party of the ESID collaborates closely with the EBMT IEWP.
>400,000 in EBMT database	The EBMT collects baseline and follow-up data on patients who have received HCT in Europe to support retrospective studies; the EBMT also conducts educational activities and prospective clinical trials in HCT The IEWP is an international collaboration to (1) develop guidance for HCT in PIDs, which is posted to the EBMT IEWP and ESID Web sites and (2) improve knowledge in PIDs by conducting retrospective research using the EBMT/SCETIDE and ESID registries.	IEWP membership includes physicians of the EBMT and international community interested in clinical research in PIDs. The IEWP is a working party of the EBMT, which collaborates closely with the ESID Bone Marrow Transplantation and Gene Therapy Working Party. The IEWP undertakes collaborative retrospective outcomes studies in HCT for patients with PIDs. An independent annual meeting of the IEWP is convened in Europe; HCT guidance and projects are reviewed and further developed.
1500 in SCETIDE database, see note Note: Reference, Gennery et al (2010) ²	The SCETIDE includes disease-specific information and outcomes data on transplantations performed in patients with PIDs in Europe.	Data on individual patients with PID undergoing HCT is acquired to complement the EBMT database and support the research projects of the EBMT/IEWP, as needed.
The Web site lists 244 PID genes; 266 PID diseases; 234 genes having mutations; and 5086 unique mutations, see note Note: Web site accessed April 2013	1) Web-based compendium of molecular alterations in patients with PIDs; the site hosts information on sequence variations and expression at the mRNA and protein levels of all genes reported to be involved in patients with PIDs. 2) Detailed information pertaining to genes and proteins involved in patients with PID diseases is provided. 3) The tool "Mutation Viewer" is able to predict deleterious and novel mutations and also obtain mutation-based 3-dimensional structures for PID genes. See note. Note: Reference, Keerthikumar et al ³	This Web-based resource is freely available to the academic community. RAPID can be queried by various search options, including gene symbol, protein name, mouse phenotypes, chromosome number, and PID category.

provide HCT for patients likely to benefit because of their low/absent neutrophil oxidase activity?¹⁷

- How does the clinical status and genotype/phenotype of the patient with CGD affect the choice of transplantation regimen?
- Should or should not carrier donors be used in HCT for X-linked and autosomal recessive CGD? Are the oxidase production levels of carrier donors stable over time, and will the expression in a recipient be the same as in the donor?
- For which forms of PIDs other than SCID would it be beneficial for the PIDTC or the PIDTC in collaboration with the IEWP-EBMT to study outcomes by using natural

history studies? Such studies are expected to form the basis for planning future prospective treatment clinical trials.

ADULT UNRELATED DONORS AND CORD BLOOD AS GRAFT SOURCES FOR HCT

In view of the experience that only approximately 10% to 20% of patients with SCID have a matched sibling donor available for HCT, alternative donors will continue to be important. Recent data indicate that for nonmalignant disease, very good to excellent survival is observed after HCT from fully matched unrelated donors (MUDs), although not as good as

TABLE III. PID gene transfer studies currently open

Study	Center(s)	Sponsor(s)	Vector	Treatment regimen	Publications
X-SCID					
Activation date: 2011; recruiting Registration: ClinicalTrials.gov NCT01129544 (London and Paris); ClinicalTrials.gov NCT01175239 (Boston Mass; Cincinnati, Ohio; and Los Angeles, Calif)	Parallel European and North American studies Europe: Great Ormond Street Hospital, London, United Kingdom; Hôpital Necker-Enfants Malades, Paris, France United States: Children's Hospital, Boston, Mass; Children's Hospital Medical Center, Cincinnati, Ohio; University of California, Los Angeles, Calif	United Kingdom: Great Ormond Street Hospital, NHS Foundation Trust (PI: A. Thrasher) France: Assistance Publique-Hôpitaux Paris (PI: A. Fischer) United States: NIAID, NIH (PI: D. A. Williams)	Virus: Gammaretrovirus Insert: IL-2 receptor γ chain Modifications: WPRE posttranslational regulatory element to enhance expression Safety modifications: EFS (EF1 α short) cellular internal promoter; U3 deletion in LTR (SIN configuration) Vector development: C. Baum, Hannover Medical School, Germany Vector manufacture: University of Cincinnati, Cincinnati, Ohio Target: Bone marrow CD34 ⁺ cells	Conditioning: None	Zychlinski et al ³⁵ Pai S-Y et al ³⁶ Hacein-Bey-Abina et al ³⁷ (report of follow-up for earlier studies using a gammaretrovirus vector) Fischer et al ³⁸ (review)
Activation date: 2012, recruiting Registration: ClinicalTrials.gov NCT01512888	St Jude Children's Research Hospital, Memphis, Tenn	NHLBI, NIH (PI: B. Sorrentino)	Virus: Lentivirus Insert: IL-2 receptor γ chain Safety modifications: EFS (EF1 α short) cellular internal promoter; U3 deletion in LTR (SIN configuration); enhancer blocking insulator sequence(s) Vector development: B. Sorrentino, St Jude, Memphis, Tenn Target: Bone marrow CD34 ⁺ cells	Conditioning: None	NA
X-linked SCID in older children					
Activation date: 2010; recruiting Registration: ClinicalTrials.gov NCT01306019	NIAID, NIH Clinical Center, Bethesda, Md	NIAID, NIH (PI: S. S. DeRaven, H. L. Malech)	Virus: Lentivirus Insert: IL-2 receptor γ chain Safety modifications: EFS (EF1 α short) cellular internal promoter; U3 deletion in LTR (SIN configuration); enhancer blocking insulator sequence(s) Vector development: B. Sorrentino, St Jude, Memphis, Tenn Target: PBSC CD34 ⁺ cells	Conditioning: Busulfan, 6 mg/kg	NA
ADA-SCID					
Activation date: May 2013; recruiting Registration: ClinicalTrials.gov NCT01852071	University of California, Los Angeles, Calif; NHGRI, NIH Clinical Center, Bethesda, Md	NIAID, NIH (PI: D. B. Kohn)	Virus: Lentivirus Modifications: Codon-optimized human ADA cDNA, WPRE posttranslational regulatory element to enhance expression Safety modifications: EFS (EF1 α short) cellular internal promoter; U3 enhancer deletion in LTR (SIN configuration) Vector manufacture: IUVPF Target: Bone marrow CD34 ⁺ cells	PEG-ADA: Discontinue Conditioning: Myeloablative busulfan, 4 mg/kg	Candotti et al ³⁹ (previous work of this group in ADA-SCID using a gammaretrovirus vector) Gaspar ⁴⁰ (editorial)

(Continued)

TABLE III. (Continued)

Study	Center(s)	Sponsor(s)	Vector	Treatment regimen	Publications
Activation date: November 2011; recruiting Registration: ClinicalTrials.gov NCT01380990	Great Ormond Street Hospital, London, United Kingdom	Great Ormond Street Hospital, NHS Foundation Trust (PI: H. B. Gaspar, A. Thrasher)	Virus: Lentivirus Modifications: Codon- optimized human ADA cDNA, WPRE posttranslational regulatory element to enhance expression Safety modifications: EFS (EF1 α short) cellular internal promoter; U3 enhancer deletion in LTR (SIN configuration) Vector manufacture: IUVPF Target: Bone marrow CD34 ⁺ cells	PEG-ADA: Discontinue Conditioning: Myeloreductive busulfan, 4 mg/kg	
X-CGD					
Activation date: 2006 Registration: ClinicalTrials.gov NCT00394316	NIAID, NIH Clinical Center, Bethesda, Md	NIAID, NIH (PI: E. Kang, H. L. Malech)	Virus: Gammaretrovirus MFGS Insert: gp91phox Target: PBSC CD34 ⁺ cells	Conditioning: Busulfan, 10 mg/kg	Kang et al ⁴¹ Kang and Malech ⁴²
Activation date: In development Registration: Pending	NIAID, NIH Clinical Center, Bethesda, Md	NIAID, NIH (PI: E. Kang, H. L. Malech)	Virus: Lentivirus Insert: gp91phox Safety modifications: EFS (EF1 α short) cellular internal promoter; U3 deletion in LTR (SIN configuration); enhancer blocking insulator sequence(s) Target: PBSC CD34 ⁺ cells	Conditioning: TBA	
Activation date: In development Registration: Pending	Great Ormond Street Hospital, London, United Kingdom; Hôpital Necker-Enfant Malades, Paris, France; University Hospital Frankfurt and Institute for Biomedical Research, Georg-Speyer-Haus, Frankfurt, Germany; University Children's Hospital Zurich, Switzerland	Great Ormond Street Hospital, NHS Foundation Trust (PI: A. Thrasher)	Virus: Lentivirus Insert: gp91phox Modifications: Regulated promoter (chimeric CatG/ cFes promoter with mutated TATA box contains binding sites for transcription factors needed for commitment and differentiation of myeloid cells to granulocyte lineage) Vector manufacture: Genethon, Paris, France Target: PBSC CD34 ⁺ cells	Conditioning: TBA	Santilli et al ⁴³
WAS					
Activation date: 2006-2009; recruitment complete, follow-up continuing Registration: German Clinical Trials Register no. DRKS00000330	Hannover Medical School Children's Hospital, Hannover, Germany	Deutsche Forschungsgemeinschaft and Bundesministerium für Bildung und Forschung (PI: C. Klein)	Virus: GALV pseudotyped CMMP, a novel derivative of MFG, which is a type of MLV gammaretrovirus Insert: WAS protein Modifications: MLV LTRs are replaced with the corresponding MPSV LTRs (this is a strong viral promoter) and the normal MLV tRNA primer binding site is replaced by a glutamine tRNA primer binding site. Vector manufacture: Hannover Medical School, Hannover, Germany Target: PBSC CD34 ⁺ cells	Conditioning: Partially myeloablative Busulfan 8 mg/kg	Boztug et al ⁴⁴ Paruzynski et al ⁴⁵ (report of insertional mutagenesis resulting in leukemia)

(Continued)

TABLE III. (Continued)

Study	Center(s)	Sponsor(s)	Vector	Treatment regimen	Publications
Activation date: 2011; recruiting	Europe: Great Ormond Street Hospital, London, United Kingdom; San Raffaele Telethon (London); ClinicalTrials.gov NCT01347242	United Kingdom: Great Ormond Street Hospital, NHS Foundation Trust (PI: A. Thrasher)	Virus: Lentivirus Insert: WAS protein	Preconditioning: Anti-CD20 mAb	Aiuti et al ⁴⁶ Scaramuzza et al ⁴⁶
Registration: ClinicalTrials.gov NCT01515462 (Milan); ClinicalTrials.gov NCT01347346 (Paris); ClinicalTrials.gov NCT01410825 (Boston)	Raffaele Telethon Institute of Gene Therapy, Milan, Italy; Hôpital Necker-Enfants Malades, Paris, France United States: Children's Hospital, Boston, Mass	Italy: IRCCS San Raffaele and Fondazione Telethon (PI: A. Aiuti, M. G. Roncarolo) France: Assistance Publique-Hôpitaux Paris (PI: A. Fischer) United States: GTRP, NHLBI, Bethesda, Md (PI: D. A. Williams, S.-Y. Pai, L. Notarangelo)	Modifications: WPRE posttranslational regulatory element to enhance expression Safety modifications: Human WAS endogenous promoter Vector manufacture: Genethon, Paris, France Target: PBSC CD34 ⁺ cells	Conditioning: Reduced-intensity busulfan (4 mg/kg), fludarabine (120 mg/m ²); ATG if autoimmune manifestations	Biasco et al ⁴⁷

Gammaretrovirus and lentivirus vectors have been/are used in patients with PIDs; adeno-associated virus is not persistent in proliferating bone marrow stem cells and lymphocytes (and therefore cannot be used for GT for PIDs). The necessity to transfect CD34 *ex vivo* or lymphocytes *ex vivo* is cumbersome but relatively effective.

GTRP, Gene Therapy Resource Program, NHLBI, NIH; IRB, institutional review board; IUVPF, Indiana University, Indianapolis, Indiana, Vector Production Facility; JAK3, Janus kinase 3; LTR, long terminal repeat; MFGS, MLV vector with MLV LTR and MLV envelope splice acceptor site; MLV, Moloney murine leukemia virus; MPSV, myeloproliferative sarcoma virus; NA, not applicable; PBSC, Peripheral blood stem cell; PI, primary investigator; SIN, self-inactivating; WPRE, Woodchuck hepatitis virus posttranscriptional regulatory element.

with an HLA-matched sibling donor.¹⁸⁻²⁰ However, the search for an MUD can take several months, posing some risk to patients with SCID. To circumvent this problem, cord blood donors have been increasingly used, especially when 1 or both haplotypes are rare, as an alternative to T cell-depleted haploidentical transplantation. Thus far, it is clear that greater degrees of HLA disparity are tolerated in cord blood transplants.²¹ However, the more immature immunologic status of this new resource requires further characterization, and the implications of using such grafts for transplantation outcomes requires further study.^{22,23}

HCT REGIMENS

Given that PIDs are rare, it is difficult to enroll the number of patients needed for prospective treatment studies to investigate variables, such as type of preparative regimen, if any, and graft source. Indeed, it has been necessary to study these variables in patients with PIDs by means of either relatively small prospective studies conducted at a single center or large retrospective observational analyses (see Table E3 in this article's Online Repository at www.jacionline.org).

The use of pre-HCT conditioning for patients with SCID continues to be controversial, with some centers avoiding it altogether and others using only fully myeloablative therapy.^{10-12,24} This topic was debated at the PIDTC Second Annual Scientific Workshop in April 2012, and the details have been published.¹² The minimal goal of HCT for SCID is obtaining durable and robust hematopoietic stem cell engraftment with a high degree of donor T-cell chimerism. The ideal goal is to achieve T- and B-cell immune reconstitution. Given the potential for toxic effects of conditioning regimens, it is desirable to avoid the use of conditioning altogether or use minimal-intensity conditioning regimens.¹² Because the patient's immune system is theoretically unable to reject the graft, this approach is feasible, at least for permissive types of SCID, such as when an HLA-matched sibling is available, when the recipient has

NK⁺ SCID, or when there is maternal engraftment at birth and the mother is the donor.²⁵ However, especially in NK⁺ SCID phenotypes with HLA-mismatched donors, graft rejection is often seen when immunosuppressive therapy is not provided.^{14,25} Furthermore, a finite degree of durable donor stem cell engraftment might be necessary to achieve recovery of B-cell function in most SCID genotypes/phenotypes, especially in forms of SCID in which the genetic defect affects B-cell function (eg, γ c or Janus kinase 3 deficiency) or development (as in defects of VDJ recombination). For these cases, some degree of myeloablation sufficient to allow B-cell reconstitution might be needed.

For non-SCID diseases, such as WAS and CGD, rejection of the graft by recipient T and NK cells occurs even with matched sibling donors, so that immune myeloablation is needed to achieve engraftment. Although partial chimerism of the myeloid lineage might be sufficient to obtain clinical cure in patients with WAS and CGD, further research in this area is needed to determine whether mixed chimerism is associated with the risk of persistence or *de novo* development of inflammatory and autoimmune manifestations and whether it is sufficient to attain full correction of the disease phenotype. If this is the case, as some recent data from the literature suggest,²⁶ there is a need to define target levels of hematopoietic stem cell engraftment and to design and test appropriate reduced-intensity conditioning regimens that permit engraftment sufficient to prevent autoimmune complications while minimizing short- and long-term toxicity in prospective randomized studies.

Alternative approaches to achieving engraftment with immune reconstitution are an area of active investigation, such as targeting recipient bone marrow stem cells with mAbs²⁷⁻²⁹ or mobilizing autologous hematopoietic stem cells,³⁰ before infusion of the graft. Other potential strategies include use of megadoses of donor CD34⁺ hematopoietic stem cells.^{25,31} Finally, the role of donor lymphocyte infusion in supporting donor engraftment after HCT in patients with severe PIDs needs to be further evaluated.⁹

GENE THERAPY AS A TREATMENT OPTION FOR PIDS

An update of current investigations of GT as treatment for PIDs is an integral part of the PIDTC Annual Scientific Workshop (Table III),³²⁻⁴⁸ and GT is included in the PIDTC natural history studies for SCID and WAS (Table I). Autologous CD34⁺ hematopoietic stem cells are positively selected, transduced by means of *ex vivo* culture with retroviral or lentiviral vectors containing the corrective gene, and then reinfused into the patient. Experience with GT for X-SCID,^{37,38} adenosine deaminase (ADA) deficiency,^{39,40,49} CGD,^{41,42,50,51} and WAS⁴⁴ have offered proof of principle that this might represent an effective form of treatment for patients with severe PIDs and other disorders. However, in the case of X-linked SCID, CGD, and WAS, the reported success of GT has been tempered by demonstration of leukemic proliferation (caused by insertional mutagenesis) in several patients,^{32-34,38} although similar adverse events have not been reported after GT for ADA-SCID. Clinical trials with novel, hopefully safer vectors have been initiated in Europe and the United States. It will likely be several years before GT for PIDs can become more widely available.

PROSPECTIVE TREATMENT PROTOCOL FOR SCID IDENTIFIED BY MEANS OF NBS

Infants with SCID who receive a diagnosis and are treated with HCT before 3.5 months of age have the best outcome.⁵² An increasing number of states in the United States have initiated or committed to starting NBS.^{7,8} Of the first 50 patients with SCID or SCID variants entered into the PIDTC prospective study, 25 were given diagnoses at birth based on the results of newborn screening (*n* = 13) or a positive family history (*n* = 12).⁴ A study of the first 2 years of screening nearly 1 million newborns in California for SCID found 14 infants with SCID and leaky SCID who were promptly given a diagnosis and treated, several in PIDTC studies, with 93% survival.⁵³

Treating newborns with SCID has raised a number of issues for investigation. The most important question is this: What is the best approach to conditioning to achieve durable T- and B-cell immunity while minimizing short- and long-term toxicities?^{54,55} Other variables include when to start prophylactic medications, whether to keep the child in the hospital until definitive therapy can be administered and sufficient immune reconstitution is achieved, and whether switching from breast-feeding to formula feeding is deemed necessary to prevent cytomegalovirus infection when the mother is seropositive.

FUTURE OPPORTUNITIES FOR CLINICAL STUDIES IN PIDS

Natural history studies

Initially, CGD and WAS were selected for study among the non-SCID disorders, given the significant questions regarding the efficacy of and optimal approach to HCT for each of them, as described above, and because the affected patient population in North America is believed to be sufficiently large to answer these questions. However, similar issues exist for other very rare PIDs, including CD40 ligand deficiency; immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; NEMO deficiency; MHC class II deficiency; DOCK8 deficiency; and disorders of T-cell function, such as ζ chain-associated protein

of 70 kDa (ZAP70) deficiency and Ca²⁺ signaling defects (see Table E1 in Griffith et al¹⁵).

A collaboration of North American and European investigators is desirable to evaluate treatment options for patients with very rare PIDs because of the limited number of patients available for study. In preparation for the PIDTC Third Annual Scientific Workshop held in May 2013 (Houston, Texas), a subcommittee of the PIDTC and IEWP met in advance to identify diseases and treatments of potential interest.

Database resources

Key components in any multicenter study of rare PIDs are the databases that are currently available (Table II) and the patient advocacy groups for these disorders (see Table E1). The USID-NET is an NIAID-funded multi-institutional collaboration with the primary goal of collecting longitudinal data on patients with a variety of PIDs. A total of 3025 patients have been reported to the USIDNET registry through 2012. The CIBMTR/National Marrow Donor Program and EBMT are international collaborations that collect detailed HCT data on patients with malignant and nonmalignant disorders. The IEWP of ESID/EBMT has developed the comprehensive registry of Stem Cell Transplant for Immunodeficiencies in Europe (SCETIDE), which collects information on patients with PIDs receiving HCT. Analysis of survival and other outcomes for patients included in the SCETIDE registry is used by the EBMT IEWP and ESID to develop and update guidelines for HCT in PIDs (Table II). At the end of 2012, 16,547 patients with PIDs had been reported to the ESID registry. Finally, the patient advocacy groups have generated large e-mail lists of patients with PIDs that could be used to inform patients and parents of possible studies, as well as survey patients and parents regarding current clinical status and quality of life.

Prospective treatment trials

For many, if not all, of the non-SCID disorders, resolution of questions regarding optimal conditioning will require the enrollment of large numbers of subjects in prospective randomized treatment trials. For example, a growing experience with treosulfan in Europe and the United States suggests that it might be more efficacious and less toxic than the standard drug busulfan in conditioning for HCT. Collaboration of European and US investigators might be needed to achieve sufficient enrollment; careful consideration will need to be given to the differing requirements of the regulatory agencies of the respective countries.

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

PIDTC high-priority research goals for the near future include the following: (1) identify optimal treatment using HCT for newborns with SCID; (2) enroll virtually all children receiving diagnoses of SCID as newborns in the United States into PIDTC studies; (3) characterize all children with low T-cell receptor excision circle numbers at birth; (4) determine which children with CGD should receive a transplant; (5) determine whether full donor chimerism is essential to prevent posttransplantation autoimmunity in patients with WAS; (6) develop joint studies

with the IEWP; (7) initiate retrospective, prospective, and cross-sectional studies of other rare non-SCID PIDs; and (8) answer questions raised by the research studies in SCID (Table I and see Table E2) for PIDTC Protocol 6902.

In conclusion, the PIDTC now looks forward to the analysis of outcomes for our present protocols and the development of future collaborative clinical studies directed to improving our understanding of the cause of disease and best treatments for patients with these rare life-threatening disorders.

We thank Elizabeth Dunn (San Francisco, Calif, 2011) and Luisa Raleza and Emily Buehrens (Boston, Mass, 2012) for expert coordination and management of the PIDTC Annual Scientific Workshops, which contributed to the success of these meetings.

Trudy Nan Small, MD, of the Departments of Pediatric Hematology/Oncology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, our valued colleague and friend, passed away in June 2013. Her special expertise included transplantation for PIDs, recovery of the immune system after HCT, and vaccination strategies to prevent infectious complications after transplantation and in immune-compromised infants and children. We are grateful for her contributions to the NIH consensus meetings in Bethesda that provided the scientific foundation for the PIDTC, including the Laboratory Testing Working Group (2008), and for cochairing the group on Management of Children with PIDs after HCT (2009). Trudy was a loyal and enthusiastic advocate of the PIDTC mission from the outset, and we will miss her.

REFERENCES

- Griffith LM, Cowan MJ, Kohn DB, Notarangelo LD, Puck JM, Schultz KR, et al. Allogeneic hematopoietic cell transplantation for primary immune deficiency diseases: current status and critical needs. *J Allergy Clin Immunol* 2008;122:1087-96.
- Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? *J Allergy Clin Immunol* 2010;126:602-10.e1-11.
- Keerthikumar S, Raju R, Kandasamy K, Hijikata A, Ramabadran S, Balakrishnan L, et al. RAPID: resource of Asian primary immunodeficiency diseases. *Nucleic Acids Res* 2009;37:D863-7.
- Dvorak CC, Cowan MJ, Logan BR, Notarangelo LD, Griffith LM, Puck JM, et al. The natural history of children with severe combined immunodeficiency: baseline features of the first fifty patients of the Primary Immune Deficiency Treatment Consortium Prospective Study 6901. *J Clin Immunol* 2013;33:156-64.
- Brown L, Xu-Bayford J, Allwood Z, Slatter M, Cant A, Davies EG, et al. Neonatal diagnosis of severe combined immunodeficiency leads to significantly improved survival outcome: the case for newborn screening. *Blood* 2011;117:3243-6.
- Dvorak CC, Cowan MJ. Radiosensitive severe combined immunodeficiency disease. *Immunol Allergy Clin North Am* 2010;30:125-42.
- Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles. *J Allergy Clin Immunol* 2012;129:607-16.
- Borte S, von Döbeln U, Hammarström L. Guidelines for newborn screening of primary immunodeficiency diseases. *Curr Opin Hematol* 2013;20:48-54.
- Taigland CL, Parrott RE, Buckley RH. Long-term outcome of non-ablative booster BMT in patients with SCID. *Bone Marrow Transplant* 2013;48:1050-5.
- Veys P, Gaspar HB. Primary immunodeficiency diseases. In: Treleaven J, Barrett AJ, editors. *Hematopoietic stem cell transplantation in clinical practice*. Edinburgh (United Kingdom): Churchill Livingstone Elsevier; 2009. pp. 153-64.
- Chiesa R, Veys P. Reduced-intensity conditioning for allogeneic stem cell transplant in primary immune deficiencies. *Expert Rev Clin Immunol* 2012;8:255-67.
- Haddad E, Leroy S, Buckley RH. B-cell reconstitution for SCID: should a conditioning regimen be used in SCID treatment? *J Allergy Clin Immunol* 2013;131:994-1000.
- Cavazzana-Calvo M, Andre-Schmutz I, Fischer A. Haematopoietic stem cell transplantation for SCID patients: where do we stand? *Br J Haematol* 2013;160:146-52.
- Yu GP, Nadeau KC, Berk DR, de Saint Basile G, Lambert N, Knapnougel P, et al. Genotype, phenotype, and outcomes of nine patients with T-B+NK+ SCID. *Pediatr Transplant* 2011;15:733-41.
- Griffith LM, Cowan MJ, Notarangelo LD, Puck JM, Buckley RH, Candotti F, et al. Improving cellular therapy for primary immune deficiency diseases: recognition, diagnosis, and management. *J Allergy Clin Immunol* 2009;124:1152-60.
- Kuhns DB, Alvord WG, Heller T, Feld JJ, Pike KM, Marciano BE, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. *N Engl J Med* 2010;363:2600-10.
- Kang EM, Marciano BE, DeRavin SS, Zarembka KA, Holland SM, Malech HL. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2011;127:1319-26.
- Woolfrey A, Lee SJ, Gooley TA, Malkki M, Martin PJ, Pagel JM, et al. HLA-allele matched unrelated donors compared to HLA-matched sibling donors: role of cell source and disease risk category. *Biol Blood Marrow Transplant* 2010;16:1382-7.
- Kim H, Kim BS, Kim DH, Hyun MS, Kim SH, Bae SH, et al. Comparison between matched related and alternative donors of allogeneic hematopoietic stem cells transplanted into adult patients with acquired aplastic anemia: multivariate and propensity score-matched analysis. *Biol Blood Marrow Transplant* 2011;17:1289-98.
- Eapen M, Horowitz MM. Alternative donor transplantation for aplastic anemia. *Hematology Am Soc Hematol Educ Program* 2010;2010:43-6.
- Eapen M, Klein JP, Sanz GF, Spellman S, Ruggieri A, Anasetti C, et al. Effect of donor-recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis. *Lancet Oncol* 2011;12:1214-21.
- Szabolcs P, Cairo MS. Unrelated umbilical cord blood transplantation and immune reconstitution. *Semin Hematol* 2010;47:22-36.
- Kim Y-J, Broxmeyer HE. Immune regulatory cells in umbilical cord blood and their potential roles in transplantation tolerance. *Crit Rev Oncol Hematol* 2011;79:112-26.
- Parikh S, Szabolcs P. Reduced-intensity conditioning (RIC) in children with nonmalignant disorders (NMD) undergoing unrelated donor umbilical cord blood transplantation (UCBT). *Biol Blood Marrow Transplant* 2012;18(Suppl):S53-5.
- Dvorak CC, Hung G-Y, Horn B, Dunn E, Oon C-Y, Cowan MJ. Megadose CD34+ cell grafts improve recovery of T cell engraftment but not B cell immunity in patients with severe combined immunodeficiency disease undergoing haplocompatible nonmyeloablative transplantation. *Biol Blood Marrow Transplant* 2008;14:1125-33.
- Moratto D, Giliani S, Bonfim C, Mazzolari E, Fischer A, Ochs HD, et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980-2009: an international collaborative study. *Blood* 2011;118:1675-84.
- Chen Y, Kornblit B, Hamlin DK, Sale GE, Santos EB, Wilbur DS, et al. Durable donor engraftment after radioimmunotherapy using alpha-emitter astatine-211-labeled anti-CD45 antibody for conditioning in allogeneic hematopoietic cell transplantation. *Blood* 2012;119:1130-8.
- Schulz AS, Glatting G, Hoenig M, Schuetz C, Gatz SA, Grewendorf S, et al. Radioimmunotherapy-based conditioning for hematopoietic cell transplantation in children with malignant and nonmalignant diseases. *Blood* 2011;117:4642-50.
- Straathof KC, Rao K, Eyrych M, Hale G, Bird P, Berrie E, et al. Haematopoietic stem cell transplantation with antibody-based minimal-intensity conditioning: a phase 1/2 study. *Lancet* 2009;374:912-20.
- Chen J, Larochelle A, Fricker S, Bridger G, Dunbar CE, Abkowitz JL. Mobilization as a preparative regimen for hematopoietic stem cell transplantation. *Blood* 2006;107:3764-71.
- Czechowicz A, Weissman IL. Purified hematopoietic stem cell transplantation: the next generation of blood and immune replacement. *Immunol Allergy Clin North Am* 2010;30:159-71.
- Kohn DB, Pai S-Y, Sadelain M. Gene therapy through autologous transplantation of gene-modified hematopoietic stem cells. *Biol Blood Marrow Transplant* 2013;19(Suppl):S64-9.
- Cavazzana-Calvo M, Fischer A, Hacein-Bey-Abina S, Aiuti A. Gene therapy for primary immunodeficiencies: part 1. *Curr Opin Immunol* 2012;24:580-4.
- Aiuti A, Bacchetta R, Seger R, Villa A, Cavazzana-Calvo M. Gene therapy for primary immunodeficiencies: part 2. *Curr Opin Immunol* 2012;24:585-91.
- Zychlinski D, Schambach A, Modlich U, Maetzig T, Meyer J, Grassman E, et al. Physiological promoters reduce the genotoxic risk of integrating gene vectors. *Mol Ther* 2008;16:718-25.
- Pai S-Y, Notarangelo LD, Harris C, Cattaneo F, Wladkowski M, Armant M, et al. Somatic gene therapy for X-linked severe combined immunodeficiency using a self-

- inactivating modified gammaretroviral vector results in an improved preclinical safety profile and early clinical efficacy in a human patient. *Blood* 2011;118:80-1.
37. Hacein-Bey-Abina S, Hauer J, Lim A, Picard C, Wang GP, Berry CC, et al. Efficacy of gene therapy for X-linked severe combined immunodeficiency. *N Engl J Med* 2010;363:355-64.
 38. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M. 20 years of gene therapy for SCID. *Nat Immunol* 2010;11:457-60.
 39. Candotti F, Shaw KL, Muul L, Carbonaro D, Sokolic R, Choi C, et al. Gene therapy for adenosine deaminase-deficient severe combined immune deficiency: clinical comparison of retroviral vectors and treatment plans. *Blood* 2012;120:3635-46.
 40. Gaspar HB. Gene therapy for ADA-SCID: defining the factors for successful outcome. *Blood* 2012;120:3628-9.
 41. Kang EM, Choi U, Theobald N, Linton G, Long Priel DA, Kuhns D, et al. Retrovirus gene therapy for X-linked chronic granulomatous disease can achieve stable long-term correction of oxidase activity in peripheral blood neutrophils. *Blood* 2010;115:783-91.
 42. Kang EM, Malech HL. Gene therapy for chronic granulomatous disease. *Methods Enzymol* 2012;507:125-54.
 43. Santilli G, Almarza E, Brendel C, Choi U, Beilin C, Blundell MP, et al. Biochemical correction of X-CGD by a novel chimeric promoter regulating high levels of transgene expression in myeloid cells. *Mol Ther* 2011;19:122-32.
 44. Boztug K, Schmidt M, Schwarzer A, Banerjee PP, Diez IA, Dewey RA, et al. Stem cell gene therapy for the Wiskott-Aldrich syndrome. *N Engl J Med* 2010;363:1918-27.
 45. Paruzynski A, Boztug K, Ball C, Nowrouzi A, Arens A, Lulay C, et al. High-level clustering of vector integrations in the German WAS clinical gene therapy trial. *Mol Ther* 2012;20(Suppl):S212.
 46. Aiuti A, Biasco L, Scaramuzza S, Ferrua F, Cicalese MP, Baricordi C, et al. Lentiviral hematopoietic stem cell gene therapy in patients with Wiskott-Aldrich syndrome. *Science* 2013;341:1233151.
 47. Scaramuzza S, Ferrua F, Castiello MC, Giannelli S, Cicalese MP, Evangelio C, et al. Lentiviral vector transduced CD34+ cells for the treatment of Wiskott-Aldrich syndrome. *Mol Ther* 2012;20(Suppl):S211-2.
 48. Biasco L, Baricordi C, Dionisio F, Calabria A, Scaramuzza S, Pellin D, et al. Integration site analysis of Wiskott-Aldrich syndrome patients treated with lentiviral vector gene therapy. *Mol Ther* 2012;20(Suppl):S86.
 49. Aiuti A, Cattaneo F, Galimberti S, Benninghoff U, Cassani B, Callegaro L, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. *N Engl J Med* 2009;360:447-58.
 50. Stein S, Ott MG, Schultze-Strasser S, Jauch A, Burwinkel B, Kinner A, et al. Genomic instability and myelodysplasia with monosomy 7 consequent to Evi1 activation after gene therapy for chronic granulomatous disease. *Nat Med* 2010;16:198-204.
 51. Segal BH, Veys P, Malech H, Cowan MJ. Chronic granulomatous disease: lessons from a rare disorder. *Biol Blood Marrow Transplant* 2011;17(Suppl):S123-31.
 52. Railey MD, Lokhnygina Y, Buckley RH. Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. *J Pediatr* 2009;155:834-40.
 53. Kwan A, Church JA, Cowan MJ, Agarwal R, Kapoor N, Kohn DB, et al. Newborn screening for severe combined immunodeficiency and T cell lymphopenia in California: results of the first 2 years. *J Allergy Clin Immunol* 2013;132:140-50.e7.
 54. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;349:1157-67.
 55. Law J, Cowan MJ, Dvorak CC, Musick L, Long-Boyle JR, Baxter-Lowe LA, et al. Busulfan, fludarabine, and alemtuzumab as a reduced toxicity regimen for children with malignant and nonmalignant diseases improves engraftment and graft-versus-host disease without delaying immune reconstitution. *Biol Blood Marrow Transplant* 2012;18:1656-63.

APPENDIX E1**PARTICIPANTS: PIDTC FIRST ANNUAL SCIENTIFIC WORKSHOP, SAN FRANCISCO, CALIFORNIA, APRIL 7-9, 2011****Workshop Co-Chairs and Organizing Committee**

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APPENDIX E2

EXPERT OPINION AND PARTICIPANTS: PIDTC SECOND ANNUAL SCIENTIFIC WORKSHOP, BOSTON, MASSACHUSETTS, APRIL 26-28, 2012

Working Group Expert Opinion: Prospective Treatment Trial for Newborn SCID

Working Group I: Pre-HCT Evaluation and Management

Jennifer M. Puck, John M. Routes (Co-Chairs); Neena Kapoor, Angela Smith

Working Group II: Objectives & Endpoints; Inclusion Exclusion Criteria; Treatment Regimen; Statistical Analysis

Morton J. Cowan, Sung-Yun Pai, Brent R. Logan (Co-Chairs); Rebecca H. Buckley, Lauri Burroughs, Christopher C. Dvorak, Donald B. Kohn, Janel R. Long-Boyle, Richard J. O'Reilly, Michael A. Pulsipher

Working Group III: Supportive Care

Christopher C. Dvorak, Caridad Martinez (Co-Chairs); Janel R. Long-Boyle, Suzanne Skoda-Smith, Angela Smith

Working Group IV: Post-Transplant Evaluation; Immune Reconstitution; Follow-Up

Thomas Fleisher, Trudy Small (Co-Chairs); Jack J. H. Blesing

Working Group V: Research Studies

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REFERENCES

- E1. Modell V, Gee B, Lewis DB, Orange JS, Roifman CM, Routes JM, et al. Global study of primary immunodeficiency diseases (PI) – diagnosis, treatment and economic impact: an updated report from the Jeffrey Modell Foundation. *Immunol Res* 2011;51:61-70.
- E2. Griffith LM, Cowan MJ, Kohn DB, Notarangelo LD, Puck JM, Schultz KR, et al. Allogeneic hematopoietic cell transplantation for primary immune deficiency diseases: current status and critical needs. *J Allergy Clin Immunol* 2008;122:1087-96.
- E3. Rao K, Amrolia PJ, Jones A, Cale CM, Naik P, King D, et al. Improved survival after unrelated donor bone marrow transplantation in children with primary immunodeficiency using a reduced-intensity conditioning regimen. *Blood* 2005;105:879-85.
- E4. Bhattacharya A, Slatter MA, Chapman CE, Barge D, Jackson A, Flood TJ, et al. Single centre experience of umbilical cord stem cell transplantation for primary immunodeficiency. *Bone Marrow Transplant* 2005;36:295-9.
- E5. Sato T, Kobayashi R, Toita N, Kaneda M, Hatano N, Iguchi A, et al. Stem cell transplantation in primary immunodeficiency disease patients. *Pediatr Int* 2007;49:795-800.
- E6. Straathof KC, Rao K, Eylich M, Hale G, Bird P, Berrie E, et al. Hematopoietic stem cell transplantation with antibody-based minimal-intensity conditioning: a phase 1/2 study. *Lancet* 2009;374:912-20.
- E7. Frangoul H, Wang L, Harrell FE, Manes B, Calder C, Domm J. Unrelated umbilical cord blood transplantation in children with immune deficiency: results of a multicenter study. *Bone Marrow Transplant* 2010;45:283-8.
- E8. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? *J Allergy Clin Immunol* 2010;126:602-10.e1-11.
- E9. Antoine C, Muller S, Cant A, Cavazzana-Calvo M, Veys P, Vossen J, et al. Long-term survival and transplantation of hematopoietic stem cells for immunodeficiencies: report of European experience 1968-99. *Lancet* 2003;361:553-60.
- E10. Slatter MA, Rao K, Amrolia P, Flood T, Abinun M, Hambleton S, et al. Treosulfan-based conditioning regimens for hematopoietic stem cell transplantation in children with primary immunodeficiency: United Kingdom experience. *Blood* 2011;117:4367-75.
- E11. Morio T, Atsuta Y, Tomizawa D, Nagamura-Inoue T, Kato K, Ariga T, et al. Outcome of unrelated umbilical cord blood transplantation in 88 patients with primary immunodeficiency in Japan. *Br J Haematol* 2011;154:363-72.
- E12. Schulz AS, Glatting G, Hoenig M, Schuetz C, Gatz SA, Grewendorf S, et al. Radioimmunotherapy-based conditioning for hematopoietic cell transplantation in children with malignant and nonmalignant diseases. *Blood* 2011;117:4642-50.
- E13. DiNardo L, Brown V, Perez E, Bunin N, Sullivan KE. A single-center study of hematopoietic stem cell transplantation for primary immune deficiencies (PIDD). *Pediatr Transplant* 2012;16:63-72.
- E14. Eapen M, Ahn KW, Orchard PJ, Cowan MJ, Davies SM, Fasth A, et al. Long-term survival and late deaths after hematopoietic cell transplantation for primary immunodeficiency diseases and inborn errors of metabolism. *Biol Blood Marrow Transplant* 2012;18:1438-45.
- E15. Dvorak CC, Hung G-Y, Horn B, Dunn E, Oon C-Y, Cowan MJ. Megadose CD34+ cell grafts improve recovery of T cell engraftment but not B cell immunity in patients with severe combined immunodeficiency disease undergoing haplocompatible nonmyeloablative transplantation. *Biol Blood Marrow Transplant* 2008;14:1125-33.
- E16. Railey MD, Likhnygina Y, Buckley RH. Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. *J Pediatr* 2009;155:834-40.
- E17. Sarzotti-Kelsoe M, Win CM, Parrott RE, Cooney M, Moser BK, Roberts JL, et al. Thymic output, T-cell diversity, and T-cell function in long-term human SCID chimeras. *Blood* 2009;114:1445-53.
- E18. Buckley RH, Win CM, Moser BK, Parrott RE, Sagaroff E, Sarzotti-Kelsoe M. Post-transplantation B cell function in different molecular types of SCID. *J Clin Immunol* 2013;33:96-110.
- E19. Iguchi A, Kawamura N, Kobayashi R, Takezaki S-I, Ohkura Y, Inamoto J, et al. Successful reduced-intensity SCT from unrelated cord blood in three patients with X-linked SCID. *Bone Marrow Transplant* 2011;46:1526-31.
- E20. Yu GP, Nadeau KC, Berk DR, de Saint Basile G, Lambert N, Knapnougel P, et al. Genotype, phenotype, and outcomes of nine patients with T-B+NK+ SCID. *Pediatr Transplant* 2011;15:733-41.
- E21. Fernandes JF, Rocha V, Labopin M, Neven B, Moshous D, Gennery AR, et al. Transplantation in patients with SCID: mismatched related stem cells or unrelated cord blood? *Blood* 2012;119:2949-55.
- E22. Hassan A, Booth C, Brightwell A, Allwood Z, Veys P, Rao K, et al. Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency. *Blood* 2012;120:3615-24.
- E23. Ozaiah H, Cavazzana-Calvo M, Notarangelo LD, Schulz A, Thrasher AJ, Maz-zolari E, et al. Long-term outcome following hematopoietic stem-cell transplantation in Wiskott-Aldrich syndrome: collaborative study of the European Society for Immunodeficiencies and European Group for Blood and Marrow Transplantation. *Blood* 2008;111:439-45.
- E24. Friedrich W, Schutz C, Schulz A, Benninghoff U, Honig M. Results and long-term outcome in 39 patients with Wiskott-Aldrich syndrome transplanted from HLA-matched and -mismatched donors. *Immunol Res* 2009;44:18-24.
- E25. Moratto D, Giliani S, Bonfim C, Mazzolari E, Fischer A, Ochs HD, et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980-2009: an international collaborative study. *Blood* 2011;118:1675-84.
- E26. Filipovich AH, Stone JV, Tomany SC, Ireland M, Kollman C, Pelz CJ, et al. Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. *Blood* 2001;97:1598-603.
- E27. Shin CR, Kim M-O, Li D, Bleesing JJ, Harris R, Mehta P, et al. Outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome. *Bone Marrow Transplant* 2012;47:1428-35.
- E28. Gungor T, Halter J, Klink A, Junge S, Stumpe KDM, Seger R, et al. Successful low toxicity hematopoietic stem cell transplantation for high-risk adult chronic granulomatous disease patients. *Transplant* 2005;79:1596-606.
- E29. Soncini E, Slatter MA, Jones LBKR, Hughes S, Hodges S, Flood TJ, et al. Unrelated donor and HLA-identical sibling hematopoietic stem cell transplantation cure chronic granulomatous disease with good long-term outcome and growth. *Br J Haematol* 2009;145:73-83.
- E30. Schuetz C, Hoenig M, Gatz S, Speth F, Benninghoff U, Schulz A, et al. Hematopoietic stem cell transplantation from matched unrelated donors in chronic granulomatous disease. *Immunol Res* 2009;44:35-41.
- E31. Tewari P, Martin PL, Mendizabal A, Parikh SH, Page KM, Driscoll TA, et al. Myeloablative transplantation using either cord blood or bone marrow leads to immune recovery, high long-term donor chimerism and excellent survival in chronic granulomatous disease. *Biol Blood Marrow Transplant* 2012;18:1368-77.

TABLE E1. Patient advocacy group resources for patients with PIDs in the United States

Group	Leadership and financial resource(s)	Disease(s)	Year started	Purpose, goal, and activities
Immune Deficiency Foundation (IDF), Towson, Md Contact: www.primaryimmune.org/	Marcia Boyle; nonprofit with corporate sponsorship	PID	1980	1) US national patient organization for PID diseases dedicated to improving the diagnosis, treatment, and quality of life of persons with PID diseases through advocacy, education, and research 2) Administrative oversight of the USIDNET (Table II)
Jeffrey Modell Foundation (JMF), New York, NY Contact: http://www.info4pi.org/jmf/	Vicki and Fred Modell; nonprofit with corporate sponsorship	PID	1987	Global nonprofit organization dedicated to early diagnosis, meaningful treatments, and, ultimately, cures through research, physician education, public awareness, advocacy, patient support, and newborn screening; there are >100 Jeffrey Modell Diagnostic and Research Centers and 230 Referral Centers worldwide. Reference: Modell et al ^{E1}
Chronic Granulomatous Disease Association, San Marino, Calif Contact: http://www.cgdassociation.org/index.php	Mary and Alan Hurley; nonprofit with corporate sponsorship	CGD	1993	Patient organization dedicated to helping those with CGD and advancing research toward a cure
Wiskott-Aldrich Foundation, Smyrna, Ga Contact: http://www.wiskott.org/	Sumathi Iyengar, MD; nonprofit with corporate sponsorship	WAS, including hereditary X-linked thrombocytopenia	2003	Dedicated to funding research to find improved cures for WAS and providing up-to-date information and support for families living with WAS worldwide
Severe Combined Immunodeficiency Family Network Contact: http://www.scid.net/ Affiliated with the Immune Deficiency Foundation (IDF)	Barbara Ballard; Listserv and Web site	SCID	1997	1) Maintain SCID e-mail Listserv Support Group; contact: mailgroup@scid.net 2) Self-help support group and a resource guide to families afflicted with SCID designed to promote education, awareness, diagnosis, newborn screening, and research related to SCID
Severe Combined Immunodeficiency Angels for Life Foundation, Lakeland, Fla Contact: http://www.scidangelsforlife.com/	Heather Smith; nonprofit with corporate sponsorship	SCID	2008	To increase awareness, benefit research, and provide parent and family education for those affected by SCID

TABLE E2. PIDTC progress to address key questions in HCT for patients with SCID and non-SCID

Item	Question	PIDTC progress and/or approach
SCID: Key questions from 2008 Consensus Workshop (Griffith et al ^{E2})		
1	How are the extent and durability of T-cell, B-cell, and NK cell lineage-specific reconstitution and function after HCT affected by the transplantation regimen/strategy used? Is full donor chimerism needed?	<i>Progress:</i> To address these questions, PIDTC Protocols 6901 and 6902 for SCID will capture as baseline data the type of donor and transplantation regimen used; in Protocol 6902, for subjects who survive ≥ 2 years after HCT, immunologic reconstitution and function and lineage-specific chimerism will be assessed. We anticipate it will be possible to study at least 400 subjects in a cross-sectional visit for Protocol 6902.
2	To minimize toxic effects yet achieve full and durable immune reconstitution, what are the best transplantation strategies?	<i>Progress:</i> PIDTC Protocols 6901 and 6902 will examine the importance of the baseline genetic defect, immune phenotype, graft type, and transplantation regimen for post-HCT outcomes, including lineage-specific chimerism and immune function.
3	What is the overall survival and long-term clinical status of patients with SCID treated with HCT in North America?	<i>Progress:</i> PIDTC Protocol 6902 will capture baseline data, including the transplantation approach, and assess long-term outcomes, including survival, growth, organ function, quality of life, and complications, such as late recurrence of immune deficiency, development of autoimmune diseases, chronic infections, or malignancies. To avoid a survival bias, each participating center has submitted for eligibility on Protocol 6902 their entire cohort of patients undergoing transplantation or with intention to transplantation for SCID, including those who have expired in the interim.
4	How do the specific SCID genotypes affect transplantation outcomes, including engraftment, sustained thymopoiesis, and function of B-cell and NK cell populations?	<i>Progress:</i> To study the importance of genotype and phenotype for outcome of HCT in children with SCID, PIDTC Protocol 6901 will capture this information prospectively. For Protocol 6902, the consortium will endeavor to obtain samples and genotype all subjects enrolled on the cross-sectional study, if this testing was not performed or was not available for these historic cases.
5	What is the significance of the recipient's residual T-cell immunity before HCT, as observed in patients with CID, and how does this affect selection of an optimal donor, conditioning regimen, and graft manipulation?	<i>Progress:</i> PIDTC Protocols 6901 and 6902, in addition to enrolling "true SCID" (stratum A), also include patients with residual T-cell immunity, including "leaky SCID," Omenn syndrome, and reticular dysgenesis (stratum B). The importance of donor type, conditioning regimen, and graft manipulation for HCT outcomes will be analyzed.
6	When the donor graft is T-cell depleted, what is the relation of the method used, source of cells, and extent of T-cell depletion on posttransplantation GVHD (with or without GVHD prophylaxis)?	<i>Progress:</i> The databases for PIDTC Protocols 6901 and 6902 will include information about graft source and manipulation, and if the subject experienced GVHD, so that the importance of aspects of the graft for post-HCT outcomes, including GVHD, can be assessed.
7	If an HLA-matched related graft is unavailable, can we develop an algorithm to identify next-best graft source and HCT regimen for patients with SCID?	<i>Progress:</i> PIDTC Protocols 6901 and 6902 will capture information on HLA typing of the donor and recipient, graft source, and HCT regimen for each patient with SCID in an effort to analyze the importance of these variables for outcomes.
8	Patients undergoing transplantation for SCID, particularly those who have received HLA-haplotype disparate T cell-depleted grafts, constitute a unique clinical model for examining interactions between donor and host cells that shape the immune repertoire, and contribute to tolerance.	<i>Progress:</i> For subjects enrolled in the cross-sectional study of PIDTC Protocol 6902 who received T cell-depleted haploidentical HCT without MAC, samples will be obtained to investigate the current status of immune reconstitution. Of particular interest is the state of mixed chimerism that has been observed in such patients, with T cells of donor origin and other hematopoietic elements, including antigen-presenting cells of myeloid lineages and in some patients also B cells of host type.
9	For long-term SCID survivors who received treatments other than transplantation, a similar retrospective analysis and comprehensive evaluation of lymphoid populations and their function is also urgently needed.	<i>Progress:</i> PIDTC Protocols 6901 and 6902 are inclusive of patients with ADA-SCID who have received PEG-ADA enzyme replacement therapy and of all patients with SCID who have received GT. Data sets inclusive of lymphoid populations comparable with those for patients receiving HCT for SCID will be collected, and outcomes will be analyzed.
10	What is the role of HCT vs GT for a specific gene defect, if available?	<i>Progress:</i> It is anticipated that factors important for risk/benefit of the HCT procedure will be identified in PIDTC Protocols 6901, 6902, 6903, and 6904, which aim to assemble the comprehensive experience of HCT in North America for SCID, WAS, and CGD. This information will further the decision-making process regarding HCT vs GT for a specific gene defect in an individual patient.

(Continued)

TABLE E2. (Continued)

Item	Question	PIDTC progress and/or approach
SCID: New key questions		
1	Regarding T-cell, B-cell, and NK cell reconstitution after HCT for SCID, what determines kinetics, level of reconstitution, durability, and quality of immune reconstitution? Can a preparative regimen be designed to facilitate the reconstitution of particular lineage(s) while minimizing patient toxicity? What is the role of the thymus in this process? What differences in outcomes are attributable to the patients' underlying genetic defects? What is the contribution of CD34 ⁺ stem cell vs common lymphoid progenitor engraftment in determining long-term T-cell reconstitution? Are there aspects of recovery of T-cell numbers, phenotype, and function that affect the recovery of B-cell function? What are the critical determinants of reconstitution of B-cell function, and are they distinct among SCID genotypes?	<i>Approach:</i> For each subject enrolled in PIDTC 6901, the prospective observational study, lineage-specific engraftment data will be studied for each subject to determine the kinetics, level of reconstitution, durability, and quality of immune reconstitution. Baseline clinical information, as well as content of the preparative regimen and type of graft, will also be recorded, and the importance of these factors for lineage-specific engraftment and for reconstitution of immune function, including T-cell and B-cell function will be assessed.
2	What is the role of autologous NK cells in transplantation outcome for patients with SCID, in particular, in T ⁻ B ⁻ NK ⁺ SCID, which includes the RAG and Artemis genetic defects? What is the role of NK cells in graft rejection, can NK cells be suppressed/ablated by using nonchemotherapy approaches, and can the NK cell-specific receptors and ligands be manipulated to promote engraftment and reduce the risk of GVHD after transplantation?	<i>Approach:</i> For each subject enrolled in PIDTC 6901, the presence or absence of autologous NK cells at baseline pretreatment will be recorded, and where data are available, posttransplantation NK cell chimerism will be studied and correlated with clinical events. Hypotheses generated regarding the role of autologous NK cells in engraftment and GVHD will then be considered for future hypothesis-driven preclinical and/or clinical studies in HCT for SCID.
Non-SCID: Key questions from 2008 Workshop (Griffith et al ^{E2})		
1	How does immune function compare for age-matched patients with WAS who have or have not received HCT?	<i>Progress:</i> For each patient with WAS enrolled in PIDTC Protocol 6904, their baseline pre-HCT and post-HCT immune function will be assessed so that these can be compared; however, control subjects who have not received transplant will not be studied as a part of the protocol.
2	How do the specific gene mutations, ages, disease manifestations, and prior treatments (eg, splenectomy) influence the risk vs benefit of HCT for patients with WAS?	<i>Progress:</i> Demographics, including age and baseline variables, such as the specific gene mutation, disease manifestations, and prior treatments, including splenectomy, will be included in the outcomes analyses of PIDTC Protocol 6904.
3	Does attaining full donor lymphoid and myeloid chimerism reduce the risk of post-HCT autoimmune and inflammatory complications for WAS?	<i>Progress:</i> Data concerning extent of lymphoid and myeloid lineage-specific donor chimerism and the occurrence of autoimmune and inflammatory complications after HCT will be collected in PIDTC Protocol 6904.
4	What degree of donor chimerism in the myeloid compartment is required for clinical cure of CGD?	<i>Progress:</i> Data concerning extent of myeloid lineage-specific donor chimerism after HCT and the oxidase activity of the subject's myeloid cells both before and after HCT will be collected in PIDTC Protocol 6903.
5	For CGD, does the burden of infectious and inflammatory manifestations relate to the biochemical consequences of the underlying genotype?	<i>Progress:</i> In PIDTC Protocol 6903 subject variables, including the genotype of their defect and their baseline burden of infectious and inflammatory manifestations before HCT, will be collected.
6	On the basis of the biochemical profile and clinical course of individual patients with CGD, is it possible to develop guidelines as to those patients most likely to benefit from HCT?	<i>Progress:</i> PIDTC Protocol 6904 aims to assemble the comprehensive experience of HCT in North America for CGD; it is anticipated that factors important for risk/benefit decisions regarding the HCT procedure for individual patients will be identified.
7	Do the recent advances in HCT regimens, such as high-resolution HLA matching for unrelated donor selection and the newer reduced-intensity and non-MAC regimens, offer possible advantages for patients with non-SCID PIDs?	<i>Progress:</i> Information about HLA matching for MUD or unrelated cord blood donor selection and the type of conditioning regimen used will be collected for subjects enrolled on PIDTC Protocols 6903 for CGD and 6904 for WAS, so that the importance of these variables of for HCT outcomes can be analyzed.
Non-SCID: New key questions		
1	What are the mechanisms of pretransplantation and posttransplantation autoimmune/inflammatory complications in patients with non-SCID PIDs? Is autoimmunity after HCT related to the extent of donor chimerism, and in particular, what is the contribution of mixed chimerism in the myeloid and B-cell lineages? What are the best approaches to transplantation of patients with WAS with autoimmune disease, and should full donor chimerism be the goal?	<i>Approach:</i> For PIDTC Protocols 6903 and 6904, baseline incidence of autoimmune/inflammatory complications will be recorded and compared with the posttransplantation incidence. Posttransplantation lineage-specific chimerism will be correlated with the incidence of autoimmune/inflammatory complications. These outcomes will be used to develop hypotheses regarding the relation of myeloid and/or B-cell donor chimerism to autoimmune/inflammatory events for patients with WAS and best approach to transplantation, to be addressed in future prospective clinical studies.

(Continued)

TABLE E2. (Continued)

Item	Question	PIDTC progress and/or approach
2	What is the importance of the CGD genotype or phenotype in the decision to move forward with HCT? New research indicates the level of oxidase activity in a patient with CGD is directly related to overall survival; is this the best indicator of need for HCT? When is the best time to provide HCT for patients likely to benefit because of their low/absent neutrophil oxidase activity?	<i>Approach:</i> For PIDTC Protocol 6903, the relation of CGD genotype and/or phenotype, including level of oxidase activity, to survival will be compared for subjects who receive HCT vs those who do not. The survival data will be used to generate hypotheses regarding the best time to provide HCT depending on the patient's genotype/phenotype, which is to be investigated in future clinical studies.
3	How does the clinical status and genotype/phenotype of the patient with CGD affect the choice of transplantation regimen?	<i>Approach:</i> In PIDTC Protocol 6903 the current experience in selection of transplantation regimens for HCT in patients with CGD will be analyzed. The importance of clinical status at baseline, as well as subject genotype/phenotype, in choice of the transplant regimen will be assessed.
4	Should or should not carrier donors be used in HCT for X-linked and autosomal recessive CGD? Are the oxidase production levels of carrier donors stable over time, and will the expression in a recipient be the same as in the donor?	<i>Approach:</i> Information about the oxidase levels of carrier donors and, where available, the stability of these oxidase levels over time will be a part of the baseline assessments in Protocol 6903. Recipient oxidase expression will be compared with that of the donor.
5	For which forms of PID other than SCID would it be beneficial for the PIDTC or the PIDTC in collaboration with the IEWP-EBMT to study outcomes by means of natural history studies? Such studies are expected to form the basis for planning future prospective treatment clinical trials.	<i>Approach:</i> A feasibility study for future longitudinal observational and cross-sectional studies in HCT for rare PIDs will be conducted before selection of the next study the PIDTC will undertake.

RAG, Recombination-activating gene.

TABLE E3. Transplantation summary for patients with SCID, WAS, and CGD: selected publications, 2005 to the present

Study (year)	SCID	WAS	CGD	Other non-SCID PID	Other disease(s)	Design	Comments
Rao et al (2005) ^{E3}	6	4	NA	23	NA	Prospective treatment, single arm, single center	RIC regimen
	7	1	NA	11	NA	Retrospective cohort, center same as above	MAC regimen
Bhattacharya et al (2005) ^{E4}	8	NA	NA	6	NA	Retrospective, single center	Cord blood graft, various regimens
Sato et al (2007) ^{E5}	3	5	NA	1	NA	Retrospective, single center	Various regimens
Straathof et al (2009) ^{E6}	9	NA	NA	7	NA	Prospective treatment, single arm, single center	Antibody-based MIC regimen (anti-CD45 and anti-CD52/ Campath)
Frangoul et al (2010) ^{E7} Registration: ClinicalTrials.gov NCT00000603	4	5	NA	15	340	Prospective treatment, single arm; multicenter (27 centers) Cord Blood Transplantation Study (COBLT) sponsored by NHLBI, NIH	Cord blood graft, MAC regimen
Gennery et al (2010), ^{E8} incorporates previous Antoine et al (2003) ^{E9}	699	168	41	574	NA	Retrospective, multicenter; 37 centers participating in SCETIDE database of EBMT/ESID	Various regimens
Slatter et al (2011) ^{E10}	27	7	0	36	NA	Retrospective, 2 centers	Treosulfan-based regimens
Morio et al (2011) ^{E11}	40	23	7	18	NA	Prospective, observational, multicenter	Cord blood graft, various regimens
Schulz et al (2011) ^{E12}	4	0	2	6	18	Prospective treatment, single center	Antibody-based (⁹⁰ Y-labeled anti-CD66) MIC regimen for SCID or MAC regimen for non-SCID
DiNardo et al (2012) ^{E13}	25	2	0	12	NA	Retrospective, single center	Various regimens
Eapen et al (2012) ^{E14}	201	144	17	244	348, all with inborn errors of metabolism	Retrospective, multicenter, from >450 centers participating in CIBMTR database	Study of survivors >2 y after HCT; various regimens
SCID							
Dvorak et al (2008) ^{E15}	15	NA	NA	NA	NA	Prospective treatment, single center	Graft: megadoses of haplocompatible CD34 ⁺ hematopoietic stem cells with a fixed dose of CD3 ⁺ T cells; no preparative regimen given except that fludarabine was used when maternal engraftment was present
Railey et al (2009) ^{E16} and Sarzotti-Kelsoe et al (2009), ^{E17} and Buckley et al (2012) ^{E18}	161	NA	NA	NA	NA	Retrospective, single center	Graft: related donor transplants Regimen: no patient received pretransplantation chemotherapy or posttransplantation GVHD prophylaxis

(Continued)

TABLE E3. (Continued)

Study (year)	SCID	WAS	CGD	Other non-SCID PID	Other disease(s)	Design	Comments
Iguchi et al (2011) ^{E19}	3 (X-linked SCID only)	NA	NA	NA	NA	Retrospective, single center	Cord blood graft, various regimens
Yu et al (2011) ^{E20}	9 (T ⁺ B ⁺ NK ⁺ SCID only)	NA	NA	NA	NA	Retrospective, single center	Various regimens
Fernandes et al (2012) ^{E21}	249 (SCID or Omenn syndrome)	NA	NA	NA	NA	Retrospective, multicenter, 32 centers participating in EUROCORD and/or SCETIDE, EBMT/ESID databases	Cord blood or T-cell depleted haplo-matched graft; various regimens
Hassan et al (2012) ^{E22}	106 (ADA-SCID only)	NA	NA	NA	NA	Retrospective, multicenter; 37 centers participating in SCETIDE database of EBMT/ESID	Various regimens
WAS							
Ozsahin et al (2008) ^{E23}	NA	96	NA	NA	NA	Retrospective, multicenter; European centers identified through IEWP EMBT and/or the ESID WAS database	Study of survivors >2 y after HCT; various MAC regimens
Friedrich et al (2009) ^{E24}	NA	39	NA	NA	NA	Retrospective, single center	Various MAC regimens
Moratto et al (2011), ^{E25} includes 8 patients reported by Ozsahin et al (2008) ^{E23} and includes 66 patients reported by Filipovich et al (2001) ^{E26}	NA	194	NA	NA	NA	Retrospective, multicenter; European and US centers	Various MAC regimens
Shin et al (2012) ^{E27}	NA	47	NA	NA	NA	Retrospective, single center	Various regimens, most are MAC
CGD							
Gungor et al (2005) ^{E28}	NA	NA	3	NA	NA	Retrospective, single center	Adult subjects with significant comorbidities; RIC regimen
Soncini et al (2009) ^{E29}	NA	NA	20	NA	NA	Retrospective, single center	Various MAC regimens
Schuetz et al (2009) ^{E30}	NA	NA	12	NA	NA	Retrospective, single center	Various MAC regimens
Tewari et al (2012) ^{E31}	NA	NA	12	NA	NA	Retrospective, single center	Graft: Cord blood or bone marrow; various MAC regimens

MIC, Minimal-intensity conditioning; NA, not applicable; RIC, reduced-intensity conditioning.