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Primary Immune Deficiency Treatment Consortium (PIDTC) update



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The Primary Immune Deficiency Treatment Consortium (PIDTC) is a collaboration of 41 North American centers studying therapy for rare primary immune deficiency diseases (PIDs), including severe combined immune deficiency (SCID), Wiskott-Aldrich syndrome (WAS), and chronic granulomatous disease (CGD). An additional 3 European centers have partnered with the PIDTC to study CGD. Natural history protocols of the PIDTC analyze outcomes of treatment for rare PIDs in multicenter longitudinal retrospective, prospective, and cross-sectional studies. Since 2009, participating centers have

enrolled more than 800 subjects on PIDTC protocols for SCID, and enrollment in the studies on WAS and CGD is underway. Four pilot projects have been funded, and 12 junior investigators have received fellowship awards. Important publications of the consortium describe the outcomes of hematopoietic cell transplantation for SCID during 2000-2009, diagnostic criteria for SCID, and the pilot project of newborn screening for SCID in the Navajo Nation. The PIDTC Annual Scientific Workshops provide an opportunity to strengthen collaborations with junior investigators, patient advocacy

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Information on participants in the PIDTC Leadership Workshop (Bethesda, Md: April 19-20, 2015) and the PIDTC Annual Scientific Workshops (Houston, Tex: May 2-4, 2013 [3rd]; Seattle, Wash: May 1-3, 2014 (4th); and Montreal, Quebec, Canada: April 30-May 2, 2015 (5th) with Education Day (April 29-30, 2015) is provided in [Appendices E1 and E2](#) in this article's Online Repository at www.jacionline.org.

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groups, and international colleagues. Funded by the National Institute of Allergy and Infectious Diseases and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, the PIDTC has recently received renewal for another 5 years. Here we review accomplishments of the group, projects underway, highlights of recent workshops, and challenges for the future. (*J Allergy Clin Immunol* 2016;138:375-85.)

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

The study of primary immune deficiency diseases (PIDs) is challenged by the rarity of these disorders and, until recently, the relative lack of known causative genetic defects.^{1,2} Treatment of PIDs is in turn compromised by a paucity of therapies based on specific mechanisms of disease, and only a few prospective clinical trials have been performed to date. The Primary Immune Deficiency Treatment Consortium (PIDTC) was formed in 2009³ to bring together investigators in North America. By means of natural history protocols, the PIDTC pools individual patient data from multiple participating sites to analyze outcomes of treatment approaches for rare PIDs and thereby identify best practices. This report updates our previous account,⁴ with a focus on the effect of accomplishments to date, recent workshop proceedings, and future plans and challenges of the consortium.

PIDs ARE RARE DISEASES

Rare diseases, as defined by the US Rare Diseases Act of 2002, affect fewer than 200,000 subjects⁵ or about 1 in 1500 persons. Incidence data for PIDs,⁶ including severe combined immune deficiency (SCID; previous estimate of 1 in 100,000 live births, but now with use of newborn screening [NBS], the estimate is 2-fold higher at 1 in 58,000 live births [see below]),⁷ chronic granulomatous disease (CGD; at least 1 in 250,000),^{8,9} and Wiskott-Aldrich syndrome (WAS; about 1 in 100,000 to 1 in 1,000,000 male subjects),¹⁰ indicate the necessity of multicenter collaboration to improve our understanding of the pathogenesis and approaches to treatment of these disorders.

PIDTC MISSION, GROWTH, AND PROGRESS

The primary mission of the PIDTC has been to conduct multicenter natural history studies of treatments for SCID, WAS, and CGD (Table I). Initially funded in 2009 by a U54 cooperative agreement from the National Institute of Allergy and Infectious Diseases (NIAID) and the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), administrative operations are centralized at the University of California, San Francisco and the Data Management and Coordinating Center at the University of South Florida. Recently, the PIDTC was renewed for 5 years. With R13 conference funding from the NIAID and ORDR, the PIDTC has held 5 Annual Scientific Workshops to date.

This consortium has been built by the participating investigators. Groundwork included a consensus of leadership in PIDs regarding elements needed for a successful consortium, assessment of the feasibility of ascertaining target patient populations, and formulation of key questions to be addressed,³ followed by a successful investigator-initiated application to the

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
GT:	Gene therapy
HCT:	Hematopoietic cell transplantation
IEWP:	Inborn Errors Working Party
MSD:	Matched sibling donor
MUD:	Matched unrelated donor
NBS:	Newborn screening
NCATS:	National Center for Advancing Translational Sciences
NIAID:	National Institute of Allergy and Infectious Diseases
NIH:	National Institutes of Health
ORDR:	Office of Rare Diseases Research
OS:	Omenn syndrome
PAG:	Patient advocacy group
PID:	Primary immune deficiency disease
PIDTC:	Primary Immune Deficiency Treatment Consortium
RD:	Reticular dysgenesis
SCID:	Severe combined immune deficiency
TREC:	T-cell receptor excision circle
WAS:	Wiskott-Aldrich syndrome
X-SCID:	X-linked severe combined immune deficiency

National Institutes of Health (NIH) for initial funding and renewal of the consortium.

Growth and progress of the PIDTC has been rapid since the beginning for several reasons. First, there is a clear perception of need by the PID caregiver community, as evidenced by the participation of 33 centers in North America during the first 5-year funding period and 41 centers in addition to 3 European centers during the present cycle. Vital collaborations directed to leverage existing resources, including the Center for International Blood and Marrow Transplant Research (CIBMTR), Milwaukee, Wisconsin, and the United States Immune Deficiency Network, Towson, Maryland,¹¹ and international colleagues in the Inborn Errors Working Party-European Group for Blood and Marrow Transplantation (IEWP-EBMT), were established at the outset (see Griffith et al,⁴ Table II). Several aspects of consortium framework have benefited from the capability of the ORDR/NCATS, in studying rare diseases, including the importance of enlisting patient advocacy groups (PAGs) to encourage broad registration of subjects; mentoring and training of young investigators; and conducting pilot projects, as described in greater detail in Griffith et al.⁴ Study protocols in patients with SCID, CGD, and WAS were developed by disease-specific teams and reviewed by the NIAID and the Data Management and Coordinating Center.

Dedicated contributors at North American centers worked to obtain approval for PIDTC protocols from their institutional review boards, meet consortium regulatory requirements for site qualification, and enter extensive patient data. The CIBMTR has contributed expert multivariable statistical analysis of transplantation outcomes for all PIDTC studies, as well as data from the CIBMTR database for prospective studies. Recently, the PIDTC has initiated collaborations with investigators from other countries for retrospective studies of rare PIDs and to participate in PIDTC Protocol 6903 in CGD.

TABLE I. Mission and vision: Primary Immune Deficiency Treatment Consortium (PIDTC)

Mission Statement	To foster collaborations across North America among researchers, physicians, allied health care workers, and patient advocacy groups with interest and expertise in primary immunodeficiency diseases. By working together, the PIDTC aims to promote research into basic, translational, and clinical science of blood and marrow transplantation, enzyme replacement, gene therapy, and related treatments for primary immunodeficiency diseases.
Vision Statement	Through collaborative research, including multicenter prospective interventional trials, the PIDTC aims to enhance our understanding of primary immunodeficiency diseases and their therapies, with the goal of improving survival and quality of life for patients living with these rare medical conditions.

Currently, 4 protocols are open and enrolling, as described below and in [Table II](#) and [Table E1](#) in this article's Online Repository at www.jacionline.org. PIDTC has published 3 manuscripts from the databases of Protocols 6901 and 6902 ([Table III](#)), several collaborative manuscripts ([Table IV](#)), and workshop reports (see [Table E2](#) in this article's Online Repository at www.jacionline.org).

To date, PIDTC has funded 4 pilot/demonstration projects (see [Table E3](#) in this article's Online Repository at www.jacionline.org) and 12 research fellowships (see [Table E4](#) in this article's Online Repository at www.jacionline.org) to encourage research that is early in development and to involve young investigators in the field of PIDs. In addition, based on multinational collaborations of the PIDTC, several articles have been published ([Table IV](#)), with additional projects underway.

PIDTC CLINICAL STUDIES

PIDTC protocols for prospective and cross-sectional studies in SCID are open and recruiting. Since opening in 2010, more than 160 subjects (target 259) have been enrolled in the prospective study (Protocol 6901), and about 90 subjects (target 200) have been enrolled in the cross-sectional study (Protocol 6902); more than 700 subjects (target 600) have been enrolled in the retrospective study for SCID (Protocol 6902, [Table II](#) and see [Table E1](#) and also Griffith et al,⁴ [Table I](#)). Thus since 2011, the consortium has enrolled about 200 subjects per year into these 2 protocols (see [Table E1](#)), accruing more than 800 total participants with SCID. Notably, for the SCID retrospective data set, research of historic data as old as 30 years has been needed. For this rare disease, assembly of such a resource is an exceptional effort. For the first time, given this sample size, the relative importance of different factors affecting long-term survival and other outcomes after hematopoietic cell transplantation (HCT) can be analyzed for patients with SCID treated in North America. The databases for Protocols 6901 and 6902 are the basis of PIDTC publications to date, as described below and in [Table III](#).

The CGD (PIDTC Protocol 6903) and WAS (PIDTC Protocol 6904) protocols have been finalized. Center institutional review boards are in the process of completing approvals, and enrollment is proceeding at participating sites ([Table II](#) and see [Table E1](#); and also Griffith et al,⁴ [Table I](#)).

SIGNIFICANCE AND EFFECT OF PIDTC PUBLICATIONS

Essentially, all studies of SCID demonstrate that HCT from an HLA-matched sibling donor (MSD) leads to the best recovery of immune function. The findings that HCT for SCID before 3.5 months of life or at any age in the absence of infection leads

to optimal survival and that use of haplocompatible donors (when no MSDs are available) without conditioning is safest for patients who are infected at the time of HCT ([Table III](#)),¹² together with wide-spread adoption of NBS for the disease in the United States ([Table IV](#)),¹³ are practice changing. It was also found that surviving patients who received reduced-intensity conditioning or myeloablative conditioning as therapy before HCT were more likely to have normal T-cell immunity and be free from gammaglobulin replacement at 5 years after transplantation.¹² These studies reinforce the importance of NBS, followed by timely HCT or other definitive therapy, for the treatment of SCID.

IEWP-EBMT and PIDTC investigators have collaborated to address 2 important issues ([Table IV](#)) related to a prospective interventional clinical trial (described below). The PIDTC plans to conduct a study on best transplantation approaches for infants given a diagnosis of SCID at birth and who lack an MSD. First, a comparison of outcomes after unconditioned HCT for SCID using MSDs versus matched unrelated donors (MUDs) has demonstrated similar survival and engraftment of donor T cells but infrequent recovery of myeloid and B cells, with an increased incidence of graft-versus-host disease in patients receiving MUD compared with MSD transplants.¹⁴ Second, the group has undertaken the first study of busulfan pharmacokinetic monitoring in small infants, demonstrating that model-predicted clearance increases 1.7-fold in early life and must be carefully monitored in this patient population.^{15,16}

The report of NBS for SCID in 11 public health programs (10 states plus the Navajo Nation)¹³ indicates an incidence of typical and leaky SCID about twice previous estimates (1 in 58,000 rather than 1 in 100,000) in the United States. The PIDTC pilot study of NBS conducted on the Navajo Reservation ([Table III](#))¹⁷ was the prototype for comprehensive NBS in the United States today. Among patients identified in all localities by using NBS for SCID, it appears that a larger than previously appreciated proportion have leaky SCID, and a new group of infants has been identified who have persistently low numbers of T lymphocytes but do not meet the criteria for typical or leaky SCID.¹⁸ Further clinical studies of this group are needed to establish disease definitions and causes and determine best management.

For Protocol 6901, the PIDTC prospective study of newly diagnosed SCID, analysis of subjects' baseline data shows that today, an increasing proportion of newborns with SCID are identified at birth because of either a prior family history of PIDs or NBS.¹⁹ At 1 year, survival is 92% for typical SCID and 86% for leaky SCID or Omenn syndrome (OS) for this contemporary cohort but lower for those with reticular dysgenesis (RD).²⁰ Clearly, many questions remain, and further work is needed to optimize transplantation approaches, as discussed further below.

TABLE II. PIDTC protocols

PIDTC no., ClinicalTrials.gov identifier, and version history	Title, mechanistic studies, and analyses currently underway
PIDTC 6901; NCT01186913 <i>Version 1.0 date:</i> May 19, 2010 <i>Current version:</i> V3.0; August 28, 2012 (V4.0 pending release)	<p><i>Title:</i> A prospective natural history study of diagnosis, treatment and outcomes of children with SCID disorders</p> <p><i>Mechanistic studies:</i></p> <ol style="list-style-type: none"> 1. T cells: post-HCT TRECs; repertoire diversity by spectratyping or Vβ use 2. B cells: post-HCT reconstitution, function, and dysregulation; analysis of gamma chain expression on CD19⁺ cells and plasmablast differentiation (limited to X-SCID and JAK3 deficiency [PIDTC Pilot Project]) <p><i>Analyses:</i></p> <ol style="list-style-type: none"> 1. One-year outcomes for the first 100 subjects enrolled on this protocol are to be described in an article that is in preparation. The T-cell mechanistic studies will be included in this article. 2. A separate article reporting the B-cell mechanistic studies for Protocols 6901 and 6902 combined is in development. 3. Data from Protocols 6901 and 6902 will be combined to study outcomes of HCT, GT, or ERT for ADA-SCID. 4. Other potential cohort analyses might include, for example, patients identified by means of NBS and genotype-specific studies. <p><i>Comments:</i></p> <ol style="list-style-type: none"> 1. V4.0 will include an option to enroll the protocol beyond the target number of subjects required by power analyses to perform the analyses planned and to follow subjects long-term. 2. Currently, Protocol 6901 is anticipated to enroll about 50 subjects during 2015 (see Table E1); this is consistent with predictions given the US birth rate and the incidence of SCID, as revised by NBS data to date.
PIDTC 6902; NCT01346150 <i>Version 1.0 date:</i> November 30, 2010 <i>Current version:</i> V3.0; August 29, 2012 (V4.0 pending release)	<p><i>Title:</i> A retrospective and cross-sectional analysis of patients treated for SCID since January 1, 1968</p> <p><i>Mechanistic studies (cross-sectional analysis):</i></p> <ol style="list-style-type: none"> 1. T cells: post-HCT TRECs; repertoire diversity by spectratyping or Vβ use 2. T-cell exhaustion: study after HCT (limited to SCID [PIDTC Pilot Project]) 3. T-cell HLA restriction: compare antigen-specific HLA-restricted responses by engrafted donor-derived T cells vs the donor's own T cells after unmodified or T cell-depleted transplantations (limited to selected subjects) 4. B cells: post-HCT reconstitution, function, and dysregulation; analysis of gamma chain expression on CD19⁺ cells and plasmablast differentiation (limited to X-SCID and JAK3 deficiency [PIDTC Pilot Project]) 5. NK cells: functional and phenotypic attributions of NK tolerance in long-term SCID survivors after unmodified or T cell-depleted transplantations 6. CD34⁺ progenitor cells: quantitate proportion of donor-derived clonogenic CD34⁺ cells in peripheral blood 7. Molecular diagnosis: genotyping; mutation (if not performed previously; separate research protocol and consent) <p><i>Analyses:</i></p> <ol style="list-style-type: none"> 1. The retrospective Stratum A (typical SCID) has been closed to further accrual and is in the process of clean-up before analysis and preparation of an article. TREC analysis and repertoire diversity will be included in this study. Importance of variables for survival (eg, genotype, decade of transplant, donor source, and conditioning regimen) will be examined. 2. A separate article reporting the B-cell mechanistic studies for Protocols 6901 and 6902 combined is in development. 3. Data from Protocols 6901 and 6902 will be combined to study outcomes of HCT, GT, or ERT for ADA-SCID. 4. PIDTC and IEWP-EBMT anticipate collaboration to study very long-term (>20 years) outcomes of HCT for SCID. 5. Stratum B (leaky SCID, OS, and RD) will be closed in the near future to undertake clean-up, analysis, and preparation of an article. 6. Other potential cohort analyses might include, for example, genotype-specific studies and subjects requiring retransplantation.

(Continued)

TABLE II. (Continued)

PIDTC no., ClinicalTrials.gov identifier, and version history	Title, mechanistic studies, and analyses currently underway
	<p><i>Comments:</i></p> <ol style="list-style-type: none"> 1. Additional enrollment of subjects for the cross-sectional analysis is needed; because the retrospective analysis is fully enrolled, this should be feasible. In V4.0 of the protocol, PIDTC will encourage centers to comprehensively recognize and follow-up their living subjects.
PIDTC 6903; NCT02082353 <i>Version 1.0 Date:</i> December 23, 2013 <i>Current version:</i> V1.0; December 23, 2013	<p><i>Title:</i> Analysis of patients treated for chronic granulomatous disease since January 1, 1995</p> <p><i>Mechanistic studies (cross-sectional analysis):</i></p> <ol style="list-style-type: none"> 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 <p><i>Analyses:</i> This protocol has recently opened to enrollment.</p> <p><i>Comments:</i></p> <ol style="list-style-type: none"> 1. Protocol 6903 is unique among PIDTC studies to date in that it includes a conventional therapy arm. Clinical outcomes after HCT will be compared with standard management. 2. CGD is an example of a PID in which the patient's marrow contains all lineages before transplantation, and a full donor chimera might not be needed to achieve therapeutic effect. Therefore use of reduced-intensity preparative regimens might be sufficient. Analysis of patient lineage-specific chimerism and relation to therapeutic benefit will be needed.
PIDTC 6904; NCT02064933 <i>Version 1.0 date:</i> October 28, 2013 <i>Current version:</i> V1.0; October 28, 2013	<p><i>Title:</i> Analysis of patients treated for Wiskott-Aldrich syndrome since January 1, 1990</p> <p><i>Mechanistic studies (prospective and/or cross-sectional analysis):</i></p> <ol style="list-style-type: none"> 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. Chimerism: lineage-specific by means of flow cytometry (WAS protein expression) 4. Autoantibodies: microarray analysis 5. Autoimmunity: investigation of the molecular and cellular mechanisms of autoimmunity in patients with WAS undergoing HCT (PIDTC Pilot Project) <p><i>Analyses:</i> This protocol has recently opened to enrollment.</p> <p><i>Comments:</i></p> <ol style="list-style-type: none"> 1. Mechanistic studies for this protocol will focus on identification of potential biomarkers of autoimmunity after HCT. 2. WAS is an example of a PID in which the patient marrow contains all lineages before transplantation, however, a full donor chimera might be needed to achieve resolution of the disease without the complication of autoimmunity after HCT. That is, a myeloablative preparative regimen resulting in a full donor chimera might be needed for therapeutic effect.

ADA-SCID, ADA-deficient SCID; BAFF/APRIL, B-cell activating factor/a proliferation-inducing ligand; ERT, enzyme replacement therapy; JAK3, Janus kinase 3; KRECs, kappa-deletion recombination excision circles; NK, natural killer.

Definitions of SCID, leaky SCID, and OS developed by the PIDTC from review of potential subjects for the 6901 and 6902 SCID protocols are now being used worldwide.¹⁸ Importantly, review of this experience illustrates that failure

to demonstrate either impaired lymphocyte proliferation to PHA or maternal T-cell engraftment is the most common reason for lack of a definitive diagnosis of SCID, emphasizing the need for communication of the most current guidance on

TABLE III. Significant findings and effect of PIDTC protocol studies

Protocol(s)	Study (reference)	Results	Effect/future outlook
PIDTC 6902	Transplantation outcomes for severe combined immunodeficiency 2000-2009 (Pai SY, Logan BR, Griffith LM, et al <i>N Engl J Med</i> 2014;371:434-46)	Found an overall survival of at least 5 years among nearly three quarters of 240 infants with SCID from 25 clinical centers who received HCT. Regardless of donor type, survival rates were high for infants undergoing transplantation within the first 3.5 months of life (94%) and those of any age without evidence of infection at the time of transplantation (for older infants, 90% among those without prior infection and 82% after resolution of infection).	Emphasizes the importance of early diagnosis and absence of infection for achieving best transplantation outcomes in patients with SCID. The positive effect of treating this disease early in life supports use of NBS to ensure early diagnosis. This is the first collaborative retrospective study of HCT outcomes for SCID ever conducted in North America and demonstrates the feasibility of this approach for study of this rare disease.
PIDTC 6901 and 6902	Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the PIDTC experience. (Shearer WT, Dunn E, Notarangelo LD, et al. <i>J Allergy Clin Immunol</i> 2014;133:1092-8)	Found failure to demonstrate either impaired lymphocyte proliferation to PHA or maternal T-cell engraftment is the most common reason for lack of definitive diagnosis of SCID and related disorders, even when detection of a genotype predictive of an SCID phenotype is also accepted as an alternative, among 322 children treated at 27 North American centers.	Indicates, unexpectedly, that in the recent decade (2000-2009), lack of complete laboratory evaluation of patients continues to present a significant barrier to definitive diagnosis of SCID and related disorders. Emphasizes the need for continued work to refine diagnostic criteria for SCID. Demonstrates the need for communication of the most current guidance on diagnostic testing for PIDs among those involved in direct patient care.
PIDTC 6901	The natural history of children with severe combined immunodeficiency: baseline features of the first fifty patients of the PIDTC Prospective Study 6901. (Dvorak CC, Cowan MJ, Logan BR, et al. <i>J Clin Immunol</i> 2013;33:1156-64)	For the first 50 sequential subjects, most (92%) had mutations in a known SCID gene. Half were given a diagnosis based on NBS or family history and were younger than those given a diagnosis based on clinical signs (median, 15 vs 81 days) and went to transplantation earlier (median, 67 vs 214 days of life).	Supportive of NBS to ensure early diagnosis. Notably, in this prospective cohort most (92%) received a genetic diagnosis of their PIDs.
PIDTC 6901	Early hematopoietic cell transplant outcomes of children with severe combined immunodeficiency (SCID): the first seventy-four patients of the Primary Immune Deficiency Treatment Consortium (PIDTC) prospective study 6901 (Heimall J, Logan BR, Cowan MJ, et al. <i>Biol Blood Marrow Transplant</i> 2015;21:S289-S291)	At 1 year, survival for 74 sequential subjects who received HCT for typical SCID, leaky SCID, OS, or RD was 88% (92% for 27 with typical SCID). Deaths were most commonly related to infection or conditioning toxicities. GVHD affected about 20%. Conditioning improved certain aspects of immune recovery and decreased the need for a second transplant.	Optimizing transplantation outcomes for patients with SCID and related disorders will require investigation specific to this population of variables contributing to GVHD, the toxicities of conditioning regimens, the relation of conditioning to immune reconstitution, and late effects and quality of life.
PIDTC Pilot Project	SCID diagnosed by newborn screening in Navajo Native Americans (Kwan A, Hu D, Song M, et al. Successful newborn screening for SCID in the Navajo Nation. <i>Clin Immunol</i> 2015; 158:29-34.)	A pilot study at 2 Navajo hospitals demonstrated feasibility of NBS in this population, which has a founder mutation for Artemis SCID. Of 7900 infants screened from February 2012 to July 2014, 4 had undetectable TRECs and were referred for HCT; 1 had low TREC counts and was given a diagnosis of non-SCID lymphopenia.	The experience of NBS in this community served as the lead for programs recently implemented in multiple states in the United States. Because of a higher frequency of SCID mutations, risk and incidence are higher among Navajo infants compared with the general population.

GVHD, Graft-versus-host disease.

diagnostic testing for PIDs among those involved in direct patient care.

ANNUAL SCIENTIFIC WORKSHOPS

Key themes presented during recent PIDTC Annual Scientific Workshops include the following.

NBS

To date, NBS is underway in 33 states, the District of Columbia, Puerto Rico, and the Navajo Nation, providing for more than 75% of US births, with additional US states and Canadian provinces planning to implement testing within 1 to 2 years (<http://primaryimmune.org/idf-advocacy-center/>)

TABLE IV. Significant findings and effect of PIDTC collaborations

Collaboration	Study (reference)	Results	Effect/future outlook
NBSTRN	Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States (Kwan A, Abraham RS, Currier R, et al. JAMA 2014;312:729-38)	Found that SCID affects about 1 in 58,000 newborns in the United States. The distribution of genetic defects among 52 subjects identified with SCID is different from that described previously; only 19% had X-linked disease, and in 19% the genetic defect was unknown. Data were gathered from more than 3 million newborns in 10 states and the Navajo nation.	Demonstrated that the incidence of SCID at birth is about twice as high as previously appreciated. The higher than expected incidence of SCID without a known defect provides an opportunity for discovery of new SCID-causing genes. Revealed a group of patients with T-cell lymphopenia who might not meet all accepted criteria for typical SCID and will require further study. Emphasizes the importance of NBS programs for SCID.
PIDTC centers in California and the CA NBSTRN	Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California: results of the first 2 years (Kwan A, Church JA, Cowan MJ, et al. J Allergy Clin Immunol 2013;132:140-50)	Experience in standardization and application of a high-throughput quantitative TREC screening test to a large population of nearly 1 million infants is described. Of 50 infants with significant T-cell lymphopenia, 11 had typical SCID, 3 had leaky SCID or Omenn Syndrome, and 6 had variant SCID or combined immunodeficiency; the remainder had other conditions.	Demonstrates feasibility to implement screening for SCID and related conditions in a large population of newborns in the state of California. Further work is needed to define best follow-up care for diagnoses of SCID and other conditions with T-cell lymphopenia.
IEWP-EBMT	Comparison of outcomes of hematopoietic stem cell transplantation without chemotherapy conditioning by using matched sibling and unrelated donors for treatment of severe combined immunodeficiency (Dvorak CC, Hassan A, Slatter MA, et al. J Allergy Clin Immunol 2014;134:935-43, e15)	Outcomes after unconditioned transplantations for SCID using HLA-matched sibling donors (MSDs) vs MUDs are compared. Survival and engraftment of donor T cells were similar; however, recovery of donor myeloid and B cells was infrequent, and the incidence of GVHD was higher in MUDs compared with MSDs.	Children who will receive MUD transplants and are ineligible for chemotherapy preparative regimens for HCT because of infection or other reasons might benefit from this approach; however, further work is needed to improve outcomes.
IEWP-EBMT	Effect of weight and maturation on busulfan clearance in infants and small children undergoing hematopoietic cell transplantation (Savic R, Cowan MJ, Dvorak CC, et al. Biol Blood Marrow Transplant 2013;19:1608-14)	Pharmacokinetics of busulfan in small infants (≤ 12 kg) is studied in 149 patients from 8 centers. A model based on busulfan therapeutic concentration at steady state of 600-900 ng/mL (AUC, 900-1350 $\mu\text{M} \cdot \text{min}$) is developed. Actual body weight and age are important clinical covariates affecting busulfan pharmacokinetics, and model-predicted clearance increases 1.7-fold between 6 weeks and 2 years of life.	Busulfan is a chemotherapeutic agent commonly used in preparative regimens for HCT. This is the first study of busulfan pharmacokinetics in small infants. Metabolic pathways for metabolism of busulfan might not be fully developed in newborns, and therefore data acquired in adults might not be applicable.

AUC, Area under the curve; GVHD, graft-versus-host disease; NBSTRN, Newborn Screening Translational Research Network.

[idf-scid-newborn-screening-campaign/](#)).¹³ The majority of infants with typical SCID, leaky SCID, OS, or RD enrolled on PIDTC Protocol 6901¹⁹ have low T-cell receptor excision circle (TREC) numbers at birth. It will be critical to develop uniform protocols for assessing, managing, and correcting SCID disorders with HCT, gene therapy (GT), or enzyme replacement therapy.

Successful implementation of NBS has led to new and unexpected research and patient care challenges. Different

states do not have uniform practices for referral and immunologic work-up for these vulnerable infants with low TREC numbers. Furthermore, some infants have been found to have persistently low TREC numbers and low T-lymphocyte counts yet do not meet the diagnostic criteria for typical SCID, OS, leaky SCID, or RD; the natural history and standard of care for this group remain to be defined.¹³

Prospective trial for newborn SCID: Potential PIDTC protocol 6905

Although infants affected with SCID are now given a diagnosis earlier in their disease course than previously, optimal strategies for HCT in newborns with SCID have yet to be defined. For example, some centers use myeloablative conditioning for all of their patients, including those with SCID, regardless of age, genotype, or donor match, whereas some centers use no conditioning for patients with typical SCID, and still others adjust conditioning regimens based on the individual children's phenotype/genotype, donor type, and clinical status, including presence of infections. Thus it is difficult to compare outcomes, especially because we now know that the drugs used in transplant conditioning regimens, such as busulfan and fludarabine, are metabolized differently by newborns compared with older infants, children, and adults. PIDTC investigators aim to study the special needs of infants undergoing HCT for SCID and define the minimal busulfan dose exposure that will allow robust and sustained multilineage engraftment with minimal short- and long-term side effects. It is anticipated that during 2015-2016, investigators of the PIDTC will submit an application to the NIAID for funding of a prospective clinical study comparing 2 low-dose exposures of busulfan as conditioning for HCT for the treatment of SCID.

Other considerations for preparative regimens and graft preparation

When a chemotherapy preparative regimen is indicated, busulfan is generally used for HCT in patients with PIDs as the agent for opening marrow niches because of its myeloablative properties, accumulated experience, and known toxicity profile. The related alkylating agent treosulfan has recently become available in Europe,^{21,22} and clinical testing in the United States is underway (see ClinicalTrials.gov NCT02048800; NCT02349906).²³ Although potential advantages of treosulfan for use in infants might include reduced hepatic toxicity and lower central nervous system penetration compared with busulfan, further pharmacokinetic and clinical toxicity data are needed. The experience with busulfan or treosulfan in infants is very limited,¹⁹ and long-term follow-up with lineage-specific chimerism testing, developmental and cognitive function assessment, and quality of life are needed.

A major controversy for treating SCID continues to be the use of myeloablative and/or immunosuppressive conditioning before HCT because of associated toxicity.²⁴ Furthermore, minimizing exposure to alkylating agents and ionizing radiation might be important for certain types of SCID caused by defects in the nonhomologous end-joining DNA repair pathway (see [Table E2](#)).²⁵ Nontoxic approaches to clear the stem cell niche and enhance engraftment are in early stages of development and include use of anti-CD117 (anti-c-kit) to deplete recipient hematopoietic stem cells.^{26,27}

Lymphodepletion through CD34 stem cell selection and/or other approaches might be a critical step in graft preparation for non-MSD donors, depending on the PID indication for HCT, the graft source, and the extent of donor-recipient HLA mismatch. Two new approaches to lymphodepletion include T-cell receptor α/β and B-cell CD19 depletion of the graft *ex vivo* before infusion²⁸ and *in vivo* T-cell depletion by post-HCT cyclophosphamide.^{29,30}

GT for PIDs

Experience with GT for adenosine deaminase (ADA) deficiency and X-linked severe combined immune deficiency (X-SCID) has offered proof of principle. This might represent effective treatment for severe PIDs and other disorders when an MSD is unavailable.^{7,31,32} However, for patients with X-SCID, the reported success of GT has been tempered by demonstration of leukemic proliferation (because of insertional mutagenesis) in 5 of 20 patients.^{33,34} Similar adverse events have recently been demonstrated in patients receiving GT for CGD or WAS but not for ADA-deficient SCID. Clinical trials with novel and putatively safer vectors have been initiated in Europe and the United States. Initial results with these self-inactivating vectors in patients with X-SCID have demonstrated efficacy without leukemic proliferation to date, although the number of patients treated thus far is limited.³⁵ Updates of GT clinical trials for PIDs currently open in Europe and the United States are summarized in [Table E5](#) in this article's Online Repository at www.jacionline.org.

WAS and CGD

Controversy remains regarding optimal timing of transplantation for patients with CGD or WAS, the necessity for full donor chimerism to correct all aspects of immune deficiency and prevent autoimmunity, and the relative importance of non-HCT therapy.^{36,37} Recent presentations related to WAS have included a debate on indications for splenectomy,³⁸ a discussion of B-cell mechanisms of cell-mediated autoimmunity,³⁹ and a PAG-sponsored survey on quality of life in families of patients with this disease.

Thymus, T-cell development, and reconstitution of the immune system after HCT

Many key questions as to mechanisms of reconstitution of the immune system and the role of the thymus after HCT in patients with PIDs remain. The origins and role of thymic epithelial cells⁴⁰ in T-cell development⁴¹ are an area of active research. Thymic transplantation has been used as therapy for patients with DiGeorge syndrome^{42,43} but is not widely available. Other topics presented at the PIDTC Annual Scientific Workshop have included discussion of common lymphoid progenitors,⁴⁴⁻⁴⁶ regulatory T cells,^{47,48} and B-cell maturation and function.^{49,50} Adoptive cell therapy, including virus-specific T cells, might provide therapeutic benefit before full reconstitution of the recipient immune system.^{51,52}

Emerging immunodeficiencies

New technologies for the characterization of immune deficiency have made possible the definition of new categories of disease and advanced our understanding of immune mechanisms in patients with PIDs. Although only 15 years ago about 50 genetic defects for specific PIDs were known, nearly 240 have been identified today.^{1,2} Thus more PIDs are now understood based on both the specific genetic defect and phenotype. Furthermore, an enlarging group of autoimmune diseases are slowly being accepted as part of the spectrum of PIDs.^{1,2} Natural history studies of these defined PIDs should now be possible. Based on genotype, phenotype, and the natural history of the

PID, hopefully, prospective treatment studies (clinical trials) directed toward well-defined PID cohorts will become available in the near future.

Emerging indications for HCT in patients with PIDs

Experiences in HCT for patients with very rare PIDs have been the subject of several recent PIDTC presentations and retrospective reports (see Table E6 in this article's Online Repository at www.jacionline.org). For example, the relative advantages of HCT compared with classical management for common variable immune deficiency^{53,54} were presented at the recent 2015 workshop. This ongoing evaluation is helpful to identify categories of PIDs potentially treatable with HCT versus standard medical management. PIDTC is currently collaborating with IEWP-EBMT to evaluate outcomes after HCT for immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

Practice survey: Communication among medical specialists

It has become increasingly evident that PIDTC outreach and communication with the immunology, infectious diseases, and hematology experts at our institutions is needed for efficient operations for future clinical trials and for continuity of individual patient care. In an informal practice survey conducted by PIDTC during 2014-2015, centers indicated that immunologists, infectious disease experts, and hematologists provide diagnosis and most of the referrals of patients with PID for HCT. About half of patients undergoing transplantation are transferred back to the referring specialist for care after HCT. Because many of the immunologists who care for patients with PIDs participate in the Clinical Immunology Society, this group hosted a session dedicated to the PIDTC at their Annual Meeting in Houston in 2015. We look forward to similar opportunities to facilitate teamwork in the future.

PAG collaborations

Presentations from the PAGs and discussions on topics they have selected are an integral component of the PIDTC Annual Scientific Workshop. Recent topics have included the effect of hospitalization for HCT on families, quality of life for families of patients with WAS, and transitioning patients from pediatric to adult medical care. A discussion panel was convened at the 2015 workshop to share experiences of families newly informed of a NBS TREC result for their newborn. Importantly, all members of the panel were in agreement that a physician immunologist with subject matter expertise is the best health care provider to inform parents of an NBS TREC test result. This is because the immunologist has the medical knowledge needed to answer questions about SCID and treatment of PIDs. Other guidance from this group included the recommendation that health care providers speak of "treatment" not "cure," "delivery of an immune system" not "transplant," and "positive screen for very low T cells" rather than "SCID," when initially meeting with families. Finally, the exceptional stress that the diagnosis of newborn SCID places on a family was addressed. It was apparent that there is pressing need for further study of the effect on caregivers of the combination of postpartum depression,

cessation of breast-feeding in cytomegalovirus-seropositive mothers, immediate hospitalization and isolation of the infant, and preparation for HCT.

Workshop Education Day

Workshop events directed to trainees/junior faculty have included breakout sessions, presentations from the fellowship awardees (see Table E4) and invitations for oral presentation of the best abstracts selected by the PIDTC abstract review committee from among those submitted by each of the participating PIDTC sites. In 2015, a dedicated Education Day was initiated that included teaching sessions on the clinical aspects of selected PIDs and treatment approaches, including HCT and GT, with trainees actively participating through abstract presentations and discussions.

Other potential projects

At present, there is no standard of practice in the community for long-term follow-up of patients with PIDs who have received HCT. Investigators in the field of PIDs attempted to address this need at a workshop sponsored by the NIH in 2009 (Griffith et al).⁵⁵ Development of a more formal guidance document might now be timely, with the goal of educating non-PIDTC centers, as well as third-party payers, on best clinical care for these vulnerable patients.

An additional gap area is the lack of long-term developmental studies of pediatric patients after HCT for PIDs. These studies are needed to understand the effects of HCT preparative regimens on the future development of these patients. To date, such studies in pediatrics have focused on treatment for hematologic malignancies, where very large doses of chemotherapy, radiotherapy, or both are required for primary treatment of the malignancy in addition to the preparative regimen for HCT.⁵⁶ Studies of patients who received HCT for SCID are available, but patients with ADA-deficient SCID and those with radiation-sensitive SCID have developmental comorbidities that might confound outcomes.^{57,58}

FUTURE CHALLENGES FOR PIDTC

In the spring of 2015, the PIDTC convened a Leadership Workshop at the NIH in Bethesda, Maryland, to identify goals and define timelines for the consortium for the next 5 years and beyond. Progress reports for the PIDTC protocols and practical operational challenges were also presented.

Future progress of the PIDTC is dependent on meeting the objectives of the current cooperative agreement during this 5-year funding period. Also, given the recent growth and success of the consortium, it has become increasingly apparent that the current award as described (RFA-13-TR-002) is insufficient to sustain all of the projects PIDTC would like to undertake. Application for additional grant support (eg, RFA-AI-13-151; RFA-AI-15-040) will be made for prospective clinical trials to be conducted by PIDTC.

In the near future, PIDTC will consider whether to retain a focus on natural history studies of rare PIDs, evolve into a prospective clinical trials consortium, or both. Furthermore, should consortium studies be limited to HCT and cellular therapies or expand to consider other potential biologic therapies,

such as Janus kinase inhibitors or cytokine inhibitors? This is a time of unprecedented opportunity, and PIDTC looks forward to our continued collaborations and leadership role in future advances in clinical research and patient care in PIDs.

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REFERENCES

- Picard C, Al-Herz W, Bousfiha A, Casanova J-L, Chatila T, Conley ME, et al. Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency 2015. *J Clin Immunol* 2015;35:696-726.
- Bousfiha A, Jeddane L, Al-Herz W, Ailal F, Casanova J-L, Chatila T, et al. The 2015 IUIS phenotypic classification for primary immunodeficiencies. *J Clin Immunol* 2015;35:727-38.
- 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;122:1087-196.
- Griffith LM, Cowan MJ, Kohn DB, Notarangelo LD, Puck JM, Pai S-Y, et al. Primary Immune Deficiency Treatment Consortium (PIDTC) report. *J Allergy Clin Immunol* 2014;133:335-47.
- Rare Diseases Act of 2002, Pub L No. 107-280 (2002).
- Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol* 2010;125(suppl):S182-94.
- Kohn DB. Eliminating SCID row: new approaches to SCID. *Hematology Am Soc Hematol Educ Program* 2014;2014:475-80.
- Marciano BE, Spalding C, Fitzgerald A, Mann D, Brown T, Osgood S, et al. Common severe infections in chronic granulomatous disease. *Clin Infect Dis* 2015;60:1176-83.
- Gennery A. Severe infections in patients with chronic granulomatous disease. *Clin Infect Dis* 2015;60:1184-5.
- Worth AJ, Thrasher AJ. Current and emerging treatment options for Wiskott-Aldrich syndrome. *Expert Rev Clin Immunol* 2015;11:1015-32.
- Sullivan KE, Puck JM, Notarangelo LD, Fuleihan R, Caulder T, Wang C, et al. USIDNET: a strategy to build a community of clinical immunologists. *J Clin Immunol* 2014;34:428-35.
- Pai S-Y, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. *N Engl J Med* 2014;371:434-46.
- Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA* 2014;312:729-38.
- Dvorak CC, Hassan A, Slatter MA, Honig M, Lankester AC, Buckley RH, et al. Comparison of outcomes of hematopoietic stem cell transplantation without chemotherapy conditioning by using matched sibling and unrelated donors for treatment of severe combined immunodeficiency. *J Allergy Clin Immunol* 2014;134:935-43.
- Savic RM, Cowan MJ, Dvorak CC, Pai SY, Pereira L, Bartelink IH, et al. Effect of weight and maturation on busulfan clearance in infants and small children undergoing hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2013;19:1608-14.
- Long-Boyle JR, Savic R, Yan S, Bartelink I, Musick L, French D, et al. Population pharmacokinetics of busulfan in pediatric and young adult patients undergoing hematopoietic cell transplant: a model-based dosing algorithm for personalized therapy and implementation into routine clinical use. *Ther Drug Monit* 2015;37:236-45.
- Kwan A, Hu D, Song M, Gomes H, Brown DR, Bourque T, et al. Successful newborn screening for SCID in the Navajo Nation. *Clin Immunol* 2015;158:29-34.
- Shearer WT, Dunn E, Notarangelo LD, Dvorak CC, Puck JM, Logan BR, et al. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. *J Allergy Clin Immunol* 2014;133:1092-8.
- 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;33:1156-64.
- Heimall J, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck J, et al. Early hematopoietic cell transplant (HCT) outcomes of children with severe combined immunodeficiency disease (SCID): the first seventy four patients of the Primary Immune Deficiency Treatment Consortium (PIDTC) prospective study 6901. *Biol Blood Marrow Transplant* 2015;21(suppl):S289-91.
- 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.
- Slatter MA, Boztug H, Potschger U, Sykora K-W, Lankester A, Yaniv I, et al. Treosulfan-based conditioning regimens for allogeneic haematopoietic stem cell transplantation in children with non-malignant diseases. *Bone Marrow Transplant* 2015;50:1536-41.
- Burroughs LM, Nemecek ER, Torgerson TR, Storer BE, Talano JA, Domm J, et al. Treosulfan-based conditioning and hematopoietic cell transplantation for nonmalignant diseases: a prospective multicenter trial. *Biol Blood Marrow Transplant* 2014;12:1996-2003.
- 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.
- Cowan MJ, Gennery AR. Radiation-sensitive severe combined immunodeficiency: the arguments for and against conditioning before hematopoietic cell transplantation—what to do? *J Allergy Clin Immunol* 2015;136:1178-85.
- Czechowicz A, Kraft D, Weissman IL, Bhattacharya D. Efficient transplantation via antibody-based clearance of hematopoietic stem cell niches. *Science* 2007;318:1296-9.
- Straathof KC, Rao K, Eyrich 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.
- Airoldi I, Bertina A, Prigione I, Zorzoli A, Pagliara D, Cocco C, et al. Gamma-delta T-cell reconstitution after HLA-haploidentical hematopoietic transplantation depleted of TCR-alpha-beta+ / CD19+ lymphocytes. *Blood* 2015;125:2349-58.
- Fuchs EJ. Haploidentical transplantation for hematologic malignancies: where do we stand? *Hematology Am Soc Hematol Educ Program* 2012;2012:230-6.
- Kanakry CG, Tsai HL, Bolanos-Meade J, Smith BD, Gojo I, Kanakry JA, et al. Single-agent GVHD prophylaxis with posttransplantation cyclophosphamide after myeloablative, HLA-matched BMT for AML, ALL, and MDS. *Blood* 2014;124:3817-27.
- Kuo CY, Kohn DB. Gene therapy for the treatment of primary immune deficiencies. *Curr Allergy Asthma Rep* 2016;16:39.
- Williams DA, Thrasher AJ. Concise review: lessons learned from clinical trials of gene therapy in monogenic immunodeficiency diseases. *Stem Cells Transl Med* 2014;3:636-42.
- 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.
- Gaspar HB, Parsley KL, Howe S, King D, Gilmour KC, Sinclair J, et al. Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector. *Lancet* 2004;364:2181-7.
- Hacein-Bey-Abina S, Pai SY, Gaspar HB, Armant M, Berry CC, Blanche S, et al. A modified gamma-retrovirus vector for X-linked severe combined immunodeficiency. *N Engl J Med* 2014;371:1407-17.
- Kang EM, Marciano BE, DeRavin SS, Zarembek KA, Holland SM, Malech HL. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2011;127:1319-26.
- 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.
- Conley ME, Saragoussi D, Notarangelo L, Etzioni A, Casanova J-L. PAGID; ESID. An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. *Clin Immunol* 2003;109:272-7.
- Becker-Herman S, Meyer-Bahlburg A, Schwartz MA, Jackson SW, Hudkins KL, Liu C, et al. WASp-deficient B cells play a critical, cell-intrinsic role in triggering autoimmunity. *J Exp Med* 2011;208:2033-42.
- Dumont-Lagacé M, Brochu S, St-Pierre C, Perreault C. Adult thymic epithelium contains non-senescent label-retaining cells. *J Immunol* 2014;192:2219-26.
- Krenger W, Blazar BR, Hollander GA. Thymic T-cell development in allogeneic stem cell transplantation. *Blood* 2011;117:6768-76.
- Li B, Li J, Devlin BH, Markert ML. Thymic microenvironment reconstitution after postnatal human thymus transplantation. *Clin Immunol* 2011;140:244-59.
- Markert ML, Devlin BH, McCarthy EA. Thymus transplantation. *Clin Immunol* 2010;135:236-46.

44. Ji H, Ehrlich LI, Seita J, Murakami P, Doi A, Lindau P, et al. Comprehensive methylome map of lineage commitment from haematopoietic progenitors. *Nature* 2010;467:338-42.
45. Inlay MA, Bhattacharya D, Sahoo D, Serwold T, Seita J, Karsunky H, et al. Ly6d marks the earliest stage of B-cell specification and identifies the branchpoint between B-cell and T-cell development. *Genes Dev* 2009;23:2376-81.
46. Fathman JW, Bhattacharya D, Inlay MA, Seita J, Karsunky H, Weissman IL. Identification of the earliest natural killer cell-committed progenitor in murine bone marrow. *Blood* 2011;118:5439-47.
47. Smigiel KS, Srivastava S, Stolley JM, Campbell DJ. Regulatory T-cell homeostasis: steady-state maintenance and modulation during inflammation. *Immunol Rev* 2014;259:40-59.
48. Gratz IK, Campbell DJ. Organ-specific and memory Treg cells: specificity, development, function, and maintenance. *Front Immunol* 2014;5:333.
49. Matthews A, Zheng S, DiMenna LJ, Chaudhuri J. Regulation of immunoglobulin class-switch recombination: choreography of noncoding transcription, targeted DNA deamination, and long-range DNA repair. *Adv Immunol* 2014;122:1-57.
50. Vuong BQ, Herrick-Reynolds K, Vaidyanathan B, Pucella JN, Ucher AJ, Donghia NM, et al. A DNA break- and phosphorylation-dependent positive feedback loop promotes immunoglobulin class-switch recombination. *Nat Immunol* 2013;14:1183-9.
51. Koehne G, Hasan A, Doubrovina E, Prockop S, Tyler E, Wasilewski G, et al. Immunotherapy with donor T cells sensitized with overlapping pentadecapeptides for treatment of persistent cytomegalovirus infection or viremia. *Biol Blood Marrow Transplant* 2015;21:1663-78.
52. Saglio F, Hanley PJ, Bollard CM. The time is now: moving toward virus-specific T cells after allogeneic hematopoietic stem cell transplantation as the standard of care. *Cytotherapy* 2014;16:149-59.
53. Wehr C, Gennery AR, Lindemans C, Schulz A, Hoenig M, Marks R, et al. Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency. *J Allergy Clin Immunol* 2015;135:988-97.e6.
54. Cunningham-Rundles C. How I treat common variable immunodeficiency. *Blood* 2010;116:7-15.
55. 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.
56. Shah AJ, Epport K, Azen C, Killen R, Wilson K, De Clerck D, et al. Progressive declines in neurocognitive function among survivors of hematopoietic stem cell transplantation for pediatric hematologic malignancies. *J Pediatr Hematol Oncol* 2008;30:411-8.
57. Lin M, Epport K, Azen C, Parkman R, Kohn DB, Shah AJ. Long-term neurocognitive function of pediatric patients with severe combined immune deficiency (SCID): pre- and post-hematopoietic stem cell transplant (HSCT). *J Clin Immunol* 2009;29:231-7.
58. Grunebaum E, Cohen A, Roifman CM. Recent advances in understanding and managing adenosine deaminase and purine nucleoside phosphorylase deficiencies. *Curr Opin Allergy Clin Immunol* 2013;13:630-8.