

Advances in basic and clinical immunology in 2007

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In 2007, there was significant progress in the area of basic immunology, including investigations that led to a better understanding of the function of antigen-presenting cells, such as the secretion of cytokines that inhibit or induce allergic inflammation on antigen stimulation. Mechanisms of IgE function were better characterized, and the clonality of IgE-producing B cells in allergic responses of monosensitized patients was demonstrated. The hygiene hypothesis was re-examined, with most of the evidence suggesting that the increase of atopy prevalence is best explained by the absence of T_H1 responses rather than the absence of regulatory T cells. The effects of the environment in the allergic inflammation of the lung received new emphasis. Similar progress took place in the area of clinical immunology. Immune adverse reactions to drugs, such as the toxicity of carbamazepine-specific T cells and the safety and efficacy of drugs for the treatment of hereditary angioedema, were better characterized. There were advances in the molecular characterization of primary immunodeficiencies and their management, remarkably the discovery of signal transducer and activator of transcription 3 gene mutations as the cause of hyper-IgE syndrome. Long-term outcomes of bone marrow transplantation for severe combined immunodeficiencies confirmed the efficacy of this therapy. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Basic immunology, antigen presentation, IgE, regulatory T cells, lung immunology, clinical immunology, immunodeficiency, hereditary angioedema, mastocytosis, common variable immunodeficiency, HIV infection

The publication of high-quality original and review articles on basic and clinical immunology has achieved new levels of excellence. The objectives of this report are to review and summarize the literature in the fields of basic and clinical immunology published in the *Journal of Allergy and Clinical Immunology* in 2007, with focus on those articles of most relevance to the readers of the *Journal* (Table I).

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Abbreviations used

BMT:	Bone marrow transplantation
CVID:	Common variable immunodeficiency
DC:	Dendritic cell
HAE:	Hereditary angioedema
HIES:	Hyper-IgE syndrome
NK:	Natural killer
SOCS:	Suppressor of cytokine signaling
STAT:	Signal transducer and activator of transcription
TACI:	Transmembrane activation and calcium modulation cyclophilin interactor
TLR:	Toll-like receptor

BASIC IMMUNOLOGY

Understanding antigen presentation in the development of the immune response

The suppressive effect of IL-10 on the ability of dendritic cells (DCs) to induce airway allergic inflammation was demonstrated by Koya et al¹ using DCs isolated from mice immunized with ovalbumin. When these ovalbumin-specific cells were generated after the mice were treated with IL-10, they expressed lower levels of CD11, CD80, and CD86, as well as lower levels of IL-4, IL-5, and IL-12. Naive mice receiving these cells and challenged with nebulized ovalbumin did not experience airway hypersensitivity and airway eosinophilia, suggesting a suppressive role of IL-10 in the development of airway inflammation. Antigen-specific T cells secreting IL-10 were also demonstrated to play a role in the immune mechanisms associated with long-term efficacy of sublingual immunotherapy.² An interesting observation by Triggiani et al³ might explain the stimulatory effect of histamine in inflammation. Working with monocyte-derived macrophages, these investigators demonstrated that macrophages increased their expression of histamine receptor 1 during differentiation, resulting in an acquired capacity to be activated by histamine. Ebner et al⁴ reported that thymic stromal lymphopoietin could induce differentiation of epidermal Langerhans' cells into DCs with increased expression of costimulatory molecules and ability to induce naive T cells to secrete IL-4, IL-5, and IL-13. Thymic stromal lymphopoietin is highly expressed in keratinocytes, and this mechanism provides an additional explanation for the chronicity of atopic dermatitis. T_H2 cytokines were also induced when antigen presentation was performed coupled with Lewis trisaccharides, a complex glycan found in pollen allergen.⁵

Immunomodulation by presentation of antigens that have been altered by amino acid substitution was explored by Kinnunne et al.⁶ This group modified an epitope of Bos d 2, an allergen of cow dander, with an amino acid substitution. When the altered peptide was exposed to T-cell lines obtained from 6 patients with cow dust-induced asthma, they were more likely to secrete

TABLE I. Key advances in basic and clinical immunology in 2007**Basic immunology**

1. Cytokines participating in antigen presentation modify the allergic inflammatory response.
2. The diversity of allergen-specific repertoire in atopic patients was found to be limited.
3. Regulatory T cells are decreased in patients with asthma and allergy.
4. Exposure to tobacco smoke and other air pollutants induces allergic inflammation in the lung.

Clinical immunology

1. Hypersensitivity to iodinated contrast media agents presents with cross-reactivity and is cell mediated.
2. Isoproterenol can induce T_H2 -type cytokine secretion.
3. Kallikrein inhibitors are effective in reducing HAE symptoms.
4. Molecular and clinical characteristics of HIES were associated with *STAT3* mutations.
5. *TACI* defects contribute to the severity of clinical complications in patients with CVID.
6. BMT for severe combined immunodeficiency and complete DiGeorge syndrome results in long-term survival.
7. CD4/CD8 ratio is a sensitive marker to predict HIV infection in infants.

IFN- γ and less likely to secrete IL-4, suggesting deviation into a T_H1 phenotype. In contrast, exposure of T-cell clones to the natural peptide induced a T_H2 phenotype. Ando et al⁷ showed that TGF- β could be orally administered and reduce allergen-specific IgE and T-cell responses in a murine model of oral allergic sensitization with ovalbumin.

Biology of IgE

Significant advances in the immunobiology of IgE antibodies were reported. Takhar et al⁸ used PCR-based methods to document that class-switch recombination to IgE occurred in the bronchial mucosa and was more frequently found in biopsy specimens taken from asthmatic patients than from healthy control subjects. To characterize the diversity of the IgE repertoire, Persson et al⁹ constructed an IgE library from B cells of a subject who was allergic to timothy grass. Using a phage display protocol and a panel of timothy peptide allergens, these authors determined that the IgE library was limited to a few allergens, and the IgE specific to the timothy panel constituted as much as 25% of the total IgE. Supporting these data, a limited number of B-cell clones were identified in atopic subjects by studying their heavy chain third complementary region. Lim et al¹⁰ used CDR3 spectratyping and also found that there were a limited number of IgE-secreting clones expanded, with preference of V_H3b , V_H3a , and V_H4 use, which is similar to IgM and IgG repertoires. A new method to identify cross-reactivity among allergen extracts was described by Soeria-Atmadja et al.¹¹ These authors collected recorded allergen-specific IgE measurements from 1011 individuals and used information technology to find significant associations. The data obtained are consistent with previous concepts based on amino acid or protein similarity, for the most part, with a particular exception of dust mite and seafood, which were expected to be but were not associated based on sharing the allergen tropomyosin. Whether these findings have clinical significance was not tested. There was a report of the synergism of IL-9 and IL-4 to induce IgE secretion by tonsillar B cells,¹² which also upregulate IL-13 receptors after CD40 activation.¹³

Klunker et al¹⁴ reported the use of anti-IgE (omalizumab) to reduce side effects and increased efficacy in rush immunotherapy,

possibly mediated by direct inhibition of IgE-allergen binding. Omalizumab was reported as a successful therapy for 3 patients with refractory angioedema and normal complement component C1 inhibitor level and function.¹⁵ Allen et al¹⁶ developed a fusion protein combining the CH3 domain of the immunoglobulin γ chain and the CH2 and CH4 domains of the ϵ heavy chain to develop a molecule with inhibitory properties on cell activation as a result of cross-linking the cell-surface receptors Fc ϵ RI and Fc γ RIIb. In a related study Yoshioka et al¹⁷ measured the cell-surface expression of Fc ϵ RI and reported that lipoteichoic acid, a component of the bacterial wall, downregulates this receptor on mast cells through Toll-like receptor (TLR) 2.

Regulatory T cells and atopy

Increasing attention has been given to the role of regulatory T cells in allergic disease. Jartti et al¹⁸ measured peripheral blood CD4⁺CD25⁺ T cells in a cohort of 151 children at age 6 years and found a significantly positive correlation with the spring season compared with the winter season, suggesting that environmental factors might influence the presence of regulatory T cells. Similarly, Hartl et al¹⁹ measured CD4⁺CD25⁺ regulatory cells in peripheral blood and bronchoalveolar lavage fluid of 18 children with asthma and compared the results with those seen in children with only cough or control children. A much higher percentage of these regulatory T cells were found in the bronchoalveolar lavage fluid compared with peripheral blood, and there was a positive correlation with the use of inhaled corticosteroids. Interestingly, CD4⁺CD25⁺ cells isolated from untreated asthmatic patients did not have the capacity to inhibit T_H2 responses. The proportion of Foxp3⁺CD4⁺ cells in total PBMCs in 37 patients with allergic disease and 27 healthy control subjects was analyzed by Orihira et al.²⁰ They found that this cell subset was significantly decreased in the allergic patients and correlated inversely with the total IgE level, eosinophil number, and serum IFN level. Maggi et al²¹ studied specific regulatory T cells to dust mite allergen and demonstrated that they were equally present in both nonatopic and atopic individuals, indicating that caution should be used to state that atopic disease is only caused by deficiency of regulatory T cells.

The hygiene hypothesis

The deficiency of regulatory T cells might not be convincing by itself to explain the hygiene hypothesis, which links the increasing incidence of allergic disorders to decreasing exposure to infections.²² Rother et al²³ studied a cohort of 362 infants and found decreased IgE levels at 3 years of life if the children had attended daycare by 3 months of age. Janson et al²⁴ measured specific IgG titers against 7 common infections in a large cohort in northern Europe and found that individuals with less than 3 specific IgG antibodies against those infections were about 2 times more likely to present with atopic symptoms. Decreased atopic sensitization associated with living in a farm was explored by Debarry et al²⁵ by studying bacteria found in cowsheds. They chose the 2 most abundant bacteria they found, *Acinetobacter lwoffii* and *Lactococcus lactis*, and described their ability to polarize the immune response toward the secretion of T_H1 cytokines in a murine model. Further support for the hygiene hypothesis was obtained with a model of ovalbumin-induced allergic airway inflammation that was reduced with concomitant chronic, but not acute, helminth infection.²⁶ This suppression of an inflammatory response was shown to be IL-10 dependent. IL-13 plays an opposite role, as shown in a

cynomolgus monkey model for eosinophilic lung inflammation induced by sensitization to *Ascaris* species, in which the use of a specific anti-IL-13 mAb reduced this inflammatory response.²⁷

Environmental pollutants and the immune system

Wang et al²⁸ developed an animal model of exposure to tobacco smoke to study cytokines and lymphocyte subsets. They demonstrated an increase of neutrophils and inflammatory cytokines in primates exposed to tobacco smoke compared with those exposed to filtered air. Human CD34⁺-derived DCs exposed *in vitro* to air particulate pollutants induced the expression of the costimulatory molecules CD80, CD86, and CD40 and decreased TLR-2 and TLR-4 expression, similar to the effects of LPS.²⁹ However, the cytokines induced by tobacco smoke had a T_H2 pattern compared with the T_H1 pattern induced by LPS. A possible mechanism for inhibition of T_H1 responses is provided by Kim et al,³⁰ who showed suppression of delayed hypersensitivity responses by glutathione depletion induced by diethyl maleate, an alkylating agent, and inhibited by acetyl cysteine, an antioxidant agent.

Immunomodulatory mechanisms in the lung

Several research articles described immune mechanisms that mediate inflammation in the lung in the pathogenesis of asthma. Gernez et al³¹ showed that the intracellular levels of phosphorylated signal transducer and activator of transcription (STAT) 6 of peripheral CD4⁺CD161⁺ cells are increased in patients with allergic asthma and decreased in those receiving corticosteroids. CD161 is a lectin receptor, a marker of effector T cells, including the invariant natural killer (NK) T cells, which are of particular interest in asthma.³² Using patients with chronic beryllium disease and granulomatous lung inflammation, Palmer et al³³ established that the increased CD57 expression in antigen-specific CD4⁺ T cells obtained from peripheral blood or bronchoalveolar lavage fluid can also be used as a marker of lung inflammation. Consistent with the Koya et al¹ report in mice, Prasse et al³⁴ demonstrated an increase of the IL-10-secreting monocyte population in atopic patients. These monocytes differentiate into activated alveolar macrophages, which expressed high levels of suppressor of cytokine signaling (SOCS) 3 and favor the T_H2 immune response. The role of SOCS3 and other SOCS proteins in allergic inflammation was comprehensively reviewed by Knitz and Rothman,³⁵ explaining their role in the inhibition of STAT proteins and modulation of the cytokine-induced cell activation. Wells et al³⁶ demonstrated that CD8⁺ T cells might have a regulatory role in specific allergic responses by transferring transgenic, ovalbumin-specific, class I- or class II-restricted T cells (CD8⁺ or CD4⁺ T cells, respectively) labeled with fluorescent dye into naive mice. When these mice were sensitized with ovalbumin intranasally, CD4⁺ T cells induced T_H2-like cytokines and allergic inflammation, whereas CD8⁺ T cells divided up to 9 times in response to allergen and also suppressed lung allergic inflammation, with decreased IL-5 and increased IL-12 levels being detected in bronchoalveolar lavage fluid. The role of filaggrin in asthma was elucidated by 2 studies published in the *Journal*. Although Palmer et al³⁷ found that filaggrin null mutations were associated with increased asthma severity in children, Rogers et al³⁸ later made it clear that this association was actually stronger when concomitant atopic dermatitis was considered. Furthermore, Howell et al³⁹ showed that T_H2 cytokines decreased filaggrin expression in patients with atopic dermatitis.

In the search for novel therapies for the control of allergic inflammation, investigators have demonstrated that a nebulized lidocaine analog was able to decrease inflammatory cells in an ovalbumin-induced lung inflammation model and reduce allergen-induced histamine release without the anesthetic or epileptic side effects of intact lidocaine.⁴⁰ Another therapy target found was the expression of CCR8, which is present in T_H2 cells. In a murine model of allergic inflammation induced by fungal sensitization, it was shown that lack of expression of CCR8 leads to early clearance of fungal antigens, increased secretion of IFN and IL-12, and decreased expression of IL-4 and IL-13.⁴¹

CLINICAL IMMUNOLOGY

Drugs and immune responses

Jerch et al⁴² showed broad cross-reactivity of 2 iodinated contrast media, iohexol and iomeprol, when their allergenicity was assessed in 2 individuals by means of immediate and delayed-type hypersensitivity skin test and proliferative responses. Skin prick test responses were negative, but patch test results were positive, suggesting participation of cellular mechanisms in these responses. Wu et al⁴³ generated T-cell clones from 5 patients with anticonvulsant hypersensitivity syndrome and demonstrated secretion of IL-5 and IFN- γ and cytotoxic activities that help explain the clinical manifestations of this syndrome. The effects of the β -agonist isoproterenol and prostaglandin E₂ in peripheral lymphocytes stimulated with IL-2 and with the mAbs anti-CD3 and anti-CD28 were studied by Loza et al.⁴⁴ After 6 days in culture, they found that the proportion of cells expressing IL-13 increased when the cells were exposed to isoproterenol but not when they were exposed to prostaglandin E₂, an effect that was likely mediated by increased survival of cells secreting T_H2 cytokines. A clinically interesting report by Wood et al⁴⁵ described skin test reactions to common vaccines in 20 healthy subjects. They concluded that no reactions should occur with skin prick testing; however, most vaccines tested intradermally and at full strength produced irritant responses.

Hereditary angioedema

Guarino et al⁴⁶ described the detection of different mutations in the gene *C1INH*, which causes hereditary angioedema (HAE), by means of denaturing HPLC after PCR amplification. A family with both male and female members presenting with HAE type III was reported by Martin et al.⁴⁷ This rare HAE type III was previously thought to occur exclusively in women. In a follow-up study the long-term use of stanozolol was summarized by Sloane et al.⁴⁸ Twenty-one patients with HAE benefit from stanozolol therapy up to 2 mg daily for more than 25 years. Treatment-related symptoms, predominantly hirsutism, menstrual cycle disorders, and weight gain, developed in 10 patients, but these were easily controlled with dose reduction. Farkas et al⁴⁹ reported the use of a human C1 inhibitor concentrate therapy for 468 acute attacks in 61 patients with HAE, including 22 children, with efficacy in more than 90% of cases and no reported adverse effects. Based on the advances in the understanding of angioedema pathogenesis involving the activation of kallikrein to generate bradykinin, Schneider et al⁵⁰ conducted a randomized, placebo-controlled trial of 48 patients with HAE to determine the efficacy of ecallantide, a kallikrein inhibitor. The authors found a reduction of HAE attack symptoms in 72.5% of their patients, and the drug was well tolerated.

Mastocytosis

Systemic mastocytosis is characterized by clonal expansion of mast cells, and most patients present with a genetic mutation in the stem cell factor receptor (*KIT*) gene, which confers constitutive activation to the encoding protein. Some of these patients present with eosinophilia and clinical manifestations that might overlap with the hypereosinophilic syndrome. Bohm et al⁵¹ reviewed the cases of 9 patients with systemic mastocytosis and persistent eosinophilia. Seven of them had the typical *KIT* gene mutation, and the other 2 had chronic eosinophilic leukemia and cardiac eosinophilic infiltration. One of these patients presented with the Fip1-like1/platelet-derived growth factor receptor alpha (*FIP1L1/PDGFRα*) fusion gene defect. There was an excess of mortality in all 9 patients with systemic mastocytosis and eosinophilia compared with that seen in those who did not have increased eosinophil counts. The association of mastocytosis and eosinophilia was further studied by Maric et al.⁵² These authors compared 12 patients with systemic mastocytosis and persistent eosinophilia and 17 patients with chronic eosinophilic leukemia and created a clinical score that was effective to distinguish these 2 conditions based on eosinophil count, serum tryptase level, mast cell aggregates in bone marrow, sex, and pulmonary, cardiac, and gastrointestinal symptoms.

Primary immunodeficiencies

More than 40 years after the first clinical description, 2 groups recently described *STAT3* gene mutations to result in the autosomal dominant form of hyper-IgE syndrome (HIES).^{53,54} This finding was preceded by reports improving the immunologic and clinical characterization of this syndrome. Simon and Seger⁵⁵ reported on a patient with HIES with an IL-4-producing T-cell clone comprising more than 25% of his T cells and postulated that in some instances this syndrome might be caused by the expansion of cytokine-producing cells. Freeman et al⁵⁶ reviewed causes of mortality in their cohort of patients with HIES. Prominent among the causes of death was cystic lung disease with pneumonia caused by *Pseudomonas* species and invasive fungal disease, suggesting that intense prophylaxis against gram-negative bacteria and fungal infection might be required for patients with HIES with cystic lung disease.

Other progress in genetic causes of primary immunodeficiencies include a report of a patient with a CD25 expression defect presenting with a clinical picture similar to immune dysregulation, polyendocrinopathy, enteropathy, X-like syndrome⁵⁷; a patient with diagnosis of complete DiGeorge syndrome without a deletion in 22q11 or 10p13.14 but with a genetic defect in the chromodomain helicase DNA-binding 7 (*CHD7*) gene⁵⁸; and a female patient with ectodermal dysplasia and immunodeficiency caused by a genetic mutation in the *IKBA* gene that results in functional nuclear factor κ B haploinsufficiency.⁵⁹ Further insight into NK cell development was provided by a double-transgenic mouse model with disruption of the activating transcription factor 2 (*ATF2*) gene and overexpression of IL-15,⁶⁰ producing accumulation of immature NK cells in the bone marrow and the periphery, similar to reports of patients with chronic NK cell lymphocytosis.

Clinical description of the recently defined IL-1 receptor-associated kinase 4 deficiency was improved with the report of Lavine et al,⁶¹ who described 3 siblings with not only defects in innate immunity but also lymphopenia, absence of response to antigens, and deficiency of antipolysaccharide responses, linking

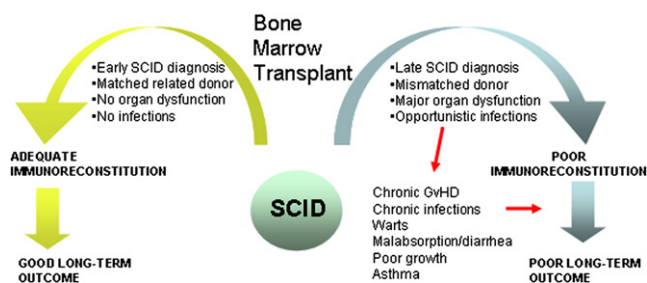


FIG 1. The long-term follow-up of patients with severe combined immunodeficiency (SCID) who received BMT is determined by several variables at the time of treatment: age of diagnosis, degree of donor compatibility, concomitant diseases, and opportunistic infections. *GvHD*, Graft-versus-host disease.

both innate and adaptive immunity. By studying the immune response to vaccinia virus, researchers demonstrated that the increased susceptibility of patients with atopic dermatitis to skin viral infections is associated with decreased expression of β -defensin 3⁶² and macrophage inflammatory protein 3 α .⁶³ Aspalter et al⁶⁴ provided further insight into common variable immunodeficiency (CVID) by showing defective activation of TNF- α receptor II, possibly explaining the T-cell deficiency observed in patients with CVID. Zhang et al⁶⁵ further examined the role of the transmembrane activation and calcium modulation cyclophilin ligand interactor gene (*TACI*) in CVID, noting that many healthy patient relatives who present with a disease-associated mutation in this gene are not susceptible to infections and have a normal *in vitro* B-cell response, questioning the role of *TACI* defects in patients with CVID. However, half of those patients with CVID who had a mutation in *TACI* developed autoimmune cytopenias. The authors concluded that *TACI* mutations might determine the severity of CVID, but they are not solely responsible for the molecular events leading to hypogammaglobulinemia. *TACI* binding might work with CD40 and IL-4 signaling to induce naive B-cell differentiation into plasma cells and increased antibody production, with little effect on B-cell proliferation, as suggested by Castigli et al.⁶⁶ Moschese et al⁶⁷ examined the predictive value of memory B-cell percentage in infancy for discrimination between transient and permanent humoral immunodeficiency. Although there was a statistical difference between groups, there was also significant overlap.

Progress in the treatment of inherited immunodeficiencies with bone marrow transplantation (BMT) was reflected by reports on long-term outcomes. Land et al⁶⁸ described 2 patients with complete DiGeorge syndrome who received BMT and were leading normal lives free of frequent infections 18 and 20 years later. Their T cells were of donor origin and with limited repertoire; however, they were sufficient for adequate T-cell function and humoral responses. The authors also reviewed 7 additional cases published in the literature recently, with only 1 death. This report supports BMT as an alternative for thymus transplantation, for which the number of experts in this procedure are limited. Outcomes of BMT for severe T-cell deficiencies (Fig 1) of 40 patients followed up for at least 5 years in a single center were described by Mazzolari et al.⁶⁹ Most patients showed complete immunoreconstitution, although many had pretransplantation conditions leading to chronic complications after treatment, such as severe viral infections resulting in neurologic damage. Other significant contributions were the report of a successful haploidentical BMT by using myeloablative conditioning in a girl with reticular dysgenesis, a rare type of severe

combined immunodeficiency that has previously been difficult to treat and achieve hematologic engraftment.⁷⁰ The role of maternal T cells acquired transplacentally in 2 patients with severe combined immunodeficiency was reported by Palmer et al.⁷¹ The authors propose that these cells can mediate rejection against paternal cells but might be favorable for maternal cell engraftment.

HIV infection

New clinical investigations continue to improve the diagnosis and treatment of HIV infection. Shearer et al.⁷² analyzed a large cohort of HIV-exposed infants and found that a CD4/CD8 ratio of 1.8 or less at 3 months of age was more sensitive than CD4⁺ T-cell counts to predict HIV infection. This finding has application to resource-poor communities without access to virology laboratories. Pahwa et al.⁷³ investigated the effects of intermittent subcutaneous IL-2 in 12 perinatally HIV-infected children with severe immunosuppression while receiving an effective combination of antiretroviral agents. The response to IL-2 therapy was an increase of CD4⁺ T cells; however, the viral load remained high. The specific IgG response to pneumococcal vaccine in bronchoalveolar lavage fluid and serum was measured in 19 HIV-infected subjects with normal CD4⁺ T cells and in 22 HIV-negative subjects.⁷⁴ All immunized subjects showed adequate specific response to the 4 serotypes tested in both fluids, which confirms previous findings and supports the observed reductions in pneumococcal disease in this population. Fletcher et al.⁷⁵ presented pediatric pharmacokinetic data of a fusion protein bearing the CD4 molecule and the immunoglobulin molecule IgG2. This molecule is designed to neutralize HIV infection and might enter clinical efficacy trials in the near future, possibly in combination with other anti-HIV therapy. Foster et al.⁷⁶ described the immunoreconstitution of CD4⁺ T cells as a risk factor for asthma in HIV-infected children and young adults, a process that might have implications for the understanding of the increase in asthma prevalence in the general population.

CONCLUSIONS

The pulse of research publications in the fields of basic and clinical immunology grew stronger in 2007. Novel findings in the presentation of antigen by antigen-presenting cells and the understanding of IgE formation and function expanded our knowledge of immunologic mechanisms. In the field of clinical immunology, research articles focused on the immune response to drugs, such as iodinated media contrast; management of HAE; mastocytosis; primary immunodeficiencies; and HIV infection. Novel immunologic therapies will continue to be developed based on the discoveries in molecular mechanisms, such as those published in the *Journal* in 2007.

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