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Ocular Inflammatory Diseases: Molecular Pathogenesis and Immunotherapy

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Abstract

Uveitis is a diverse group of potentially sight-threatening intraocular inflammatory diseases of infectious or autoimmune etiology and accounts for more than 10% of severe visual handicaps in the United States. Pathology derives from the presence of inflammatory cells in the optical axis and sustained production of cytotoxic cytokines and other immune-regulatory proteins in the eye. The main therapeutic goals are to down-regulate the immune response, preserve the integrity of the ocular architecture and eventually eliminate the inciting uveitogenic stimuli. Current therapy is based on topical or systemic corticosteroid with or without second line agents and serious adverse effects of these drugs are the impetus for development of less toxic and more specific therapies for uveitis. This review summarizes the pathophysiology of uveitis, molecular mechanisms that regulate the initiation and progression of uveitis and concludes with emerging strategies for the treatment of this group of potentially blinding diseases.

Keywords

B cell therapy; IL-12 cytokines; IL-35-expressing Breg cell (i35-Breg); interleukin 35 (IL-35); regulatory B cells (Breg); therapeutic cytokines; uveitis

INTRODUCTION

The vertebrate eye is a highly specialized sensory organ comprised of the retina, cornea, lens, iris, ciliary body, choroid, sclera, aqueous humor and vitreous body (Fig. 1) and its function is to receive and convert incident light rays into visual images [1]. The photo-transduction process is sensitive to minimal anatomic or minute biochemical distortions as alterations in the intraocular environment can reduce the visual image to a blur. Thus, the optical axis (cornea, anterior chamber, lens and vitreous body) through which the light is transmitted must be transparent to ensure the fidelity of the visual image [1]. Inflammation

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

in the eye is therefore highly undesirable because it compromises the transparency of the optical axis and cytokines, growth factors and other inflammatory mediators secreted by the inflammatory cells promote angiogenesis, fibrosis and tissue destruction. Ocular immunity is therefore predicated on mounting a limited immune response with minimal collateral damage to ocular structures and eliminating inflammatory cells from the visual axis upon resolution of the inflammatory challenge. Treatment of ocular inflammatory conditions has generally been with systemic immunosuppressive drugs, such as corticosteroids, cyclosporin A, methotrexate, azathioprine, chlorambucil, cyclophosphamide and colchicine [2]. However, sight-threatening inflammation requires aggressive immunosuppression, which can be associated with significant morbidity and mortality and this has been the impetus for interest in developing non-steroidal anti-inflammatory drugs (NSAIDs). In this review, a major goal is to briefly discuss the pathophysiology of uveitis, highlight potential therapeutic targets and emerging strategies for treating uveitis.

UVEITIS (INTRAOCULAR INFLAMMATORY DISEASES)

Uveitis is a diverse group of potentially sight-threatening intraocular inflammatory diseases. It is classically defined as inflammation of the uveal tract [3]. It can be classified as anterior, intermediate, posterior uveitis or panuveitis on the basis of its anatomic location. Anterior uveitis or inflammation of the anterior segment manifests as iritis or iridocyclitis, with inflammatory cell infiltration and leakage of protein into the aqueous humor. Intermediate uveitis, also described as peripheral exudative retinitis, cyclochorio-retinitis or peripheral uveoretinitis, is characterized by vitritis and peripheral retinal vasculitis and can manifest as vascular sheathing with evidence of increased vascular permeability on fluorescein angiography. Posterior uveitis is inflammation of the posterior segment, including the retina, choroid and vitreous and both intermediate and posterior uveitis can be complicated by cystoid macular edema. Uveitis can be of infectious or non-infectious etiology, although majority of cases are thought to be autoimmune in nature. In fact, there is substantial evidence that Fuchs' heterochromic iridocyclitis, serpiginous choroidopathy, birdshot retinochoroidopathy, multifocal choroiditis, intermediate uveitis of the pars planitis and sympathetic ophthalmia are of autoimmune etiology [3]. In addition, uveitis can also be associated with systemic diseases such as sarcoidosis, psoriatic arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis (JRA), multiple sclerosis, Vogt-Koyanagi-Harada's disease, Behçet's disease, systemic lupus erythematosus (SLE) and a variety of collagen vascular diseases [3]. The most common symptoms of uveitis are blurred vision, pain and photophobia, with long-term sequelae including increase in intraocular pressure, cataract, retinal detachment, retinal atrophy, macular edema and retinal neovascularization [3].

ANIMAL MODELS OF UVEITIS

Most of our knowledge of the pathophysiology of human uveitis has come from studies in animals and the development of animal models that exhibit essential features of human uveitis has played a central role in expanding our understanding of immunopathogenic mechanisms that initiate acute and chronic uveitis. Animal models have also been extensively utilized in efforts to develop new therapies and provide a template for evaluating biologics and immunomodulatory strategies that might be useful in the treatment of uveitis.

There are two well-characterized models of anterior uveitis endotoxin-induced uveitis (EIU) [4, 5] and experimental autoimmune anterior uveitis (EAAU), also called experimental melanin-induced uveitis (EMIU) [6, 7]. On the other hand, the model of posterior uveitis is experimental autoimmune uveitis (EAU), a model of posterior uveitis (Fig. 2) [8–10].

Experimental Models of Anterior Uveitis

Endotoxin-induced uveitis (EIU) is a well-characterized rodent model of acute inflammation in the anterior segment of the eye [11]. It is induced by systemic subcutaneous or intraperitoneal injection of Lipopolysaccharide (LPS) and characterized by an intense infiltration of inflammatory cells and protein exudation into the anterior segment. Although EIU is similar in many ways to human anterior uveitis, it is of very short duration (< 72 h) and the inflammatory cells recruited into the anterior segment do not cause lasting tissue damage [11]. On the other hand, EAAU is more representative of human anterior uveitis. EAAU is induced by peripheral administration of proteins bound to melanin granules and similar to EIU the disease is characterized by massive infiltration of mononuclear and polymorphonuclear cells into the anterior chamber, iris and ciliary body vessels, with minimal posterior segment involvement. Although none of these models manifest the full spectrum of clinical and histopathological features of human uveitis, each contributes to our understanding of particular aspects of the disease process.

Experimental Autoimmune Uveitis: Model of Posterior Uveitis

Experimental autoimmune uveitis (EAU) is a predominantly T-cell-mediated intraocular inflammatory disease induced in susceptible species by active immunization with ocular-specific proteins (or peptides derived from them) and is transferable to naive syngeneic animals by injection of *in vitro* activated CD4+, MHC class II restricted, T cells specific to retinal antigens [8–10]. Since the seminal studies by Wacker and colleagues showing that intradermal injection of retinal extracts can induce uveitis, a number of retinal proteins have also been found to be uveitogenic [8]. Two of the best-characterized uveitogenic retinal proteins are S-Antigen (S-Ag or arrestin) and interphotoreceptor retinoid-binding protein (IRBP). S-Ag is a 48 kDa retinal protein involved in phototransduction [12, 13], whereas IRBP is a 140 kDa retinal glycoprotein that functions in the transport of retinoids between the neural retina and the retinal pigment epithelium [14]. Other ocular proteins that are uveitogenic include recoverin, rhodopsin, opsin, phosducin and melanin associated protein [15, 16]. The experimental animal used in the majority of early studies on EAU is the Lewis rat, an inbred strain that is highly susceptible to EAU induced by all known uveitogenic antigens [17–19]. Other animal species including mice and non-human primates have also been used. Severe ocular inflammation develops in monkeys of different species following immunization with S-Ag or IRBP, suggesting that these proteins may also induce disease in humans [20]. Histologically, EAU exhibits many immunopathologic features of human uveitis, such as vitritis, retinal vasculitis, exudative retinal detachment, destruction of photoreceptor layer, retinal edema, infiltration of inflammatory cells into the choroid, iris and ciliary body [21]. EAU is thus considered a useful model of posterior uveitis.

CELLULAR AND MOLECULAR MECHANISMS THAT MEDIATE AUTOIMMUNE UVEITIS

Despite the valuable insights gained from the study of animal models of uveitis, mechanisms that initiate acute uveitis or perpetuate remitting and recurrent chronic uveitis are still poorly understood. In fact, the putative retinal antigens involved in human uveitis have not been defined. Although many uveitis patients have cellular responses to retinal S-Ag, it remains to be established whether the autoreactive T-lymphocytes are indeed the etiologic agents or if the response is secondary to retinal tissue damage caused by an on-going disease process. However, the fact that a number of retinal antigens induce disease in rodents and non-human primates that mimics human uveitis is highly suggestive of their role in the disease process. Nevertheless, none of the animal models of uveitis manifests the full spectrum of clinical features of human uveitis although each has contributed to our understanding of particular aspects of the disease process. Here, we summarize our current understanding of the pathophysiology of uveitis, with particular focus on: (i) molecular and cellular defects that lead to autoimmune pathology and susceptibility to autoimmune uveitis, (ii) autoreactive lymphocytes that mediate acute and chronic uveitis.

Central Tolerance Mechanism and Autoreactivity

The vertebrate immune system provides the primary defense against foreign pathogens and neo-antigenic determinants that have never been encountered before in the course of evolution. Its immense capacity to detect and respond to diverse antigens derives from a correspondingly great diversity of clonally distributed heterodimeric antigen receptors expressed on T lymphocytes [22]. Each T cell receptor (TCR) is generated by somatic recombination of variable (V), diversity (D), junctional (J) and constant (C) gene segments (VDJ recombination) and a consequence of the random combinatorial mechanisms is the inevitable generation of lymphocytes that can respond to self antigens and cause autoimmunity [23]. Thus, immature T cells learn to discriminate between self and non-self antigens as part of their development program in the thymus through an elaborate positive and negative selection process known as mechanism of central tolerance [24]. Positive selection for T cells occurs in the cortex of the thymus where the developing thymocytes that do not bind to self-MHC molecules expressed on cortical thymic epithelial cells die by deprivation of survival signals. The positively selected T cells are next subjected to negative selection, a process where developing T cells encounter a myriad of self-peptides presented by thymic epithelial cells and T cell clones that bind with high affinity to the self-antigens are eliminated [25]. Thus, only T cells that develop tolerance towards the self-antigens encountered in the thymus exit the thymus and enter secondary lymphoid organs and the peripheral circulation. Self-antigens that mediate negative selection are produced through the agency of the transcription factor, AIRE, which allows the expression of organ-specific antigens in the thymus [26]. Although most of the self-proteins are expressed at relatively high levels, others are below the threshold required for tolerance induction, resulting in the escape of potentially pathogenic autoreactive T cells into the periphery. Autoimmunity mediated by these renegade autoreactive T cells is thought to be the cause of organ-specific autoimmune diseases [27]. Nonetheless, these potentially pathogenic T cells are present at very low levels and kept at bay in the immune-competent host by mechanisms of peripheral

tolerance including, immune ignorance, and generation of regulatory T cells that suppress self-reactive T lymphocytes [28].

Susceptibility to Uveitis Correlates with Level of Ocular Autoantigen Expressed in Thymus

It was long assumed that ocular proteins are anatomically sequestered away from the peripheral immune system and thus not accessible to the thymus for tolerance induction. Potent immune-pathogenicity of several ocular-specific antigens also suggested that lymphocytes that mediate uveitis might not be rendered tolerant to the sequestered ocular proteins by the central tolerance mechanism described above. However, studies in the late nineties revealed that ocular proteins are indeed expressed in the thymus but their relative expression levels differed even among animals of the same species [19, 29, 30]. Ocular antigens detected in mouse thymus in these studies included lens- (αA- and γ-crystallins, major intrinsic protein (MIP)) and retina-specific proteins (S-Ag, IRBP, recoverin and opsin) [15, 19]. The mRNA transcripts of genes coding for these proteins were also detected and the proteins were present at levels that are physiologically relevant for formation of peptide: MHC complexes.

Analysis of four inbred mouse strains of known susceptibility to EAU uncovered a strong correlation between the level of expression of S-Ag or IRBP in the thymus and susceptibility or resistance to EAU development [19]. All the strains (BALB/c, AKR/J, B10.A and B10.RIII mice) that were resistant to S-Ag-induced EAU had relatively high expression levels of S-Ag mRNA in their thymi while BALB/c and AKR/J mice, which were also resistant to IRBP-induced disease, expressed IRBP in their thymi [19]. In contrast, IRBP mRNA and protein were not detectable in thymus of B10.A or B10.RIII, two strains that are susceptible to IRBP-induced disease. While IRBP-specific staining was detected in thymi of three mouse strains resistant to EAU induced by this protein (AKR/J, BALB/c and FVB/N), it was not detectable in the thymi of the susceptible B10.RIII mouse strain. In parallel, transgenic B10.RIII mice expressing high levels of uveitogenic IRBP epitopes in the thymus were also resistant to EAU induced by this antigen [31]. The correlation between the expression of high levels of uveitogenic proteins in the thymus and resistance to EAU development also extends to rats and non-human primates (Table 1). Lewis rats are highly susceptible to EAU induced by S-Ag or IRBP [17, 32] and transcripts of both proteins could not be detected in the Lewis rat thymus. Brown Norway rats are susceptible to IRBP-induced EAU they are partially resistant to S-Ag-induced disease. Thus, IRBP transcript was not detected in the thymi of Brown Norway rats, whereas low levels of S-Ag transcripts were detected, albeit in very low quantity, further underscoring the correlation between thymic expression of ocular autoantigens and susceptibility to EAU [19]. In Rhesus monkeys low level expression of S-Ag mRNA was detected in the thymus of one of four tested monkeys [19], an observation in accord with the high susceptibility of monkeys to EAU induction by both S-Ag or IRBP in most but not all tested monkeys [20, 33, 34]. Taken together these observations provide a mechanistic explanation for the differences in susceptibility to autoimmune uveitis and suggest that resistance to autoimmune uveitis may be regulated at least in part by capacity to establish central tolerance to retinal autoantigens.

Th17 and Th1 Lymphocytes Mediate the Development and Recovery from Uveitis

Although the cause of non-infectious uveitis is largely unknown, mounting evidence from mouse and human studies points to possible involvement of Th17 T-helper lymphocyte subset in the development of uveitis while Th1 cells are suspected to mediate recovery from the disease (Fig. 3). The blood of patients with uveitis contained more Th17 cells than blood of healthy individuals [35]. In addition, Th17 levels were found to increase during active uveitis and decrease following treatment, suggesting that Th17 cells may sustain inflammatory disease in these patients. These observations have been validated in EAU studies as Th17 cells were detected in the retina of mice with EAU but not normal mouse retina and the presence of Th17 cells in the retina temporally correlated with the onset of EAU [35]. Moreover, treatment with antibody to IL-17 reduced the severity of EAU, providing direct evidence for the involvement of Th17 cells in EAU pathogenesis [35]. Although both Th17 and Th1 cells are present in the eye during EAU, the former are most abundant in the retina at early stages of the disease, whereas the latter are most abundant at late stages associated with resolution of the disease [35]. These observations thus establish a positive correlation between the increase in Th17 cells and the pathogenicity of EAU, while the increase in Th1 cells correlates with recovery from EAU. Interestingly, IL-2 promotes Th17 expansion in human PBMC while IFN-γ, produced by Th1 cells inhibits Th17 expansion by up-regulating IL-27 expression, suggesting that inhibition of Th17 cells by IFN-γ and IL-27 could be exploited for treatment of uveitis.

It is however interesting to note that Th17 is one of the five major T-lymphocyte subtypes (Th1, Th2, Th17, Tfh, Treg) that mediate immunity in mammals and in comparison to other T-helper subsets, Th17 cells are invariably implicated in the etiology of most organ-specific autoimmune diseases. Although the reasons for the remarkable success of Th17 cells as etiologic agents is not fully understood, recent studies have provided mechanistic explanation for the frequent involvement of Th17 cells in uveitis. Genetic ablation studies in mice revealed that the quintessential Th17 transcription-factor, STAT3, collaborates with Class-O Forkhead transcription-factors in conferring survival advantages to Th17 phenotype by limiting IL-2 production to very low levels that do not provoke IL-2-induced activation-induced-cell-death and yet sufficient to promote their homeostatic expansion [36]. These thus allow Th17 effector cells to survive and persist in peripheral tissues and promote chronic inflammation. Physiological relevance of IL-2-expressing Th17 cells (Th17-DP) is suggested by the findings that the majority of Th17 in human blood and substantial percentage of autoreactive T cells that mediate EAU are Th17-DP [37].

Chronic Uveitis and Pathogenic T Cells That Mediate Recurrent Uveitis

A vexing and important issue pertinent to the development of effective treatment for uveitis and other CNS autoimmune diseases is the age-old question of where autoreactive pathogenic memory T cells reside in between episodes of acute inflammation and how to deprive them of factors that promote their survival. This is particularly relevant to Behçet's disease, a recurrent disease that can lead to permanent vision loss in 20% of cases. It is characterized by unpredictable recurrent inflammatory attacks that can subside spontaneously with no evidence of overt inflammation in between attacks. Although EAU shares essential features with human uveitis, it is generally considered a self-limiting

inflammatory disease and the insidious and clinically important manifestations of chronic uveitis are not usually observed in the mouse EAU model. Lack of a useful animal model of chronic human uveitis has therefore been an impediment to a comprehensive understanding of the natural history and pathophysiology of chronic uveitis. This limitation of the EAU model has been overcome by the recent development and adaptation of non-invasive instrumentation utilized in ophthalmology such as Fundoscopy, Optical Coherence Tomography (OCT) and Electroretinography (ERG) for use in the mouse [38–40]. Thus, the establishment of a mouse model of chronic uveitis characterized by progressive photoreceptor cell loss, retinal degeneration, focal retinitis, retinal vasculitis, multifocal choroiditis, and choroidal neovascularization, now provides a useful model for studying the etiology of chronic uveitis and the long-term pathological consequences of chronic inflammation of the neuroretina [21]. Direct *in vivo* tracking of uveitogenic T cells in host tissues of EAU mice revealed a time-dependent relocation of autoreactive pathogenic memory T cells that mediated acute uveitis from the retina to the bone marrow (BM) where they resided in a resting state [21]. This study demonstrated that resting BM memory T cells converted into pathogenic effectors upon re-stimulation with ocular autoantigen and induced uveitis in adoptive transfer studies. It is of note that the recruitment and retention of the autoreactive T cells in the BM required up-regulation of α4β1 and osteopontin expression through STAT3-dependent mechanisms [21]. Identifying the BM as survival-niche for the memory T cells, suggests that BM stromal cells that support survival of IRBP-specific autoreactive memory T cells are potential therapeutic targets that can be exploited to selectively deplete memory T cells that drive chronic inflammation.

CURRENT TREATMENT OF OCULAR INFLAMMATORY DISEASES

Anterior uveitis is the most common form of uveitis and is treated with topical corticosteroid and periocular corticosteroid injections are used to treat severe unilateral anterior, intermediate or posterior uveitis, especially if accompanied by cystoid macular edema, a significant cause of vision loss. The standard of care for treatment of vision-threatening uveitis is systemic immunosuppression with an oral corticosteroid such as prednisone and if corticosteroid is ineffective, it is used at a lower dose in combination with cyclosporin A, antimetabolites (methotrexate, azathioprine) or an anti-inflammatory (colchicine) (see Table 2). In cases where use of corticosteroid in combination with these second line drugs fails to reduce sight-threatening ocular inflammation, then, alkylating agents such as cyclophosphamide or chlorambucil is recommended. However, use of alkylating agents is associated with high risk of adverse effects and is therefore employed as a last resort. Of particular concern is the overall risk of systemic immunosuppression, increased risk of infections and malignancy and a decreased lifespan that is associated with prolonged use of corticosteroids. The adverse effects of anti-inflammatory (corticosteroids), cytotoxic (alkylating agents) and powerful immunosuppressive (cyclosporin A, FK-506, rapamycin) drugs have been the impetus for the urgent need to develop less toxic and more specific therapies for uveitis and other organ-specific autoimmune diseases.

EMERGING STRATEGIES FOR THE TREATMENT OF UVEITIS

Therapeutic intervention in uveitis or other autoimmune diseases presents formidable challenges, due the need to strike a balance between controlling pathogenic immune responses and preventing generalized immunosuppression that can undermine vital immune surveillance mechanisms. Data from the clinic and animal models of uveitis over the past decade form the basis of emerging strategies for the treating uveitis and these include: (i) Therapeutic inhibition of T-lymphocyte activity by anti-IL-2R therapy or neutralization of IFN-γ; (ii) Anti-TNF-α therapy by use of Etanercept (Enbrel®), Infliximab (Remicade®) or Thalidomide, (iii) targeting of the CD4 molecule or immune modulatory molecules (adhesion or costimulatory molecules). Several excellent reviews [41–44] have addressed these strategies of inhibiting T-lymphocyte functions and they will not be covered here. Instead, we will discuss new strategies based on targeting signal transduction pathways that regulate the functions of inflammatory and ocular cells and the therapeutic use of IL-12 family cytokines and fusokines (Table 3).

Targeting STAT3 Pathways

Discovery that expansion of Th17 cells in normal human blood is a potential cause of human uveitis suggests that blocking the development or biological activities of Th17 cells can be exploited as a treatment for uveitis and other potentially blinding ocular inflammatory diseases. The Th17 subset is induced by IL-6 and TGF-β1 and characterized by a unique transcriptional program dependent on STAT3 and SMAD signal transduction pathways, respectively [45, 46]. The transcription factors, retinoic-acid-receptor-related orphan receptors gamma (ROR-γt) and alpha (RORα) are two factors essential for Th17 development and expansion. They induce expression of the IL-23 receptor through STAT3-dependent mechanisms, rendering the differentiating cells responsive to IL-23, an innate immune cell cytokine that stabilizes the Th17 phenotype. Consistent with the critical role of STAT3 in Th17 differentiation, mice with targeted deletion of STAT3 in $CD4^+$ T-cells (CD4-STAT3KO) cannot generate Th17 and do not develop EAU due in part to defective expression of α4β1 or α4β7 expression, intergrins required for trafficking into the retina [38, 47]. As described above, re-localization of autoreactive uveitogenic memory T cells from the retina to the bone marrow is dependent on STAT3, suggesting a role of STAT3 in establishment of chronic uveitis [21]. Thus, STAT3 and Th17 cells are potential therapeutic targets. Several therapeutic strategies for uveitis are described below.

STAT3 Inhibitors—Several compounds that inhibit STAT3 pathway and Th17 cells *in vitro* have been developed. One of these is ORLL-NIH001, a synthetic 406-kDa small chemical compound that has recently been shown to inhibit EAU [48]. ORLL-NIH001 substantially reduced levels of Th17 cells, as well as, the IFN-γ-expressing Th17 subset that correlates with development of EAU [48]. Its inhibitory effects derive in part from down-regulating the expression of α4β1, α4β7, CCR6 and CXCR3, immune-modulatory proteins required for lymphocyte trafficking into the retina [48]. Importantly, ORLL-NIH001 suppressed EAU in mice that received the drug after EAU had been established, suggesting that ORLL-NIH001 may be used in treating pre-existing uveitis [48]. However, a drawback

to therapeutic use of ORLL-NIH001 is its bioavailability, as frequent administration of the drug is required.

Synthetic Chemical Inhibitors of Th17 Developmental Pathway—In addition to STATs, the Th17 master transcription factors, ROR-γt and RORα are potential therapeutic targets in Th17-mediated disease. Two drugs, Digoxin, a cardiac glycoside used for the treatment of heart conditions and SR1001, a derivative of the benzenesulphonamide drug T0901317, have recently been used to block the activities of RORα and ROR-γt and prevent Th17 differentiation by inhibiting the expression of Th17 signature genes including IL23R, IL-17A, IL-17F and IL-22 [49, 50]. Most importantly, both drugs delayed the onset and reduced the severity of EAE. Thus, Digoxin and SR1001 are potential drugs that can be exploited for the treatment of uveitis.

Immunomodulation of Suppressors of Cytokine Signaling (SOCS) Proteins

The JAK/STAT pathway is an evolutionarily conserved signal transduction mechanism that regulates, temporally and spatially, a myriad of physiological processes in mammals. STAT activation must by necessity be transient and the initiation, duration, and intensity of STAT signals is therefore under stringent regulation [51, 52]. Regulators of JAK/STAT pathways include cytoplasmic inhibitory proteins (PIAS, SHP-1, and SHIP-2) and suppressors of cytokine signaling (SOCS) and unbridled activation of STAT proteins is associated with a variety of pathological conditions including chronic auto-inflammatory diseases [53]. In context of immune modulation therapy, much interest has centered on SOCS proteins, particularly SOCS1 and SOCS3 that are induced by cytokines during lymphocyte activation and constitute a negative feedback loop that regulate cytokine-mediated inflammatory responses [54, 55]. Because SOCS proteins are intracellular proteins, a major impediment to their use in inhibiting inflammatory disease has been finding efficient means of delivering SOCS proteins into cells. Two promising approaches have now been developed to enhance the negative regulatory functions of SOCS1 and SOCS3 *in vivo* and are described below.

Cell-Penetrating SOCS1 (CP-SOCS1) and CP-SOCS3 Proteins—Recombinant cell-penetrating SOCS1 (CP-SOCS1) and CP-SOCS3 proteins have been generated by fusing SOCS1 or SOCS3 to a 12 amino acid hydrophobic sequence of the signal peptide of the Karposi FGF4 protein as described [54]. Delivery of MTS-SOCS1 into macrophages inhibits IFN-γ-induced STAT1 activation while MTS-SOCS3 inhibited expansion of pathogenic Th17 cells *in vitro.* Of particular interest in context of immunotherapy, delivery of CP-SOCS3 protein into immune cells has been used to protect mice from lethal effects of staphylococcal enterotoxin B (SEB) and lipopolysaccharide challenge [54]. These studies have thus laid the foundation for eventually utilizing MTS-SOCS proteins in treating auto-inflammatory diseases such as uveitis.

SOCS1 and SOCS3 Mimetic Peptides—Some SOCS proteins possess a KIR Kinase inhibitory Region (KIR) that binds to tyrosine-phosphorylated JAKs and suppress JAK activities [56, 57]. SOCS1 and SOCS3 KIR mimetics inhibit STAT pathways and the small peptide mimetics of SOCS1 has been used to effectively inhibit IL-6 and IFN-γ signaling *in vitro* and *in vivo* by targeting JAK/STAT pathway [58–60]. Several SOCS1 mimetic

peptides (Table 3) are effective in inhibiting JAK2 kinase activity including some designed to deliver the KIR mimetics attached to lipophilic palmitoyl-lysine and arginine groups. It is of note that the SOCS1 mimetics have been used to inhibit Th17 expansion immune functions in EAE [58–60]. Treatment with tyrosine kinase inhibitor peptide (Tkip) mimetics prevented the development of acute EAE in 75% of treated New Zealand White mice, and completely protected SJL/J mice from the chronic relapsing/ remitting form of EAE [61]. Orally administered SOCS1 mimetics antagonize STAT3 activation and inhibit production of IL-17, IFN-γ, TNF-α and IL-23 by inflammatory cells [62]. Because they readily cross the blood brain barrier (BBB), SOCS1-KIR are considered to be more clinical efficacious than therapeutic antibodies that have difficulty in crossing the BBB.

Therapeutic Cytokines

Cytokines play crucial roles in shaping immune responses by influencing cell-fate decisions of differentiating T-cells while effective defense against pathogens depends on cytokines produced by activated immune cells. IL-12 family of cytokines have emerged as important regulators of T-helper cell lineage commitment and the differentiation, growth and functions of a variety hematopoietic cells that regulate host immunity. The IL-12 family of cytokines is comprised of four heterodimeric cytokines, IL-12 (IL12p35/IL12p40), IL-23 (IL23p19/IL12p40), IL-27 (IL27p28/Ebi3) and IL-35 (IL12p35/Ebi3). Each member is composed of an α-subunit with a helical structure similar to type 1 cytokine, IL-6, and a β-subunit structurally related to the soluble IL-6 receptor (IL-6Rα). Chain-pairing promiscuity is a distinctive feature that accounts for their involvement in many aspects of host immunity [63]. While some members (IL-12 and IL-23) exert dominant immunostimulatory functions and are implicated in the pathogenesis of several chronic inflammatory diseases, others (IL-27 and IL-35) possess potent immunosuppressive activities and mitigate autoimmune diseases [63]. Although we do not fully understand the mechanisms that underlie the positive and negative feedback controls on many cell types by IL-12 family cytokines, they provide unique opportunities for therapeutic applications. Studies in mouse models of uveitis have established involvement of IL-12, IL-23, IL-27 and IL-35 in ocular inflammatory diseases, our focus here is on recent studies that have utilized IL-27, IL-35 and their single chain subunits to inhibit EAU.

IL-27p28 Single Chain Protein—Th17 cells have been implicated in the etiology of uveitis and IL-27 production by retinal cells has been shown to inhibit Th17 expansion in the retina during EAU through STAT1-dependent mechanism [64]. These results suggest that antagonism of Th17 by IL-27 can be exploited for treatment of uveitis. However, IL-27 signals through STAT1 and STAT3 and is a functionally flexible cytokine endowed with either immunosuppressive or immune-stimulatory properties, depending on the physiological or differentiation state of its target cell. Thus, therapeutic use of IL-27 must be approached with caution. Recent studies have therefore examined the specific role of each of its two subunits, IL-27p28 and Ebi3 to determine whether the diametrically opposite functions of IL-27 can be attributed to a specific subunit. Biologically active recombinant IL-27p28 suppresses T cell proliferation of primary T cell and it was therefore used to examine whether the single chain subunit possesses suppressive or stimulatory activities independent of the heterodimeric IL-27. These studies revealed that administration

of IL-12p28 at the time of EAU induction inhibited Th17 expansion and mitigated EAU pathology [65].

IL-27p28/IL-12-p40 Fusokine—An attractive approach that has been used to create novel therapeutic cytokines is to combine the cytokine with a ligand that can serve to target the therapeutic cytokine or protein to a receptor or target tissue of choice. Fusion proteins combining different bioactive ligands are termed fusokines and have been used in modulating immune responses to therapeutic advantage. This concept led to the bioengineering of the IL-27p28/IL-12-p40 fusokine [65]. IL-12p40 is a subunit of the IL-12 or IL-23 cytokines and when secreted as a homodimer functions as an antagonist by competing with IL-12 for IL-12Rα [66]. Similarly, IL-27p28 antagonizes IL-6 by preventing the binding of IL6 to the gp130 receptor chain [67]. The IL-27p28/IL-12-p40 fusokine was thus generated to harness the suppressive activities of the IL-12p40 and IL-27p28 proteins. In a proof-concept study, *in vivo* administration of the IL-27p28/IL-12-p40 fusokine suppressed EAU by inhibiting the differentiation and inflammatory responses of both Th17 and Th1 cells while promoting expansion of regulatory T cells (Tregs) [65]. Furthermore, adoptive transfer of uveitogenic cells from mice treated with the IL-27p28/IL-12-p40 fusokine blocked EAU induced in naive syngeneic mice [65]. Notably, mechanisms underlying the suppressive effects of IL-27p28 single chain protein or the IL-27p28/IL-12-p40 fusokine derived in part from inhibiting the activation of STAT3 and STAT1 pathways induced by IL-6 and IL-27, both of which signal through gp130 receptor. Interestingly, the IL-27p28/IL-12-p40 fusokine also inhibits signaling downstream IL-12Rβ1, an effect that may explain the concomitant suppression of Th17 (mediated by IL-6 and thus gp130) and Th1 (mediated by IL-12Rβ1) responses [65]. These observations thus suggest that by inhibiting IL-6 signaling and Th17 expansion, the IL-27p28/IL-12-p40 fusokine might skew the immune response towards to Treg differentiation thereby promoting immunosuppressive Treg-mediated responses.

Single-chain IL-35 Subunits (IL-12p35 and Ebi3)—IL-35 has been shown to possess potent immunosuppressive function in mouse and human studies [68]. It mediates its biological functions through IL-35 receptors, IL12Rβ2-gp130, IL-12Rβ2-IL-12Rβ2, IL-12Rβ2-IL-27Rα or gp130-gp130 and activates STAT1, STAT3 and/or STAT4 [69, 70]. The IL-35 heterodimeric cytokine was recently engineered in a bicistronic vector and showed that IL-35 preparations contain significant levels of p35:p35 and Ebi3:Ebi3 homodimers that antagonize the heterodimeric IL-35 [69]. Whereas the single-chain IL-12p35 could not activate STAT1 and STAT3 it inhibited IL-6-induced STAT3 activation while enhancing IL-27-induced activation of STAT1 [69]. This observation is reminiscent of the findings that IL-27p28 and IL-12p40 could not activate STATs but suppressed T cell proliferation by inhibiting STAT1, STAT3 and STAT4 activation by IL-27, IL-6 and IL-12, respectively [65, 67]. The finding that IL-12p35 and Ebi3 inhibit proliferation of T and B lymphocytes, suggests that IL-12p35 and Ebi3 possess intrinsic immune suppressive activities independent of the heterodimeric IL-35 and can be exploited therapeutically to inhibit uveitis and other autoinflammatory diseases [69].

Interleukin 35 Therapy—IL-35 exerts its anti-inflammatory effects by inhibiting effector T cell responses through expansion of IL-10- and/or IL-35-producing regulatory T cells or iTR5 [68] or regulatory B cells that produce IL-10 (Bregs) or IL-35 (i35-Bregs) [69, 71]. Of note, treatment of mice with IL-35 confers protection from EAU, and mice lacking IL-35 (IL12-p35 or Ebi3 knockout mice) or defective in IL-35 signaling (IL-12Rβ2 knockout mice) produce less Breg cells and i35-Bregs and develop severe uveitis [69]. Adoptive transfer of ex-vivo generated Breg cells suppressed EAU when transferred to mice with established disease by inhibiting pathogenic Th17 cells while promoting expansion of Tregs. IL-35 also induces the conversion of human B cells into Breg cells, suggesting that IL-35 can be used to induce autologous Breg and IL-35+ Breg cells and treat uveitis and other ocular inflammatory diseases. Therapeutic cytokines and autologous tolerogenic B cell therapy thus provide novel approaches for treatment of autoimmune uveitis with potentially less undesirable off-target effects mediated by corticosteroid-based therapies.

CONCLUSION

The development of animal models of intraocular inflammatory diseases has immeasurably contributed to our understanding of the molecular mechanisms that underlie the etiology and susceptibility to uveitis. The remarkable advances in ocular immunology and in the development of Biologics over the past two decades have ushered in a new era of targeted treatment modalities for this family of potentially blinding diseases that are a major cause of morbidity. In this review, we have summarized some of the key mechanisms that contribute to the development of uveitis and noted potential therapeutic targets that can be exploited to mitigate or modulate uveitis. Use of Biologics such as humanized monoclonal Abs specific to the IL-2R (Anti-Tac mAb), soluble TNF receptor (Etanercept or Enbrel), TNF-α (Infliximab or Remicade) or soluble IFN-γ receptor are efficacious to varying degrees. Immune modulation strategies based on targeting adhesion and chemotactic molecules (mAb against LFA-1 and ICAM-1), blocking signal transduction pathways (Rapamycin, cyclosporine A, CTLA4) or oral tolerance using soluble retinal proteins and HLA peptides that mimic ocular antigens are all exciting new therapeutic strategies gleaned from studies in animal studies. Identification of the Th17 subset and its implication in the etiology of human and mouse uveitis revealed additional therapeutic targets that can be used to treat uveitis. Thus, inhibitors of transcription factors that regulate Th17 development, small synthetic compounds that inhibit STAT3 or ROR-γT as well as, SOCS mimetics have yielded promising results. However, the most exciting therapeutic and promising experimental therapeutic strategy is cell based therapy and in this context, the use of autologous tolerogenic B-cells or Breg/i35-Breg therapy has been shown to be effective in ameliorating uveitis in the EAU model.

Biography

C.E. Egwuagu

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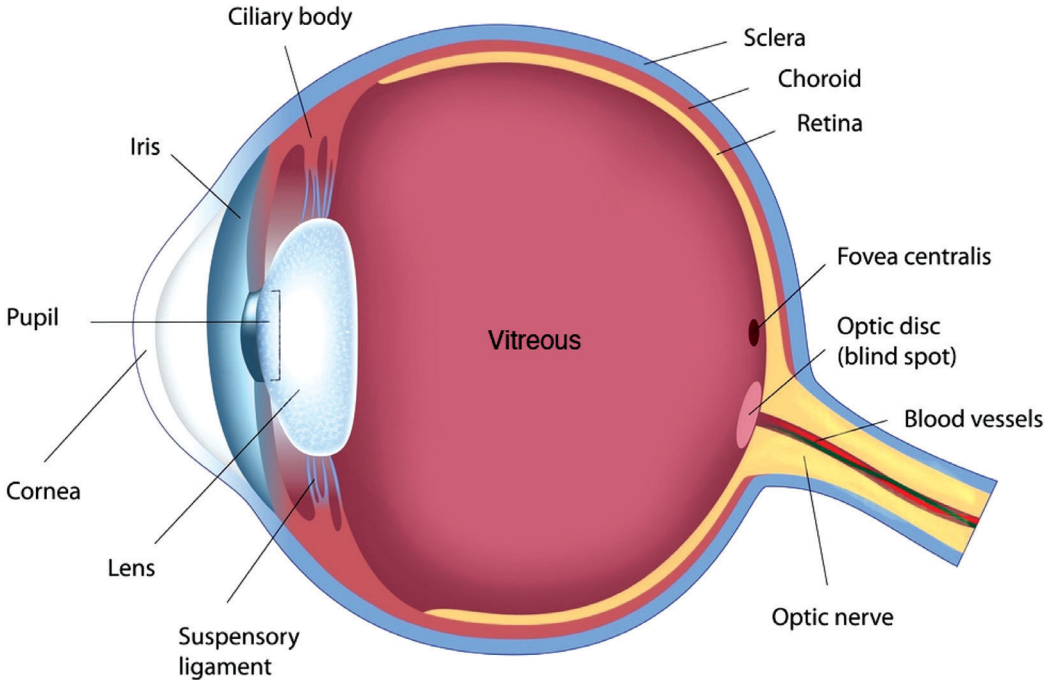
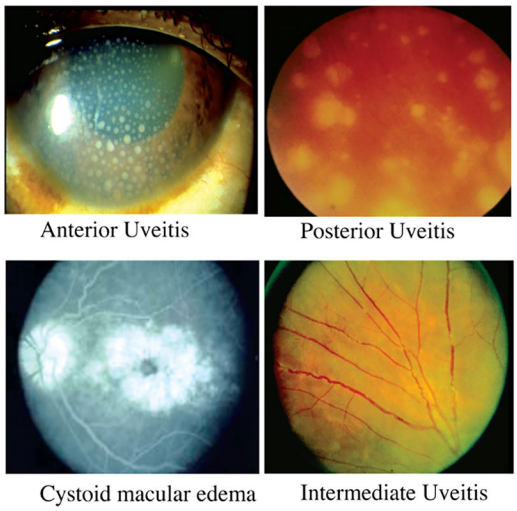


Fig. (1).

Anatomy of the Eye. The eye is a complex sensory organ, which is essential to the visual system that allows vertebrates to assimilate light rays from their surroundings, processes and converts them into neuronal signals that are interpreted as an image. The retina plays a critical role in the process of vision, hence, damage to the retina can cause permanent visual lose.



Causes of Anterior Uveitis:
Idiopathic
Ankylosing spondylitis
Reiter's syndrome
Inflammatory bowel disease
Psoriatic arthritis
Juvenile rheumatoid arthritis
Fuchs' heterochromic iridocyclitis
Sarcoidosis
Syphilis
Glaucomatocyclitic crisis
Masquerade syndromes

Cause of intermediate uveitis:
Sarcoidosis
Inflammatory bowel disease
Multiple sclerosis
Lyme disease
Intermediate uveitis/pars planitis subtype

Causes of Posterior Uveitis:
Focal retinitis
- Toxoplasmosis
- Onchocerciasis
- Cysticercosis
- Masquerade syndromes

Focal choroiditis
- Toxocariasis
- Tuberculosis
- Nocardiosis
- Masquerade syndromes

Multifocal choroiditis
- Histoplasmosis
- Sympathetic ophthalmia
- Vogt-Koyanagi-Harada disease
- Sarcoidosis
- Serpiginous choroidopathy
- Birdshot choroidopathy
- Masquerade syndromes

Fig. (2).

Classification and manifestations of uveitis. Uveitis is a group of inflammatory eye diseases that affect the lens, retina, optic nerve, and vitreous, resulting in visual impairment or blindness. Based on the scheme proposed by the International Uveitis Study Group (Bloch-Michel and Nussenblatt 1987), uveitis can be classified as anterior, intermediate, or posterior uveitis and panuveitis depending on the anatomic position of inflammation.

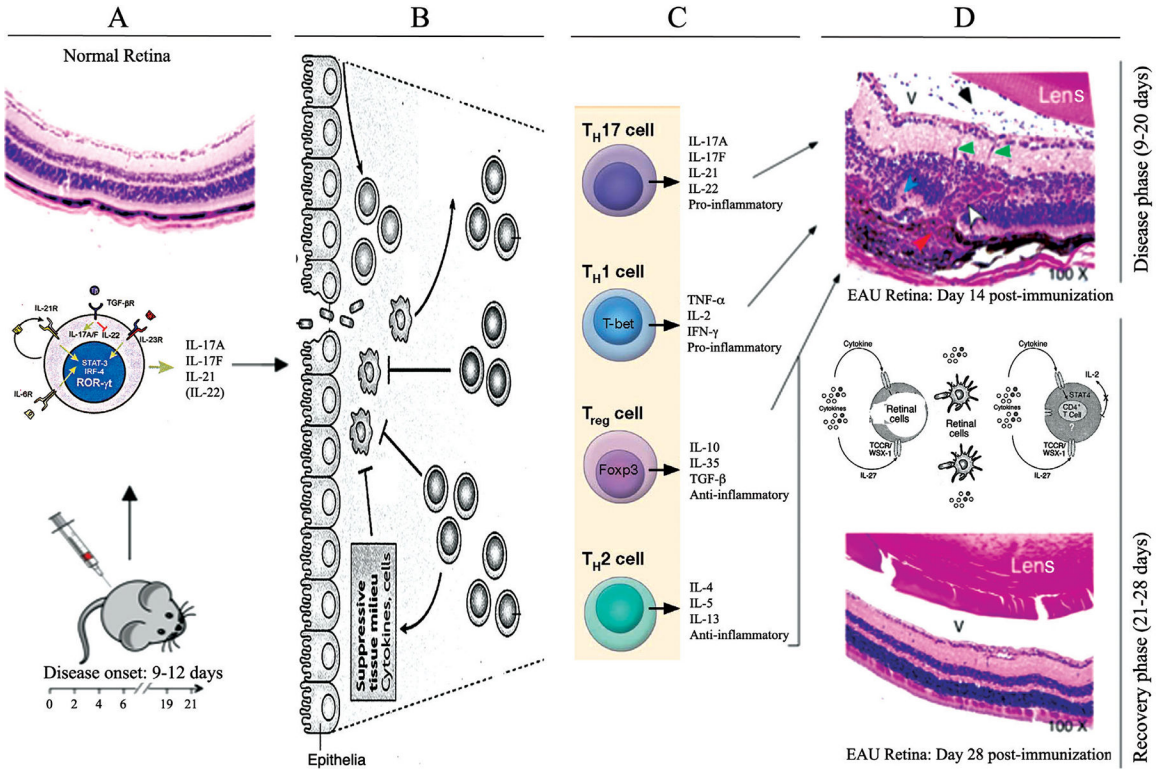


Fig. (3).

Schematic representation of early events associated with loss of immune privilege of the eye and induction of retinal protective mechanism in rodent model of uveitis. (**A**) Immunization of susceptible mouse strains with retinal proteins in the context of complete Freund's adjuvant (CFA) elicits a Th17 and Th1 mediated immune response. (**B**, **C**) Effector molecules such as granzyme and pro-inflammatory cytokines secreted by Th17 cells facilitate breakdown of blood ocular barrier (BOB) accompanied by influx of other inflammatory cells (such as Th1, Th2, monocytes). The inflammatory cells entering the eye encounter hostile environment of the retina consisting of anti-inflammatory molecules and resident retinal cells express inhibitory cell surface associated proteins (TGF-β, FAS/FAS ligand, CD46 and CD59). (**D**) Incidental elimination of pathogenic cells from retina derives from endogenous adaptive ocular mechanisms that maintain immune privilege. IFN-γ/STAT1-induced IL-27 production of IL-27, SOCS1 and SOCS3 by resident ocular cells contribute to mitigation of uveitis.

Table 1.

Inverse correlation between thymic expression of retina specific antigens and degree of susceptibility to EAU.

Species	Thymic Expression	Susceptibility to EAU
B10.RIII mice	− (IRBP)	+ +
	+ (S-Ag)	−
B10.A mice	− (IRBP)	+ +
	+ (S-Ag)	−
BALB/c mice	+ (IRBP)	−
	+ (S-Ag)	−
AKR/J mice	+ (IRBP)	−
	+ (S-Ag)	+/−
Lewis Rats	− (IRBP)	+ + + +
	− (S-Ag)	+ + + +
Brown Norway Rats	− (IRBP)	+ +
	+ (S-Ag)	+/−
Rhesus Monkeys	− (IRBP)	+ + +
	+/− (variable S-Ag)	+ + +

Inverse correlation between thymic expression of IRBP and/or S-Ag mRNA transcripts and degree of susceptibility to uveitis in rodents and non-human primates (+ indicates expression and − indicates no expression).

Table 2.

Immunosuppressive drugs used to treat inflammatory ocular diseases.

Immunosuppresive Drugs	Side Effects
Cyclophosphamid	Hemorrhagic cystitis, bone marrow (BM) suppression*, secondary malignancy, bladder carcinoma, alopecia, teratogenicity, pulmonary damage, cardiotoxicity
Chlorambucil	BM suppression*, gonadal dysfunction, secondary malignancy, pulmonary fibrosis
Methotrexate	Interstitial pneumonitis and pulmonary fibrosis, hepatotoxicity, ulcerative stomatitis, diarrhea, BM suppression*, nausea, ocular irritation, alopecia, gastrointestinal distress
Corticosteroid	Diabetes mellitus, avascular necrosis of the femoral neck, hypertension, seizure, psychosis, pancreatitis. Osteoporosis, myopathy, ulcer, hypokalemia, adrenal suppression, obesity, cataract, growth suppression, striae
Azathioprine	BM suppression*, nausea, alopecia, hepatotoxicity secondary malignancy
Cyclosporin A	Neurotoxicity, hypertension, hyperuricemia, hepatotoxicity, renal toxicity, temperature hypersensitivity, hypertrichosis, gingival hyperplasia, common drug interactions, angioedema
Dapsone	Hemolytic anemia (glucose-6-phosphate deficiency), nausea, mononucleosis-like syndrome, blurred vision, methemoglobinemia, peripheral neuropathy, psychosis
Colchicine	Hemorrhagic gastroenteritis, nausea, vomiting, BM suppression*, nephrotoxicity, ascending paralysis of central nervous system, azospermia, alopecia, myopathy, vascular damage
Newer Agents	Side Effects
Rapamycin	Increased susceptibility to infection and the possible development of lymphoma and other malignancies stomach pain, headache, constipation, diarrhea, nausea, joint pain
FK506	Headache, uncontrollable shaking, diarrhea, constipation, nausea, vomiting, heartburn, stomach pain, loss of appetite, insomnia, dizziness, weakness, back or joint, pain, burning, numbness, pain, or tingling in the hands or feet, rash, itching
Mycophenolate motetil	Increased risk of loss of a pregnancy (miscarriage) and higher risk of birth defects, Increased risk of getting serious infections, Increased risk of lymphoma and skin cancers
Daclizumab	Increased susceptibility to infection, upset stomach, nausea, or vomiting, diarrhea or constipation, tremor or dizziness, headache, swelling of the hands, feet or legs

*Bone marrow suppression, pancytopenia, leukopenia, thrombocytopenia and anemia.

Table 3.

New therapeutic approaches to treat autoimmune diseases.

Class	Targeted Pathways
STAT3 inhibitors: ORLL-NIH001, S31-201	STAT3-Th17 axis
Synthetic chemical inhibitors: Digoxin, SR1001	STAT3-Th17 axis
Cell-penetrating SOCS proteins: CP-SOCS1, CP- SOCS3	JAK-STAT pathways
SOCS mimetics: SOCS1-KIR, SOCS1-KIR2A, tKIP	JAK-STAT pathways
IL-6/12 Family Cytokines and Single-Chain Subunits	**Targeted Lymphocytes**
IL-27p28	Antagonizes IL-6 and IL-27: Inhibits induction of Th17 and Th1 cells
IL-12p40	Antagonizes IL-12: Inhibits induction of Th1 cells
IL-12p40/IL-12p40	Antagonizes IL-12: Inhibits induction of Th1 cells
IL-27	Promotes Tr1 Induction, Inhibits Th17 expansion
IL-35	Induces i35B and iT35 regulatory cells, promotes Breg expansion, Inhibits Th1 and Th17 induction, inhibits Th1 expansion, Converts Th2 cells into iT35 cells
Fusokines	**Targeted Lymphocytes**
IL-27p28/IL-12p40	Antagonizes IL-6 and IL-12: Inhibits induction of Th17 and Th1 cells
GIFT15 (GM-CSF-IL-15)	Promotes an regulatory B cell population with anti-inflammatory properties