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Advances in Basic and Clinical Immunology 2009

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Abstract

In 2009, reports on basic and clinical immunology had an increased focus on human disease mechanisms and management. The molecular pathogenesis of familial angioedema associated with estrogen was further explored to find possible factors affecting severity, including polymorphisms in enzymes and receptors related to bradykinin pathways. A placebo-controlled clinical trial of C1INH concentrate in hereditary angioedema patients demonstrated the safety of its use and the efficacy to reduce duration of angioedema attacks. The interaction of innate immunity and adaptive responses was further examined in several reports establishing the significant role of toll-like receptor stimulation for the development of optimal specific antibody responses. The 2009 update of the classification of primary immunodeficiencies introduced over 15 new genetic defects related to the immune response, including *DOCK8* mutations responsible for the autosomal recessive form of the hyper IgE syndrome. Other reports expanded the clinical spectrum of disease and improved the characterization of conditions such as warts, hypogammaglobulinemia and myelokathexis (WHIM) syndrome, or the occurrence of mucormycosis and *Serratia* infections in chronic granulomatous disease. The frequent presentation of gastrointestinal disorders in humoral immunodeficiencies was recognized and recommendations for management were reviewed. Clinical research focused in severe combined immunodeficiency included the development and implementation of a state-wide newborn screening program for this condition, a desired goal considering the significant reduction of mortality rate when diagnosis is made early before opportunistic infections occur.

Keywords

basic immunology; B cells; T regulatory cells; TH17; clinical immunology; primary immunodeficiency; hyper IgE syndrome; hereditary angioedema; hematopoietic stem cell transplantation; space immunology; HIV infection

Introduction

Following the trend of the last three decades, progress in basic and clinical immunology in 2009 was documented by the significant number of published reports. Research findings from animal and *in vitro* experimental models have been translated to similar investigations in patients presenting with immunological conditions, thus providing insights into the biology of

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human immunity and leading to the description of additional human gene defects causing immune dysfunction. (Table I). This article reviews the reports on basic and clinical immunology published in the *Journal of Allergy and Clinical Immunology* in 2009.

Angioedema and capillary leak syndrome: immunobiology and treatment

Advances in the immunobiology of angioedema included molecular investigations of patients presenting with this clinical manifestation and with normal complement C1 esterase inhibitor (C1INH) level and function. Hentges and colleagues¹ reported 4 female patients with recurrent angioedema attacks and normal levels and function of the C1-INH. All of these patients were taking oral estrogen contraceptives, however, only one presented with a gain-of-function mutation of factor XII. The authors were able to demonstrate that the four patients had evidence of activation of the contact system with demonstration of complete cleavage of the high molecular weight kininogen, or HMWK. (Figure 1) They concluded that mutations in multiple genes may explain this phenotype, which was supported by data provided by Joseph et al.² that demonstrated the production of bradykinin by prekallikrein in absence of Factor XII. Duan and collaborators³ reported three affected members of a family with estrogen-dependent angioedema that added further support to the multifactorial pathogenesis of estrogen-dependent angioedema. These patients were heterozygous for the missense mutation Thr328Lys in *F12*, which increases Factor XII activity, and in addition, they presented with polymorphisms in the genes encoding the aminopeptidase enzyme APP and the angiotensin-I convertase (ACE) that are associated with decreased degradation of bradykinin. The combination of mutations in these three genes may explain the variability in the risk of angioedema attacks.

Idiopathic systemic capillary leak syndrome (ISCLS) is included in the differential diagnoses of angioedema, and is characterized by intermittent attacks of hypotension, hemoconcentration, hypoalbuminemia, renal failure, increased weight, and edema. Dowden et al.⁴ studied 3 patients with this condition, two adults and a 6 year-old boy in whom angioedema diagnosis was ruled-out, and reported that they all had elevated serum levels of TNF- α . Based on this finding and subsequent therapeutic response to TNF- α inhibitors, they proposed the use of a two-tier management approach for ISCLS: initially to use theophylline and terbutaline, and if no response was evident, to use TNF- α inhibitors such as infliximab. Bossi and collaborators⁵ developed elegant *in vitro* and *in vivo* experimental models to measure vascular permeability to proteins after exposure to plasma obtained from patients suffering an angioedema attack. They showed that, in addition to the bradykinin receptor 2, bradykinin receptor 1 also has a significant role in the increased vascular leakage. Furthermore, they showed that inhibition of the interaction of kininogens and the receptor for the globular head of the C1q protein resulted in complete inhibition of vascular leakage induced by the plasma samples. These findings suggest that both the bradykinin receptor 1 and the receptor for C1q are potential therapeutic targets for the control and relief of angioedema attacks.

A multicenter randomized placebo-controlled trial involving 125 patients with hereditary angioedema demonstrated the safety and efficacy of a human C1INH concentrate product for facial and abdominal attacks in patients with hereditary angioedema.⁶ Overall, there was a significant reduction of time to relief from 1.5 hrs to 0.5 hrs using this preparation at a dose of 20 U/kg within the first 6 hrs of onset. The effect was more significant for severe attacks and for facial swelling than for abdominal symptoms. A dose of 10 U/Kg did not have an effect that was significantly different from placebo. Safety was assessed by monitoring adverse events possibly related to the administration of C1INH and extensive testing of blood-borne viruses. No significant safety differences between placebo and treatment groups were found.

Innate immunity and inflammatory disorders

Autoinflammatory syndromes result from mutations in genes involved in the control of inflammatory responses. Goldbatch-Mantsky and Kastner reviewed the genetic causes of these rare conditions,⁷ which have helped to improve our understanding of the mechanisms of inflammation and the role of the initial immune response to trigger the adaptive immunity. Most of these genes encode proteins that participate in an intracellular molecular complex called “inflammasome”, and leads to the secretion of the pro-inflammatory cytokine IL-1. These conditions include the familial mediterranean fever, TNF- α receptor associated periodic syndrome, cryopyrin associated periodic syndrome, and hyper-IgD syndrome. The progress in the understanding of these diseases has led to clinical trials using IL-1 inhibitors such as anakinra, with promising results. The therapy of these inflammatory disorders was reviewed by Hoffman,⁸ who pointed out that these disorders have been traditionally managed with colchicine, but both TNF- α inhibitors and IL-1 receptor antagonists were increasingly used because of their mechanism of action were based on the pathogenesis of the disease, resulting in less adverse effects.

Investigations in animal models help to further refine the action of molecules involved in inflammation. As an example, it was shown that the mutation of a tyrosine in position 145, but not in position 112 and 128 of the lymphocyte cytosolic protein 2 (SLP-76) abrogates the development of inflammation in a serum-induced arthritis mouse model.⁹ SLP-76 regulates cell signaling in myeloid cells mediated by Fc γ R and specific integrins. Similar findings are directed to identify novel targets for the treatments of inflammatory conditions.

Investigations on cytokines

Gold and collaborators studied the cytokine responses to stimulation with mitogens, antigens and TLR-agonists in mononuclear cells of 558 cord blood samples.¹⁰ They analyzed the association of differences in these responses with variables such as presence of maternal allergic disease, infection or season of birth. Those associations that were statistically significant included the presence of maternal asthma and RSV infection associated with decreased response of pro-inflammatory cytokines. Interferon- α responses were higher if babies were born in January-March as compared to the other 3-month seasons. The authors concluded that innate cytokine responses were associated with maternal allergic disease and season of birth, as well as somatic growth and ethnicity. Cytokine responses were also studied in a space flight model using the head-tilted bed-rest position to simulate anti-gravity effect.¹¹ TNF- α levels were increased and associated with impaired kinetics of antibody responses to immunization with the neoantigen Phi174. Interestingly, routine exercise used as a counter measure ablated the increase of TNF- α , possibly related to concomitant increase of the levels of the IL-1 receptor antagonist and of the chemokine RANTES.

Fibronectin was identified as a T_H1 specific molecule by comparing mRNA expression of T_H1 and T_H2 differentiated cells, using microarray techniques. Sandig et al.¹² showed that T_H1 cells but not T_H2 cells secrete fibronectin and, after binding to receptors in macrophage, secretion of the pro-inflammatory cytokine IL-6 was induced. These findings further define the molecular events regulating cytokines and other chemical messengers that regulate the immune response.

Primary immunodeficiencies (PID)

Classification and policy guidelines

The field of primary immunodeficiencies was significantly represented in the progress achieved in basic and clinical immunology in 2009. The International Union of Immunological

Societies Expert Committee on Primary Immunodeficiencies reported on the biennial update of the classification of primary immunodeficiencies, in an article by Notarangelo et al.¹³ In this updated classification, the relative frequency of each condition among PIDs based on published reports was included. Several new gene defects have been included in each of the 8 PID categories, and some of them are described below.

Particularly expanded are those affecting the innate immunity and atypical genetic immunodeficiencies such as the one conferring susceptibility to trypanosomiasis, attributed to mutations in the gene encoding the apolipoprotein I (APOLI). In a Primary Immunodeficiency Treatment Consortium report by Griffith et al.,¹⁴ experts from North American academic centers that focus on the management of primary immunodeficiencies authored guidelines for the recognition of PIDs, indications for hematopoietic stem cell transplant (HSCT), and the care before and after HSCT, with emphasis in antimicrobial prophylaxis. Limitations of the available literature about the management of these rare diseases were recognized, as well as the need of National Institutes of Health-sponsored multicenter efforts to provide with evidence and consensus for future clinical trials.

New findings on rare immunodeficiency disorders

McCarl et al.¹⁵ studied the immunodeficiency caused by defects in the Ca^{2+} -release activated Ca^{2+} (CRAC) channels, encoded by the *ORAI* genes. The dysfunction of intracellular calcium release results in immunodeficiency, autoimmunity associated with myopathy and ectodermal dysplasia. This clinical presentation may also be caused by pathogenic mutations in the ER protein stromal interaction molecule 1 (STIM1), which is involved in the activation of ORAI1. The authors characterized six patients from 3 families with *ORAI1* mutations, who presented with characteristic clinical features and decreased lymphoproliferative responses to mitogens and antigens. Their *in vitro* experiments demonstrated that all mutations resulted in impaired calcium mobilization. In a similar effort to improve characterization of a rare immunodeficiency syndrome, Tassone and collaborators¹⁶ studied ten patients with deleterious mutations in the gene encoding for the chemokine receptor CXCR4, which is defective in the warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome. These ten patients were identified after analyzing the CXCR4 gene sequence of 53 patients who presented with chronic neutropenia. The authors found that 3 of the ten patients had hypogammaglobulinemia, and 4 patients had serum IgG levels close to the lower limit of normal range. All patients had recurrent infections, mainly respiratory, with only one presenting with genital warts. The authors concluded that *CXCR4* gene analysis should be considered in patients with chronic neutropenia even in the absence of hypogammaglobulinemia and warts. Renner et al.¹⁷ reported several defective immunological parameters, especially defective isotype switching and B cell memory, in 9 patients with the Comel-Netherton syndrome, a complex genetic disease caused by mutations of the *SPINK5* gene. The clinical phenotype of this syndrome is characterized by ichthyosis, bamboo hair, recurrent infections and allergic disease. Interestingly, five patients with suboptimal antibody responses reported clinical benefit after initiation of IVIG at replacement doses, with decreased skin inflammation and healthier scalps. Two reports advanced our knowledge of infections by pathogens that present selectively in chronic granulomatous disease: molds and *Serratia* sp. Vihn et al.¹⁸ found four patients with invasive mucormycosis from a cohort of 278 patients evaluated at the National Institutes of Health. All patients had intensive steroid-based regimen 3 or more weeks immediately before the presentation of their infections. Although the total number of patients who received a similar steroid treatment was not reported, this finding suggests that NADPH oxidase-independent mechanisms are important for the development of mucormycosis. This research group also reported their experience with *Serratia* sp infections in 15 CGD patients 8–39 years of age.¹⁹ The most significant findings were: 1) *Serratia* sp. osteomyelitis was uncommon beyond infancy, 2) skin infections require prolonged antibiotic

treatment, and 3) isolated *Serratia* sp. pneumonias were unlikely to become systemic and spread to other organs.

Two case reports were illustrative of the complex nature of primary immunodeficiencies and provided with valuable teaching points. The importance of the history and physical examination in the evaluation of primary immunodeficiencies was underscored by the report by Shah and colleagues,²⁰ who described a 5 year-old patient with recurrent infections, short stature and skeletal dysmorphism, and was later diagnosed with Schwachman-Bodian-Diamond syndrome. Further investigations revealed a hypocellular bone marrow and low absolute counts of B cell and NK cells as well as evidence of pancreatitis, supporting the clinical diagnosis. Fiorini et al.²¹ showed two different genetic mechanisms leading to an autosomal recessive condition. They reported a case of leukocyte adhesion deficiency type I caused by a nonsense mutation in *ITGB2*, the gene encoding the integrin beta 2, inherited with the maternal allele, and a *de novo* deleted ring 21 chromosome comprising 69 genes including *ITGB2*. This case emphasizes the importance of cytogenetic analysis in patients with complex clinical phenotypes.

Hyper IgE syndrome

One of the newly described gene defects is one affecting the dedicator of cytokinesis 8 (DOCK8) signal transducer, which is associated with autosomal recessive hyper IgE syndrome (AR-HIES).²² Both microdeletions involving this gene and deleterious mutations in *DOCK8* were found in 21 patients with AR-HIES, a syndrome characterized by recurrent pneumonia, skin abscesses and viral infections (especially molluscum contagiosum and herpes viruses), very high eosinophilia and elevated serum IgE level, but, in contrast to the autosomal dominant form, does not present with skeletal or dental disease. Kim and colleagues²³ reported a missense mutation in the linker domain of the signal transducer and activator of transcription 3 (STAT3) in a patient with autosomal dominant HIES, expanding the range of genetic defects causing this syndrome, since previous reports had found mutations in either the DNA-binding domain transactivation domain or the SH2 domain. Of note, this 5 year-old boy did not have any skeletal or dental anomalies. He did have impairment in *in vitro* T_H17 differentiation. Alkhatib et al.²⁴ showed that impaired T_H17 differentiation was a characteristic of all HIES patients, regardless of the causative gene defect. These investigators studied a cohort of 25 Turkish children with HIES diagnoses, and while only six individuals had mutations in the *STAT3* gene, all studied patients had decreased T_H17 responses with conserved T_H1 responses. The pathways involving the described gene products STAT3, tyrosine kinase 2 (TYK2) and DOCK8 leading to T_H17 differentiation and their role in HIES have not been well defined. Burgler et al.²⁵ studied the *in vitro* differentiation of human T_H17 cells and demonstrated high expression of the retinoic acid orphan receptor (ROR) C2, a human homologue of the mouse ROR γ . This group stimulated naïve T cells with TGF- β , and induction of IL-17A and IL-17F secretion were achieved by exposing the cells to IL-6, IL-23 and IL-1 β . However, TGF- β also induced differentiation of T regulatory cells (Tregs) when also exposed to anti-IL-12 and anti-IFN- γ antibodies. Furthermore, Tregs also expressed RORC2. The authors emphasized that human T_H17 cells need to be identified by IL-17 secretion and not by RORC2 expression. Further definition of the clinical features of HIES included the work of Melia et al.²⁶ to investigate the frequency of non-tuberculous mycobacterial infections in AD-HIES. All of those patients with lung structural damage in the form of bronchiectasis or lung cysts were investigated for mycobacterial infections. Five of 32 patients were found with positive cultures and with clinical criteria to define active infection. All five responded to antimycobacterial therapy.

Antibody immunodeficiencies

Agarwal and Mayer²⁷ reviewed gastrointestinal conditions that commonly present in patients with deficiency of antibody responses. They classified these conditions in 4 groups: infections, malignancies, autoimmune conditions, and inflammatory disorders. They postulated that their clinical characteristics are more likely the result of cellular immunity dysfunction accompanying the antibody defect, and that treatment may need to be patient-tailored, because it is often necessary to use immunomodulators in these immunocompromised patients. The authors focused on the description of pathologies occurring in three conditions: X-linked agammaglobulinemia (XLA), selective IgA deficiency, and common variable immunodeficiency (CVID). They noted that the gastrointestinal conditions in these diseases resemble common illnesses such as ulcerative colitis and celiac sprue, however they do not have a typical clinical picture, suggesting different pathogenesis mechanisms from those that explain the same diseases in immunocompetent individuals.

Yu et al.²⁸ reported impaired activation of CVID B cells mediated by toll-like receptors (TLR)-7 and TLR-9. The authors showed impaired cell proliferation, immunoglobulin production, and expression of activation-induced deaminase (AID), when patient B cells were stimulated with TLR-7, TLR-7/8 and TLR-9 agonists, strongly suggesting a role of innate immunity in the pathogenesis of this immunodeficiency. The effect of the TLR-7 agonist resiquimod was shown to induce IgG production in normal naïve B cells, especially when costimulated with IL-2 and IL-10.²⁹ This effect was also seen with B cells from a patient with X-linked hyper IgM syndrome, indicating that class-switch and IgG production may occur in absence of B-cell receptor cross-linking and CD40-CD40 ligand interaction. Additional evidence of the role of TLR stimulation in the immunoglobulin production by B cells was provided by Ozcan et al.³⁰ They used a mouse model to demonstrate the synergism of lipopolysaccharide (LPS), a TLR-4 agonist, and a proliferation-inducing ligand (APRIL) to induce B cell proliferation, differentiation and immunoglobulin secretion. APRIL binds to the B cell receptor TACI, which has been found defective in a subset of patients with CVID.

Other advances related to humoral immunodeficiencies included a small trial to compare the use of immunoglobulin supplementation by intravenous and subcutaneous routes.³¹ Twelve patients were enrolled in a randomized, 2-arm crossover trial, with six months in each route and same total monthly dose. There were no differences in systemic adverse effects or incidence of infection between the two arms of the study. The authors concluded that the results of this pilot trial supported the need of a larger protocol with greater statistical power to compare the efficacy of these two routes of administration for IgG replacement. Of interest, von Gunten et al.³² studied the anticarbohydrate antibodies present in 3 commercial IVIG preparations, using a glycan microarray with high throughput testing. They found that antibodies to half of over 370 different glycans tested were present in the different preparations. Depletion of IgG2 did not eliminate the carbohydrate specific antibodies, suggesting that IgG1 also targets carbohydrate moieties and that T cell immunity is likely to be involved in the generation of anti-carbohydrate antibodies. Specificity to endogenous carbohydrates was absent, and the most frequent antibodies specificities corresponded to glycans found in bacteria. The authors pointed out that these findings are of potential significance for the development of vaccines, with the consideration of new targets. Hare and collaborators³³ found that many patients had elevated concentrations of antibodies against the different serotype antigens included in the non-conjugated 23-valent pneumococcal serotype vaccine and estimated preimmunization values at which the chance of achieving a four-fold increase of titers post-immunization was nearly zero. These data are of clinical value in the often difficult interpretation of antibody responses.

Severe Combined Immunodeficiency (SCID)

Advances in the diagnosis and management of SCID reported in 2009 included the first development of a state-wide newborn screening program for the early diagnosis of this condition. Baker et al.³⁴ reported their efforts to implement this program in Wisconsin. They tested 5,766 dried blood spot samples obtained from newborn screening cards by measuring T-cell receptor excision circles (TRECs) using real-time quantitative PCR. The absence of TRECs strongly indicates a SCID diagnosis. With an estimated frequency of 1 in 50,000 live births, a larger number of samples needed to be tested to identify these patients. The demonstration of its feasibility constituted significant progress, considering the improved outcomes of treatment with HSCT when diagnosis is made early. This publication was followed by the same group reporting the outcomes of this program over 12 months.³⁵ After 71,000 samples were tested, 8 infants with T cell lymphopenia were subsequently diagnosed with DiGeorge syndrome (n=2), idiopathic CD4 T cell lymphopenia (n=2), extravascular extravasation of lymphocytes (n=3) and Rac2 deficiency (n=1). Early diagnosis of SCID is of utmost importance to reduce frequency of severe infections, and also to avoid adverse consequences of administering live vaccines in an immunocompromised patient, as demonstrated by reports of intractable diarrhea when rotavirus immunization has inadvertently been given to 2-month-old infants as scheduled, before SCID diagnosis was made.³⁶

Patel et al.³⁷ reported the outcomes of 23 SCID patients who received a hematopoietic stem cell transplant at a single institution between 1998 and 2007. Five of the patients received HSCT using matched related donors, and all have survived. The other eighteen received HSCT using a haploidentical related donor or a matched unrelated donor, with all but one patient receiving a conditioning regimen. The one-year survival rate was 72%. No significant differences were obtained when this outcome was compared with previous reported experience in the same center consisting of 25 SCID patients who were transplanted without conditioning regimens. The assessment of risks and benefits of pre-transplant conditioning regimens require further follow up of these patients and similar cohorts from other centers.

Other significant progress related to SCID included the description of two interesting cases presenting with Omenn syndrome. Sheehan et al.³⁸ reported the association of Omenn syndrome and aniridia, in which further genetic investigation revealed microdeletion of chromosome 11p13 including the genes recombination activating gene (*RAG*)1, *RAG*2 and paired box gene 6 (*PAX6*) in one allele, and missense mutations in the second allele. The authors call to our attention that in autosomal recessive disease, apparent homozygous mutation in autosomal chromosomes may be further investigated to rule-out heterozygous deletions. Somech et al.³⁹ studied one patient with *RAG*2 deficiency who presented with erythrodermia, lymphadenopathy, splenomegaly and *Pneumocystis pneumonia*. T cell oligoclonality was demonstrated as well as absence of TRECs. The authors found that this patient had reduced expression in peripheral blood of the autoimmune regulator (AIRE) protein, but not forkhead box P3 (FOXP3) and hypothesized that central tolerance, and not T regulatory cells, plays a role in the autoimmunity associated with Omenn syndrome. This group also described one patient with partial adenosine deaminase (ADA) deficiency and mild immunodeficiency who started treatment with polyethylenglycol (PEG)-ADA at 20 months, because of interstitial pneumonitis.⁴⁰ This patient had also developed autoimmune hepatitis that did not improve with this treatment but ultimately responded to prednisone. They concluded that PEG-ADA improves lung disease but not liver disease in partial adenosine deaminase deficiency.

The development of a functional diagnostic assay based on IL-2 induced STAT5 phosphorylation was reported to identify SCID patients with defects in the Janus kinase 3 (JAK3) and γ c pathways.⁴¹ These patients characteristically present with absence of T cells and NK cells, and with dysfunctional B cells. However, this phenotype may be modified by the presence of maternally engrafted cells, oligoclonal T cell expansion or extrinsic factors that

induce lymphopenia. In these cases, and in those in which genetic analysis is equivocal, functional studies such as the one described in this report may prove to be clinically useful.

Conclusions

Scientific reports published in 2009 reflect the progress in basic and clinical immunology increasingly focused on the elucidation of mechanisms that regulate the human immune response and results in immunological diseases (Table II). New genetic lesions were described, such as mutations in *DOCK8*, responsible for the autosomal form of HIES, or familial angioedema not mediated by a defective C1INH. The role of effector cells and molecules of the innate immunity to trigger inflammation and efficient antibody responses have been further defined. From the molecular characterization of individual patients or small case series, research efforts are being translated into matters of public health to reduce the burden of the most severe forms of the primary immunodeficiency diseases, by early detection with universal neonatal screening.

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Abbreviations

APC	Antigen-presenting cells
STAT	signal transduction and activation transcription
IFN	interferon
TLR	toll-like receptor
HAE	hereditary angioedema
HIE	Shyper IgE syndrome
CGD	chronic granulomatous disease
HSCT	hematopoietic stem cell transplantation
SCID	severe combined immunodeficiency
CVID	common variable immunodeficiency.

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Figure.

Mechanisms of bradykinin-induced vasodilation in angioedema. Increased activation of Factor XII, or decreased activity of C1 inhibitor esterase leads to increased levels of kallikrein, which induced the formation of bradykinin from high molecular weight kininogen (HMWK).

TABLE I**New diseases reported in the 2009 update of the PID classification**

I.	Combined T and B cell immunodeficiencies
a.	T-B+ SCID: Coronin-1A deficiency
b.	T-B– SCID: DNA PK deficiency
c.	Reticular dysgenesis due to mutation in <i>AK2</i>
II.	Predominantly antibody deficiencies
a.	with normal or low B cell number: BAFF receptor deficiency, TACI deficiency
III.	Other well-defined immunodeficiency syndromes
a.	DNA repair defects: Immunodeficiency with centromeric instability and facial abnormalities, PMS2 deficiency (defective mismatch repair)
b.	Immuno-osseous dysplasias: Comel-Netherton syndrome
c.	Hyper IgE syndromes : autosomal recessive due to mutations in <i>DOCK8</i>
d.	Chronic mucocutaneous candidiasis due to mutations in <i>CARD9</i>
IV.	Diseases of immune regulation
a.	lymphoproliferative syndromes: ITK deficiency
V.	Congenital defects of phagocytes
a.	Neutropenia with cardiac and urogenital malformations: mutations in <i>G6PC3</i>
b.	Glycogen storage disease type 1b, mutations in <i>G6PT1</i>
c.	Pumonary alveolar proteinosis due to defects in GCSF signaling
VI.	Defects in innate immunity
a.	MyD88 deficiency
b.	Susceptibility to trypanosomiasis due to mutations in <i>APOL1</i>
VII.	Autoinflammatory disorders
a.	Deficiency of the IL-1 receptor antagonist
VIII.	Complement deficiencies
a.	Immunodeficiency associated to ficolin 3 deficiency

Table II

Key advances in basic and clinical immunology in 2009

1.	Increased vascular protein leakage is mediated by activation of both bradykinin receptors 1 and 2.
2.	Innate cytokine responses in cord blood cells are associated with maternal allergic disease and season of birth
3.	Increased TNF- α and impaired antibody responses to neoantigens were observed in a space flight model
4.	Fibronectin was identified as a T _H 1-specific molecule
5.	<i>CXCR4</i> gene defects were identified in patients with chronic neutropenia who did not present with warts or hypogammaglobulinemia
6.	<i>DOCK8</i> gene defects lead to the autosomal recessive form of hyper IgE syndrome.
7.	B cells from CVID patients present with impaired activation mediated by TLR-7 and TLR-9 agonists
8.	APRIL and LPS can induce B cell proliferation, differentiation and immunoglobulin secretion.
9.	The feasibility of newborn screening for SCID was demonstrated