

Advances in basic and clinical immunology in 2011Javier Chinen, MD, PhD, and William T. Shearer, MD, PhD *Houston, Tex*

Investigations of basic immunologic mechanisms and clinical studies of primary immunodeficiencies were most prevalent in 2011. Significant progress was achieved in the characterization of T_H17 cell differentiation and associated cytokines in the setting of inflammatory disorders, HIV infection, and immunodysregulation disorders. The role of transmembrane activator and calcium modulator and cyclophilin ligand interactor (*TACI*) mutations in the pathogenesis of CVID was further described and reported to be likely mediated by impaired *TACI* expression affecting B-cell function. The frequency of autoimmunity in patients with partial DiGeorge syndrome was estimated at 8.5%, predominantly resulting in blood cytopenias and hypothyroidism. Several reports emphasized the presentation of neoplasias, most often lymphomas, as the first manifestation of several primary immunodeficiencies. Novel strategies for newborn screening of B-cell lymphopenia by measuring immunoglobulin κ chain-deletion recombinant excision circles and for adenosine deaminase deficiency using tandem mass spectrometry were demonstrated to be feasible at a large scale. Progress in the treatment of primary immunodeficiencies included increased success with unrelated HLA-compatible donors for hematopoietic stem cell transplantation and the development of new gene therapy approaches with improved safety features. Induced pluripotent stem cells were developed from patients with primary immunodeficiencies, providing a virtually unlimited resource for pathophysiology and gene correction studies. New findings in several of the uncommon immunodeficiencies, such as the increased susceptibility to severe viral infections caused by defects in the activation of the Toll-like receptor 3 pathway, overall contributed to the understanding of their immunologic basis and provided for the design of effective diagnostic and therapeutic strategies. (*J Allergy Clin Immunol* 2012;■■■:■■■-■■■.)

Key words: Immunology, primary immunodeficiencies, intravenous immunoglobulin, transmembrane activator and calcium modulator and cyclophilin ligand interactor, common variable immunodeficiency, cell immunity, severe combined immunodeficiency, newborn screening

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Abbreviations used

ADA:	Adenosine deaminase
ATM:	Ataxia-telangiectasia mutated
CGD:	Chronic granulomatous disease
CHH:	Cartilage-hair hypoplasia
CMV:	Cytomegalovirus
CVID:	Common variable immunodeficiency
HIR:	Histamine receptor 1
HIES:	Hyper-IgE syndrome
HSCT:	Hematopoietic stem cell transplantation
IVIG:	Intravenous immunoglobulin
KREC:	κ Recombination excision circle
MMP:	Matrix metalloproteinase
NEMO:	Nuclear factor κ B essential modulator
SCID:	Severe combined immunodeficiency
TACI:	Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TLR:	Toll-like receptor
TREC:	T-cell receptor excision circle
WAS:	Wiskott-Aldrich syndrome
WASP:	Wiskott-Aldrich syndrome protein
WIP:	Wiskott-Aldrich syndrome protein-interacting peptide
XLA:	X-linked agammaglobulinemia
XLP:	X-linked lymphoproliferative disease

This Advances article reviews the research work in the areas of basic and clinical immunology published in the *Journal* from January to December 2011 (Table I). Contributions investigating the immunologic basis of inherited immunodeficiencies has led to an exponential increase in our understanding of human molecular and immunologic mechanisms of disease and provided the conceptual basis for the design of specific diagnostic and therapeutic interventions.

CYTOKINES

Akdis et al¹ reviewed the current understanding of the immunologic actions of IL-1 to IL-37 and IFN- γ . Their role in the pathogenesis of different diseases was discussed within the context of their modulatory role in the inflammatory response, as well as their function against infectious agents. The cytokines were classified into the following 7 groups: the IL-1 family, the common γ -chain cytokine family, the IL-10 family, the IL-12 family, T_H2-like cytokines, interleukins with chemokine activity, and other cytokines. The authors predicted that many more new cytokines would be characterized as interleukins or chemokines. Some of the recently described cytokines have helped to explain the pathogenesis of diseases such as Behçet disease. T_H17 cell responses, but not T_H1 responses, were found to be increased in patients with active Behçet disease² and were associated with high

TABLE I. Selected key advances in basic and clinic immunology in 2011

T_H17 cells
• IL-21 modulates T_H17 cells in patients with Behçet disease. • IL-13 attenuates IL-17A production. • Forkhead box protein 3 (<i>FOXP3</i>) mutations lead to increased T_H17 cell numbers and regulatory T-cell instability. • <i>Bacillus anthracis</i> toxin promotes T_H17 development • IVIG inhibits T_H17 cell differentiation
TACI
• The C76R <i>TACI</i> mutation disrupts B-cell function in heterozygous and homozygous mice. • TLR9, TACI, and CD40 synergize in causing B-cell activation. • TACI haploinsufficiency results in B-cell dysfunction in patients with Smith-Magenis syndrome.
Immunoregulation
• Adhesion of pneumococci to epithelial cells increases when exposed to urban particulate matter. • <i>FCGR2B</i> gene variants are associated with response to IVIG in patients with Kawasaki disease.
Primary immunodeficiency
• Plasma metalloproteinase levels are dysregulated in patients with HIES. • <i>XIAP</i> most often presents with hemophagocytic lymphohistiocytosis. • Frequency of autoimmunity in patients with partial DiGeorge syndrome is 8.5%. • NEMO deficiency phenotype includes increased susceptibility to severe viral infections. • Granulomatous disease in patients with CVID might be associated with CMV infection. • κ Recombination excision circles might be used for newborn screening of B-cell lymphopenia. • HSCT has been successful for patients with CD3δ deficiency, dedicator of cytokinesis 8 deficiency, and CVID. • Gene therapy for WAS restores B-cell function. • Immunoreconstitution for ADA deficiency does not result in early immunosenescence. • Induced pluripotent stem cells for the study of human primary immunodeficiencies have been developed.

expression of IL-21, suggesting a possible causative role of this cytokine for Behçet disease. One example of the complex interaction of interleukins was provided by Newcomb et al.³ They observed that IL-13 downregulated murine T_H17 T-cell differentiation and showed that human T_H17 T cells expressed IL-13 α 1, which mediated inhibition of IL-17A production. The authors suggested that strategies targeting IL-13's effects on asthma and allergic diseases might increase T_H17 responses.

HIV INFECTION

Research into HIV pathogenesis continued to reveal new aspects of human immunology. Clark et al⁴ showed that the number and frequency of T_H1/T_H17 CD4 T cells were reduced in HIV-infected patients and were only partially reconstituted with antiretroviral treatment, indicating a possible contributing factor to the increased prevalence of allergic disease in this patient population. Also in these patients Pallikkuth et al⁵ reported that increases in memory B-cell frequencies and serum levels of B-cell activating factor and a proliferation inducing ligand were

associated with good antibody titers against influenza vaccine, suggesting that there was a threshold of B-cell function necessary to produce specific antibody responses.

IMMUNOMODULATORY MECHANISMS

Of interest, Pescovitz et al⁶ studied antibody responses during B-cell depletion in patients with autoimmune diabetes who received 4 weekly doses of rituximab. Titers of specific antibodies to routine childhood immunizations were not different in B cell-depleted patients and healthy control subjects, likely because of the persistence of CD20⁺ memory B cells and plasma cells. In contrast, attempts to induce new antibody responses during the B-cell lymphopenia stage by using the hepatitis A vaccine or the neoantigen ϕ X174 were not successful.

Johansen et al⁷ investigated the immunomodulatory properties of clemastine, a histamine receptor 1 (H1R)-specific antagonist, using a murine model of *Listeria* species infection. They found an increased mortality caused by infection in those mice that received 100 μ g of clemastine daily. This dose is about a hundred times the equivalent therapeutic dose in human subjects. Similar increases of *Listeria* species in the spleen were obtained with 100 μ g of clemastine or desloratadine but not cetirizine or dimetindene. The authors also showed that clemastine induced less expression of the proinflammatory cytokines IL-6 and TNF- α in mice and human cells exposed to LPS. Interestingly, the effect of clemastine in *Listeria* species-induced mortality of H1R knockout mice and wild-type mice was not different, suggesting that the immunosuppressive effect was not H1R dependent.

The deleterious influence of pollution in immunity and susceptibility to infections was noted to contribute to the increased frequency of respiratory tract infections in urban areas. Mushtaq et al⁸ reported that particulate matter induced increased bacterial adhesion to human airway epithelial cells, potentially explaining the association with infections. They also demonstrated that this observation was mediated by the platelet-activating factor receptor because bacterial adhesion could be inhibited by a platelet-activating factor receptor blocker.

de Roock et al⁹ suggested that the increased tolerogenic immune responses observed in newborns might be related to the increased expression of the receptor programmed death 1 in newborn CD4 T cells, which induced regulatory T cells twice as efficiently as adult cells.

Paccani et al¹⁰ showed a strong induction of T_H17 cell differentiation when CD4 T cells were exposed to the adenylate cyclase toxin of *Bacillus anthracis* and hypothesized that this function contributes to the generation of robust memory immunity, which is of importance for the design of vaccines.

IMMUNOLOGY OF PRIMARY IMMUNODEFICIENCIES

An increase in T_H17 cell counts in patients with immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) was demonstrated by Paserini et al,¹¹ who also pointed out that dysfunctional, epigenetically imprinted regulatory T cells were present and might contribute to the inflammatory manifestations of this condition. Papinazath et al¹² studied thymocyte development in a murine model of purine nucleoside phosphorylase deficiency and reported on the essential role of this enzyme in the survival of double-positive thymocytes, which underwent

apoptosis when exposed to deoxyguanosine. T-cell proliferation and T-cell receptor (TCR) diversity were not affected, and the restoration of purine nucleoside phosphorylase prevented the observed apoptosis.

Considering the potential role of matrix metalloproteinases (MMPs) in the development of pneumatocoles and aneurysms and the presence of signal transducer and activator of transcription 3-binding sites in promoter regions of genes encoding these enzymes, plasma levels of these enzymes were investigated in patients with hyper-IgE syndrome (HIES).¹³ MMP8 and MMP9 levels were found to be increased along with decreased expression of MMP3 in patients with HIES compared with levels seen in control subjects, suggesting a possible pathogenetic mechanism.

TRANSMEMBRANE ACTIVATOR AND CALCIUM MODULATOR AND CYCLOPHILIN LIGAND INTERACTOR

Several studies aimed to clarify the role of transmembrane activator and calcium modulator and cyclophilin ligand interactor (*TACI*) mutations in the development of common variable immunodeficiency (CVID). Bacchelli et al¹⁴ demonstrated that the murine mutation C76R, corresponding to the common *TACI* mutation in human subjects, C104R, significantly alters B-cell function both *in vitro* and *in vivo*. Knock-in mice harboring this gene mutation in 1 allele and wild-type *TACI* in the other allele showed marginal-zone B-cell expansion, decreased antibody production, and splenomegaly. The authors postulate that this is likely the result of gene haploinsufficiency because these mice presented with reduced *TACI* expression and suggested that genetic or environmental modifiers determined the penetrance of this gene defect. The work of Ozcan et al¹⁵ supported this concept by showing in both human and murine cells that *TACI* synergizes with Toll-like receptor (TLR) 9 stimulation and CD40 signaling in the activation of class-switch recombination, B-cell proliferation, and subsequent B-cell differentiation into plasma cells. Fried et al¹⁶ tested the *in vitro* expression and function of 10 common deleterious *TACI* mutations that have been associated with CVID. Mutations that affected *TACI* binding or signaling did not have a dominant negative effect.

The hypothesis of impairment of B-cell function by *TACI* gene mutations caused by haploinsufficiency was further supported by the study of patients with Smith-Magenis syndrome by Chinen et al.¹⁷ Patients with Smith-Magenis syndrome present with a heterozygous microdeletion in chromosome 18 that includes the *TACI* gene in most cases. In this study *TACI* intracellular and extracellular expression from the remaining allele was variable and correlated with the degree of B-cell activation and ability to develop antibodies to pneumococcal polysaccharides.

INFLAMMATORY DISORDERS AND USE OF INTRAVENOUS IMMUNOGLOBULIN

Yildirim-Toruner and Diamond¹⁸ reviewed the therapeutic armamentarium for the treatment of systemic lupus erythematosus, dividing the treatment agents into 4 categories: treatment directed to systemic inflammation, B cell–targeted antibodies, anticytokine antibodies, and therapies targeting costimulatory signaling. The first category includes medications that have been used for the past 30 years, such as antimalarial drugs, corticosteroids, cyclophosphamide, mycophenolate, azathioprine, and methotrexate.

Agents in the new categories are still experimental, such as therapeutic antibodies to deplete B cells or inhibit costimulatory molecules. Few trials in human patients have been conducted with these agents, and more data are needed to establish the safety and efficacy of these novel treatments.

A lung-specific inflammatory condition caused by exposure to beryllium was studied by Martin et al.¹⁹ Measurement of beryllium-specific, IFN- γ -producing CD4 T cells was used to determine sensitization to beryllium in 260 workers from a beryllium-machining facility and shown to be of predictive value for the development of chronic beryllium disease.

The immunologic mechanisms that support the efficacy of intravenous immunoglobulin (IVIG) in inflammatory disorders were reviewed by Ballow.²⁰ IVIG modulates immune effector pathways, mainly by blocking Fc receptor signals and modulating T- and B-cell function. Shreshta et al²¹ asked whether polymorphisms in the *FCGR2B* gene, which encodes the Fc γ RIIb inhibitory receptor, might be associated with the response to IVIG in patients with Kawasaki disease. The authors found that 1 allele of 3 single nucleotide polymorphisms studied (A at *FCGR2B* –120 T/a), which is located in the gene promoter region, was absent in patients of Asian and African descent, and its presence was indeed associated with IVIG responses, adding to the evidence supporting the role of Fc γ RIIb in the anti-inflammatory mechanisms of IVIG. Chua et al²² confirmed the direct relationship between titers of anti-pneumococcal, anti-*Haemophilus* species, and anti-tetanus IgG antibodies and total IgG serum levels in patients with hypogammaglobulinemia receiving IVIG.

The association of anti-IgA antibodies and the occurrence of adverse reactions to IVIG were studied by Rachid et al.²³ They found 35 patients presenting with undetectable serum IgA after screening 425 patients with immunodeficiency receiving IVIG and reviewed their medical records. There were only mild adverse events secondary to IVIG administration. Three of the 35 patients had high levels of anti-IgA IgG, and only 1 of them had an anaphylactic reaction to an IVIG product, which contained less than 10 μ g/mL IgA. Maddur et al²⁴ investigated the effect of IVIG in human T_H17 cells *in vitro* using IVIG at 25 mg/mL compared with human albumin (10 mg/mL). IVIG reduced 50% differentiation and proliferation of T_H17 cells, with decreased expression of their most significant transcription factor, the retinoic acid–related orphan receptor C. These experiments suggest other mechanisms for the anti-inflammatory action of IVIG.

PROGRESS IN PRIMARY IMMUNODEFICIENCIES

Micol et al²⁵ reviewed a French cohort of 240 patients with ataxia-telangiectasia born from 1954 to 2005 and analyzed their clinical presentation with regards to the specific mutation in the causative ataxia-telangiectasia mutated (*ATM*) gene. They confirmed that patients with null *ATM* mutations had lower life expectancy because of earlier onset of cancer compared with patients with mutations allowing *ATM* protein expression. In contrast, the first cause of mortality in those patients with hypomorphic *ATM* mutations was severe respiratory tract infection.

The frequency of autoimmune disorders in patients with partial DiGeorge syndrome was reviewed by Tison et al²⁶ in a large cohort of pediatric patients. Autoimmunity was found in 10 (8.5%) of 130 patients, a frequency similar to that seen in a previous study in a different institution. The most common autoimmune conditions were cytopenias and hypothyroidism. Children with high

or normal naive CD4 T-cell counts early in childhood had a lower risk of autoimmune disease.

Although primary immunodeficiencies usually present with increased susceptibility to infections, they can also present with neoplastic diseases. One of these conditions is X-linked lymphoproliferative disease (XLP-1), which is caused by mutations in the SH2 domain-containing gene 1A (*SH2D1A*). Another gene, X-linked inhibitor of apoptosis (*XIAP*; XLP-2), is usually mutated in patients with XLP when there are not pathogenic mutations in the *SH2A* gene. Horn et al²⁷ presented 2 families with *XIAP* mutations not previously described and reviewed the published literature of patients with this gene defect. Patients with XLP-2 appeared not to have an increased risk of lymphoma, but they might present with hemophagocytic lymphohistiocytosis. Three reports illustrated the development of neoplastic disease in other primary immunodeficiencies. Newell et al²⁸ reported a case of ζ chain-associated protein kinase 70 (ZAP70) deficiency in a patient who presented with an EBV-associated lymphoma in infancy that was unresponsive to chemotherapy. Slatter et al²⁹ reported 2 cases of IL-2 receptor γ -deficient severe combined immunodeficiency (SCID) in patients who presented with an intracranial Hodgkin-like, EBV-negative lymphoma. Hodgkin lymphoma was reported in 2 patients with chronic granulomatous disease (CGD),³⁰ emphasizing the notion that these neoplastic disorders also occur in patients with innate immune deficiencies. A review of the primary immunodeficiencies known to be most associated with increased occurrence of malignancies and viral infections included the following conditions: XLP; IL-2-inducible T-cell kinase (ITK) deficiency; epidermodysplasia verruciformis; warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome; autosomal recessive HIES; X-linked agammaglobulinemia (XLA); and CVID.³¹ The authors commented that neoplastic diseases in these patients are often a consequence of impaired immunologic surveillance against oncogenic viruses and malignant cells. Consistent with this observation, Marashi et al³² found cytomegalovirus (CMV)-specific CD8 T-cell counts to be increased in CVID patients with inflammatory complications compared with those seen in patients without inflammation in addition to evidence of active CMV replication. Inflammatory disease occurred more frequently in patients with CVID with evidence of CMV infection (31/43 patients) than in CMV-naïve patients (8/31 patients).

The use of current molecular biology technology to characterize genetic complex diseases, such as CVID, was reported by Orange et al.³³ They studied 363 patients with CVID and genotyped single nucleotide polymorphisms genome-wide to identify possible gene defects that might cause this condition. Several gene loci were significantly associated with CVID, which is in agreement with the observed heterogeneity of this disease. The information obtained might be useful for gene discovery and possible insight into mechanisms of humoral immunity.

Other contributions to the understanding of primary immunodeficiencies included the report of development of glomerulonephritis in patients with CD19 deficiency³⁴ and the diagnosis of CVID in adult patients after herpes simplex virus-induced encephalitis.³⁵ These patients were not receiving immunoglobulin replacement, underscoring the importance of herpes simplex virus-specific IgG in the protection against disease. A comparison of the pulmonary function of 29 patients with CVID and 8 patients with XLA showed an accelerated decrease

in those with XLA, which was partially attributed to increased years of smoking and the presence of bronchiectasis.³⁶

Hanna and Etzioni³⁷ discussed the immunologic mechanisms conferring increased susceptibility to localized fungal infections, emphasizing the recent progress in the discovery of cytokines involved in T_H17 responses. They described the monogenic diseases that include mucocutaneous candidiasis in their presentation, such as those caused by deleterious mutations in the genes autoimmunity, polyendocrinopathy, candidiasis, and ectodermal dystrophy (*AIRE*), signal transducer and activator of transcription 3 (*STAT3*; autosomal dominant HIES), caspase recruitment domain family, member 9 (*CARD9*), and in IL-12 deficiency. An immunodeficiency syndrome characterized by cutaneous candidiasis, CMV infection, and autoimmunity was reported to be associated with the amino acid sequence variant L412F of the TLR3 protein.³⁸ Fourteen of 21 patients with chronic mucocutaneous candidiasis were heterozygous for this variant and also showed autoimmune pancytopenia, arthritis, and vitiligo. The authors demonstrated decreased interferon production and low nuclear factor κ B activation to TLR3 stimulation in cells expressing the L412F variant. The TLR3 signaling pathway was explored to understand the occurrence of severe herpes simplex encephalitis in a patient with a hypomorphic nuclear factor κ B essential modulator (NEMO) mutation.³⁹ IFN- α and IFN- β expression in response to TLR3 agonists were reduced in cell lines with the NEMO mutation compared with that seen in control cells. These findings suggest that patients with NEMO deficiency have increased susceptibility to severe viral infections.

Immunologic studies in a series of 18 patients with cartilage-hair hypoplasia (CHH),⁴⁰ with 14 of them bearing the same genetic mutation, although with different histories of severe infections, showed a reduced number of naive T cells and increased apoptosis of their T cells, even in those without clinical evidence of immunodeficiency. Parameters of the B-cell compartment were not different from those seen in healthy control subjects. Two patients with reticular dysgenesis were reported to have myelodysplastic syndrome after a myeloablative HLA-haploidentical bone marrow transplantation resulted in mixed chimerism.⁴¹

Additional case reports showed hypogammaglobulinemia and hemophagocytic lymphohistiocytosis in a 3-year-old boy with a mutation in the *FAS* gene death domain, reminding us of the heterogeneity of presentation of autoimmune lymphoproliferative syndrome,⁴² and a hypomorphic mutation in *IL2RG*, pD134V, was associated with CD4 T lymphopenia and increased susceptibility of infections, suggesting causality.⁴³

NEWBORN SCREENING OF PRIMARY IMMUNODEFICIENCIES

The diagnosis of *Rac2* mutation immunodeficiency as the result of neonatal screening for T-cell lymphopenia provided additional insight into the essential role of *Rac2* in lymphocyte development in addition to neutrophil function.⁴⁴ Knutsen et al⁴⁵ offered a word of caution by reporting the case of a child with partial DiGeorge syndrome who had absent T-cell receptor excision circles (TRECs) with a normal percentage of CD4CD45RA T cells and was treated as having complete DiGeorge syndrome until 8 months of age, when his immune response measurements no longer indicated immunodeficiency.

An effort to develop a newborn screening method for B-cell lymphopenia was reported by Suri et al.⁴⁶ They measured κ

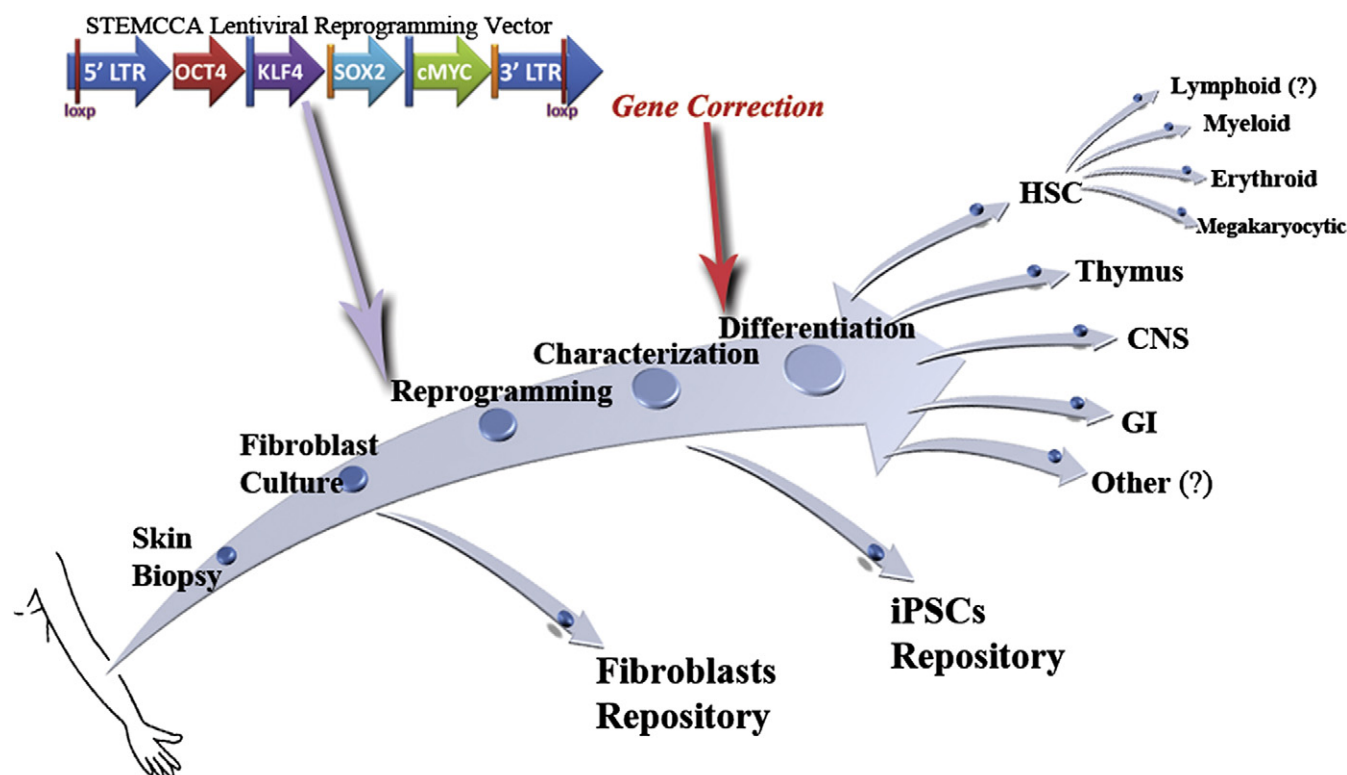


FIG 1. Development of induced pluripotent stem cells (iPSCs) and differentiation into different cell lineages. Fibroblasts are obtained from a skin biopsy specimen and reprogrammed into iPSCs by expressing 4 genes (OCT4, KLF4, SOX2, and cMYC) introduced by the STEMCCA lentiviral vector. Different cell lineages can be differentiated *in vitro* by using specific culture conditions.⁵⁹ CNS, Central nervous system; GI, gastrointestinal; HSC, hematopoietic stem cell; LTR, long terminal repeat.

recombination excision circles (KRECs) using a similar methodology to the measurement of TRECs. KRECs were undetectable in neonatal Guthrie cards of 8 patients with B-cell lymphopenia and detectable in 133 healthy control subjects.

Azzari et al⁴⁷ presented newborn screening for adenosine deaminase (ADA) deficiency–SCID using tandem mass spectrometry to detect adenine metabolites in neonatal Guthrie cards. No false-positive or indeterminate results were found after screening 12,000 newborn Guthrie cards. The authors discussed the superior cost-effectiveness of this method over TREC analysis for this form of SCID.

NEW DEVELOPMENTS IN THE TREATMENT OF PRIMARY IMMUNODEFICIENCIES

A potential therapeutic molecule for Wiskott-Aldrich syndrome (WAS) was suggested by investigations of Masaad et al.⁴⁸ They demonstrated that a short form of the WAS protein (WASP)–interacting peptide (WIP) stabilizes mutated WASPs if these are expressed, as occurs in patients with X-linked thrombocytopenia. The investigators assayed T- and B-cell lines, each bearing one of 8 WASP missense mutations in the WIP-binding region, showing WASP recovery to normal levels when exposed to WIP.

Chinn and Markert⁴⁹ discussed issues involved in achieving immunologic tolerance of parental parathyroid grafts when done simultaneously with allogeneic thymus transplantations in patients with complete DiGeorge syndrome. They suggested that matching HLA class II antigens between the thymus and

parathyroid grafts might determine parathyroid graft survival and long-term functionality.

The outcomes of hematopoietic stem cell transplantation (HSCT) of 13 patients with CD3 δ deficiency treated at different centers were summarized by Marcus et al.⁵⁰ Only 2 of 7 patients treated with HLA-mismatched related donors survived, whereas all those who received matched grafts were alive. Kang et al⁵¹ reviewed current concepts and considerations of HSCT for patients with CGD. HSCT for CGD used to be indicated only when an HLA-compatible sibling donor was available. Recent data suggest that HSCT with HLA-mismatched and unrelated HLA-compatible donors can be safely performed in patients with CGD, with survival of greater than 95% and resolution of infections and inflammatory complications. Other progress in the treatment of CGD included the restoration of microbicidal activity against *Aspergillus* species spores by neutrophils from patients with CGD after gene therapy, which is thought to be mediated by neutrophil extracellular traps and dependent on the oxidative burst.⁵²

The empiric use of anti-TNF- α inhibitors for the management of granulomatous complications in patients with CGD was challenged by Deffert et al.⁵³ They showed that TNF- α levels were not significantly increased in granulomas induced by intradermal injection of β -glucan in mice. The investigators also showed that the use of etanercept in this animal model of granuloma did not reduce the granuloma size and that TNF- α –deficient and CGD double-knockout mice produced a similar inflammatory response than CGD mice, suggesting that the role of TNF- α might be negligible.

The use of anti-TNF- α antibodies for granulomatous diseases was similarly addressed by Moshous et al⁵⁴ in patients with CHH. Four of 21 patients with CHH had cutaneous and subcutaneous granulomatous inflammation and were treated with infliximab, resulting in partial regression in 3 cases. However, 1 patient had progressive multifocal encephalopathy and subsequently died. The authors concluded that the risk of severe infection is a major concern when considering anti-TNF- α agents for the treatment of granulomatous inflammation in immunodeficient patients.

Two primary immunodeficiencies, dedicator of cytokinesis 8 deficiency and an early-onset form of the recently described monocyte-B cell-NK cell deficiency, were reported to be successfully treated with myeloablative HLA-identical HSCT protocols.^{55,56} The outcomes of HSCT for 4 patients with CVID with severe hematologic complications were reported by Rizzi et al.⁵⁷ There was 1 mortality and a diversity of outcomes, however, providing some evidence of feasibility to induce significant clinical improvement in CVID.

Pessach and Notarangelo⁵⁸ summarized the achievements of gene therapy efforts for primary immunodeficiencies and highlighted current limitations for widespread use, such as insertional mutagenesis resulting in leukemia. These limitations have motivated the development of new viral vectors to increase safety by including self-inactivating features or by using lentivirus vectors. In addition, new efforts to provide gene correction with locus-specific targeting are underway using endonucleases, zinc finger nucleases, and transposons.

Pessach et al⁵⁹ presented evidence of the generation of 25 induced pluripotent stem cells obtained from fibroblasts of patients with primary immunodeficiencies, thus providing a source material to support the development of new therapeutic approaches (Fig 1).⁵⁹

Fischer et al⁶⁰ summarized the gene therapy trials conducted for ADA deficiency, X-linked SCID, and WAS in the last 10 years, which has included more than 60 patients who have benefited with significant immunoreconstitution; however, 5 children had leukemia, and 1 died as a result of this therapy. The authors discussed the insights provided by these trials regarding the nature of retroviral integration in the host genome and offered considerations for the development of new gene vectors.

Selleri et al⁶¹ reported T-cell homeostasis studies in a cohort of patients with ADA-SCID who were reconstituted with gene therapy and HSCT. They showed that both new naive T cells and peripheral T-cell expansion contribute to T-cell reconstitution and suggested that accelerated immunosenescence was not occurring in these patients.

Of note, Grunebaum et al⁶² reported the development of an adipose tumor with incomplete correction of purine metabolism 3 years in a patient with ADA-SCID after gene therapy, underscoring the limitations of hematopoietic stem cell-based gene therapy for the treatment of multiorgan disease.

Bosticardo et al⁶³ expanded on the clinical evidence supporting gene therapy for WAS and showed reconstitution of B-cell function, as well as the presence of WASP in B cells of the splenic marginal zone and improvement of splenic architecture in a WAS murine model.

CONCLUSIONS

This year in review witnessed an increased number of contributions investigating primary immunodeficiencies. The role of

Th17 cells in inflammatory disorders, HIV infection, and immunodeficiencies was further defined. New evidence was published supporting the effect of *TACI* mutations in the development of CVID mediated by haploinsufficiency and not by a dominant negative function. HSCT with unrelated HLA-compatible grafts has proved to be of clinical benefit in an increasing number of primary immunodeficiencies, whereas gene therapies continue to be developed to provide increased safety.

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