REVIEW

Recent advances in primary immunodeficiency: from molecular diagnosis to treatment [version 1; peer review: 3 approved]

Giorgia Bucciol [1,2], Isabelle Meyts [1,2]

[1]Inborn Errors of Immunity, Department of Immunology, Microbiology and Transplantation, KU Leuven, Herestraat 49, Leuven, 3000, Belgium
[2]Childhood Immunology, Department of Pediatrics, University Hospitals Leuven, ERN-RITA Core Member, Herestraat 49, Leuven, 3000, Belgium

v1 **First published:** 19 Mar 2020, **9**(F1000 Faculty Rev):194 (https://doi.org/10.12688/f1000research.21553.1)
Latest published: 19 Mar 2020, **9**(F1000 Faculty Rev):194 (https://doi.org/10.12688/f1000research.21553.1)

Abstract
The technological advances in diagnostics and therapy of primary immunodeficiency are progressing at a fast pace. This review examines recent developments in the field of inborn errors of immunity, from their definition to their treatment. We will summarize the challenges posed by the growth of next-generation sequencing in the clinical setting, touch briefly on the expansion of the concept of inborn errors of immunity beyond the classic immune system realm, and finally review current developments in targeted therapies, stem cell transplantation, and gene therapy.

Keywords
primary immunodeficiency, inborn error of immunity, next generation sequencing, targeted therapy, hematopoietic stem cell transplantation

Open Peer Review

Reviewer Status ✓ ✓ ✓

	Invited Reviewers		
	1	**2**	**3**
version 1 19 Mar 2020	✓	✓	✓

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1 **Andrew L Snow**, Uniformed Services University of the Health Sciences, Bethesda, USA

2 **Helen C. Su**, National Institutes of Health, Bethesda, USA

3 **Trine H. Mogensen**, Aarhus University, Aarhus, Denmark

Any comments on the article can be found at the end of the article.

Corresponding author: Isabelle Meyts (isabelle.meyts@uzleuven.be)

Author roles: Bucciol G: Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing; **Meyts I**: Data Curation, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: IM is supported by a CSL Behring Chair in Primary Immunodeficiency (paid to institution). GB declares that she has no competing interests.

Grant information: GB is supported by the Research Foundation - Flanders (project G0C8517N). IM is supported by the Jeffrey Modell Foundation, the Research Foundation - Flanders (project G0C8517N), and the CSL Behring Chair in Primary Immunodeficiency in Children.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Bucciol G and Meyts I. **Recent advances in primary immunodeficiency: from molecular diagnosis to treatment [version 1; peer review: 3 approved]** F1000Research 2020, **9**(F1000 Faculty Rev):194 (https://doi.org/10.12688/f1000research.21553.1)

First published: 19 Mar 2020, **9**(F1000 Faculty Rev):194 (https://doi.org/10.12688/f1000research.21553.1)

Introduction

Perhaps more than other medical disciplines, the field of primary immunodeficiency is expanding rapidly thanks to recent advances in sequencing, gene editing tools, and the introduction of new biological drugs and small molecules that target specific checkpoints relevant to immunity, inflammation, and cancer. We have witnessed, first of all, a rapid rise in the number of described monogenic inborn errors of immunity (IEIs), and more than 400 distinct defects were included in the International Union of Immunological Societies (IUIS) classification of 2019[1]. This represents an increase of 200 new genes and diseases in 10 years and reveals a paradigm shift from "primary immunodeficiencies" as fundamental defects in the immune response to infection toward the broader concept of "inborn errors of immunity" as a comprehensive group of different phenotypes, including infection, autoinflammation, autoimmunity, allergy, and malignancy[1,2]. Indeed, a relatively new concept in IEIs is immune dysregulation caused by the innate components of immunity, in juxtaposition with adaptive immunity-driven autoimmunity. Autoinflammatory disorders are caused by an over-activation of pro-inflammatory cytokines or pathways, mostly components of the inflammasomes. They typically manifest as fevers, skin rashes, systemic inflammation, and variable arthritis and lymphadenopathy, although some forms can also present with immunodeficiency and other clinical phenotypes[3]. A subgroup of these disorders is represented by interferonopathies, characterized by constitutively activated type I interferon (IFN) responses[4].

New insight into the pathogenesis of IEIs has introduced targeted treatments next to substitution and symptomatic therapy (immunoglobulin replacement, antimicrobial and anti-inflammatory, or immunosuppressive treatments) on one side and replacement of the flawed immune system by hematopoietic stem cell transplantation (HSCT) or gene therapy on the other[2]. Moreover, the latter have greatly benefited from the new advances in cell and gene manipulation, expanding the number of diseases to be successfully treated and increasing the survival chances of affected individuals[5]. In this review, we focus on some of the most recent advances over the last 3 years in the diagnosis and therapy of human IEIs.

Molecular diagnosis of inborn errors of immunity

Sequencing in general and next-generation sequencing (NGS) techniques in particular are becoming technically more accurate, fast, affordable and therefore widely available to researchers and physicians. Apart from the obvious result of increasing the sheer number of defined IEIs, this rapid expansion has highlighted the phenotypic heterogeneity and genetic pleiotropy of these disorders. On the other hand, many novel IEIs are studied in a single kindred or a small number of kindreds, thus providing little information on the penetrance and phenotype[1]. Moreover, the pathophysiology often remains to be unraveled. For example, heterozygous mutations in cell division cycle 42 (*CDC42*), encoding a small GTP/GDP-binding protein involved in eukaryotic actin cytoskeleton dynamics, cause a wide range of different developmental phenotypes with or without autoinflammation, depending on the affected protein domain[6–12]. Patients with biallelic mutations in lariat debranching enzyme 1 (*DBR1*) have a very rare brainstem viral encephalitis through a defect of cell-intrinsic immunity that is still entirely unexplained[13]. A relevant example of phenotypic heterogeneity is the deficiency of adenosine deaminase 2 (DADA2): originally reported as a small-vessel vasculitis manifesting with polyarteritis nodosa, livedo racemosa, stroke, and mild immunodeficiency, the phenotype has significantly expanded to include pure red cell aplasia, other cytopenias, lymphoproliferation, and lymphoma[14–30].

In at least 10 genes responsible for IEI, both gain-of-function (GOF) and loss-of-function (LOF) mutations have been described, resulting in different biological effects and clinical phenotypes (Table 1)[31–55].

Mutations of signal transducer and activator of transcription 1 (*STAT1*) are exemplary. Biallelic LOF mutations cause either complete or partial STAT1 deficiency: the first impairs type I and II IFN responses and produces a severe phenotype of mycobacterial and viral susceptibility, which invariably is fatal if not corrected by HSCT; the second has a similar but milder presentation[46,47,56–60]. Heterozygous mutations with a dominant-negative LOF effect impair mainly type II IFN signaling and cause mendelian susceptibility to mycobacterial disease (MSMD) and salmonellosis[48,57,61]. Finally, heterozygous *STAT1* GOF mutations affect interleukin-17 (IL-17) immunity and cause autosomal dominant (AD) chronic mucocutaneous candidiasis (CMC), bacterial and viral infections, autoimmunity, and cerebral aneurysms[49,50,57,62]. A similar situation can be seen in defects of caspase recruitment domain family 11 (*CARD11*). Homozygous null mutations in fact cause a profound combined immunodeficiency, heterozygous dominant-negative LOF mutations cause combined immunodeficiency with severe atopic disease, and heterozygous GOF mutations instead cause B-cell expansion with nuclear factor kappa B (NF-κB) and T-cell anergy (BENTA) disease[51–55,63,64]. These examples of additional phenotypes progressively connected to different mutations in the same genes highlight the risk of labeling heterozygous variants as irrelevant to the observed clinical phenotype without functional testing.

With NGS methods routinely available for diagnosis and with a shift from the fixed gene panel and whole exome sequencing (WES) toward whole genome sequencing (WGS), we also learned that deep intronic variants can be disease-causing[65,66]. For example, various deep intronic mutations in *UNC13D*, underlying familial hemophagocytic lymphohistiocytosis (HLH), are very commonly found in patients of European, North American, or Asian origin[67–71]. Similarly, intronic mutations were found in a number of IEI-causing genes: in *IL7R* and Janus kinase 3 (*JAK3*) in patients with severe combined immunodeficiency (SCID); in *ZAP70*, encoding the zeta chain-associated protein kinase, in a child with severe T-cell immunodeficiency; in *STAT3* in a patient with hyper IgE syndrome; in the NF-κB essential modulator (*NEMO*) in two patients with ectodermal dysplasia and immunodeficiency (EDA-ID); in *POLA1*, encoding DNA polymerase α, in

Table 1. PID genes in which GOF and LOF mutations have been described.

Protein	Gene	OMIM n. disease	Inheritance	Immunological phenotype	Infectious phenotype	Non-infectious phenotype	Autoinflammation	Therapy
STAT1	*STAT1*	613796	AR Complete/partial LOF	Deficient intracellular pathogen killing by monocytes and T cells; impaired IFN type I response to viral infections	Lethal viral diseases and susceptibility to mycobacterial infection	N/A	No	N/A
		614892	AD Dominant-negative LOF	Deficient intracellular pathogen killing by monocytes and T cells	Mendelian susceptibility to mycobacterial disease	N/A	No	IFN-γ
		614162	AD GOF	Low Th17 proportions ± low memory B cells	Chronic mucocutaneous candidiasis, bacterial and viral infections, invasive fungal infections, mycobacterial disease	Intracranial aneurysms, autoimmunity, enteropathy, bronchiectasis	Yes	JAK inhibitor (ruxolitinib) HSCT
CARD11	*CARD11*	615206	AR LOF	Defective NF-κB signaling with B- and T-cell functional impairment, hypogammaglobulinemia	*Pneumocystis jirovecii* pneumonia	N/A	No	HSCT
		617638	AD Dominant-negative LOF	Defects in T-cell activation, increased IgE, and eosinophilia	Recurrent or severe infections, including pneumonia, molluscum, abscesses, and bacteremia	Moderate to severe atopic dermatitis, asthma, allergies, ulcerative colitis, T-cell lymphoma	No	N/A
		616452	AD GOF	B-cell expansion with NF-κB and T-cell anergy (BENTA), decreased T-cell proliferative responses and vaccine responses	Recurrent upper respiratory infections	Splenomegaly, lymphadenopathy, autoimmunity, chronic lymphocytic leukemia	No	N/A
WASP	*WAS*	301000	X-linked recessive LOF	Lymphopenia, hypogammaglobulinemia, eosinophilia, decreased vaccine responses	Recurrent bacterial infections, molluscum	Microthrombocytopenia, eczema, autoimmunity, hematological malignancies, inflammatory bowel disease	Yes	HSCT, gene therapy
		300299	X-linked recessive GOF	Severe congenital neutropenia, monocytopenia, natural killer cell deficiency, increased $CD8^+$ T cells	Severe bacterial infections	N/A	No	Granulocyte-colony-stimulating factor
MDA5	*IFIH1*	-	AR/AD LOF	Respiratory epithelial cells and fibroblasts	Rhinovirus and other respiratory viral infections	N/A	No	N/A
		615846	GOF	Aicardi–Goutieres syndrome: type I interferonopathy	Not reported	Pseudo-TORCH syndrome: basal ganglia calcification, microcephaly, developmental delay, spasticity, autoimmunity	Yes	JAK inhibitor (ruxolitinib)

F1000Research 2020, 9(F1000 Faculty Rev):194 Last updated: 19 MAR 2020

Protein	Gene	OMIM n. disease	Inheritance	Immunological phenotype	Infectious phenotype	Non-infectious phenotype	Autoinflammation	Therapy
STAT3	*STAT3*	147060	AD Dominant-negative LOF	Hyper IgE syndrome, eosinophilia, T-cell defect with Th17 deficiency, decreased vaccine responses	Recurrent Staphylococcal infections, fungal infections,	Coarse facial appearance, abnormal dentition, hyperextensibility of the joints, and bone fractures	No	HSCT?
		615952	AD GOF	T-cell lymphopenia, hypogammaglobulinemia, increased double-negative T cells	Recurrent infections, including fungal infections	Autoimmunity, dermatitis, arthritis, interstitial lung disease, short stature, lymphadenopathy, splenomegaly	Yes	HSCT?
STAT2	*STAT2*	616636	AR LOF	Defective type I IFN-STAT signaling	Increased susceptibility to viral infections and to disseminated disease after live vaccines (measles)	Defect of mitochondrial fission and fusion	No	N/A
		-	AR GOF	Type I interferonopathy	Not reported	Severe early-onset autoinflammation	Yes	N/A (possibly JAK inhibitor)
Complement factor B	*CFB*	615561	AR LOF	Inactive alternative complement pathway	Infections with encapsulated bacteria	N/A	No	Vaccination, prophylactic antibiotics
		612924	AD GOF	Decreased C3 and increased C3b	Not reported	Atypical hemolytic uremic syndrome	No	N/A
C3	*C3*	613779	AR LOF	C3 deficiency	Recurrent bacterial infections, mainly by Gram-negative bacteria	Immune complex-mediated autoimmune disease, glomerulonephritis	No	N/A
		612925	AD GOF/LOF	None	Not reported	Atypical hemolytic uremic syndrome	No	N/A
JAK1	*JAK1*	-	AR LOF	Progressive T-cell lymphopenia, increased IgG	Mendelian susceptibility to mycobacterial disease, warts, parasitic and fungal infections	Early-onset bladder carcinoma	No	N/A
		-	AD GOF	Eosinophilia	Not reported	Hepatosplenomegaly, liver cysts, severe atopic dermatitis, allergy, autoimmunity, failure to thrive	No	JAK inhibitor (ruxolitinib)
ZAP70	*ZAP70*	269840	AR LOF	Selective T-cell defect with $CD8^+$ deficiency and $CD4^+$ impairment	Severe combined immunodeficiency phenotype: bacterial, viral and opportunistic infections	N/A	No	HSCT
		617006	AR LOF + GOF	Mild T- and B-cell lymphopenia, reduced $CD8^+$ T cells, decreased T-cell proliferative responses	Not reported	Bullous pemphigoid, inflammatory bowel disease, autoimmunity	Yes	HSCT

AD, autosomal dominant; AR, autosomal recessive; GOF, gain of function; HSCT, hematopoietic stem cell transplantation; IFN, interferon; JAK, Janus kinase; LOF, loss of function; N/A, not available/not applicable; NF-κB, nuclear factor kappa B; STAT, signal transducer and activator of transcription; Th, T helper; TORCH, toxoplasmosis, rubella, cytomegalovirus, herpes.

F1000Research 2020, 9(F1000 Faculty Rev):194 Last updated: 19 MAR 2020

patients with X-linked recessive reticulate pigmentary disorder (XLPDR); in *CYBB*, encoding p91-PHOX, in patients with chronic granulomatous disease (CGD); in *ATM* in patients with ataxia-telangiectasia; and in *CD40LG* in patients with hyper IgM syndrome[72–85]. RNA sequencing can be an invaluable tool in the validation of these deep intronic variants but also of synonymous and splice-site variants[75,76,86,87]. In particular, it can highlight the partial or complete loss of gene expression in the proband compared with controls, which would be missed by traditional sequencing. The increase in diagnostic rate of rare diseases obtained by WGS versus WES can be as high as 6 to 11%, and the use of tissue-specific RNA sequencing can aid the diagnostic process and help clarify the pathophysiology of the disease[86,87]. Interestingly, in the case of monogenic rare diseases, RNA sequencing as the first molecular approach led to a diagnosis in 7 to 17% of cases[87]. No hematological/immunological disorders were among those successfully diagnosed in this cohort, which consisted mostly of patients affected by neuromuscular disorders. A lower success rate in IEIs could also be a reflection of the difficulty of comparing normal controls with patients with significant blood cell abnormalities.

The benefit of diagnostic NGS comes at a cost: the necessity of unequivocal functional validation of new variants, albeit in known IEI-related genes. Still too often the pathogenicity of a given variant is based only on the available *in silico* prediction tools, which can be misleading. Indeed, the validation of variants of unknown significance represents one of the biggest hurdles in making WES and NGS technologies the norm in clinical practice. This is because of not only the financial cost but also the time and competence required first to analyze and study a variant and afterwards to interpret the results and translate them into clinical treatment and care. More than anything, this calls for collaboration and sharing of data for the benefit of the patients. With limited research resources, the further development of more robust prediction tools/validation models becomes a necessity. Finally, as physician-scientists, we wish to stress the importance of the clinical phenotype as a beacon in the era of so-called unbiased sequencing approaches.

Inborn errors of immunity in other diseases

As previously mentioned, the concept of what constitutes an immunodeficiency is steadily shifting from a focus on defects of hematopoietic immune system components, such as leukocytes and immunoglobulins, to conditions affecting immunity at the organism level[88]. Classic examples are cystic fibrosis and sickle cell disease: the first is a chloride channel defect with primarily pulmonary and digestive manifestations, the second is a red blood cell disease caused by mutations in the β-globin gene, and both have recurrent and life-threatening infections as major symptoms (secondary to functional asplenia in the case of sickle cell disease)[88–93]. All cells and tissues exert essential host defense functions that range from physical and chemical barriers to pathogen sensing, cytokine production, and protein secretion and activation of the immune response upon infection, representing cell-intrinsic immunity. Infection and inflammation in fact can arise in several disorders of organs other than the classic hematopoietic immune system. The importance of these cell-specific immune responses is apparent when we consider those IEI characterized by the involvement of a single non-hematopoietic tissue, such as the central nervous system (CNS)-specific lack of resistance against herpesviruses in case of mutations of the Toll-like receptor 3/IFN pathway, or the keratinocyte-restricted susceptibility to beta-papillomavirus infections in epidermodysplasia verruciformis (due to null mutations in transmembrane channel-like protein 6 [*TMC6*], *TMC8* [encoding EVER1 and EVER2, respectively], or *CIB1*, encoding calcium- and integrin-binding protein 1)[94–104]. More generally, inherited defects of the skin or mucosal barriers cause at the very least a detrimental secondary effect on immune protection, as well exemplified by genodermatoses and inflammatory bowel diseases.

Several defects of the skin barrier frequently cause secondary infection of the affected epithelia and can also present with additional features resembling known IEIs[105], such as Netherton syndrome (caused by autosomal recessive [AR] defects in *SPINK5*), hyper IgE syndrome (caused by defects in *STAT3*, *DOCK8*, *IL6ST*, *ZNF341*, or phosphoglucomutase 3 [*PGM3*]), or immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome (caused by X-linked *FOXP3* defects). Defects in desmoglein 1 (DSG1) or desmoplakin (DSP), structural desmosomal proteins, cause severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome, a severe multisystemic disease resembling IPEX syndrome at least clinically[106,107]. Recent reports have highlighted the complex clinical and immunological phenotype of this disease, including recurrent sepsis and mucocutaneous HSV-1 infection in a patient and T helper 1 (Th1)/Th17/IL-23 skewing in the skin and Th17/IL-22 skewing in the blood of another patient, which merit further research[108–110].

The immunological effects of glycosylation defects and metabolic diseases have also recently gained interest in the IEI field. Glycosylation is crucial in many mechanisms of the immune response, such as pathogen recognition and cell–cell interaction, and glycoimmunology is a rapidly expanding field of research[111–119]. Among the currently known congenital disorders of glycosylation (CDGs) (around 133 heterogenous diseases), 23 show a relevant degree of immune impairment; in 10 of these, immunodeficiency is a prominent trait of the disease[118]. Two of these CDGs manifest as severe congenital neutropenia caused by defects in Jagunal homolog 1 (*JAGN1*) and glucose-6-phosphatase catalytic 3 (*G6PC3*), one is a leukocyte adhesion deficiency type II due to defects in solute carrier family 35 member C1 (*SLC35C1*), one is a glycogen storage disease type I with neutropenia or neutrophil dysfunction (or both) caused by defects in *SLC37A4*, and the others show various degrees of lymphocyte and immunoglobulin impairment[118,120–125]. Additionally, AR *PGM3* mutations cause glycosylation defects that lead to atopy, immune deficiency with hyper IgE, autoimmunity, and neurocognitive impairment[126]. Finally, a recent study highlighted the role of impaired glycosylation in the pathogenesis of X-linked immunodeficiency with magnesium defect, Epstein–Barr virus (EBV) infection, and neoplasia (XMEN) disease, caused by hemizygous

LOF mutations in the magnesium transporter 1 (*MAGT1*) gene[127,128]. On the other side, the study of differentially glycosylated antibodies and their diverse antigen reactivity will teach us more about the fine tuning of the immune responses by glycosylation[129].

Targeted therapies for inborn errors of immunity

Recent developments in molecular studies have allowed the identification of several possible targets for specific therapeutic interventions. Targeted therapies comprise monoclonal antibodies (mAbs) and small molecules, such as cytokines or cytokine inhibitors, employed to up- or down-regulate a particular pathway, depending on the need. They can be used instead of or in combination with traditional immunosuppressant/immunomodulating agents, also as a bridge to definitive treatment, such as HSCT or gene therapy. Well-known targeted therapies are rituximab (anti-CD20) to treat autoimmune and lymphoproliferative manifestations; enzyme replacement therapy with pegylated bovine adenosine deaminase (ADA) to treat ADA-SCID; IFN-γ to increase superoxide production in the monocytes/macrophages of patients with CGD and to enhance anti-mycobacterial immunity in patients with defects of the IFN-γ/IL-12R pathway; anti-tumor necrosis factor alpha (anti-TNFα) to treat defects of the immunoproteasome causing an autoinflammatory syndrome; IL-1 signal antagonists to treat inflammasome disorders; and finally mechanistic target of rapamycin (mTOR) inhibitors to control aberrant proliferation of effector T cells in various immune dysregulation disorders, such as in IPEX, or to downregulate increased mTOR signaling, such as in activated phosphoinositide 3-kinase δ (PI3Kδ) syndrome (APDS, or PASLI)[130–136].

The latest molecular defects to be targeted in the context of IEI therapy are *PI3Kδ* activating mutations, cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*) haploinsufficiency and the closely related lipopolysaccharide (LPS)-responsive beige-like anchor (*LRBA*) deficiency, *STAT1* GOF mutations, *STAT3* GOF mutations, IFN-γ activation in the context of HLH, and activating defects in NLR family CARD domain-containing 4 (*NCLR4*).

Selective inhibitors of PI3Kδ

Patients with APDS present with recurrent respiratory tract infections, herpesvirus infections, lymphoproliferation, autoimmunity and a characteristic immunophenotype with impaired class-switch recombination, hypogammaglobulinemia, T-cell hyperactivation, and senescence with loss of naïve T cells and predominance of $CD8^+$ cells[136–142]. Two selective PI3Kδ inhibitors have been tested on patients with APDS: Leniolisib, a potent oral inhibitor of the p110δ subunit of PI3Kδ (ClinicalTrials.gov Identifier: NCT02435173), has shown significant effects on general well-being, lymphoproliferation, and immunological markers, such as normalization of B-cell subsets, reduction of senescent T cells, and reduction of IgM and of inflammatory cytokines[143,144]. Nemiralisib, an inhaled PI3Kδ inhibitor (ClinicalTrials.gov Identifier: NCT02593539), could benefit patients primarily affected by airway infection and bronchiectasis and is being trialed in patients with APDS[145].

CTLA4-IgG fusion proteins

CTLA4 haploinsufficiency causes impaired T-cell suppressor function, $CD4^+$ T-cell deficiency, progressive loss of B cells, and increase in autoreactive B cells. Clinical manifestations are recurrent sinopulmonary and viral infections, severe autoimmunity with cytopenia, lymphocytic interstitial lung disease, enteropathy, colitis, and lymphoproliferation with lymphocytic infiltration of solid organs, such as the brain and endocrine glands[146–148]. Although the pathophysiology of LRBA deficiency is still incompletely elucidated, LRBA acts a chaperone protein for CTLA4 to allow its recycling in endosomes. LRBA deficiency causes increased degradation of CTLA4 and a combined immunodeficiency disorder with hypogammaglobulinemia, infections, and severe autoimmune features, including cytopenias, enteropathy, lymphoproliferation, hepatitis, diabetes, polyarthritis, and alopecia[149–151]. CTLA4-IgG fusion proteins abatacept and belatacept have demonstrated significant results in restoring the impaired checkpoint balance and reducing symptoms in CTLA4- and LRBA-deficient patients. In particular, they could restore regulatory T (Treg) cell function and halt or (partially) resolve autoimmune, lymphoproliferative, and inflammatory symptoms, including interstitial lung disease, enteropathy, cytopenias, and other autoimmune manifestations[148,152–154].

JAK/STAT inhibitors (Jakinibs)

GOF mutations in *STAT1* cause CMC, bacterial and viral infections, autoimmunity, immune dysregulation, and a higher risk of cerebral aneurysms and vasculopathy[49,50,62]. STAT1 is a signal transducer downstream from type I and II IFN receptors and other cytokine receptors, such as IL-21R and IL-2R. GOF defects in *STAT3* cause a severe autoimmune syndrome with growth impairment, lymphoproliferation, and inflammatory features[33,155,156]. STAT3 also signals downstream from type I, II, and III IFN receptors, IL-10R, IL-23R, and IL-6R. These receptors activate STAT1 and STAT3 through JAK proteins (JAK1, JAK2, and JAK3), thus initiating the transcription of several factors relevant to the immune response, cell proliferation, differentiation, and survival. Jakinibs are small molecules that inhibit the signal transduction through JAK proteins: tofacitinib preferentially inhibits JAK1 and JAK3, ruxolitinib and baricitinib inhibit JAK1 and JAK2, and many other Jakinibs with different JAK specificity were recently discovered[157,158]. Ruxolitinib and tofacitinib have been used in patients with STAT1 or STAT3 GOF mutations, mostly with significant clinical improvement on fungal infections, autoimmune manifestations, and lymphoproliferation[159–164]. Selective inhibition of IL-6R with tocilizumab is also a valid targeted therapy in STAT3 GOF defects, especially when combined with Jakinibs[155,159].

Anti-IFN-γ mAb

HLH is a disease characterized by hyperinflammation and immune dysregulation and is fatal if not treated. It can be primary, owing to defects of cytotoxic T cells, natural killer (NK) cells, or genes required for EBV control and clearance, or secondary, owing to an exaggerated response to viral infections, malignancies, or rheumatologic disorders. Its

manifestations are fever, systemic inflammation, splenomegaly, cytopenias, and hemophagocytosis in the bone marrow, with or without CNS involvement. Isolated CNS forms have also been described[165]. Classic treatment targets the life-threatening inflammation and includes steroid therapy, chemotherapy (etoposide and intrathecal methotrexate), and HSCT[166,167]. Anti-CD52 mAb alemtuzumab has been proven effective as salvage therapy of refractory HLH[168]. Emapalumab is a recently developed mAb against IFN-γ and has been tested for treatment of HLH. An international phase II/III trial (ClinicalTrials.gov Identifier: NCT01818492) showed a good safety profile and efficacy, an overall response rate of 65%, and a complete response in 26% of cases[169,170]. However, caution is warranted as the number of patients who have received treatment is still very small and the concomitant therapies were significant.

Future applications

Treatment with Jakinibs could benefit other disorders characterized by inflammation and hyperactivation of the IFN pathways, such as interferonopathies, stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy, and HLH[171–173]. Ruxolitinib was recently used in two patients with HLH: both showed a decrease of inflammatory markers, but only one recovered from cytopenias and survived long enough to receive HSCT[174,175]. A phase I trial evaluating ruxolitinib for patients with HLH is now recruiting (ClinicalTrials.gov Identifier: NCT02400463).

Recent advances in hematopoietic stem cell transplantation and gene therapy

Since they are largely due to intrinsic defects of hematopoietic cells or their descendant, the mature blood cells, HSCT represents the treatment of choice for many IEIs. Thanks to better and faster molecular diagnosis, improvement in conditioning practices, better donor selection and graft manipulation, and development of more successful supportive therapies to guarantee engraftment while fending off infections and graft-versus-host disease (GvHD), the overall survival of immunodeficient patients after HSCT has steadily improved up to over 80%[176–179]. What then are the challenges and future perspectives in this field?

Newborn screening and hematopoietic stem cell transplantation

Newborn screening has changed the landscape of HSCT for SCID because early diagnosis allows early transplantation with a smaller burden of infection. Based on a T-cell receptor excision circle assay performed on the dried blood spots taken after birth for the other newborn screenings, it has been extensively (though not uniformly) adopted in Europe and the US in the last decade[180,181]. It allows the identification of T-cell development disorders that affect the diversity of T-cell receptor recombination, namely SCIDs. Although there is no consensus about the influence of the diagnostic method on overall survival, HSCT before the age of 3.5 months is associated with fewer infectious complications and higher survival, and event-free survival is better for children identified by newborn screening if uninfected at the time of transplant[182–184]. Indeed, the current challenge lies in protecting SCID babies identified by newborn screening from infection prior to transplantation. Early diagnosis of SCID also poses therapeutic dilemmas: while owing to the high risk of infections delaying HSCT is not recommended, there are no data on long-term neurotoxicity of conditioning regimens in young infants. Moreover, the genetic diagnosis may not be available in time to adapt the transplantation plan accordingly, and patients with radiosensitive SCIDs such as Artemis or DNA ligase IV deficiency could experience severe early toxicity and long-term sequelae after standard conditioning since chemotherapy causes DNA breakages in non-hematopoietic cells and tissues.

Conditioning

Although the level of chimerism needed to correct IEIs is not precisely defined, most IEIs do not require full donor chimerism, explaining why modified myeloablative and reduced intensity conditioning has become the practice of choice in many centers to reduce acute and long-term toxicity[185]. A promising line of research is represented by targeted antibody-based conditioning strategies, which are probably going to replace chemotherapy-based regimens in the near future[186]. These therapeutic agents work by selectively targeting bone marrow cells and leukocytes for apoptosis, either by disrupting the physiological cell proliferation/cell death cycle or by delivering a radioisotope or a drug toxic to the cell. CD45 (or common leukocyte antigen) is selectively expressed on hematopoietic cells. Rat anti-CD45 mAbs were used together with anti-CD52 (alemtuzumab) and cyclophosphamide in a small group of patients with IEIs and pre-existing organ toxicity with good outcome[187]. Further trials of radioisotope-labeled anti-CD45 mAb are ongoing in patients with myeloid disorders (ClinicalTrials.gov Identifiers: NCT00119366 and NCT01300572), and antibody–drug conjugates have shown promising results in several animal models[188–192]. Similarly, a mAb against CD117 (or c-Kit), necessary for survival, proliferation, and differentiation of hematopoietic stem cells and early progenitors, has demonstrated good preclinical results in animal models and is being tested in patients with SCID (ClinicalTrials.gov Identifier: NCT02963064)[193–195].

Gene therapy

Hematopoietic stem cells are the perfect candidate for genetic manipulation. Indeed, gene therapy has been applied to the treatment of blood-specific disorders, including IEIs, for at least three decades[196]. The first attempts at gene therapy in the field of IEIs began in the ’90s and targeted ADA-SCID and X-SCID, caused by defects in the common gamma chain of IL-2 receptor, and subsequently chronic granulomatous disease and Wiskott–Aldrich syndrome[196–202]. The technique is based on autologous stem cell infusion after *in vitro* correction of the molecular defect by gene addition, eliminating the risk of GvHD and making it an appealing alternative to HSCT. The original trials were successful in terms of genetic defect correction and clinical benefit, but the gamma-retroviral vectors in use were associated with leukemia or monoclonal expansion, except in the case of ADA-SCID[196,197,203–206]. These serious adverse events seem to have been overcome by the introduction of safer

self-inactivating lentiviral vectors, and new studies are under way for a number of IEIs, including RAG-SCID, X-linked lymphoproliferative syndrome, and perforin deficiency[197]. Whereas the earlier trials were based on gene addition (that is, the introduction by means of a viral vector of the wild-type gene in the host genome), recent approaches have investigated gene editing as a way to correct a molecular defect *in situ*. CRISPR/Cas9 has become a particularly trending method, especially if paired with the delivery of a donor template (the wild-type cDNA of the gene of interest) via a viral vector that integrates after the natural promotor of the gene to maintain physiological expression and regulation. At the moment, transfection efficiency is still lower with gene editing methods than with gene addition via lentiviral transduction, mainly due to high cell mortality during transfection procedures, and on-target and off-target side effects must be better understood[196,197]. This technique is in a preclinical stage or phase I/II trials in several IEIs, including X-linked SCID, hyper IgM syndrome, CGD, and X-linked agammaglobulinemia, and looks very promising in the context of GOF mutations[196,197,207–211]. Moreover, so-called T-cell gene therapy is being studied for the correction of T cell–intrinsic defects with encouraging results, and trials are under way for IPEX, hyper IgM syndrome, X-linked lymphoproliferative disease, Munc 13-4 deficiency, and perforin deficiency[207,212–216]. Still at a preclinical phase is base editing, a new development in gene editing techniques that would allow the correction of single point mutations without requiring the DNA cleaving step[217,218]. Future studies will need to clarify what the best positioning of gene therapy approaches versus HSCT versus conservative therapy is.

Conclusions

In this review, we have tried to provide a timely overview of recent advances in the diagnosis and treatment of primary immunodeficiencies/IEIs. With rapidly evolving molecular techniques as the leading force, the end of progress is not yet in sight. Indeed, it can be expected that we are on the verge of a further breakthrough of knowledge in primary immunodeficiency.

Challenges will lie in making these treatments and diagnostics tools available to as many patients as possible and to tailor them to specific needs. Undoubtedly, primary immunodeficiencies/IEIs as experiments of nature will continue to teach us about the magnificent and still-underestimated complexity of the human immune system.

Abbreviations

AD, autosomal dominant; ADA, adenosine deaminase; APDS, activated phosphoinositide 3-kinase δ syndrome; AR, autosomal recessive; CARD11, caspase recruitment domain family 11; CDG, congenital disorder of glycosylation; CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; CNS, central nervous system; CTLA4, cytotoxic T lymphocyte-associated antigen 4; DOCK8, dedicator of cytokinesis 8; EBV, Epstein–Barr virus; FOXP3, forkhead box P3; GOF, gain of function; GvHD, graft-versus-host disease; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; IEI, inborn error of immunity; IFN, interferon; IL, interleukin; IL6ST, interleukin 6 signal transducer; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked; JAK, Janus kinase; LOF, loss of function; LRBA, lipopolysaccharide-responsive beige-like anchor; mAb, monoclonal antibody; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa B; NGS, next-generation sequencing; PGM3, phosphoglucomutase 3; PI3Kδ, phosphoinositide 3-kinase δ; SCID, severe combined immunodeficiency; SLC37A4, solute carrier family 37 member A4; SPINK5, serine protease inhibitor Kazal type 5; STAT, signal transducer and activator of transcription; Th, T helper; TMC, transmembrane channel-like protein; WES, whole exome sequencing; WGS, whole genome sequencing; ZNF341, zinc finger 341

References

F1000 recommended

1. F Tangye SG, Al-Herz W, Bousfiha A, *et al.*: **Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee.** *J Clin Immunol.* 2020.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

2. Delmonte O, Notarangelo L: **Targeted Therapy with Biologicals and Small Molecules in Primary Immunodeficiencies.** *Med Princ Pract.* 2020; **29**(2): 101–112.
PubMed Abstract | Publisher Full Text

3. Martinez-Quiles N, Goldbach-Mansky R: **Updates on autoinflammatory diseases.** *Curr Opin Immunol.* 2018; **55**: 97–105.
PubMed Abstract | Publisher Full Text

4. Rodero MP, Crow YJ: **Type I interferon-mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview.** *J Exp Med.* 2016; **213**(12): 2527–38.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Castagnoli R, Delmonte OM, Calzoni E, *et al.*: **Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency Diseases: Current Status and Future Perspectives.** *Front Pediatr.* 2019; **7**: 295.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Takenouchi T, Kosaki R, Niizuma T, *et al.*: **Macrothrombocytopenia and developmental delay with a *de novo CDC42* mutation: Yet another locus for thrombocytopenia and developmental delay.** *Am J Med Genet A.* 2015; **167A**(11): 2822–5.
PubMed Abstract | Publisher Full Text

7. Takenouchi T, Okamoto N, Ida S, *et al.*: **Further evidence of a mutation in *CDC42* as a cause of a recognizable syndromic form of thrombocytopenia.** *Am J Med Genet A.* 2016; **170A**(4): 852–5.
PubMed Abstract | Publisher Full Text

8. Motokawa M, Watanabe S, Nakatomi A, *et al.*: **A hot-spot mutation in *CDC42* (p.Tyr64Cys) and novel phenotypes in the third patient with Takenouchi-Kosaki syndrome.** *J Hum Genet.* 2018; **63**(3): 387–90.
PubMed Abstract | Publisher Full Text

9. Gernez Y, de Jesus AA, Alsaleem H, *et al.*: **Severe autoinflammation in 4 patients with C-terminal variants in cell division control protein 42 homolog (*CDC42*) successfully treated with IL-1β inhibition.** *J Allergy Clin Immunol.* 2019; **144**(4): 1122–1125.e6.
PubMed Abstract | Publisher Full Text

10. Lam MT, Coppola S, Krumbach OHF, *et al.*: **A novel disorder involving dyshematopoiesis, inflammation, and HLH due to aberrant CDC42 function.** *J Exp Med.* 2019; **216**(12): 2778–99.
PubMed Abstract | Publisher Full Text | Free Full Text

11. F Martinelli S, Krumbach OHF, Pantaleoni F, *et al.*: **Functional Dysregulation of CDC42 Causes Diverse Developmental Phenotypes.** *Am J Hum Genet.* 2018;

102(2): 309–20.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

12. Uehara T, Suzuki H, Okamoto N, *et al.*: **Pathogenetic basis of Takenouchi-Kosaki syndrome: Electron microscopy study using platelets in patients and functional studies in a Caenorhabditis elegans model.** *Sci Rep.* 2019; **9**(1): 4418.
PubMed Abstract | Publisher Full Text | Free Full Text

13. F Zhang SY, Clark NE, Freije CA, *et al.*: **Inborn Errors of RNA Lariat Metabolism in Humans with Brainstem Viral Infection.** *Cell.* 2018; **172**(5): 952–965.e18.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

14. F Zhou Q, Yang D, Ombrello AK, *et al.*: **Early-onset stroke and vasculopathy associated with mutations in ADA2.** *N Engl J Med.* 2014; **370**(10): 911–20.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

15. F Navon Elkan P, Pierce SB, Segel R, *et al.*: **Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy.** *N Engl J Med.* 2014; **370**(10): 921–31.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

16. Hashem H, Kelly SJ, Ganson NJ, *et al.*: **Deficiency of Adenosine Deaminase 2 (DADA2), an Inherited Cause of Polyarteritis Nodosa and a Mimic of Other Systemic Rheumatologic Disorders.** *Curr Rheumatol Rep.* 2017; **19**(11): 70.
PubMed Abstract | Publisher Full Text

17. Nanthapisal S, Murphy C, Omoyinmi E, *et al.*: **Deficiency of Adenosine Deaminase Type 2: A Description of Phenotype and Genotype in Fifteen Cases.** *Arthritis Rheumatol.* 2016; **68**(9): 2314–22.
PubMed Abstract | Publisher Full Text

18. Caorsi R, Penco F, Grossi A, *et al.*: **ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study.** *Ann Rheum Dis.* 2017; **76**(10): 1648–56.
PubMed Abstract | Publisher Full Text

19. Skrabl-Baumgartner A, Plecko B, Schmidt WM, *et al.*: **Autoimmune phenotype with type I interferon signature in two brothers with ADA2 deficiency carrying a novel CECR1 mutation.** *Pediatr Rheumatol Online J.* 2017; **15**(1): 67.
PubMed Abstract | Publisher Full Text | Free Full Text

20. Nihira H, Nakagawa K, Izawa K, *et al.*: **Fever of unknown origin with rashes in early infancy is indicative of adenosine deaminase type 2 deficiency.** *Scand J Rheumatol.* 2017; **47**(2): 170–2.
PubMed Abstract | Publisher Full Text

21. Keer N, Hershfield M, Caskey T, *et al.*: **Novel compound heterozygous variants in CECR1 gene associated with childhood onset polyarteritis nodosa and deficiency of ADA2.** *Rheumatology (Oxford).* 2016; **55**(8): 1145–7.
PubMed Abstract | Publisher Full Text

22. Hashem H, Egler R, Dalal J: **Refractory Pure Red Cell Aplasia Manifesting as Deficiency of Adenosine Deaminase 2.** *J Pediatr Hematol Oncol.* 2017; **39**(5): e293–e296.
PubMed Abstract | Publisher Full Text

23. Alsultan A, Basher E, Alqanatish J, *et al.*: **Deficiency of ADA2 mimicking autoimmune lymphoproliferative syndrome in the absence of livedo reticularis and vasculitis.** *Pediatr Blood Cancer.* 2018; **65**(4).
PubMed Abstract | Publisher Full Text

24. Trotta L, Martelius T, Siitonen T, *et al.*: **ADA2 deficiency: Clonal lymphoproliferation in a subset of patients.** *J Allergy Clin Immunol.* 2018; **141**(4): 1534–1537.e8.
PubMed Abstract | Publisher Full Text

25. Michniacki TF, Hannibal M, Ross CW, *et al.*: **Hematologic Manifestations of Deficiency of Adenosine Deaminase 2 (DADA2) and Response to Tumor Necrosis Factor Inhibition in DADA2-Associated Bone Marrow Failure.** *J Clin Immunol.* 2018; **38**(2): 166–73.
PubMed Abstract | Publisher Full Text

26. Cipe FE, Aydogmus C, Serwas NK, *et al.*: **Novel Mutation in *CECR1* Leads to Deficiency of ADA2 with Associated Neutropenia.** *J Clin Immunol.* 2018; **38**(3): 273–7.
PubMed Abstract | Publisher Full Text

27. Hsu AP, West RR, Calvo KR, *et al.*: **Adenosine deaminase type 2 deficiency masquerading as GATA2 deficiency: Successful hematopoietic stem cell transplantation.** *J Allergy Clin Immunol.* 2016; **138**(2): 628–630.e2.
PubMed Abstract | Publisher Full Text | Free Full Text

28. Elbracht M, Mull M, Wagner N, *et al.*: **Stroke as Initial Manifestation of Adenosine Deaminase 2 Deficiency.** *Neuropediatrics.* 2017; **48**(2): 111–4.
PubMed Abstract | Publisher Full Text

29. Meyts I, Aksentijevich I: **Deficiency of Adenosine Deaminase 2 (DADA2): Updates on the Phenotype, Genetics, Pathogenesis, and Treatment.** *J Clin Immunol.* 2018; **38**(5): 569–78.
PubMed Abstract | Publisher Full Text | Free Full Text

30. Moens L, Hershfield M, Arts K, *et al.*: **Human adenosine deaminase 2 deficiency: A multi-faceted inborn error of immunity.** *Immunol Rev.* 2019; **287**(1): 62–72.
PubMed Abstract | Publisher Full Text

31. Slade C, Bosco J, Unglik G, *et al.*: **Deficiency in complement factor B.** *N Engl J Med.* 2013; **369**(17): 1667–9.
PubMed Abstract | Publisher Full Text

32. F Goicoechea de Jorge E, Harris CL, Esparza-Gordillo J, *et al.*: **Gain-of-function mutations in complement factor B are associated with atypical hemolytic uremic syndrome.** *Proc Natl Acad Sci U S A.* 2007; **104**(1): 240–5.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

33. F Flanagan SE, Haapaniemi E, Russell MA, *et al.*: **Activating germline mutations in *STAT3* cause early-onset multi-organ autoimmune disease.** *Nat Genet.* 2014; **46**(8): 812–4.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

34. F Minegishi Y, Saito M, Tsuchiya S, *et al.*: **Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome.** *Nature.* 2007; **448**(7157): 1058–62.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

35. Botto M, Fong KY, So AK, *et al.*: **Molecular basis of polymorphisms of human complement component C3.** *J Exp Med.* 1990; **172**(4): 1011–7.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Frémeaux-Bacchi V, Miller EC, Liszewski MK, *et al.*: **Mutations in complement C3 predispose to development of atypical hemolytic uremic syndrome.** *Blood.* 2008; **112**(13): 4948–52.
PubMed Abstract | Publisher Full Text | Free Full Text

37. Devriendt K, Kim AS, Mathijs G, *et al.*: **Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia.** *Nat Genet.* 2001; **27**(3): 313–7.
PubMed Abstract | Publisher Full Text

38. Derry JM, Ochs HD, Francke U: **Isolation of a novel gene mutated in Wiskott-Aldrich syndrome.** *Cell.* 1994; **78**(4): 635–44.
PubMed Abstract | Publisher Full Text

39. Villa A, Notarangelo L, Macchi P, *et al.*: **X-linked thrombocytopenia and Wiskott-Aldrich syndrome are allelic diseases with mutations in the WASP gene.** *Nat Genet.* 1995; **9**(4): 414–7.
PubMed Abstract | Publisher Full Text

40. Del Bel KL, Ragotte RJ, Saferali A, *et al.*: ***JAK1* gain-of-function causes an autosomal dominant immune dysregulatory and hypereosinophilic syndrome.** *J Allergy Clin Immunol.* 2017; **139**(6): 2016–2020.e5.
PubMed Abstract | Publisher Full Text

41. Eletto D, Burns SO, Angulo I, *et al.*: **Biallelic JAK1 mutations in immunodeficient patient with mycobacterial infection.** *Nat Commun.* 2016; **7**: 13992.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Lamborn IT, Jing H, Zhang Y, *et al.*: **Recurrent rhinovirus infections in a child with inherited MDA5 deficiency.** *J Exp Med.* 2017; **214**(7): 1949–72.
PubMed Abstract | Publisher Full Text | Free Full Text

43. F Rice GI, Del Toro Duany Y, Jenkinson EM, *et al.*: **Gain-of-function mutations in *IFIH1* cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling.** *Nat Genet.* 2014; **46**(5): 503–9.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

44. F Chan AY, Punwani D, Kadlecek TA, *et al.*: **A novel human autoimmune syndrome caused by combined hypomorphic and activating mutations in ZAP-70.** *J Exp Med.* 2016; **213**(2): 155–65.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

45. Arpaia E, Shahar M, Dadi H, *et al.*: **Defective T cell receptor signaling and CD8$^+$ thymic selection in humans lacking zap-70 kinase.** *Cell.* 1994; **76**(5): 947–58.
PubMed Abstract | Publisher Full Text

46. Chapgier A, Wynn RF, Jouanguy E, *et al.*: **Human complete Stat-1 deficiency is associated with defective type I and II IFN responses *in vitro* but immunity to some low virulence viruses *in vivo*.** *J Immunol.* 2006; **176**(8): 5078–83.
PubMed Abstract | Publisher Full Text

47. Chapgier A, Kong XF, Boisson-Dupuis S, *et al.*: **A partial form of recessive STAT1 deficiency in humans.** *J Clin Invest.* 2009; **119**(6): 1502–14.
PubMed Abstract | Publisher Full Text | Free Full Text

48. F Dupuis S, Dargemont C, Fieschi C, *et al.*: **Impairment of mycobacterial but not viral immunity by a germline human *STAT1* mutation.** *Science.* 2001; **293**(5528): 300–3.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

49. F Liu L, Okada S, Kong XF, *et al.*: **Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis.** *J Exp Med.* 2011; **208**(8): 1635–48.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

50. F van de Veerdonk FL, Plantinga TS, Hoischen A, *et al.*: ***STAT1* mutations in autosomal dominant chronic mucocutaneous candidiasis.** *N Engl J Med.* 2011; **365**(1): 54–61.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

51. Stepensky P, Keller B, Buchta M, *et al.*: **Deficiency of caspase recruitment domain family, member 11 (CARD11), causes profound combined immunodeficiency in human subjects.** *J Allergy Clin Immunol.* 2013; **131**(2): 477–85.e1.
PubMed Abstract | Publisher Full Text

52. Greil J, Rausch T, Giese T, *et al.*: **Whole-exome sequencing links caspase recruitment domain 11 (*CARD11*) inactivation to severe combined immunodeficiency.** *J Allergy Clin Immunol.* 2013; **131**(5): 1376–83.e3.
PubMed Abstract | Publisher Full Text

53. Dadi H, Jones TA, Merico D, *et al.*: **Combined immunodeficiency and atopy caused by a dominant negative mutation in caspase activation and recruitment domain family member 11 (CARD11).** *J Allergy Clin Immunol.* 2018; **141**(5): 1818–1830.e2.
PubMed Abstract | Publisher Full Text

54. F Ma CA, Stinson JR, Zhang Y, *et al.*: **Germline hypomorphic *CARD11***

mutations in severe atopic disease. *Nat Genet.* 2017; **49**(8): 1192–201.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

55. Snow AL, Xiao W, Stinson JR, *et al.*: **Congenital B cell lymphocytosis explained by novel germline *CARD11* mutations.** *J Exp Med.* 2012; **209**(12): 2247–61.
PubMed Abstract | Publisher Full Text | Free Full Text

56. Dupuis S, Jouanguy E, Al-Hajjar S, *et al.*: **Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency.** *Nat Genet.* 2003; **33**(3): 388–91.
PubMed Abstract | Publisher Full Text

57. Boisson-Dupuis S, Kong XF, Okada S, *et al.*: **Inborn errors of human STAT1: allelic heterogeneity governs the diversity of immunological and infectious phenotypes.** *Curr Opin Immunol.* 2012; **24**(4): 364–78.
PubMed Abstract | Publisher Full Text | Free Full Text

58. Naviglio S, Soncini E, Vairo D, *et al.*: **Long-Term Survival After Hematopoietic Stem Cell Transplantation for Complete STAT1 Deficiency.** *J Clin Immunol.* 2017; **37**(7): 701–6.
PubMed Abstract | Publisher Full Text

59. Kong XF, Ciancanelli M, Al-Hajjar S, *et al.*: **A novel form of human STAT1 deficiency impairing early but not late responses to interferons.** *Blood.* 2010; **116**(26): 5895–906.
PubMed Abstract | Publisher Full Text | Free Full Text

60. Kristensen IA, Veirum JE, Møller BK, *et al.*: **Novel STAT1 alleles in a patient with impaired resistance to mycobacteria.** *J Clin Immunol.* 2011; **31**(2): 265–71.
PubMed Abstract | Publisher Full Text

61. Chapgier A, Boisson-Dupuis S, Jouanguy E, *et al.*: **Novel STAT1 Alleles in Otherwise Healthy Patients with Mycobacterial Disease.** *PLoS Genet.* 2006; **2**(8): e131.
PubMed Abstract | Publisher Full Text | Free Full Text

62. Toubiana J, Okada S, Hiller J, *et al.*: **Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype.** *Blood.* 2016; **127**(25): 3154–64.
PubMed Abstract | Publisher Full Text | Free Full Text

63. F Dorjbal B, Stinson JR, Ma CA, *et al.*: **Hypomorphic caspase activation and recruitment domain 11 (CARD11) mutations associated with diverse immunologic phenotypes with or without atopic disease.** *J Allergy Clin Immunol.* 2019; **143**(4): 1482–95.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

64. Brohl AS, Stinson JR, Su HC, *et al.*: **Germline CARD11 Mutation in a Patient with Severe Congenital B Cell Lymphocytosis.** *J Clin Immunol.* 2015; **35**(1): 32–46.
PubMed Abstract | Publisher Full Text | Free Full Text

65. Meyts I, Bosch B, Bolze A, *et al.*: **Exome and genome sequencing for inborn errors of immunity.** *J Allergy Clin Immunol.* 2016; **138**(4): 957–69.
PubMed Abstract | Publisher Full Text | Free Full Text

66. Vaz-Drago R, Custódio N, Carmo-Fonseca M: **Deep intronic mutations and human disease.** *Hum Genet.* 2017; **136**(9): 1093–111.
PubMed Abstract | Publisher Full Text

67. Meeths M, Chiang SCC, Wood SM, *et al.*: **Familial hemophagocytic lymphohistiocytosis type 3 (FHL3) caused by deep intronic mutation and inversion in UNC13D.** *Blood.* 2011; **118**(22): 5783–93.
PubMed Abstract | Publisher Full Text

68. Qian Y, Johnson JA, Connor JA, *et al.*: **The 253-kb inversion and deep intronic mutations in UNC13D are present in North American patients with familial hemophagocytic lymphohistiocytosis 3.** *Pediatr Blood Cancer.* 2014; **61**(6): 1034–40.
PubMed Abstract | Publisher Full Text

69. Entesarian M, Chiang SCC, Schlums H, *et al.*: **Novel deep intronic and missense UNC13D mutations in familial haemophagocytic lymphohistiocytosis type 3.** *Br J Haematol.* 2013; **162**(3): 415–8.
PubMed Abstract | Publisher Full Text

70. Seo JY, Song JS, Lee KO, *et al.*: **Founder effects in two predominant intronic mutations of UNC13D, c.118-308C>T and c.754-1G>C underlie the unusual predominance of type 3 familial hemophagocytic lymphohistiocytosis (FHL3) in Korea.** *Ann Hematol.* 2013; **92**(3): 357–64.
PubMed Abstract | Publisher Full Text

71. Schulert GS, Zhang M, Husami A, *et al.*: **Brief Report: Novel UNC13D Intronic Variant Disrupting an NF-κB Enhancer in a Patient With Recurrent Macrophage Activation Syndrome and Systemic Juvenile Idiopathic Arthritis.** *Arthritis Rheumatol.* 2018; **70**(6): 963–70.
PubMed Abstract | Publisher Full Text | Free Full Text

72. Butte MJ, Haines C, Bonilla FA, *et al.*: **IL-7 receptor deficient SCID with a unique intronic mutation and post-transplant autoimmunity due to chronic GVHD.** *Clin Immunol.* 2007; **125**(2): 159–64.
PubMed Abstract | Publisher Full Text | Free Full Text

73. Stepensky P, Keller B, Shamriz O, *et al.*: **Deep intronic mis-splicing mutation in JAK3 gene underlies T–B+NK– severe combined immunodeficiency phenotype.** *Clin Immunol.* 2016; **163**: 91–5.
PubMed Abstract | Publisher Full Text

74. Picard C, Dogniaux S, Chemin K, *et al.*: **Hypomorphic mutation of ZAP70 in human results in a late onset immunodeficiency and no autoimmunity.** *Eur J Immunol.* 2009; **39**(7): 1966–76.
PubMed Abstract | Publisher Full Text

75. F Khourieh J, Rao G, Habib T, *et al.*: **A deep intronic splice mutation of STAT3 underlies hyper IgE syndrome by negative dominance.** *Proc Natl Acad Sci U S A.* 2019; **116**(33): 16463–72.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

76. F Boisson B, Honda Y, Ajiro M, *et al.*: **Rescue of recurrent deep intronic mutation underlying cell type-dependent quantitative NEMO deficiency.** *J Clin Invest.* 2019; **129**(2): 583–97.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

77. Jørgensen SE, Bøttger P, Kofod-Olsen E, *et al.*: **Ectodermal dysplasia with immunodeficiency caused by a branch-point mutation in *IKBKG*/*NEMO*.** *J Allergy Clin Immunol.* 2016; **138**(6): 1706–1709.e4.
PubMed Abstract | Publisher Full Text

78. F Starokadomskyy P, Gemelli T, Rios JJ, *et al.*: **DNA polymerase-α regulates the activation of type I interferons through cytosolic RNA:DNA synthesis.** *Nat Immunol.* 2016; **17**(5): 495–504.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

79. Meyts I, Casanova JL: **A human inborn error connects the α's.** *Nat Immunol.* 2016; **17**(5): 472–4.
PubMed Abstract | Publisher Full Text

80. Bustamante J, Aksu G, Vogt G, *et al.*: **BCG-osis and tuberculosis in a child with chronic granulomatous disease.** *J Allergy Clin Immunol.* 2007; **120**(1): 32–8.
PubMed Abstract | Publisher Full Text

81. Rump A, Rösen-Wolff A, Gahr M, *et al.*: **A splice-supporting intronic mutation in the last bp position of a cryptic exon within intron 6 of the *CYBB* gene induces its incorporation into the mRNA causing chronic granulomatous disease (CGD).** *Gene.* 2006; **371**(2): 174–81.
PubMed Abstract | Publisher Full Text

82. Noack D, Heyworth PG, Newburger PE, *et al.*: **An unusual intronic mutation in the *CYBB* gene giving rise to chronic granulomatous disease.** *Biochim Biophys Acta.* 2001; **1537**(2): 125–31.
PubMed Abstract | Publisher Full Text

83. Cavalieri S, Pozzi E, Gatti RA, *et al.*: **Deep-intronic *ATM* mutation detected by genomic resequencing and corrected *in vitro* by antisense morpholino oligonucleotide (AMO).** *Eur J Hum Genet.* 2013; **21**(7): 774–8.
PubMed Abstract | Publisher Full Text | Free Full Text

84. Coutinho G, Xie J, Du L, *et al.*: **Functional significance of a deep intronic mutation in the ATM gene and evidence for an alternative exon 28a.** *Hum Mutat.* 2005; **25**(2): 118–24.
PubMed Abstract | Publisher Full Text

85. Lee WI, Torgerson TR, Schumacher MJ, *et al.*: **Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome.** *Blood.* 2005; **105**(5): 1881–90.
PubMed Abstract | Publisher Full Text

86. Lee H, Huang AY, Wang LK, *et al.*: **Diagnostic utility of transcriptome sequencing for rare Mendelian diseases.** *Genet Med.* 2020; **22**(3): 490–499.
PubMed Abstract | Publisher Full Text

87. F Frésard L, Smail C, Ferraro NM, *et al.*: **Identification of rare-disease genes using blood transcriptome sequencing and large control cohorts.** *Nat Med.* 2019; **25**(6): 911–9.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

88. F Zhang SY, Jouanguy E, Zhang Q, *et al.*: **Human inborn errors of immunity to infection affecting cells other than leukocytes: from the immune system to the whole organism.** *Curr Opin Immunol.* 2019; **59**: 88–100.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

89. Riquelme SA, Lozano C, Moustafa AM, *et al.*: **CFTR-PTEN-dependent mitochondrial metabolic dysfunction promotes *Pseudomonas aeruginosa* airway infection.** *Sci Transl Med.* 2019; **11**(499): pii: eaav4634.
PubMed Abstract | Publisher Full Text | Free Full Text

90. Balázs A, Mall MA: **Mucus obstruction and inflammation in early cystic fibrosis lung disease: Emerging role of the IL-1 signaling pathway.** *Pediatr Pulmonol.* 2019; **54 Suppl 3**: S5–S12.
PubMed Abstract | Publisher Full Text

91. Elborn JS: **Cystic fibrosis.** *Lancet.* 2016; **388**(10059): 2519–31.
PubMed Abstract | Publisher Full Text

92. F Piel FB, Steinberg MH, Rees DC: **Sickle Cell Disease.** *N Engl J Med.* 2017; **376**(16): 1561–73.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

93. Cannas G, Merazga S, Virot E: **Sickle Cell Disease and Infections in High- and Low-Income Countries.** *Mediterr J Hematol Infect Dis.* 2019; **11**(1): e2019042.
PubMed Abstract | Publisher Full Text | Free Full Text

94. F Casrouge A, Zhang SY, Eidenschenk C, *et al.*: **Herpes simplex virus encephalitis in human UNC-93B deficiency.** *Science.* 2006; **314**(5797): 308–12.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

95. Herman M, Ciancanelli M, Ou YH, *et al.*: **Heterozygous *TBK1* mutations impair TLR3 immunity and underlie herpes simplex encephalitis of childhood.** *J Exp Med.* 2012; **209**(9): 1567–82.
PubMed Abstract | Publisher Full Text | Free Full Text

96. F Pérez de Diego R, Sancho-Shimizu V, Lorenzo L, *et al.*: **Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis.** *Immunity.* 2010; **33**(3): 400–11.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

97. Sancho-Shimizu V, Pérez de Diego R, Lorenzo L, *et al.*: **Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF**

deficiency. *J Clin Invest.* 2011; **121**(12): 4889–902.
PubMed Abstract | Publisher Full Text | Free Full Text

98. F Zhang SY, Jouanguy E, Ugolini S, *et al.*: **TLR3 deficiency in patients with herpes simplex encephalitis.** *Science.* 2007; **317**(5844): 1522–7.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

99. F Guo Y, Audry M, Ciancanelli M, *et al.*: **Herpes simplex virus encephalitis in a patient with complete TLR3 deficiency: TLR3 is otherwise redundant in protective immunity.** *J Exp Med.* 2011; **208**(10): 2083–98.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

100. Andersen LL, Mørk N, Reinert LS, *et al.*: **Functional IRF3 deficiency in a patient with herpes simplex encephalitis.** *J Exp Med.* 2015; **212**(9): 1371–9.
PubMed Abstract | Publisher Full Text | Free Full Text

101. Ramoz N, Rueda LA, Bouadjar B, *et al.*: **Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis.** *Nat Genet.* 2002; **32**(4): 579–81.
PubMed Abstract | Publisher Full Text

102. Ramoz N, Taïeb A, Rueda LA, *et al.*: **Evidence for a nonallelic heterogeneity of epidermodysplasia verruciformis with two susceptibility loci mapped to chromosome regions 2p21-p24 and 17q25.** *J Invest Dermatol.* 2000; **114**(6): 1148–53.
PubMed Abstract | Publisher Full Text

103. F de Jong SJ, Créquer A, Matos I, *et al.*: **The human CIB1-EVER1-EVER2 complex governs keratinocyte-intrinsic immunity to β-papillomaviruses.** *J Exp Med.* 2018; **215**(9): 2289–310.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

104. F Youssefian L, Vahidnezhad H, Mahmoudi H, *et al.*: **Epidermodysplasia Verruciformis: Genetic Heterogeneity and *EVER1* and *EVER2* Mutations Revealed by Genome-Wide Analysis.** *J Invest Dermatol.* 2019; **139**(1): 241–4.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

105. Lyons JJ, Milner JD: **The clinical and mechanistic intersection of primary atopic disorders and inborn errors of growth and metabolism.** *Immunol Rev.* 2019; **287**(1): 135–44.
PubMed Abstract | Publisher Full Text

106. F Samuelov L, Sarig O, Harmon RM, *et al.*: **Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting.** *Nat Genet.* 2013; **45**(10): 1244–8.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

107. McAleer MA, Pohler E, Smith FJ, *et al.*: **Severe dermatitis, multiple allergies, and metabolic wasting syndrome caused by a novel mutation in the N-terminal plakin domain of desmoplakin.** *J Allergy Clin Immunol.* 2015; **136**(5): 1268–76.
PubMed Abstract | Publisher Full Text | Free Full Text

108. F Paller AS, Czarnowicki T, Renert-Yuval Y, *et al.*: **The spectrum of manifestations in desmoplakin gene (DSP) spectrin repeat 6 domain mutations: Immunophenotyping and response to ustekinumab.** *J Am Acad Dermatol.* 2018; **78**(3): 498–505.e2.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

109. Taiber S, Samuelov L, Mohamad J, *et al.*: **SAM syndrome is characterized by extensive phenotypic heterogeneity.** *Exp Dermatol.* 2018; **27**(7): 787–90.
PubMed Abstract | Publisher Full Text

110. Vakkilainen S, Puhakka L, Klemetti P, *et al.*: **Novel DSP Spectrin 6 Region Variant Causes Neonatal Erythroderma, Failure to Thrive, Severe Herpes Simplex Infections and Brain Lesions.** *Acta Derm Venereol.* 2019; **99**(9): 789–96.
PubMed Abstract | Publisher Full Text

111. Anthony RM, Ravetch JV: **A novel role for the IgG Fc glycan: the anti-inflammatory activity of sialylated IgG Fcs.** *J Clin Immunol.* 2010; **30 Suppl 1**: S9–14.
PubMed Abstract | Publisher Full Text

112. Crespo HJ, Lau JT, Videira PA: **Dendritic cells: a spot on sialic Acid.** *Front Immunol.* 2013; **4**: 491.
PubMed Abstract | Publisher Full Text | Free Full Text

113. Priatel JJ, Chui D, Hiraoka N, *et al.*: **The ST3Gal-I sialyltransferase controls CD8$^+$ T lymphocyte homeostasis by modulating O-glycan biosynthesis.** *Immunity.* 2000; **12**(3): 273–83.
PubMed Abstract | Publisher Full Text

114. Stanley P, Guidos CJ: **Regulation of Notch signaling during T- and B-cell development by *O*-fucose glycans.** *Immunol Rev.* 2009; **230**(1): 201–15.
PubMed Abstract | Publisher Full Text

115. Baum LG, Crocker PR: **Glycoimmunology: ignore at your peril!.** *Immunol Rev.* 2009; **230**(1): 5–8.
PubMed Abstract | Publisher Full Text

116. Barral DC, Brenner MB: **CD1 antigen presentation: how it works.** *Nat Rev Immunol.* 2007; **7**(12): 929–41.
PubMed Abstract | Publisher Full Text

117. Jensen T, Galli-Stampino L, Mouritsen S, *et al.*: **T cell recognition of Tn-glycosylated peptide antigens.** *Eur J Immunol.* 1996; **26**(6): 1342–9.
PubMed Abstract | Publisher Full Text

118. F Pascoal C, Francisco R, Ferro T, *et al.*: **CDG and immune response: From bedside to bench and back.** *J Inherit Metab Dis.* 2020; **43**(1): 90–124.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

119. Monticelli M, Ferro T, Jaeken J, *et al.*: **Immunological aspects of congenital disorders of glycosylation (CDG): a review.** *J Inherit Metab Dis.* 2016; **39**(6): 765–80.
PubMed Abstract | Publisher Full Text

120. F Boztug K, Järvinen PM, Salzer E, *et al.*: **JAGN1 deficiency causes aberrant myeloid cell homeostasis and congenital neutropenia.** *Nat Genet.* 2014; **46**(9): 1021–7.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

121. Boztug K, Appaswamy G, Ashikov A, *et al.*: **A syndrome with congenital neutropenia and mutations in *G6PC3*.** *N Engl J Med.* 2009; **360**(1): 32–43.
PubMed Abstract | Publisher Full Text | Free Full Text

122. Lühn K, Wild MK, Eckhardt M, *et al.*: **The gene defective in leukocyte adhesion deficiency II encodes a putative GDP-fucose transporter.** *Nat Genet.* 2001; **28**(1): 69–72.
PubMed Abstract | Publisher Full Text

123. Lübke T, Marquardt T, Etzioni A, *et al.*: **Complementation cloning identifies CDG-IIc, a new type of congenital disorders of glycosylation, as a GDP-fucose transporter deficiency.** *Nat Genet.* 2001; **28**(1): 73–6.
PubMed Abstract | Publisher Full Text

124. Jun HS, Weinstein DA, Lee YM, *et al.*: **Molecular mechanisms of neutrophil dysfunction in glycogen storage disease type Ib.** *Blood.* 2014; **123**(18): 2843–53.
PubMed Abstract | Publisher Full Text | Free Full Text

125. Chou JY, Cho JH, Kim GY, *et al.*: **Molecular biology and gene therapy for glycogen storage disease type Ib.** *J Inherit Metab Dis.* 2018; **41**(6): 1007–14.
PubMed Abstract | Publisher Full Text

126. Zhang Y, Yu X, Ichikawa M, *et al.*: **Autosomal recessive phosphoglucomutase 3 (*PGM3*) mutations link glycosylation defects to atopy, immune deficiency, autoimmunity, and neurocognitive impairment.** *J Allergy Clin Immunol.* 2014; **133**(5): 1400–1409.e5.
PubMed Abstract | Publisher Full Text | Free Full Text

127. F Ravell JC, Matsuda-Lennikov M, Chauvin SD, *et al.*: **Defective glycosylation and multisystem abnormalities characterize the primary immunodeficiency XMEN disease.** *J Clin Invest.* 2020; **130**(1): 507–22.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

128. F Blommaert E, Péanne R, Cherepanova NA, *et al.*: **Mutations in *MAGT1* lead to a glycosylation disorder with a variable phenotype.** *Proc Natl Acad Sci U S A.* 2019; **116**(20): 9865–70.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

129. F Cheng HD, Tirosh I, de Haan N, *et al.*: **IgG Fc glycosylation as an axis of humoral immunity in childhood.** *J Allergy Clin Immunol.* 2020; **145**(2): 710–713.e9.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

130. Hennig C, Baumann U, Ilginus C, *et al.*: **Successful treatment of autoimmune and lymphoproliferative complications of patients with intrinsic B-cell immunodeficiencies with Rituximab.** *Br J Haematol.* 2010; **148**(3): 445–8.
PubMed Abstract | Publisher Full Text

131. Rao VK, Price S, Perkins K, *et al.*: **Use of rituximab for refractory cytopenias associated with autoimmune lymphoproliferative syndrome (ALPS).** *Pediatr Blood Cancer.* 2009; **52**(7): 847–52.
PubMed Abstract | Publisher Full Text | Free Full Text

132. Gobert D, Bussel JB, Cunningham-Rundles C, *et al.*: **Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients.** *Br J Haematol.* 2011; **155**(4): 498–508.
PubMed Abstract | Publisher Full Text | Free Full Text

133. Naderi beni F, Fattahi F, Mirshafiey A, *et al.*: **Increased production of nitric oxide by neutrophils from patients with chronic granulomatous disease on interferon-gamma treatment.** *Int Immunopharmacol.* 2012; **12**(4): 689–93.
PubMed Abstract | Publisher Full Text

134. Alangari AA, Al-Zamil F, Al-Mazrou A, *et al.*: **Treatment of disseminated mycobacterial infection with high-dose IFN-γ in a patient with IL-12Rβ1 deficiency.** *Clin Dev Immunol.* 2011; **2011**: 691956.
PubMed Abstract | Publisher Full Text | Free Full Text

135. Yong PL, Russo P, Sullivan KE: **Use of sirolimus in IPEX and IPEX-like children.** *J Clin Immunol.* 2008; **28**(5): 581–7.
PubMed Abstract | Publisher Full Text

136. F Lucas CL, Kuehn HS, Zhao F, *et al.*: **Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency.** *Nat Immunol.* 2014; **15**(1): 88–97.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

137. Coulter TI, Chandra A, Bacon CM, *et al.*: **Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: A large patient cohort study.** *J Allergy Clin Immunol.* 2017; **139**(2): 597–606.e4.
PubMed Abstract | Publisher Full Text | Free Full Text

138. F Angulo I, Vadas O, Garcon F, *et al.*: **Phosphoinositide 3-kinase δ gene mutation predisposes to respiratory infection and airway damage.** *Science.* 2013; **342**(6160): 866–71.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

139. Avery DT, Kane A, Nguyen T, *et al.*: **Germline-activating mutations in *PIK3CD* compromise B cell development and function.** *J Exp Med.* 2018; **215**(8): 2073–95.
PubMed Abstract | Publisher Full Text | Free Full Text

140. Edwards ESJ, Bier J, Cole TS, *et al.*: **Activating *PIK3CD* mutations impair human cytotoxic lymphocyte differentiation and function and EBV immunity.** *J Allergy Clin Immunol.* 2019; **143**(1): 276–291.e6.
PubMed Abstract | Publisher Full Text

141. F Tangye SG, Bier J, Lau A, *et al.*: **Immune Dysregulation and Disease**

Pathogenesis due to Activating Mutations in *PIK3CD*-the Goldilocks' Effect. *J Clin Immunol.* 2019; **39**(2): 148–58.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

142. Maccari ME, Abolhassani H, Aghamohammadi A, *et al.*: **Disease Evolution and Response to Rapamycin in Activated Phosphoinositide 3-Kinase δ Syndrome: The European Society for Immunodeficiencies-Activated Phosphoinositide 3-Kinase δ Syndrome Registry.** *Front Immunol.* 2018; **9**: 543.
PubMed Abstract | Publisher Full Text | Free Full Text

143. F Rao VK, Webster S, Dalm VASH, *et al.*: **Effective "activated PI3Kδ syndrome"-targeted therapy with the PI3Kδ inhibitor leniolisib.** *Blood.* 2017; **130**(21): 2307–16.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

144. Hoegenauer K, Soldermann N, Zécri F, *et al.*: **Discovery of CDZ173 (Leniolisib), Representing a Structurally Novel Class of PI3K Delta-Selective Inhibitors.** *ACS Med Chem Lett.* 2017; **8**(9): 975–80.
PubMed Abstract | Publisher Full Text | Free Full Text

145. Cahn A, Hamblin JN, Begg M, *et al.*: **Safety, pharmacokinetics and dose-response characteristics of GSK2269557, an inhaled PI3Kδ inhibitor under development for the treatment of COPD.** *Pulm Pharmacol Ther.* 2017; **46**: 69–77.
PubMed Abstract | Publisher Full Text

146. F Kuehn HS, Ouyang W, Lo B, *et al.*: **Immune dysregulation in human subjects with heterozygous germline mutations in *CTLA4*.** *Science.* 2014; **345**(6204): 1623–7.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

147. Schubert D, Bode C, Kenefeck R, *et al.*: **Autosomal dominant immune dysregulation syndrome in humans with *CTLA4* mutations.** *Nat Med.* 2014; **20**(12): 1410–6.
PubMed Abstract | Publisher Full Text | Free Full Text

148. F Schwab C, Gabrysch A, Olbrich P, *et al.*: **Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects.** *J Allergy Clin Immunol.* 2018; **142**(6): 1932–46.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

149. Lopez-Herrera G, Tampella G, Pan-Hammarström Q, *et al.*: **Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity..** *Am J Hum Genet.* 2012; **90**(6): 986–1001.
PubMed Abstract | Publisher Full Text | Free Full Text

150. Charbonnier LM, Janssen E, Chou J, *et al.*: **Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA.** *J Allergy Clin Immunol.* 2015; **135**(1): 217–27.
PubMed Abstract | Publisher Full Text | Free Full Text

151. Gámez-Díaz L, August D, Stepensky P, *et al.*: **The extended phenotype of LPS-responsive beige-like anchor protein (LRBA) deficiency.** *J Allergy Clin Immunol.* 2016; **137**(1): 223–30.
PubMed Abstract | Publisher Full Text

152. Lee S, Moon JS, Lee CR, *et al.*: **Abatacept alleviates severe autoimmune symptoms in a patient carrying a *de novo* variant in *CTLA-4*.** *J Allergy Clin Immunol.* 2016; **137**(1): 327–30.
PubMed Abstract | Publisher Full Text

153. F van Leeuwen EM, Cuadrado E, Gerrits AM, *et al.*: **Treatment of Intracerebral Lesions with Abatacept in a CTLA4-Haploinsufficient Patient.** *J Clin Immunol.* 2018; **38**(4): 464–7.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

154. F Lo B, Zhang K, Lu W, *et al.*: **AUTOIMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy.** *Science.* 2015; **349**(6246): 436–40.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

155. F Milner JD, Vogel TP, Forbes L, *et al.*: **Early-onset lymphoproliferation and autoimmunity caused by germline *STAT3* gain-of-function mutations.** *Blood.* 2015; **125**(4): 591–9.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

156. Haapaniemi EM, Kaustio M, Rajala HL, *et al.*: **Autoimmunity, hypogammaglobulinemia, lymphoproliferation, and mycobacterial disease in patients with activating mutations in *STAT3*.** *Blood.* 2015; **125**(4): 639–48.
PubMed Abstract | Publisher Full Text | Free Full Text

157. Roskoski R Jr: **Janus kinase (JAK) inhibitors in the treatment of inflammatory and neoplastic diseases.** *Pharmacol Res.* 2016; **111**: 784–803.
PubMed Abstract | Publisher Full Text

158. Banerjee S, Biehl A, Gadina M, *et al.*: **JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects.** *Drugs.* 2017; **77**(5): 521–46.
PubMed Abstract | Publisher Full Text

159. Forbes LR, Vogel TP, Cooper MA, *et al.*: **Jakinibs for the treatment of immune dysregulation in patients with gain-of-function signal transducer and activator of transcription 1 (*STAT1*) or *STAT3* mutations.** *J Allergy Clin Immunol.* 2018; **142**(5): 1665–9.
PubMed Abstract | Publisher Full Text | Free Full Text

160. Weinacht KG, Charbonnier LM, Alroqi F, *et al.*: **Ruxolitinib reverses dysregulated T helper cell responses and controls autoimmunity caused by a novel signal transducer and activator of transcription 1 (*STAT1*) gain-of-function mutation.** *J Allergy Clin Immunol.* 2017; **139**(5): 1629–1640.e2.
PubMed Abstract | Publisher Full Text | Free Full Text

161. Al Shehri T, Gilmour K, Gothe F, *et al.*: **Novel Gain-of-Function Mutation in *Stat1* Sumoylation Site Leads to CMC/CID Phenotype Responsive to Ruxolitinib.** *J Clin Immunol.* 2019; **39**(8): 776–85.
PubMed Abstract | Publisher Full Text

162. Vargas-Hernández A, Mace EM, Zimmerman O, *et al.*: **Ruxolitinib partially reverses functional natural killer cell deficiency in patients with signal transducer and activator of transcription 1 (*STAT1*) gain-of-function mutations.** *J Allergy Clin Immunol.* 2018; **141**(6): 2142–2155.e5.
PubMed Abstract | Publisher Full Text | Free Full Text

163. Bloomfield M, Kanderová V, Paračková Z, *et al.*: **Utility of Ruxolitinib in a Child with Chronic Mucocutaneous Candidiasis Caused by a Novel STAT1 Gain-of-Function Mutation.** *J Clin Immunol.* 2018; **38**(5): 589–601.
PubMed Abstract | Publisher Full Text

164. F Higgins E, Al Shehri T, McAleer MA, *et al.*: **Use of ruxolitinib to successfully treat chronic mucocutaneous candidiasis caused by gain-of-function signal transducer and activator of transcription 1 (*STAT1*) mutation.** *J Allergy Clin Immunol.* 2015; **135**(2): 551–3.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

165. Solomon IH, Li H, Benson LA, *et al.*: **Histopathologic Correlates of Familial Hemophagocytic Lymphohistiocytosis Isolated to the Central Nervous System.** *J Neuropathol Exp Neurol.* 2018; **77**(12): 1079–84.
PubMed Abstract | Publisher Full Text | Free Full Text

166. Jordan MB, Allen CE, Weitzman S, *et al.*: **How I treat hemophagocytic lymphohistiocytosis.** *Blood.* 2011; **118**(15): 4041–52.
PubMed Abstract | Publisher Full Text | Free Full Text

167. Bergsten E, Horne A, Aricó, *et al.*: **Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study.** *Blood.* 2017; **130**(25): 2728–38.
PubMed Abstract | Publisher Full Text | Free Full Text

168. Marsh RA, Allen CE, McClain KL, *et al.*: **Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab.** *Pediatr Blood Cancer.* 2013; **60**(1): 101–9.
PubMed Abstract | Publisher Full Text | Free Full Text

169. Vallurupalli M, Berliner N: **Emapalumab for the treatment of relapsed/refractory hemophagocytic lymphohistiocytosis.** *Blood.* 2019; **134**(21): 1783–6.
PubMed Abstract | Publisher Full Text

170. Al-Salama ZT: **Emapalumab: First Global Approval.** *Drugs.* 2019; **79**(1): 99–103.
PubMed Abstract | Publisher Full Text

171. F Liu Y, Jesus AA, Marrero B, *et al.*: **Activated STING in a vascular and pulmonary syndrome.** *N Engl J Med.* 2014; **371**(6): 507–18.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

172. F Das R, Guan P, Sprague L, *et al.*: **Janus kinase inhibition lessens inflammation and ameliorates disease in murine models of hemophagocytic lymphohistiocytosis.** *Blood.* 2016; **127**(13): 1666–75.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

173. Vignesh P, Rawat A, Singh S: **An Update on the Use of Immunomodulators in Primary Immunodeficiencies.** *Clin Rev Allergy Immunol.* 2017; **52**(2): 287–303.
PubMed Abstract | Publisher Full Text

174. Broglie L, Pommert L, Rao S, *et al.*: **Ruxolitinib for treatment of refractory hemophagocytic lymphohistiocytosis.** *Blood Adv.* 2017; **1**(19): 1533–6.
PubMed Abstract | Publisher Full Text | Free Full Text

175. Sin JH, Zangardi ML: **Ruxolitinib for secondary hemophagocytic lymphohistiocytosis: First case report.** *Hematol Oncol Stem Cell Ther.* 2019; **12**(3): 166–70.
PubMed Abstract | Publisher Full Text

176. F Marsh RA, Hebert KM, Keesler D, *et al.*: **Practice pattern changes and improvements in hematopoietic cell transplantation for primary immunodeficiencies.** *J Allergy Clin Immunol.* 2018; **142**(6): 2004–7.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

177. Ferrua F, Galimberti S, Courteille V, *et al.*: **Hematopoietic stem cell transplantation for CD40 ligand deficiency: Results from an EBMT/ESID-IEWP-SCETIDE-PIDTC study.** *J Allergy Clin Immunol.* 2019; **143**(6): 2238–53.
PubMed Abstract | Publisher Full Text

178. Cole T, Pearce MS, Cant AJ, *et al.*: **Clinical outcome in children with chronic granulomatous disease managed conservatively or with hematopoietic stem cell transplantation.** *J Allergy Clin Immunol.* 2013; **132**(5): 1150–5.
PubMed Abstract | Publisher Full Text

179. F Haddad E, Logan BR, Griffith LM, *et al.*: **SCID genotype and 6-month posttransplant CD4 count predict survival and immune recovery.** *Blood.* 2018; **132**(17): 1737–49.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

180. Puck JM: **Newborn screening for severe combined immunodeficiency and T-cell lymphopenia.** *Immunol Rev.* 2019; **287**(1): 241–52.
PubMed Abstract | Publisher Full Text | Free Full Text

181. King JR, Hammarström L: **Newborn Screening for Primary Immunodeficiency Diseases: History, Current and Future Practice.** *J Clin Immunol.* 2018; **38**(1): 56–66.
PubMed Abstract | Publisher Full Text | Free Full Text

182. Heimall J, Logan BR, Cowan MJ, *et al.*: **Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: A PIDTC natural history**

study. *Blood.* 2017; **130**(25): 2718–27.
PubMed Abstract | Publisher Full Text | Free Full Text

183. Dvorak CC, Puck JM, Wahlstrom JT, *et al.*: **Neurologic event–free survival demonstrates a benefit for SCID patients diagnosed by newborn screening.** *Blood Adv.* 2017; **1**(20): 1694–8.
PubMed Abstract | Publisher Full Text | Free Full Text

184. Railey MD, Lokhnygina Y, Buckley RH: **Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis.** *J Pediatr.* 2009; **155**(6): 834–840.e1.
PubMed Abstract | Publisher Full Text | Free Full Text

185. Shaw P, Shizuru J, Hoenig M, *et al.*: **Conditioning Perspectives for Primary Immunodeficiency Stem Cell Transplants.** *Front Pediatr.* 2019; **7**: 434.
PubMed Abstract | Publisher Full Text | Free Full Text

186. F George BM, Kao KS, Kwon HS, *et al.*: **Antibody Conditioning Enables MHC-Mismatched Hematopoietic Stem Cell Transplants and Organ Graft Tolerance.** *Cell Stem Cell.* 2019; **25**(2): 185–192.e3.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

187. Straathof KC, Rao K, Eyrich M, *et al.*: **Haemopoietic stem-cell transplantation with antibody-based minimal-intensity conditioning: A phase 1/2 study.** *Lancet.* 2009; **374**(9693): 912–20.
PubMed Abstract | Publisher Full Text

188. F Palchaudhuri R, Saez B, Hoggatt J, *et al.*: **Non-genotoxic conditioning for hematopoietic stem cell transplantation using a hematopoietic-cell-specific internalizing immunotoxin.** *Nat Biotechnol.* 2016; **34**(7): 738–45.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

189. Abadir E, Bryant C, Larsen S, *et al.*: **Targeting the niche: Depleting haemopoietic stem cells with targeted therapy.** *Bone Marrow Transplant.* 2019; **54**(7): 961–8.
PubMed Abstract | Publisher Full Text

190. Vo P, Gooley TA, Rajendran JG, *et al.*: **Yttrium-90-labeled anti-CD45 antibody followed by a reduced-intensity hematopoietic cell transplantation for patients with relapsed/refractory leukemia or myelodysplasia.** *Haematologica.* 2019; pii: haematol.2019.229492.
PubMed Abstract | Publisher Full Text

191. Orozco JJ, Kenoyer A, Balkin ER, *et al.*: **Anti-CD45 radioimmunotherapy without TBI before transplantation facilitates persistent haploidentical donor engraftment.** *Blood.* 2016; **127**(3): 352–9.
PubMed Abstract | Publisher Full Text | Free Full Text

192. Mawad R, Gooley TA, Rajendran JG, *et al.*: **Radiolabeled anti-CD45 antibody with reduced-intensity conditioning and allogeneic transplantation for younger patients with advanced acute myeloid leukemia or myelodysplastic syndrome.** *Biol Blood Marrow Transplant.* 2014; **20**(9): 1363–8.
PubMed Abstract | Publisher Full Text | Free Full Text

193. F Czechowicz A, Palchaudhuri R, Scheck A, *et al.*: **Selective hematopoietic stem cell ablation using CD117-antibody-drug-conjugates enables safe and effective transplantation with immunity preservation.** *Nat Commun.* 2019; **10**(1): 617.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

194. Agarwal R, Dvorak CC, Prohaska S, *et al.*: **Toxicity-Free Hematopoietic Stem Cell Engraftment Achieved with Anti-CD117 Monoclonal Antibody Conditioning.** *Biol Blood Marrow Transplant.* 2019; **25**(3 Supplement): S92.
Publisher Full Text

195. Kwon HS, Logan AC, Chhabra A, *et al.*: **Anti-human CD117 antibody-mediated bone marrow niche clearance in nonhuman primates and humanized NSG mice.** *Blood.* 2019; **133**(19): 2104–8.
PubMed Abstract | Publisher Full Text | Free Full Text

196. Booth C, Romano R, Roncarolo MG, *et al.*: **Gene therapy for primary immunodeficiency.** *Hum Mol Genet.* 2019; **28**(R1): R15–R23.
PubMed Abstract | Publisher Full Text

197. Staal FJT, Aiuti A, Cavazzana M: **Autologous Stem-Cell-Based Gene Therapy for Inherited Disorders: State of the Art and Perspectives.** *Front Pediatr.* 2019; **7**: 443.
PubMed Abstract | Publisher Full Text | Free Full Text

198. F Aiuti A, Slavin S, Aker M, *et al.*: **Correction of ADA-SCID by stem cell gene therapy combined with nonmyeloablative conditioning.** *Science.* 2002; **296**(5577): 2410–3.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

199. Cavazzana-Calvo M, Hacein-Bey S, de Saint Basile G, *et al.*: **Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease.** *Science.* 2000; **288**(5466): 669–72.
PubMed Abstract | Publisher Full Text

200. Gaspar HB, Parsley KL, Howe S, *et al.*: **Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector.** *Lancet.* 2004; **364**(9452): 2181–7.
PubMed Abstract | Publisher Full Text

201. F Ott MG, Schmidt M, Schwarzwaelder K, *et al.*: **Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of *MDS1-EVI1*, *PRDM16* or *SETBP1*.** *Nat Med.* 2006; **12**(4): 401–9.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

202. F Boztug K, Schmidt M, Schwarzer A, *et al.*: **Stem-cell gene therapy for the Wiskott-Aldrich syndrome.** *N Engl J Med.* 2010; **363**(20): 1918–27.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

203. F Hacein-Bey-Abina S, Garrigue A, Wang GP, *et al.*: **Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1.** *J Clin Invest.* 2008; **118**(9): 3132–42.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

204. Howe SJ, Mansour MR, Schwarzwaelder K, *et al.*: **Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients.** *J Clin Invest.* 2008; **118**(9): 3143–50.
PubMed Abstract | Publisher Full Text | Free Full Text

205. F Braun CJ, Boztug K, Paruzynski A, *et al.*: **Gene therapy for Wiskott-Aldrich syndrome--long-term efficacy and genotoxicity.** *Sci Transl Med.* 2014; **6**(227): 227ra33.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

206. Stein S, Ott MG, Schultze-Strasser S, *et al.*: **Genomic instability and myelodysplasia with monosomy 7 consequent to *EVI1* activation after gene therapy for chronic granulomatous disease.** *Nat Med.* 2010; **16**(2): 198–204.
PubMed Abstract | Publisher Full Text

207. Hubbard N, Hagin D, Sommer K, *et al.*: **Targeted gene editing restores regulated CD40L function in X-linked hyper-IgM syndrome.** *Blood.* 2016; **127**(21): 2513–22.
PubMed Abstract | Publisher Full Text

208. Schiroli G, Ferrari S, Conway A, *et al.*: **Preclinical modeling highlights the therapeutic potential of hematopoietic stem cell gene editing for correction of SCID-X1.** *Sci Transl Med.* 2017; **9**(411): pii: eaan0820.
PubMed Abstract | Publisher Full Text

209. F Pavel-Dinu M, Wiebking V, Dejene BT, *et al.*: **Gene correction for SCID-X1 in long-term hematopoietic stem cells.** *Nat Commun.* 2019; **10**(1): 1634.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

210. F De Ravin SS, Reik A, Liu PQ, *et al.*: **Targeted gene addition in human CD34$^+$ hematopoietic cells for correction of X-linked chronic granulomatous disease.** *Nat Biotechnol.* 2016; **34**(4): 424–9.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

211. F De Ravin SS, Li L, Wu X, *et al.*: **CRISPR-Cas9 gene repair of hematopoietic stem cells from patients with X-linked chronic granulomatous disease.** *Sci Transl Med.* 2017; **9**(372): pii: eaah3480.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

212. F Panchal N, Houghton B, Diez B, *et al.*: **Transfer of gene-corrected T cells corrects humoral and cytotoxic defects in patients with X-linked lymphoproliferative disease.** *J Allergy Clin Immunol.* 2018; **142**(1): 235–245.e6.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

213. Passerini L, Rossi Mel E, Sartirana C, *et al.*: **CD4$^+$ T cells from IPEX patients convert into functional and stable regulatory T cells by *FOXP3* gene transfer.** *Sci Transl Med.* 2013; **5**(215): 215ra174–215ra174.
PubMed Abstract | Publisher Full Text

214. F Ghosh S, Carmo M, Calero-Garcia M, *et al.*: **T-cell gene therapy for perforin deficiency corrects cytotoxicity defects and prevents hemophagocytic lymphohistiocytosis manifestations.** *J Allergy Clin Immunol.* 2018; **142**(3): 904–913.e3.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

215. Soheili T, Rivière J, Ricciardelli I, *et al.*: **Gene-corrected human Munc13-4-deficient CD8+ T cells can efficiently restrict EBV-driven lymphoproliferation in immunodeficient mice.** *Blood.* 2016; **128**(24): 2859–62.
PubMed Abstract | Publisher Full Text

216. Ferreira LMR, Muller YD, Bluestone JA, *et al.*: **Next-generation regulatory T cell therapy.** *Nat Rev Drug Discov.* 2019; **18**(10): 749–69.
PubMed Abstract | Publisher Full Text

217. F Gaudelli NM, Komor AC, Rees HA, *et al.*: **Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage.** *Nature.* 2017; **551**(7681): 464–71.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

218. Abbasi J: **DNA Base Editing Could Reverse Most Disease-Causing Point Mutations.** *JAMA.* 2017; **318**(22): 2173.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔ ✔

Editorial Note on the Review Process

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1 **Trine H. Mogensen**
Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
Competing Interests: No competing interests were disclosed.

2 **Helen C. Su**
Human Immunological Diseases Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
Competing Interests: No competing interests were disclosed.

3 **Andrew L Snow**
Department of Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
Competing Interests: No competing interests were disclosed.