

Treatment of immunodeficiency: Long-term outcome and quality of life

William T. Shearer, MD, PhD,^a Luigi D. Notarangelo, MD,^b and Linda M. Griffith, MD, PhD^c Houston, Tex, Boston, Mass, and Bethesda, Md

Key words: Hematopoietic stem cell transplantation, severe combined immunodeficiency, long-term follow-up, quality of life

Now able to treat or cure many of the most serious forms of primary immunodeficiency,¹⁻³ clinical immunologists are increasingly concerned about the long-term outcomes and quality of life issues their patients live with as a result of medical intervention.⁴ There is no better way to illustrate a very happy result of immunologic reconstitution than the Journal cover picture of life photographs of a patient with common variable immunodeficiency who was diagnosed at 11 years of age and begun on monthly intravenous immunoglobulin replacement therapy. She went on to accomplish her dreams with a college degree, medical degree, and specialty board certification. Dr Jennifer Pate now gives to other patients the healing power she was able to obtain by maintaining her own health with regular immunologic treatments. Dr Pate validates the hypothesis that definitive treatment of patients with primary immunodeficiency will enable them to live life to the fullest and take their place in society.

Perhaps the most challenging patients are those who require hematopoietic stem cell transplantation (HCT) as infants to be able to survive a world of opportunistic microbes. Severe combined immunodeficiency disease (SCID) is the title given to many types of diseases represented by severe congenital deficiencies of T lymphocytes, which may occasionally involve B and/or natural killer cells also. Clinical immunologists have been giving bone marrow transplants to patients with SCID for 40 years, initially using only HLA-compatible sibling donors,^{5,6} but later also HLA-mismatched related donors,^{7,8} HLA-matched unrelated donors,⁹ and partially HLA-matched cord blood.¹⁰ Mature T lymphocytes are removed from HLA-mismatched related

donors by soybean lectin separation,⁷ mAb-mediated lysis,¹¹ or positive selection of CD34⁺ cells¹²; these are different methods to deplete the graft of donor-derived allogeneic T cells that would otherwise produce lethal graft-versus-host disease. Prophylactic and therapeutic immunosuppressive agents have also been used to reduce the effects of graft-versus-host disease. Whether infants with SCID should be treated with conditioning agents before HCT to create a space in the bone marrow for newly transplanted stem cells remains a controversial issue. Proponents of this approach say that there is better engraftment of hematopoietic stem cells if infants with SCID are treated with drugs such as busulfan, cyclophosphamide, and fludarabine.^{2,3} Opponents claim that because infants with SCID lack mature or functional T cells, no cytoreduction is necessary, and the toxicity and bone marrow suppression of these agents are avoided.¹

Relatively few long-term outcome studies of bone marrow-transplanted children with SCID have appeared, and most of those published are from Europe.¹³⁻¹⁵ For this purpose, a consortium of institutions in North America recently came together to evaluate different methods of HCT for patients with and without SCID, with the ultimate goal to identify best practices and plan future clinical research trials.¹⁶ This conference of experts recommended (1) a comprehensive cross-sectional and retrospective analysis of survivors after HCT for SCID; (2) a prospective study of patients with SCID receiving HCT, with comparable baseline and follow-up testing across participating centers; (3) a pilot study of newborn screening for SCID to identify affected infants before compromise by infection; and (4) for the non-SCID diseases, Wiskott-Aldrich syndrome and chronic granulomatous disease, studies of the natural history of disease in patients who do or do not receive HCT. Clinical questions proposed by the consortium include (1) the genetic variant and phenotype of SCID and non-SCID diseases; (2) patient demographics and treatment history; (3) the type of HCT with respect to donor, source of stem cells, and use of conditioning; and (4) the clinical outcome of immune reconstitution. Among the latter studies, the general health of the patients, presence of graft-versus-host disease, autoimmune conditions and malignancies, function of organ systems, psychosocial development, neurobehavioral development, and neurocognition will be assessed. Among the 34 centers forming the consortium, approximately 500 of 750 transplanted infants with SCID are alive, 200 of 250 transplanted patients with Wiskott-Aldrich syndrome are alive, and 46 of 59 transplanted patients with chronic granulomatous disease are alive. The numbers of infants born with these 3 conditions per year are 50 to 60, 20 to 30, and 10 to 20, respectively. With these numbers of immunodeficient patients born each year, it will be possible to address the understudied areas of neurodevelopment and neurocognition and to follow children through adolescence and early adulthood. In a recent short-term study, Lin et al¹⁷ demonstrated

From ^athe Departments of Pediatrics and Immunology, Baylor College of Medicine, and the Allergy and Immunology Service, Texas Children's Hospital; ^bthe Division of Immunology, Children's Hospital, Harvard Medical School, Boston; and ^cthe Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda.

W.T.S. is supported by National Institutes of Health grants AI069441, AI036211, HD052102, RR0188, HL079533, HL72705, HL78522, and RAT003084A; the Pediatric Research and Education Fund, Baylor College of Medicine; and the David Fund, Pediatrics AIDS Fund, and Immunology Research Fund, Texas Children's Hospital.

Disclosure of potential conflict of interest: L. Notarangelo has served as a member of the Immune Disease Institute and as cochair of the International Union of Immunological Societies Committee on Primary Immunodeficiencies. The rest of the authors have declared that they have no conflict of interest.

Received for publication October 23, 2008; accepted for publication October 23, 2008.

Reprint requests: William T. Shearer, MD, PhD, Texas Children's Hospital, 6621 Fannin Street, (MC: FC330.01), Houston, TX 77030. E-mail: wtsheare@TexasChildrensHospital.org.

J Allergy Clin Immunol 2008;122:1065-8.
0091-6749

© 2008 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2008.10.033

significant loss of mental development and the psychomotor scale index in the first few years after hematopoietic stem cell transplantation, but the small number of children ($n = 16$) and limited follow-up (3 years) make enlarged and longer studies imperative. A larger study of infants with SCID who have received HCT in the United Kingdom demonstrated an increased long-term risk of cognitive difficulties and behavioral disorders.⁴ What is critically needed is the type of information conveyed in the cover picture of this issue of the Journal in which patients recover and go on to lead normal, productive lives. Because HCT is the treatment of choice today for SCID, it is important for consortium centers to work together to study surviving patients, and appropriate that comparable assessments be performed for the prospective patients, as proposed by the consortium.

In addition to the workshop summary on bone marrow transplantation of patients with SCID, this immunodeficiency thematic issue is spilling over with review, opinion, and original articles on primary immunodeficiency. In the first of these, Patel et al¹⁸ describe an overall 60% long-term survival rate of 25 patients with SCID transplanted between 1981 and 1995: 50% survival (10-19 years) for 20 patients given HLA-mismatched related donor bone marrow depleted of T cells with anti-CD6 mAb, and 100% survival (19-26 years) for 5 patients given unmanipulated matched related donor bone marrow. None of these 25 patients were pretreated to achieve cytorreduction of the bone marrow. The barriers to survival were identified as (1) delay in diagnosis, (2) pretransplant infection, (3) failure to engraft, and (4) chronic graft-versus-host disease. Almost all children achieved educational goals including college attendance, and 3 of the older patients have become parents of healthy children. Continuing on with articles on bone marrow transplantation for immunodeficient patients, we have a perplexing article by Pai et al¹⁹ that describes successful correction of the immunodeficiency in patients with mutations in the nuclear factor- κ B essential modulator (NEMO), but not the associated colitis. This single patient observation is illuminating because it strongly suggests that hematopoietic stem cells can correct gene defects in lymphoid and myeloid cell lineages but not those of other cell origins—mucosal epithelial cells, in this instance. This article also is valuable because it represents the first report on the use of preimplantation genetic diagnosis to identify an unaffected and HLA-matched embryo who after birth served as a donor to cure an immune deficiency (NEMO deficiency) that had been diagnosed in an affected sibling. Also pertinent to the subject of bone transplantation is the report by Somech et al²⁰ that suggests high-dose (30 mg/kg) methylprednisolone pulse therapy is effective in reducing the threat of acute and chronic graft-versus-host disease in patients with SCID treated with matched unrelated bone marrow. The consortium network of investigators, including this Toronto group, advocates long-term follow-up of these patients to guard against possible toxic effects of such novel therapies.

Turning to the review articles contained in this issue of the Journal, first, we have a current review of the genetic heterogeneity of mendelian susceptibility to mycobacterial diseases by Al-Muhsen and Casanova.²¹ Areas of the world where consanguineous marriages are common provide study cohorts in which new types of inheritance patterns of immunodeficiency are being discovered that result in an unusual susceptibility to mycobacterial infections. Six genes, if mutated, produce this rare immunodeficiency: 1 X-linked gene (NEMO) and 5 autosomal genes (IFN- γ receptors 1 and 2, signal transducer and activator of

transcription 1, IL-12 β , IL-12 receptor β 1). Of the latter, the IFN- γ receptor 2, IL-12 β , and IL-12R β deficiencies are inherited as autosomal recessive traits, signal transducer and activator of transcription 1 deficiency causing isolated mendelian susceptibility to mycobacterial diseases is autosomal dominant, and the IFN- γ receptor 1 may be autosomal dominant or recessive. The multiplicity of genetic inheritance patterns for rare immunodeficiencies offers unusual insights into their genetic origins. Equally compelling is the second review (Mechanisms of allergic diseases) article that seeks to provide insight into the long fascinating observation of high serum IgE levels in patients with profound immunodeficiencies. Ozcan et al²² focus on 4 immunodeficiencies in which strikingly high IgE levels are found: hyper-IgE syndrome; Wiskott-Aldrich syndrome; immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX); and Omenn syndrome. The authors conclude that the basis of elevation of IgE in the Wiskott-Aldrich syndrome; IPEX; and Omenn syndrome is probably related to increased T_H2 cytokine production as a result of decreased CD4⁺CD25⁺Forkhead box P3⁺ regulatory T cells, but that of the hyper-IgE syndrome remains to be discovered. The authors also note that IgE levels become elevated after bone marrow transplantation during the graft-versus-host reaction, presumably because of similar defective regulatory mechanisms.

Besides these review articles, other invited articles offer unique or provocative insights into primary immunodeficiency. The case study by De Ravin et al²³ relates an impressive number of autoimmune conditions emerging in 6 representative cases of chronic granulomatous disease, suggesting that such patients are at risk for antiphospholipid syndrome, recurrent pericardial effusion, juvenile idiopathic arthritis, IgA nephropathy, cutaneous lupus erythematosus, and autoimmune pulmonary disease. Villa et al²⁴ in a Rostrum article make a strong case for the diversity of genetic origins of the Omenn syndrome (hepatosplenomegaly, erythrodermia, respiratory infections, eosinophilia, severe immunodeficiency). Mutant recombinase activating genes (RAG) 1 and RAG2 were suspected as the genetic basis for Omenn syndrome, but subsequent experience has demonstrated the typical phenotype of Omenn syndrome in cartilage hair hypoplasia, adenosine deaminase, Artemis deficiency, DiGeorge syndrome, Coloboma, Heart anomaly, choanal Atresia, Retardation, Genital and Ear anomalies (CHARGE) syndrome, and ligase-4 deficiency.²⁵ The authors' position is that Omenn syndrome is not a distinct form of combined immunodeficiency and lacks a specific genetic defect. Rather, they maintain that it is a generalized inflammatory condition associated with multiple genetic mutations that produce T-cell deficiency. The Current Perspectives article by Notarangelo and Sorensen²⁶ addresses the pertinent question of whether clinical immunologists need to identify the molecular origins of primary immunodeficiency in their patients, a question increasingly important with third party payers and litigation experts. This article grew out of a pro/con debate at the 2008 annual meeting of the American Academy of Allergy, Asthma, and Immunology. The pro part of the debate focused on the importance of medical advances in immunodeficiency made possible by detection of mutant genes, whereas the con argument presented societal concerns such as loss of insurability and confidentiality. Both sides came to a consensus on the absolute value of detection of genetic origins, but stressed the need to validate the pathogenetic role of gene mutations by means of independent studies that analyze protein expression and/or function. The authors also emphasize the

urgency to discover biomarkers that would help identify the different forms of genetically heterogeneous diseases and facilitate more specific forms of therapy.

A number of excellent and informative original articles and letters are contained in this special issue on primary immunodeficiency. Davis et al²⁷ studied serial T-cell proliferative responses to *Candida* and tetanus antigens in 93 patients with partial DiGeorge syndrome: 46% of patients who had received 3 tetanus immunizations developed persistent *Candida* and tetanus responses, but 35% did not develop *Candida* or tetanus responses. Almost all of the latter patients had initial T-cell counts less than the 10th percentile. Protective tetanus specific IgG antibody responses (>0.10 IU/mL) were detected in all 72 patients tested, ages 2 to 85 months. The authors conclude that some patients with partial DiGeorge syndrome with low T-cell counts may not develop *Candida* and tetanus cellular immune responses. Gambineri et al²⁸ evaluated 14 patients with IPEX and documented a total of 13 missense and splice-site mutations. Similar genotypes did not always yield similar phenotypes with regard to presentation and severity of disease. Moreover, FOXP3 protein expression could not be used as the sole diagnostic test for IPEX. Hanson et al²⁹ evaluated the phenotypic presentation of 72 patients with 32 different NEMO mutations who had the following clinical conditions: ectodermal dysplasia, 81%; pyogenic infection, 76%; mycobacterial infection, 39%; viral infection, 19%; and inflammatory disorders, 21%. Hypomorphic reconstituted NEMO cells were used to define specific disease and genetic characteristics, thus providing new understanding of the genetic mutations that contribute to the phenotypic expression of a complex disease. Continuing in a similar line of investigation, Kavadas et al³⁰ compared mutations in the ribonuclease mitochondrial RNA processing (RMRP) gene with phenotypic expressions of the cartilage hair hypoplasia syndrome. Nine of the patients had severe immunodeficiencies that were associated with mutations in the gene promoter region, and CD8⁺ T lymphocytopenia was present in 4 patients. Skeletal abnormalities were not always present, although short stature was more common. These findings suggest that RMRP gene defects should be considered in SCID of unknown origin. Nahum et al³¹ report on the association of the R620W variant of lymphoid tyrosine kinase with chronic mucocutaneous candidiasis, recurrent microbial infection caused by antibody deficiency, and autoimmune conditions such as hypothyroidisms and gonadal failure. Ehlayel et al³² report the highly unusual case of a 7-year-old girl child from the Middle East with 2 rare immunodeficiencies: IL-12 receptor β 1 deficiency and ataxia telangiectasia. Last, Sheehan et al³³ report on the unusual case of Omenn syndrome with RAG point mutations on the maternal allele along with a contiguous deletion encompassing both RAG1 and RAG2 genes and paired box gene 6 (PAX6) (causes aniridia) on the corresponding region of the paternally derived chromosome 11 in a 3-month-old boy. The authors suggest that molecular cytogenetic studies should be performed in patients with a complex phenotype suggestive of a contiguous gene deletion syndrome.

In summary of this précis of the articles for this issue devoted to primary immunodeficiency, I want to return to the original theme: Improved Treatment of Immunodeficiency: Outcome and Quality of Life. The first report of the phenotypic description of an immunodeficiency was made in 1926.³⁴ In the intervening years, comprehensive studies of clinical characteristics of more than 130 immunodeficiencies have been made, genetic and molecular

bases for these diseases have been described and will continue, and vastly improved methods of diagnostic treatment of various immunodeficiencies have been devised as chronicled in special issues of the Journal devoted to primary immunodeficiency and technology.³⁵⁻³⁸ However, because the ultimate repair of genetic deficiencies by gene therapy has not been widely adapted to clinical practice, intravenous immunoglobulin and HCT have been and will continue to be used to save children and adults with serious immunodeficiencies. Particularly with cellular reconstitution that involves serious health risks, the outcome benefits must outweigh the risks, and the quality of life for rescued patients must be good. All the clinical and basic research in this issue of the Journal and in other recent issues devoted to immunodeficiency must be directed toward that purpose.

REFERENCES

- Buckley RH. Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. *Annu Rev Immunol* 2004;22:625-55.
- Dvorak CC, Cowan MJ. Hematopoietic stem cell transplantation for primary immunodeficiency disease. *Bone Marrow Transplant* 2008;41:119-26.
- Filipovich AH. Hematopoietic cell transplantation for correction of primary immunodeficiencies. *Bone Marrow Transplant* 2008;42:S49-52.
- Titman P, Pink E, Skucek E, O'Hanion K, Cole TL, Gaspara J, et al. Cognitive and behavioral abnormalities in children following haematopoietic stem cell transplantation for severe congenital immunodeficiencies. *Blood* 2008;112:3907-13.
- Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet* 1968;2:1366-9.
- Bach FH, Albertini RJ, Joo P, Anderson JL, Bortin MM. Bone marrow transplantation in a patient with the Wiskott-Aldrich syndrome. *Lancet* 1968;2:1364-6.
- Reisner TM, Kapoor N, Kirkpatrick D, Pollack MS, Cunningham-Rundles S, Dupont B, et al. Transplantation for severe combined immunodeficiency with HLA-A, B, D, DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. *Blood* 1983;61:341-8.
- Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, et al. Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. *New Engl J Med* 1999;340:508-16.
- Roifman CM, Somech R, Grunebaum E. Matched unrelated bone marrow transplant for T + combined immunodeficiency. *Bone Marrow Transplant* 2008;41:947-52.
- Knutsen AP, Wall DA. Umbilical cord blood transplantation in severe T-cell immunodeficiency disorders: two-year experience. *J Clin Immunol* 2000;20:466-76.
- Barge RMY, Starrenburg CWJ, Falkenburg JHF, Fibbe WE, Marijt EW, Willemze R. Long-term follow-up of myeloablative allogeneic stem cell transplantation using Campath "in the bag" as T-cell depletion: the Leiden experience. *Bone Marrow Transplant* 2006;37:1129-34.
- Read EJ, Carter CS. T-cell depletion of hematopoietic progenitor cell products for allogeneic transplantation. In: Sacher RA, editor. *Cellular therapy: new frontiers in transfusion medicine*. Bethesda (MD): American Association of Blood Banks; 2002. p. 29-44.
- Antoine C, Müller S, Cant A, Cavazzana-Calvo M, Veys P, Vossen J, et al. European Group for Blood and Marrow Transplantation, European Society for Immunodeficiency. Long-term survival and transplantation of haematopoietic stem cells for immunodeficiencies: report of the European experience 1968-99. *Lancet* 2003;361:553-60.
- Mazzolari E, Forino C, Guerci S, Imperti L, Lanfranchi A, Porta F, et al. Long-term immune reconstitution and clinical outcome after stem cell transplantation for severe T-cell immunodeficiency. *J Allergy Clin Immunol* 2007;120:892-9.
- Grunebaum E, Mazzolari E, Porta F, Dalleria D, Atkinson A, Reid B, et al. Bone marrow transplantation for severe combined immune deficiency. *JAMA* 2006;295:508-18.
- Griffith LM, Cowan MJ, Kohn DB, Notarangelo LD, Puck JK, Schultz KR, et al. Allogeneic hematopoietic cell transplantation for primary immune deficiency disease: current status and critical needs. *J Allergy Clin Immunol* 2008;122:1087-96.
- Lin M, Eppert K, Azen C, Parkman R, Kohn DB, Shah AJ. Long-term neurocognitive function of pediatric patients with severe combined immunodeficiency (SCID): pre- and post-hematopoietic stem cell transplant (HSCT). *J Clin Immunol* 2008; Sep 20. [Epub ahead of print].
- Patel NC, Chinen J, Rosenblatt HM, Hanson IC, Brown BS, Paul ME, et al. Long-term outcomes of nonconditioned patients with severe combined

- immunodeficiency transplanted with HLA-identical or haploidentical bone marrow depleted of T cells with anti-CD6 mAb. *J Allergy Clin Immunol* 2008;122:1185-93.
19. Pai SY, Levy O, Jabara HH, Glickman JN, Sachs J, Nurko S, et al. Allogeneic transplantation successfully corrects immune defects, but not susceptibility to colitis, in a patient with nuclear factor- κ B essential modulator deficiency. *J Allergy Clin Immunol* 2008;122:1113-8.
 20. Somech R, Kavadas F, Atkinson A, Grunebaum E, Roifman CM. High-dose methylprednisolone is effective in the management of acute graft-versus-host disease in severe combined immune deficiency. *J Allergy Clin Immunol* 2008;122:1215-6.
 21. Al-Muhsen S, Casanova JL. The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases. *J Allergy Clin Immunol* 2008;122:1043-51.
 22. Ozcan E, Notarangelo LD, Geha RS. Primary immune deficiencies with aberrant IgE production. *J Allergy Clin Immunol* 2008;122:1054-62.
 23. De Ravin SS, Naumann N, Cowen EW, Friend J, Hilligoss D, Marquesen M, et al. Chronic granulomatous disease as a risk factor for autoimmune disease. *J Allergy Clin Immunol* 2008;122:1097-103.
 24. Villa A, Notarangelo LD, Roifman CM. Omenn syndrome: inflammation in leaky severe combined immunodeficiency. *J Allergy Clin Immunol* 2008;122:1082-6.
 25. Grunebaum E, Bates A, Roifman CM. Omenn syndrome is associated with mutations in DNA ligase IV. *J Allergy Clin Immunol* 2008;122:1219-20.
 26. Notarangelo LD, Sorensen R. Is it necessary to identify molecular defects in primary immunodeficiency disease? *J Allergy Clin Immunol* 2008;122:1069-73.
 27. Davis C, Kancherla VS, Reddy A, Yeh HW, Noroski LM, Rosenblatt H, et al. Development of specific T-cell responses to *Candida* and tetanus antigens in partial DiGeorge syndrome. *J Allergy Clin Immunol* 2008;122:1194-9.
 28. Gambineri E, Perroni L, Passerini L, Bianchi L, Doglioni C, Meschi F, et al. Clinical and molecular profile of a new series of patients with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome: inconsistent correlation between forkhead box protein 3 expression and disease severity. *J Allergy Clin Immunol* 2008;122:1105-12.
 29. Hanson EP, Monaco-Shawver L, Solt LA, Madge LA, Banerjee PP, May MJ, et al. Hypomorphic nuclear factor- κ B essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. *J Allergy Clin Immunol* 2008;122:1169-77.
 30. Kavadas FD, Giliiani S, Gu Y, Mazzolari E, Bates A, Pegoiani E, et al. Variability of clinical and laboratory features among patients with ribonuclease mitochondrial RNA processing endoribonuclease gene mutations. *J Allergy Clin Immunol* 2008;122:1178-84.
 31. Nahum A, Bates A, Sharfe N, Roifman CM. Association of the lymphoid tyrosine phosphatase, R620W variant, with chronic mucocutaneous candidiasis. *J Allergy Clin Immunol* 2008;122:1220-2.
 32. Ehlayel M, de Beaucoudrey L, Fike F, Nahas SA, Feinberg J, Casanova JL, et al. Simultaneous presentation of 2 rare hereditary immunodeficiencies: IL-12 receptor β 1 deficiency and ataxia-telangiectasia. *J Allergy Clin Immunol* 2008;122:1217-9.
 33. Sheehan WJ, Delmonte OM, Miller DT, Roberts AE, Bonilla FA, Morra M, et al. Novel presentation of Omenn syndrome in association with aniridia. *J Allergy Clin Immunol* 2008. In press.
 34. Syllabe L, Henner K. Contribution a l'independance de l'athetose double idiopathique et congenitale: atteinte familiale, syndrome dystrophique, signe du reseau vasculaire conjonctival, integrite psychique. *Rev Neurol (Paris)* 1926;1:541-62.
 35. Shearer WT, Cunningham-Rundles C, Ochs HD. Editorial: primary immunodeficiency: looking backwards, looking forwards. *J Allergy Clin Immunol* 2004;113:607-9.
 36. Shearer WT. Editorial. Importance of technology for the future of allergy and immunology. *J Allergy Clin Immunol* 2004;114:406-8.
 37. Shearer WT. Editorial: the 1st 80 years in primary immunodeficiency: how far have we come, how far need we go? *J Allergy Clin Immunol* 2006;117:748-52.
 38. Shearer WT, Malech H, Puck JM. Editorial: primary immunodeficiencies: meeting the challenges. *J Allergy Clin Immunol* 2007;120:753-5.