Published in final edited form as:
J Allergy Clin Immunol. 2014 February ; 133(2): 335–347.e11. doi:10.1016/j.jaci.2013.07.052.

Primary Immune Deficiency Treatment Consortium (PIDTC) Report

A full list of authors and affiliations appears at the end of the article.

Abstract

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 (PID). 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 PID. To date, the PIDTC has funded two pilot projects: newborn screening for SCID in Navajo Native Americans; and B cell reconstitution in SCID patients following 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 two PIDTC workshops, and consideration of future consortium objectives.

Keywords

Allogeneic hematopoietic cell transplantation; gene therapy; primary immunodeficiency; clinical trial

INTRODUCTION

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

Correspondence: Linda M. Griffith, MD, PhD, Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 6610 Rockledge Dr, Rm. 6716, Bethesda, MD 20892-6610; Phone (301) 496-7104; Fax: (301) 480-1450; LGriffith@niaid.nih.gov.

transplantation (HCT) have differed according to local practice with relatively few patients treated at each individual 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 or enzyme replacement therapy for PID performed in North America. The results of these studies were envisioned to become a resource and foundation for the design of future prospective 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 PID, 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 (NCATS), NIH. PIDTC clinical studies in Severe Combined Immune Deficiency (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 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 progress of the PIDTC is to re-visit the priorities presented in the report of our consensus workshop at 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

1. Conduct of Multi-Center 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.

2. Conduct of Pilot/Demonstration Projects

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

3. 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 (UCSF) and UCSF Benioff Children's Hospital, and at the Data Management and Coordinating Center (DMCC) of the Rare Diseases Clinical Research Network (RDCRN), University of South Florida (http://rarediseasesnetwork.epi.ucsf.edu/PIDTC). The Center for International Blood and Marrow Transplant Research (CIBMTR) (Table II) collects part of the prospective data for the PIDTC natural history studies. To refer patients to PIDTC participating centers and/or for PIDTC protocols, see the ClinicalTrials.gov website for IRB-approved studies (Table I), and / or the PIDTC website above.

4. Communication with Patient Advocacy Groups

The cooperation and support of representatives of patients with PID 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; to register patients with PID in the United States Immunodeficiency Network (USIDNET), see Table II.

5. 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, ten trainees and junior faculty have been funded with one year $25,000 awards to support research in PID.

6. Scientific Collaboration Nationally and Internationally

The PIDTC has worked consistently to strengthen scientific interaction between North America and international colleagues in the field. Members from 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 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 match and any conditioning received prior to HCT. Cross-sectional studies of subjects surviving at least two years post-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 NIH in 2008[1] (see Table E2) can be analyzed. The PIDTC collaborates actively with the Center for International Blood and Marrow Transplant Research (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 fifty children diagnosed with SCID by consortium centers since 2010[2] (Protocol 6901). We are in the process of evaluating the collected outcome data for children with SCID treated by HCT in North America at PIDTC centers between January 1, 2000 and December 31, 2009 (Protocol 6902; manuscript in preparation).

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,[3] the PIDTC contributed to a pilot study to develop a NBS test in the 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,[4] 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 USA.[5,6]

GRAFT FAILURE AFTER HCT FOR SCID

Graft failure is a relatively frequent complication of HCT for SCID,[7] especially when no conditioning or a reduced intensity conditioning (RIC) regimen[8,9] is used for HCT from donors other than HLA-matched siblings, although graft failure may 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 re-transplant of SCID patients. The group defined failure of T cell engraftment as undetectable CD3+ T cells and absence of donor T cell chimerism, occurring at three months (ninety days) post-HCT for T-depleted grafts, and at two months (sixty days) post-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 transplant regimen on the extent and durability of T cell, B cell and NK cell lineage-specific reconstitution, and concerns regarding long-term toxic effects of any conditioning used, are critical questions in allogeneic HCT for SCID.[1,10,11] The consortium has reviewed the published experience of B cell reconstitution after allogeneic HCT for SCID when using no conditioning vs. using a conditioning regimen, by means of a debate during the PIDTC Second Annual Scientific Workshop in 2012.[10]

We now add the following 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 impact 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 transplant outcome for SCID, in particular, in T-B-NK+ SCID, which includes the RAG and Artemis genetic defects?[12] What is the role of NK cells in graft rejection, can NK cells be suppressed/ablated using non-chemotherapy approaches, and can the NK cell-specific receptors and ligands be manipulated to promote engraftment and reduce the risk of graft vs host disease (GVHD) post-transplant?

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

In 2008, the PIDTC recommended study of the cumulative North American experience of HCT for WAS and CGD by means of natural history studies; these are expected to open in 2013 (Table I). Cross-sectional studies of subjects surviving at least two years post-HCT will assess immune function, late effects, and 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, for resolution of the clinical symptoms[1] (see also Table E1 in Griffith et al (2009)[13]).

We now add the following questions:

1. What are the mechanisms of pre- and post-transplant autoimmune/inflammatory complications in patients with non-SCID PID? Is autoimmunity post-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 transplant of WAS patients 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 CGD patient's level of oxidase activity is directly related to overall survival;[14] is this the best indicator of need for HCT? When is the best time to provide HCT for patients likely to benefit due to their low/absent neutrophil oxidase activity?[15]
3. How does the clinical status and genotype/phenotype of the patient with CGD affect the choice of transplant regimen?
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?
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.

ADULT UNRELATED DONORS AND CORD BLOOD AS GRAFT SOURCES FOR HCT

In view of the experience that only about 10–20% of patients with SCID have a matched sibling donor (MSD) available for HCT, alternative donors will continue to be important. Recent data indicate that for non-malignant disease, while not as good as with an HLA-matched sibling donor, very good to excellent survival is observed after HCT from fully matched unrelated donors (MUD).[16–18] However, the search for a MUD may take several months, posing some risk to SCID patients. To circumvent this problem, cord blood donors have been increasingly utilized, especially when one or both haplotypes are rare, as an alternative to T cell-depleted haploidentical transplantation. So far, it is clear that greater degrees of HLA disparity are tolerated in cord blood transplants.[19] However, the more immature immunologic status of this new resource requires further characterization and the implications of using such grafts for transplant outcomes requires further study.[20,21]

HCT REGIMENS

Given that the PID are rare, it is difficult to enroll the number of subjects 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 PID by means of either relatively small prospective studies conducted at a single center, or large retrospective observational analyses (Table E3).

The use of pre-HCT conditioning for patients with SCID continues to be controversial with some centers avoiding it altogether while others use only fully myeloablative therapy.[8–10,22] At the PIDTC Second Annual Scientific Workshop in April 2012 this topic was debated and the details have been published.[10] 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 (MIC) regimens.[10] As the patient's immune system is theoretically unable to reject the graft, this approach is feasible at least for permissive types of SCID, e.g., when an HLA matched sibling is available, when the recipient has NK- SCID, and when there is maternal engraftment at birth and the mother is the donor.[23] However, especially in NK+ SCID phenotypes with HLA-mismatched donors, graft rejection is often seen when immunosuppressive therapy is not given.[12,23] Furthermore, a finite degree of durable donor stem cell engraftment may be necessary to achieve recovery of B cell function in most SCID geno/phenotypes, especially in forms of SCID in which the genetic defect affects B cell function (such as in γc or JAK3 deficiency) or development (as in defects of VDJ recombination). For these cases, some degree of myeloablation sufficient to allow B cell reconstitution may 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. While partial chimerism of the myeloid lineage may be sufficient to obtain clinical cure in 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 if it is sufficient to attain full correction of the disease phenotype. If this is the case, as some recent data from the literature suggest,[24] there is a need to define target levels of HSC engraftment and to design and test in prospective randomized studies appropriate reduced-intensity conditioning regimens that permit engraftment sufficient to prevent autoimmune complications while minimizing short and long term toxicity.

Alternative approaches to achieving engraftment with immune reconstitution are an area of active investigation, for example, targeting recipient bone marrow stem cells with monoclonal antibodies,[25–27] or mobilizing autologous hematopoietic stem cells,[28] prior to infusion of the graft. Other potential strategies include use of megadoses of donor CD34+ hematopoietic stem cells.[23,29] Finally, the role of donor lymphocyte infusion in supporting donor engraftment after HCT in patients with severe primary immunodeficiencies needs to be further evaluated.[7]

GENE THERAPY AS A TREATMENT OPTION FOR PID

An update of current investigations of gene therapy (GT) as treatment for PID is an integral part of the PIDTC Annual Scientific Workshop[30–32] (Table III), and GT is included in the PIDTC natural history studies for SCID and WAS (Table I). Autologous CD34+ HSCs are positively selected, transduced by ex vivo culture with retroviral or lentiviral vectors containing the corrective gene, and then re-infused into the patient. Experience with GT for

X-SCID, [33,34] ADA deficiency,[35–37] CGD[38–41] and WAS[42] have offered proof-of-principle that this may represent an effective form of treatment for severe PIDs and other disorders. However, in the case of X-SCID, CGD and WAS the reported success of gene therapy has been tempered by demonstration of leukemic proliferation (due to insertional mutagenesis) in several patients.[30–32, 43] 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 PID can become more widely available.

PROSPECTIVE TREATMENT PROTOCOL FOR SCID IDENTIFIED BY NBS

Infants with SCID who are diagnosed and treated with HCT before 3.5 months of age have the best outcome.[44] An increasing number of states in the US have initiated or committed to starting newborn screening for SCID.[5,6] Of the first fifty patients with SCID or SCID variants entered into the PIDTC prospective study, twenty-five were diagnosed at birth by newborn screening (n=13) or positive family history (n=12).[2] 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 diagnosed and treated, several in PIDTC studies, with 93% survival.[45]

Treating newborns with SCID has raised a number of issues for investigation, most importantly, what is the best approach to conditioning in order to achieve durable T and B cell immunity while minimizing short and long term toxicities?[46,47] Other variables include when to start prophylactic medications, whether or not 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 CMV infection when the mother is seropositive.

FUTURE OPPORTUNITIES FOR CLINICAL STUDIES IN PID

1. Natural History Studies

Initially, CGD and WAS were selected for study among the non-SCID disorders, given the significant questions regarding efficacy and optimal approach to HCT for each of them as described above, and because the affected patient population in North America is felt to be sufficiently large to answer these questions. However, similar issues exist for other very rare PIDs including CD40 ligand deficiency, IPEX, NEMO deficiency, Major Histocompatibility Class II deficiency, DOCK8 deficiency, and disorders of T cell function such as ZAP70 deficiency and Ca^{2+} signaling defects (Table E1 in Griffith et al (2009)[13]).

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

2. 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 (PAGs) for these disorders (Table E1). The USIDNET is a NIAID-funded multi-institutional collaboration with a primary goal of collecting longitudinal data on patients with a variety of PIDs. A total 0f 3025 patients have been reported to the USIDNET Registry through 2012. The CIBMTR/NMDP and EBMT are international collaborations that collect detailed HCT data on patients with malignant and non-malignant disorders. The Inborn Errors Working Party (IEWP) of ESID/EBMT has

developed the comprehensive registry of Stem Cell Transplant for Immunodeficiencies in Europe (SCETIDE) that 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 PID (Table II). At the end of 2012, 16,547 PID patients had been reported to the ESID Registry. Finally, the PAGs have generated large email lists of patients with PID that could be used to inform patients and parents of possible studies as well as survey patients/parents regarding current clinical status and quality of life.

3. 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 may be more efficacious and less toxic than the standard drug Busulfan in conditioning for HCT. Collaboration of Europe and the US may 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 diagnosed as newborns with SCID in the US into PIDTC studies; 3) characterize all children with low TRECs at birth; 4) determine which children with CGD should get a transplant; 5) determine if full donor chimerism is essential to prevent post-transplant autoimmunity in WAS; 6) develop joint studies with 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 (Tables I and 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 improve understanding of the etiology of disease and best treatments for patients with these rare life-threatening disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Linda M. Griffith, MD, PhD[a], Morton J. Cowan, MD[b], Luigi D. Notarangelo, MD[c], Donald B. Kohn, MD[d], Jennifer M. Puck, MD[b,e], Sung-Yun Pai, MD[f], Barbara Ballard[g], Sarah C. Bauer, MD[h], Jack J. H. Bleesing, MD, PhD[i], Marcia Boyle, PhD[g], Amy Brower, PhD[j], Rebecca H. Buckley, MD[k], Mirjam van der Burg, PhD[l], Lauri M. Burroughs, MD[m], Fabio Candotti, MD[n], Andrew J. Cant, MD[o], Talal Chatila, MD[p], Charlotte Cunningham-Rundles, MD, PhD[q], Mary C. Dinauer, MD, PhD[r], Christopher C. Dvorak, MD[b], Alexandra H. Filipovich, MD[s], Thomas A. Fleisher, MD[t], Hubert Bobby Gaspar, MD, PhD[u], Tayfun Gungor, MD[v], Elie Haddad, MD, PhD[w], Emily Hovermale[g], Faith Huang, MD[x], Alan Hurley[y], Mary Hurley[y], Sumathi Iyengar, MD[z], Elizabeth M. Kang, MD[aa], Brent R. Logan, PhD[bb], Janel R. Long-Boyle, PharmD, PhD[cc], Harry L. Malech, MD[aa], Sean A. McGhee, MD[dd], Fred Modell[ee], Vicki Modell[ee], Hans D. Ochs, DM[ff], Richard J. O'Reilly, MD[gg], Robertson Parkman, MD[hh], David J. Rawlings, MD[ii], John M. Routes, MD[jj], William T. Shearer,

MD, PhD[kk], Trudy N. Small, MD[ll], Heather Smith[mm], Kathleen E. Sullivan, MD, PhD[nn], Paul Szabolcs, MD[oo], Adrian Thrasher, MD[pp], Troy R. Torgerson, MD, PhD[qq], Paul Veys, MD[rr], Kenneth Weinberg, MD[ss], and Juan Carlos Zuniga-Pflucker, PhD[tt] **on behalf of the workshop participants**

Affiliations

[a]Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD [b]Division of Allergy/Immunology and Blood and Marrow Transplantation, Department of Pediatrics and UCSF Benioff Children's Hospital, University of California San Francisco, San Francisco, CA [c]Division of Immunology, the Manton Center for Orphan Disease Research, Children's Hospital, and Harvard Stem Cell Institute, Harvard Medical School, Boston, MA [d]Departments of Microbiology, Immunology and Molecular Genetics, University of California Los Angeles, Los Angeles, CA [e]Institute for Human Genetics, University of California San Francisco, San Francisco, CA [f]Pediatric Hematology/Oncology, Children's Hospital, Harvard Medical School, Boston, MA [g]Immune Deficiency Foundation, Towson, MD [h]Developmental and Behavioral Pediatrics, Lurie Children's Hospital of Chicago, Northwestern Feinberg School of Medicine, Chicago, IL [i]Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH [j]Newborn Screening Translational Research Network, American College of Medical Genetics and Genomics, Bethesda, MD [k]Pediatric Allergy and Immunology, Duke University School of Medicine, Durham, NC [l]Molecular Immunology, Erasmus Medical Center, Rotterdam, The Netherlands [m]Pediatric Hematology/Oncology, Fred Hutchinson Cancer Research Center, University of Washington School of Medicine, Seattle, WA [n]Genetics & Molecular Biology Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD [o]Pediatric Immunology and Infectious Diseases, and Pediatric Bone Marrow Transplant, Newcastle General Hospital, Newcastle upon Tyne, UK [p]Pediatric Allergy/Immunology, Children's Hospital, Harvard Medical School, Boston, MA [q]Pediatric Clinical Immunology, Mount Sinai School of Medicine, New York, NY [r]Pediatric Hematology/Oncology, Washington University School of Medicine, St. Louis, MO [s]Pediatric Clinical Immunology, Division of Hematology / Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH [t]Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, MD [u]Pediatric Immunology, Center for Immunodeficiency, Institute of Child Health, Great Ormond Street Hospital, University College London, England, UK [v]Pediatric Immunology and Blood and Marrow Transplantation, Children's Hospital Zurich, University of Zurich, Switzerland [w]Pediatric Immunology, Mother and Child Ste-Justine Hospital, Montreal, Quebec, Canada [x]Pediatric Allergy/Immunology, Mount Sinai Medical Center, New York, NY [y]Chronic Granulomatous Disease Association, San Marino, CA [z]Wiskott-Aldrich Foundation, Inc., Smyrna, GA [aa]Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD [bb]Center for International Blood and Marrow Transplant Research and Division of Biostatistics, Medical College of Wisconsin, Milwaukee, WI [cc]Department of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco, CA [dd]Pediatric Allergy/Immunology, Lucile Packard Children's Hospital, Stanford University Medical Center, Stanford, CA [ee]Jeffrey Modell Foundation, New York, NY [ff]Center for Immunity and Immunotherapy, Seattle Children's Hospital Research Institute, University of Washington School of Medicine, Seattle, WA [gg]Pediatrics and Immunology, Memorial Sloan Kettering Cancer Center, New York, NY [hh]Division of Research Immunology/B.M.T., Children's Hospital Los Angeles, Los Angeles, CA [ii]Pediatric Immunology, Seattle

Children's Research Institute, University of Washington School of Medicine, Seattle, WA [jj]Pediatric Allergy and Clinical Immunology, Children's Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee, WI [kk]Pediatric Allergy & Immunology, Texas Children's Hospital, Baylor College of Medicine, Houston TX [ll]Pediatric Bone Marrow Transplant Service, Memorial Sloan Kettering Cancer Center, New York, NY [mm]SCID Angels for Life Foundation, Lakeland, FL [nn]Pediatric Immunology, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA [oo]Bone Marrow Transplantation and Cellular Therapies, Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA [pp]Pediatric Immunology, Center for Immunodeficiency, Institute of Child Health, Great Ormond Street Hospital, University College London, England, UK [qq]Pediatric Rheumatology, Seattle Children's Research Institute, University of Washington School of Medicine, Seattle, WA [rr]Blood and Marrow Transplantation, Institute of Child Health, Great Ormond Street Hospital, London, UK [ss]Pediatric Stem Cell Transplantation, and Hematology/Oncology, Lucile Packard Children's Hospital, Stanford University School of Medicine, Stanford, CA [tt]Department of Immunology, University of Toronto, Toronto, Ontario, Canada

Acknowledgments

We thank Elizabeth Dunn (San Francisco, 2011), and Luisa Raleza and Emily Buehrens (Boston, 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, NY, our valued colleague and friend, passed away in June 2013. Her special expertise included transplantation for primary immune deficiencies, recovery of the immune system after hematopoietic cell transplantation, and vaccination strategies to prevent infectious complications post-transplant 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 co-chairing 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.

This work was supported by: the Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases; the Intramural Research Programs of the National Human Genome Research Institute and the National Institute of Allergy and Infectious Diseases; and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA; U54-AI082973 (PI: M. J. Cowan); U54-NS064808 (PI: J. P. Krischer); R13-AI094943 (PIs: M. J. Cowan, L. D. Notarangelo). **Workshops in April 2011 (San Francisco, CA) and April 2012 (Boston, MA) were also supported in part by:** the Immune Deficiency Foundation, Towson MD; the Jeffrey Modell Foundation, New York, NY; the Robert A. Good Immunology Society, St. Petersburg, FL; the Manton Center for Orphan Disease Research and the Children's Hospital Translational Research Program, Children's Hospital, Boston, MA; Baxter International, Deerfield, IL; CSL Behring, King of Prussia, PA; Sigma-Tau Pharmaceuticals, Inc., Gaithersburg, MD; and Talecris Biotherapeutics, Research Triangle Park, NC.

Abbreviations - PIDTC Interim Report and Annual Scientific Workshops 1 & 2

CGD	Chronic Granulomatous Disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CMV	Cytomegalovirus
DLI	Donor Lymphocyte Infusion
DMCC	Data Management and Coordinating Center

EBMT	European Group for Blood and Marrow Transplantation
ERT	Enzyme Replacement Therapy
ESID	European Society for Immunodeficiencies
GT	Gene Therapy
GVHD	Graft vs. Host Disease
HCT	Hematopoietic Cell Transplantation
HLA	Human Leukocyte Antigen
HSCs	Hematopoietic Stem Cells
IEWP	Inborn Errors Working Party
IPEX	Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked
MAC	Myeloablative Conditioning
MIC	Minimal Intensity Conditioning
MUD	Matched Unrelated Donors
NBS	Newborn Screening for SCID
NCATS	National Center for Advancing Translational Sciences
NEMO	Acronym of the Non-functioning Gene NF-kB Essential Modulator
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NK-SCID	Natural Killer –SCID
NMDP	National Marrow Donor Program
PAG	Patient Advocacy Group
PID	Primary Immune Deficiency (Diseases)
PIDTC	Primary Immune Deficiency Treatment Consortium
RAPID	Resource of Asian Primary Immune Deficiency Diseases
RIC	Reduced Intensity Conditioning
RDCRN	Rare Diseases Clinical Research Network
SCETIDE	Stem Cell Transplantation for Immunodeficiencies in Europe
SCID	Severe Combined Immunodeficiency
SCID-A	Artemis-Deficient SCID
TRECs	T-cell Receptor Excision Circles
UCSF	University of California San Francisco
USIDNET	United States Immunodeficiency Network
WAS	Wiskott-Aldrich Syndrome;

REFERENCES

1. 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; 122:1087–1096. [PubMed: 18992926]
2. Dvorak CC, Cowan MJ, Logan BR, Griffith L, Puck J, Notarangelo LD, 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. Jul 2.2013 :23818196. [Epub ahead of print] PMID.
3. 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; 117:3243–3246. [PubMed: 21273302]
4. Dvorak CC, Cowan MJ. Radiosensitive severe combined immunodeficiency disease. Immunol Allergy Clin N Am. 2010; 30:125–142.
5. 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; 129:607–616. [PubMed: 22285280]
6. Borte S, von Dobeln U, Hammarstrom L. Guidelines for newborn screening of primary immunodeficiency diseases. Curr Opin Hematol. 2013; 20:48–54. [PubMed: 23108220]
7. Taigland CL, Parrott RE, Buckley RH. Long-term outcome of non-ablative booster BMT in patients with SCID. Bone Marrow Transplant. Feb 11.2013 Advance online publication.
8. Veys, P.; Gaspar, HB. Primary immunodeficiency diseases. In: J, Treleaven; AJ, Barrett, editors. Hematopoietic Stem Cell Transplantation in Clinical Practice. Edinburgh, UK: Churchill Livingstone Elsevier; 2009. p. 153-164.
9. Chiesa R, Veys P. Reduced-intensity conditioning for allogeneic stem cell transplant in primary immune deficiencies. Expert Rev Clin Immunol. 2012; 8:255–267. [PubMed: 22390490]
10. 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. [PubMed: 23465660]
11. Cavazzana-Calvo M, Andre-Schmutz I, Fischer A. Haematopoietic stem cell transplantation for SCID patients: where do we stand? British J Haematol. 2013; 160:146–152.
12. 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; 15:733–741. [PubMed: 21883749]
13. 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; 124:1152–1160. [PubMed: 20004776]
14. Kuhns DB, Alvord WG, Heller T, Feld JJ, Pike KM, Marciano BE, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. New Engl J Med. 2010; 363:2600–2610. [PubMed: 21190454]
15. Kang EM, Marciano BE, DeRavin SS, Zarember KA, Holland SM, Malech HM. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2011; 127:1319–1326. [PubMed: 21497887]
16. Woolfrey A, Lee SJ, Gooley TA, Malkki M, Martin PJ, Pagel JM, Hansen JA, Petersdorf E. HLA-allele matched unrelated donors compared to HLA-matched sibling donors: role of cell source and disease risk category. Biol Blood Marrow Transplant. 2010; 16:1382–1387. [PubMed: 20447462]
17. 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; 17:1289–1298. [PubMed: 21220035]
18. Eapen M, Horowitz MM. Alternative donor transplantation for aplastic anemia. Hematology (ASH Education Program Book). 2010:43–55.
19. 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; 12:1214–1221. [PubMed: 21982422]

20. Szabolcs P, Cairo MS. Unrelated umbilical cord blood transplantation and immune reconstitution. Semin Hematology. 2010; 47:22–36.
21. Kim Y-J, Broxmeyer HE. Immune regulatory cells in umbilical cord blood and their potential roles in transplantation tolerance. Crit Rev Oncol / Hematol. 2011; 79:112–126.
22. Parikh S, Szabolcs P. Reduced-intensity conditioning (RIC) in children with nonmalignant disorders (NMD) undergoing unrelated donor umbilical cord blood transplantation. Biol Blood Marrow Transplant. 2012; 18:S53–S55. [PubMed: 22226113]
23. 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; 14:1125–1133. [PubMed: 18804042]
24. 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; 118:1675–1684. [PubMed: 21659547]
25. 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; 119:1130–1138. [PubMed: 22134165]
26. 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; 117:4642–4650. [PubMed: 21325170]
27. Straathof KC, Rao K, Eyrich 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; 374:912–920. [PubMed: 19729196]
28. Chen J, Larochelle A, Fricker S, Bridger G, Dunbar CE, Abkowitz JL. Mobilization as a preparative regimen for hematopoietic stem cell transplantation. Blood. 2006; 107:3764–3771. [PubMed: 16439683]
29. Czechowicz A, Weissman IL. Purified hematopoietic stem cells transplantation: the next generation of blood and immune replacement. Immunol Allergy Clin N Am. 2010; 30:159–171.
30. Kohn DB, Pai S-Y, Sadelain M. Gene therapy through autologous transplantation of gene-modified hematopoietic stem cells. Biol Blood Marrow Transplant. 2013; 19:S64–S69. [PubMed: 23032601]
31. Cavazzana-Calvo M, Fischer A, Hacein-Bey-Abina S, Aiuti A. Gene therapy for primary immunodeficiencies: Part 1. Curr Opin Immunol. 2012; 24:580–584. [PubMed: 22981681]
32. Aiuti A, Bacchetta R, Seger R, Villa A, Cavazzana-Calvo M. Gene therapy for primary immunodeficiencies: Part 2. Curr Opin Immunol. 2012; 24:585–591. [PubMed: 22909900]
33. 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; 363:355–364. [PubMed: 20660403]
34. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M, et al. 20 years of gene therapy for SCID. Nature Immunol. 2010; 11:457–460. [PubMed: 20485269]
35. 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; 360:447–458. [PubMed: 19179314]
36. 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; 120:3635–3646. [PubMed: 22968453]
37. Gaspar HB. Gene therapy for ADA-SCID: defining factors for a successful outcome. Blood. 2012; 120:3628–2629. [PubMed: 23118212]

38. Kang EM, Choi U, Theobald N, Linton G, Long Priel DA, Kuhns D, Malech HL. Retrovirus gene therapy for X-linked chronic granulomatous disease can achieve stable long-term correction of oxidase activity in peripheral blood neutrophils. Blood. 2010; 115:783–791. [PubMed: 19965657]
39. Kang EM, Malech HL. Gene therapy for chronic granulomatous disease. Meth Enzymol. 2012; 507:125–154. [PubMed: 22365772]
40. 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. [PubMed: 20098431]
41. Segal BH, Veys P, Malech H, Cowan MJ. Chronic Granulomatous disease: lessons from a rare disorder. Biol Blood Marrow Transplant. 2011; 17:S123–S131. [PubMed: 21195301]
42. 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; 363:1918–1927. [PubMed: 21067383]
43. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M, et al. 20 years of gene therapy for SCID. Nature Immunol. 2010; 11:457–460. [PubMed: 20485269]
44. 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 Pediatrics. 2009; 155:834–840.
45. Kwan A, Church JA, Cowan MJ, Agarwal R, Kapoor N, Kohn DB, Lewis DB, McGhee SA, Moore TB, Stiehm ER, Porteus M, Aznar CP, Currier R, Lorey F, Puck JM. Newborn screening for severe combined immunodeficiency and T cell lymphopenia in California: Results of the first 2 years. J Allergy Clin Immunol. 2013; 132:140–150. e7. [PubMed: 23810098]
46. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology – drug disposition, action, and therapy in infants and children. New Engl J Med. 2003; 349:1157–1165. [PubMed: 13679531]
47. Law J, Cowan MJ, Dvorak CC, Musick L, Long-Boyle JR, Baxter-Lowe LA, Horn B. 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; 18:1656–1663. [PubMed: 22609040]
48. 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; 126:602–610. [PubMed: 20673987]
49. 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–D867. [PubMed: 18842635]
50. Zychlinski D, Schambach A, Modlich U, Maetzig T, Meyer J, Grassman E, Mishra A, Baum C. Physiological promoters reduce the genotoxic risk of integrating gene vectors. Mol Ther. 2008; 16:718–725. [PubMed: 18334985]
51. 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(21):80–81. [PubMed: 21576698]
52. 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; 363:355–364. [PubMed: 20660403]
53. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M, et al. 20 years of gene therapy for SCID. Nature Immunol. 2010; 11:457–460. [PubMed: 20485269]
54. 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; 120:3635–3646. [PubMed: 22968453]

55. Gaspar HB. Gene therapy for ADA-SCID: defining factors for a successful outcome. Blood. 2012; 120:3628–2629. [PubMed: 23118212]

56. Kang EM, Choi U, Theobald N, Linton G, Long Priel DA, Kuhns D, Malech HL. Retrovirus gene therapy for X-linked chronic granulomatous disease can achieve stable long-term correction of oxidase activity in peripheral blood neutrophils. Blood. 2010; 115:783–791. [PubMed: 19965657]

57. Kang EM, Malech HL. Gene therapy for chronic granulomatous disease. Meth Enzymol. 2012; 507:125–154. [PubMed: 22365772]

58. 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 experession in myeloid cells. Mol Ther. 2011; 19:122–32. [PubMed: 20978475]

59. 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; 363:1918–1927. [PubMed: 21067383]

60. 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:S212.

61. 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:S211–S212.

62. 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:S86.

Table I

PIDTC Protocols

Protocol Number, Title, Principal Investigators**	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 TRECs; repertoire diversity by spectratyping or Vβ usage. **3** **B Cells**: Post-HCT reconstitution, function & dysregulation; analysis of γc expression on CD19+ cells and plasmablast differentiation (limited to XSCID 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 years post-HCT and > 200 currently alive at 10 years post-HCT	**Cross-Sectional Analysis** **1** **T Cells**: TRECs, repertoire diversity by spectratyping or Vβ usage. **2** **T Cell HLA Restriction**: Compare antigen-specific HLA restricted by engrafted, donor-derived T cells and the donor's own T cells following unmodified or T cell depleted transplants (limited to selected subjects). **3** **B Cells**: Analysis of γc expression on CD19+ cells and plasmablast differentiation (limited to XSCID and JAK3 deficiency). **4** **NK Cells**: Functional and phenotypic attributions of NK tolerance in long-term SCID survivors following unmodified or T cell depleted transplants. **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 HCT subject they are paired with, and must have been alive at the age at which the HCT subject received transplant.	In development; IRB submission anticipated 2013	60 retrospective and 12 new transplant patients/year; 120 control non-transplant patients	**Cross-Sectional Analysis** **1** **Definition of CGD Subtype**: Western blot gene testing and/or mother demonstrates X-linked carrier mosaicism by NBT 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**: GI tract and skin (Steve Holland).

Protocol Number, Title, Principal Investigators**	**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 2013	250 retrospective and 29 new patients/year; 58 currently alive at 5 years post-HCT and > 70 currently alive at 10 years post-HCT	**Prospective and/or Cross-Sectional Analysis** **1** **T Cells**: Repertoire diversity by deep sequencing. **2** **B Cells**: KRECs; repertoire diversity by deep sequencing; BAFF/April level in serum. **3** **NK Cells**: CD107a degranulation assay. **4** Lineage-specific chimerism by flow cytometry (WASp expression) **5** **Autoantibodie(s)**: microarray analysis.

Notes:

* 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 website.

Table II

Clinical Research Database Resources in PID

Database	"Owner" and Primary Financial Resource(s)	Required or Voluntary	Year Started	Enrollment to Date	Purpose or Goal	Utilization Process
United States Immunodeficiency Network (USIDNET) **Contact:** **http://www.usidnet.org** **USIDNET PID Registry**	Immune Deficiency Foundation (IDF), Towson, MD; NIH, NIAID U24 (Research Resource) Grant Award, PI: Charlotte Cunningham-Rundles, MD PhD (Mount Sinai Medical Center)..	Voluntary	1997 (CGD started 1992)	3025 in PID Registry, see Note.	The purpose and scope of this project is to assemble and maintain a registry of residents of the United States with primary immunodeficiency diseases. Objectives include: to provide a minimum estimate of the prevalence of each disorder in the United States; to provide a comprehensive clinical picture of each disorder; to provide a resource for clinical and laboratory research.	Queries to the steering committee of the registry are accepted from diverse individuals including: physicians in practice, clinical researchers, and members of the lay public.
Contact: **http://www.usidnet.org/pub/Disease-Registry**	Non-profit with US Government and corporate sponsorship			Note: Website accessed April 2013.		
Center for International Blood and Marrow Transplant Registry (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, WI; 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. Non-profit with US Government and corporate sponsorship.	Registration is required for each allogeneic transplant performed in the USA (for the SCTOD, as required by US law). Transplant centers worldwide voluntarily submit allogeneic transplant data.	1972	> 330,000 in CIBMTR database; 5245 with transplant 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* posted on the website.	CIBMTR leads a worldwide collaboration of scientists and clinicians to advance understanding and outcomes of hematopoietic cell transplantation (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 which are reviewed by the committee and CIBMTR leadership prior to writing a study protocol for outcomes research of the database.
European Society for Immuno-deficiencies (ESID) **Contact: http://www.esid.org/** **ESID Registry** **Contact:**	Non-profit with corporate sponsorship.	Voluntary	1994 (Informal Organization started 1983)	16,547 in ESID database, see Note. Note: Enrollment	The registry of the ESID includes patients in Europe diagnosed with PID. ESID promotes collaboration between medical professionals, patient advocacy groups, industry and	Membership of the Bone Marrow Transplantation and Gene Therapy Working Party includes physicians of the

Database	"Owner" and Primary Financial Resource(s)	Required or Voluntary	Year Started	Enrollment to Date	Purpose or Goal	Utilization Process
http://www.esid.org/registry **ESID Bone Marrow Transplantation and Gene Therapy Working Party** **Contact:** **http://www.esid.org/bone-marrow-transplantation**				from 96 ESID documenting centers as of December 31, 2012; website accessed April 2013.	governmental bodies to further education and research in PID. 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 PID, which is posted to the EBMT IEWP and ESID web sites: **http://www.esid.org/downloads/BMT_Guidelines_2011.pdf**	ESID interested in clinical research in PID. This working party of the ESID collaborates closely with the EBMT IEWP.
European Group for Blood and Marrow Transplantation (EBMT) **Contact:** **http://www.ebmt.org/Contents/Pages/Default.aspx** **EBMT Inborn Errors Working Party (IEWP)** **Contact:** **http://www.ebmt.org/Contents/About-EBMT/Who-We-Are/Workingparties/Pages/Workingparties.aspx**	Non-profit with corporate sponsorship.	Voluntary	1974	> 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 PID, which is posted to the EBMT IEWP and ESID web sites; and 2) improve knowledge in PID by conducting retrospective research utilizing the EBMT/SCETIDE and ESID registries.	IEWP membership includes physicians of the EBMT and international community interested in clinical research in PID. 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 PID. An independent annual meeting of the IEWP is convened in Europe; HCT guidance and projects are reviewed and further developed.
Stem Cell Transplant for Immuno-deficiencies in Europe (SCETIDE); a Collaboration of EBMT and ESID	NA	Voluntary	1968	1500 in SCETIDE database, see Note. Note: Reference, Gennery (2010).[48]	The SCETIDE includes disease-specific information and outcomes data on transplants performed in primary immune deficiencies in Europe.	Data on individual PID HCT patients is acquired to complement the EBMT database and support the research projects of the EBMT/IEWP, as needed.
Resource of Asian Primary Immune	RAPID is a joint collaboration	NA	2009	The website lists 244 PID	**1** Web-based compendium of molecular alterations in	This web-based resource is

Database	"Owner" and Primary Financial Resource(s)	Required or Voluntary	Year Started	Enrollment to Date	Purpose or Goal	Utilization Process
Deficiency Diseases (RAPID) **Contact:** **http://rapid.rcai.riken.jp/RAPID**	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.			genes; 266 PID diseases; 234 genes having mutations; and 5086 unique mutations, see Note. Note: Website accessed April 2013.	PID; the site hosts information on sequence variations and expression at the mRNA and protein levels of all genes reported to be involved in PID patients. **2** Detailed information pertaining to genes and proteins involved in PID diseases is provided. **3** The tool, "Mutation Viewer" is able to predict deleterious and novel mutations and also obtain mutation-based 3D structures for PID genes. See Note. Note: Reference, Keerthikumar (2009).[49]	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.

Abbreviations: HRSA = Health Resources and Services Administration; SCTOD = Stem Cell Transplant Outcomes Database

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 & Paris); ClinicalTrials.gov NCT01175239 (Boston MA, Cincinnati OH & Los Angeles CA)	Parallel European and North American studies. Europe: Great Ormond Street Hospital, London, UK; Hôpital Necker-Enfants Malades, Paris, FR USA: Children's Hospital, Boston MA; Children's Hospital Medical Center, Cincinnati, OH; University of California, Los Angeles, CA	UK: Great Ormond Street Hospital, NHS Foundation Trust (PI: A. Thrasher) FR: Assistance Publique-Hôpitaux Paris (PI: A. Fischer) USA: NIAID, NIH (PI: D. A. Williams)	Virus: Gamma retrovirus Insert: IL2R gamma chain Modifications: WPRE post-translational regulatory element to enhance expression Safety modifications: EFS (EF1α short) cellular internal promoter; U3 deletion in LTR (SIN configuration) Vector development: C. Baum, Hannover Medical School, Germany Vector manufacture: University of Cincinnati, OH, USA Target: BM CD34+ cells	Conditioning: None	Zychlinski (2008);[50] Pai S-Y (2011);[51] Hacein-Bey-Abina (2010) (report of follow-up for earlier studies using a gamma retrovirus vector);[52] Fischer (2010) (review).[53]
Activation Date: 2012, recruiting Registration: ClinicalTrials.gov NCT01512888	St. Jude Children's Research Hospital, Memphis, TN	NHLBI, NIH (PI: B. Sorrentino)	Virus: Lentivirus Insert: IL2R gamma chain Safety modifications: EFS (EF1α short) cellular internal promoter; U3 deletion in LTR (SIN configuration); enhancer blocking insulator sequence(s) Vector development: B. Sorrentino, St. Jude, Memphis, TN, USA Target: BM CD34+ cells	Conditioning: None	NA
X-SCID in Older Children					
Activation Date: 2010; recruiting Registration: Clinical Trials.gov NCT01306019	NIAID, NIH Clinical Center, Bethesda, MD	NIAID, NIH (PI: S. S. DeRaven, H. L. Malech)	Virus: Lentivirus Insert: IL2R gamma chain Safety modifications: EFS (EF1α short) cellular internal promoter; U3 deletion in LTR (SIN configuration);enhancer blocking insulator sequence(s) Vector development: B. Sorrentino, St. Jude, Memphis, TN Target: PBSC CD34+ cells	Conditioning: Busulfan 6mg/kg	NA
ADA SCID					

Study	Center(s)	Sponsor(s)	Vector	Treatment Regimen	Publications
Activation Date: May 2013; recruiting Registration: ClinicalTrials.gov NCT01852071	University of California, Los Angeles, CA & NHGRI, NIH Clinical Center, Bethesda, MD	NIAID, NIH (PI: D.B. Kohn)	Virus: Lentivirus Modifications: codon optimized human ADA cDNA, WPRE post-translational regulatory element to enhance expression Safety modifications: EFS (EF1α short) cellular internal promoter; U3 enhancer deletion in LTR (SIN configuration) Vector manufacture: IUVPF Target: BM CD34+ cells	PEG-ADA: Discontinue Conditioning: Myeloreductive Busulfan (4 mg/kg)	Candotti (2012)[54] (previous work of this group in ADA SCID using a gamma retrovirus vector); Gaspar (2012) [55](editorial).
Activation Date: November 2011; recruiting Registration: ClinicalTrials.gov NCT01380990	Great Ormond Street Hospital, London, UK	Great Ormond Street Hospital, NHS Foundation Trust (PI: H. B. Gaspar, A. Thrasher)	Virus: Lentivirus Modifications: codon optimized human ADA cDNA, WPRE post-translational regulatory element to enhance expression Safety modifications: EFS (EF1α short) cellular internal promoter; U3 enhancer deletion in LTR (SIN configuration) Vector manufacture: IUVPF Target: BM 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: Gamma retrovirus MFGS Insert: gp91phox Target: PBSC CD34+ cells	Conditioning: Busulfan (10 mg/kg) Graft: CD34+ dose target 5 × 10e6/kg	Kang (2010);[56] Kang (2012).[57]
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 (EF1α 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, UK; Hôpital Necker-Enfant Malades, Paris, FR; University Hospital Frankfurt and Institute for Biomedical Research, Georg-Speyer-Haus, Frankfurt, Germany; University Children's	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 & differentiation myeloid cells to granulocyte lineage) Vector manufacture: Genethon, Paris, FR Target: PBSC CD34+ cells	Conditioning: TBA	Santilli (2011).[58]

Study	Center(s)	Sponsor(s)	Vector	Treatment Regimen	Publications
	Hospital Zürich, Switzerland				
WAS					
Activation Date: 2006–2009; recruitment complete, follow-up continuing. Registration: German Clinical Trials Register Number DRKS00000330	Hannover Medical School Children's Hospital, Germany	Deutsche Forschungsgemeinschaft and Bundesministerium fur Bildung und Forschung (PI: C. Klein)	Virus: GALV pseudotyped CMMP, a novel derivative of MFG, which is a type of MLV gamma retrovirus Insert: WASp Modifications: MLV LTRs are replaced with the corresponding myeloproliferative sarcoma virus (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, Germany Target: PBSC CD34+ cells	Conditioning: Partially myeloablative Busulfan 8 mg/kg	Boztug (2010);[59] Paruzynski (2012)[60] (report of insertional mutagenesis resulting in leukemia).
Activation Date: 2011; recruiting Registration: ClinicalTrials.gov NCT01347242 (London); ClinicalTrials.gov NCT01515462 (Milan); ClinicalTrials.gov NCT01347346 (Paris); ClinicalTrials.gov NCT01410825 (Boston)	Europe: Great Ormond Street Hospital, London, UK; San Raffale Telethon Institute of Gene Therapy, Milan, IT; Hôpital Necker-Enfants Malades, Paris, FR USA: Children's Hospital, Boston MA	UK: Great Ormond Street Hospital, NHS Foundation Trust (PI: A. Thrasher) IT: IRCCS San Raffaele and Fondazione Telethon (PI: A. Aiuti, M. G. Roncarolo) FR: Assistance Publique- Hôpitaux Paris (PI: A. Fischer) USA: GTRP, NHLBI, Bethesda, MD (PI: D. A. Williams, S.-Y. Pai, L. Notarangelo)	Virus: Lentivirus Insert: WASp Modifications: WPRE post-translational regulatory element to enhance expression Safety modifications: hWAS endogenous promoter Vector manufacture: Genethon, Paris, FR; Target: PBSC CD34+ cells	Pre-Conditioning: Anti-CD20 monoclonal Ab Conditioning: Reduced intensity Busulfan (4 mg/kg), Fludarabine (120 mg/m2); ATG if autoimmune manifestations	*Science* (a manuscript is in press; not yet available); Scaramuzza (2012);[61] Biasco L (2012).[62]

Gamma-retrovirus and lentivirus vectors have been/are used in PID; adeno-associated virus is not persistent in proliferating bone marrow stem cells and lymphocytes (so cannot be used for GT for PID). The necessity to transfect CD34 ex vivo or lymphocytes ex vivo is cumbersome, but relatively effective. WPRE = Woodchuck hepatitis virus post-transcriptional regulatory element; LTR = long terminal repeat; SIN= self-inactivating; MLV = Moloney murine leukemia virus; MPSV = Myeloproliferative sarcoma virus. IUVPF = Indiana University, Indianapolis, IN, Vector Production Facility. GTRP = Gene Therapy Resource Program, NHLBI, NIH.