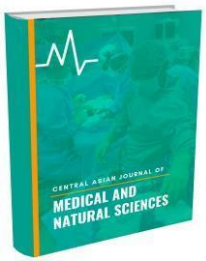

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Article

Recent Advances in Immunotherapy for Autoimmune and Inflammatory Diseases

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Abstract: Autoimmune and inflammatory diseases represent a significant global health burden, characterized by dysregulated immune responses that target the body's own tissues. Recent advances in immunotherapy have revolutionized the management of these disorders, offering more precise and effective treatment strategies. Biological agents, such as monoclonal antibodies targeting tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17), have significantly improved outcomes in conditions like rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Additionally, therapies modulating T-cell activity, such as abatacept and anti-CD20 therapies like rituximab, have shown efficacy in systemic lupus erythematosus and multiple sclerosis. The emergence of Janus kinase (JAK) inhibitors represents another promising advancement, providing oral options that disrupt intracellular signaling pathways involved in immune activation. Furthermore, tolerogenic vaccines and antigen-specific immunotherapies are being explored to re-educate the immune system and promote immune tolerance. Cellular therapies, including regulatory T cell (Treg) expansion and mesenchymal stem cell transplantation, also hold potential for long-term immune modulation. While these innovations mark a significant leap forward, challenges remain, including the risk of infections, high costs, and variable patient responses. Personalized medicine approaches, integrating genetic, immunological, and clinical data, are expected to refine treatment selection and improve efficacy. In conclusion, recent developments in immunotherapy offer new hope for patients with autoimmune and inflammatory diseases, moving toward targeted, individualized care that aims not only to control symptoms but also to modify disease progression and restore immune balance.

Keywords: Immunotherapy, Autoimmune Diseases, Inflammatory Disorders, Biologic Agents, JAK Inhibitors, Targeted Therapy

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1. Introduction

Autoimmune and inflammatory diseases are caused by aberrant immune tolerance mechanisms that activate pathogenic immune responses toward self-antigens. Over the years, treatments of different types have been developed for treating autoimmune diseases [1]. These include potent immune-suppressive drugs like corticosteroids (as monotherapy or combined with other drugs) and various immune-modulating therapies like biologics. A growing number of novel treatments acting on the immune system have been developed in recent years and have reshaped treatment options in many autoimmune and inflammatory diseases [2]. A better understanding of the immune pathogenesis of diseases has also contributed to treatment advancements. New immunotherapies harness the

body's own immune system to recognize and fix issues that cause disease rather than using calmer immune system [3].

The skin barrier protects the body from desiccation and microbial invasion and plays a key role in self-tolerance. The skin harbors almost half of the body's DCs and all subtypes can be found in the epidermis and dermis. Skin DCs convey both pro-inflammatory signals and tolerance cues to naïve T cells, thus sculpting T cell immunity. Reciprocally, Tregs play a critical role in allergen-desensitization promoting an immunosuppressive milieu that leads allergen tolerance [4]. Disruption of this fine cross-talk initiates pathogenic TH2 cell-mediated eosinophilic inflammation. There are pro-resolving mediators that can be exploited to induce tolerance against allergens like IL-9, which elicits multiple protective functions like inducing granule recruitment, enhancing skin-barrier integrity, and upregulating TH1-co-stimulatory molecules on DCs [5]. The self-healing capacity of cutaneous inflammation is also reassured by immune-regulatory innate lymphoid cells types 2 and 3. Understanding how skin lesions resolve spontaneously after scratch exposure, in the absence of exogenous IL-10, represents an unmet need, before performing clinical trials targeting this pathway. The discovery of tissue-centric regulatory T cells mindset emphasizes their protective role in tissue healing and regulation against excessive inflammation, representing a new avenue for new immunotherapy [6].

Understanding Autoimmune and Inflammatory Diseases

Diseases of immune dysregulation affect an estimated 40% of the global population. Autoimmune diseases such as type 1 diabetes, lupus, and multiple sclerosis arise from inappropriate antigen-specific immune responses to self-antigens [7]. Autoimmune pathology can be directed against a variety of molecules, including protein, lipid, and carbohydrate antigens, and inflammation during the chronic stages of disease is largely promoted by lymphocytes, principally T and B cell that have been activated by recognition of cognate antigens presented on major histocompatibility complex and stimulation by costimulatory signals. In contrast, allergic diseases are mediated by inappropriate activation of largely CD4+ T eosinophils and mast cells against non-self foreign antigens [8]. These diseases, primarily the result of Th2-biased immunity, are characterized by the production of Th2 cytokines that coordinate production of IgE, IgG, and pro-inflammatory milieu and the secretion of mediators and the release of inflammatory molecules by mast cells and eosinophils [9]. Finally, autoinflammatory diseases, largely of monogenetic origin, are caused by persistently activated myeloid cells which mediate antigen-independent innate immune pathology. The principal effectors of innate immunity are macrophages, monocytes, and dendritic cells, which produce pro-inflammatory cytokines and chemokines and phagocytose pathogens [10]. Many diseases involve a mixture of innate and adaptive immune dysregulation and most autoimmune diseases are driven by a combination of innate and adaptive immune dysregulation. Thus, it is not surprising that the chronic stages of autoimmune diseases are associated with the activation of myeloid cells and production of smoke alarm cytokines [11].

As with autoimmunity, the role of autoinflammatory pathways in driving pathogenesis of some allergic diseases has become an area of major investigation. In light of these recent advances, it is recognized that the previously clear-cut boundaries separating autoinflammatory and autoimmune diseases have become blurred. Not only have new diseases emerged with overlapping features, but an appreciation for how innate immune activation can influence T and B cells, the principal effectors of autoimmunity has significantly increased [12]. To date, most of the work on the intersection of allergy and autoinflammation has revolved around the notion that their immune responses have opposing functions. Autoimmunity and autoinflammatory responses are thought to primarily repress allergic inflammation [13]. This is largely due to the Th1-Th2 paradigm, which posits that these two subsets of effector T cells have counterregulatory roles. Many ongoing questions remain. Further, the possibility exists that legitimate safety issues may

arise as experience with medications increases and as long-term follow-up data become available [14].

Definition and Classification

Immunotherapy is a rapidly developing treatment modality that uses the body's immune system to target and attack cancer cells. Today, there are several FDA-approved and investigational immunotherapy agents that fall into different categories. These agents are often referred to as immunomodulatory agents or immune checkpoint inhibitors (ICI) [15].

Autoimmunity refers to a failure of immune tolerance mechanisms, leading to an immune response toward self-antigens, characterized as an autoimmune disease (or autoimmune disorder). During this process, immune tolerance physiological mechanisms break down, resulting in the emergence of immune cells that attack self-antigens and give rise to unwanted autoimmune/inflammatory responses, tissue injury, and organ dysfunction [16]. Autoimmune diseases can be classified by geographical distribution, estimated prevalence, ethnicity, and host genetic factors. Female exclusivity of autoimmune diseases indicates a female bias affected by hormonal status, especially during gestation. In addition to hormonal factors, improvements in hygiene, urbanization, industrialization, and environmental pollution significantly contribute to developing autoimmune diseases in industrialized countries, while genetic factors vary with ethnicity [17].

More than 80 systemic autoimmune diseases are classified, significantly impacting everyday activities and affecting social and working life quality. Pathological mechanisms of systemic autoimmune diseases evolve through the accumulation and aberrant activation of autoreactive B and T lymphocytes against nuclear components, resulting in B cell polyclonal activation, interferon biological activities, and pro-inflammatory cytokine production [18]. Systemic autoimmune diseases are complex, and the response to immunotherapy is unique and patient-dependent due to multi-organ involvement and diverse disease severity. These factors influence the cellular nature, state, and microenvironment of inflammatory cells within the affected organs, all of which play critical roles in therapeutic efficacy and immune response [19,20]]

Pathophysiology

A variety of changes in the immune system can cause a lack of self-tolerance and autoimmune disease. Although ongoing antigen exposure in the setting of chronic inflammatory diseases instills a state of increased reactivity within the immune system, it is unclear whether exhausted-like T and B cells are persistently activated and in a continuous activation loop or primed naive cells mount and reinforce an immune response against the persistent inflammatory milieu [21]. It is worth noting that this not necessarily mutually exclusive, and each, possibly in tandem, might form an aberrantly activated immune network reinforcing one another and driving chronic inflammation. Changes in various arms of the immune system can present as hyporeactive states that are associated with immune dysregulation and increased susceptibility to infections and malignancies [22,23].

An inherited deficiency of innate immunity causes an autoinflammatory syndrome with lipomatosisorange, ichthyosis, and blindness, and is caused by mutations in the factor monocytes [24]. A loss-of-function mutation causes an autoinflammatory degenerative skin disease associated with the activation of the NOD-like receptor, consistent with the involvement of the innate immunity in theaphylactic autoinflammatory disease. Also described is an autoinflammatory syndrome of early-onset periodic fevers, arthritis, and mucocutaneous ulcers caused by a mutation in the steroid receptor coactivator 3, which causes the upregulation of the prohistamine chemokines [25]. A gain-of-function mutation in the cystathionine-dependent protease discovered using a screening of systemic inflammatory diseases results in elemental xanthomas and anaphylactic shock. Cells

treated with various immune modulators had a significantly milder phenotype. Autoinflammatory diseases can be very complex and heterogeneous involving a multitude of intracellular and extracellular mechanisms and their interactions [26,27].

Epidemiology

Autoimmune and inflammatory diseases (AID) are common chronic, systemic diseases characterized by a plethora of clinical and laboratory signs and symptoms. Depending on the characteristics of the immune activation, the diseases may be classified into two broad categories: autoimmunity and autoinflammation. The latter comprises monogenic and common polygenic diseases due to dysregulation of the innate immunity [28]. The AID spectrum encompasses diseases that overlap between these two categories, such as some forms of systemic lupus erythematosus or systemic sclerosis (which are termed autoinflammatory autoimmunities), as well as conditions with features distinct from both (i.e. non-Mendelian monogenic) [29]. New avenues for treatment have opened with the advent and success of biological drugs targeting aberrant immune pathways, and with the development of small molecules that inhibit diverse components of intracellular signaling pathways triggered by many innate and adaptive immune receptors. Biological treatments have proven to be beneficial in patients with AID, preventing acute and chronic complications and significantly improving quality of life [30]. A majority of biological drugs target the cytokines central to the pathogenesis of a given disease. However, these treatments can have an incomplete effect, and long-term efficacy may significantly wane. Therefore, there is a need to innovate new classes of drugs and expand the therapeutic modality, especially in polysymptomatic, seropositive patients refractory to several biological treatments. Autoimmune and inflammatory diseases have a profound effect on the lives of those that suffer from them [31]. Even for patients who do not have any serious sequelae, the uncertainty that characterizes these diseases causes distress and limits the ability to focus on other aspects of life, such as work or raising children. Most patients with AID lose the opportunity to enter or remain in the labor market. Education and professional careers suffer major setbacks, and those affected are forced to weight professional ambitions against the need for medical treatment and attention [32].

Immunotherapy: An Overview

Immunotherapy options include compounds that influence adaptive immunity to dampen excessive TCR stimulation of effector cells. Recently developed humanized antibodies are effective against TNF-alfa, IL-1, IL-6, IL-17, and the co-stimulatory molecule CTL4. However, with widespread use, safety issues have arisen, resulting in the emergence of treatment-associated adverse events (IAE) [33]. More widespread use of IL-17 inhibitors has resulted in life-threatening IAE, particularly after the first dose. Rare hyper-IL-17A syndromes resulting in pneumonitis have also been reported. Immunotherapy with monoclonal antibodies targeting IL-6, IL-7, IL-17, and PD-1 resulted in the emergence of random type-I cytokine systemic inflammatory symptoms with neurological symptoms and trigger of de novo autoimmunity [34].

A more recent class of immune modulators, the peptides that specifically inhibit the activation of TH3 or regulatory T-cells, has been developed for inflammatory or autoimmune disorders in preclinical studies. An autoantigen-based peptide vaccine therapy has been developed to induce the immune tolerance to prevent or mitigate these diseases, where preclinical studies showed promise [35]. Clinical application should become available within a few years. Current studies focus on several other immune modulator classes targeting TH1, TH2, or B-cells, which are in various preclinical stages. These studies are expected to significantly advance the development of safer immunotherapy treatment options for the specific targeting of immune components [36].

2. Materials and Methods

Mechanisms of Action

Monoclonal antibodies (mAb) against the proinflammatory cytokines have represented the most common class of immunotherapeutic agents tested in patients with AID. Following on initial pioneering results with anti-tumor necrosis factor (TNF) mAbs, the scientific community rapidly realized that a large number of the AIDs share or are exclusively of TH17 origin. This allowed to formulate the hypothesis that targeting specifically interleukin- (IL-) 17A- or IL-23 would be a more selective, and hence potentially better tolerated, treatment for a number of these diseases. While IL-23 specific mAbs were tested in patients with psoriatic arthritis (PsA), the IL-17A hypothetical paradigm follow up was both much simpler and faster due to the clinical development of anti-IL-17A mAbs already ongoing for other indications. The most advanced immunotherapeutic in clinical development in this setting was secukinumab, originally aimed to be a treatment for RA for which interim results indicated a better efficacy of this treatment compared to the current therapy of reference at that time, methotrexate.

3. Results and Discussion

By the time of the annual EULAR Congress in June 2013, secukinumab had already been tested in a clear treatment indication for a debilitating skin disease, i.e., moderate to severe plaque psoriasis (Pso) where the results were pivotal [37], [38]. Numerous subsequent trials needed to obtain marketing authorization in both Europe and the USA in this indication were then communicated including both interim and complete results of these studies [40][40]. The interest in this kind of interventional studies was not limited to a mere scientific audience, but even more so to the pharmaceutical industry and probably even to the clinical trial competition because this new treatment could potentially replace a number of less effective, less specific and less safe treatment already in use [41].

A. Types of Immunotherapy

91% of patients with psoriatic skin lesions will develop psoriatic arthritis (PsA) - Disease modifying antirheumatic drugs (DMARDs) remain the cornerstone of therapy, but new specific drugs are desperately needed. Tumor necrosis factor (TNF)-alpha specific monoclonal antibodies (mAbs) are very efficacious, but about one in three patients will not respond and need to switch immunotherapy class [42]. The anti-interleukin (IL)-17A mAb secukinumab is the most novel and advanced anti-PsA mAb in clinical trials. Psoriasis (Pso) skin inflammation is due to hyperactive Th1 and/or Th17 lymphocytes, and TNF-alpha, IL-12, IL-23, IL-17A, and IL-22 exacerbate the disease [43]. Regardless of the initial therapeutic intervention, a subset of patients with skin Pso also develops PsA - This polyarthritis is characterized by very painful synovitis and systemic inflammation, and progressive joint destruction can occur. Anti-TNF-allergic mAbs are very efficacious for PsA - However, about one in three patients will develop secondary loss of response after a median of 2 years and need to switch immunotherapy class [44]. Cytokine blockade approaches. Most AID could share or be exclusively of Th17 origin - The Th17 lineage was proposed as a therapeutic target for IL-17A and/or IL-23 blockade. In early human clinical trials, specific mAbs against IL-17A or IL-23 p19 were tested in RA, but they have been far more successful in dermatology [45]. In psoriasis, Th1 and Th17 dominate the skin infiltrate. The most advanced IL-17A specific mAb in clinical trials is secukinumab, originally aimed to be a treatment for RA. Secukinumab proved to be highly efficacious in Pso. In pivotal phase III trials, treatment with 300 mg secukinumab with a combination of IV infusion and SC injections led to PASI50, PASI75, and PASI90 responses in 73% and 52% and 32% of patients at week 16, respectively [46]. These rates of response increased further at week 52 as complete treatment of the entire skin surface yielded clearer and softer skin. Patients on secukinumab remained clear for longer periods, and the efficiency of the drug was clear from week 4 onwards. This was in part because the two highly

specific Th17A engaging mAb were better tolerated than broadly anti-cytokine agents such as anti-TNF-alpha [47]. Trials with both IL-17 and IL-23 specific mAbs highlighted the relevance of IL-17A blockade. The efficiency of dupilumab in asthma is explicable through blockade of Th2-derived IL-4 central to triggering multiple tissue infiltrations [48].

Recent Advances in Immunotherapy

Standard pharmacologic treatment for autoimmune and autoinflammatory disorders relies primarily on immunosuppression. Corticosteroids and cytotoxic agents with broad immunosuppressive activity remain the primary treatments for these debilitating but often neglected conditions. This therapeutic approach successfully alleviates symptoms, but these off-target immunosuppressive therapies increase susceptibility to infections or malignancy [49]. Furthermore, the development of new formulations of monoclonal antibodies, fusion proteins, and small molecules that selectively inhibit inflammatory pathways has led to the emergence of disease-modifying anti-arthritis drugs. Their more specific modes of action promise a more favorable safety profile compared to conventional treatments, but experience has demonstrated that even targeted immunotherapies can induce significant adverse effects [50]. In particular, treatments that block inflammatory mediators risk tipping the immune balance toward hyperreactivity, while therapies that augment immune tolerance can promote opportunistic infections and cancers [51].

In parallel to these approaches, immunotherapies targeting, restoring, or enhancing immunoregulatory mechanisms are being developed as new therapeutic modalities, with the promise to provide beneficial options long sought after by patients. Leading the pack are strategies that aim at fueling the production, selection, or expansion of regulatory T cells, which counteract inflammation by secreting immunosuppressive cytokines or through the secretion of active enzymes that dampen the activation of effector T cells by antigen-presenting cells [52]. In addition to T cells, several therapeutic avenues also targeting antigen-presenting cells specifically and/or enhancing immunoorgans development and activity are being pursued. These alternatives to classical immunosuppressive treatments are still at early preclinical or clinical stages, and therefore, it is to be hoped that they will fulfill their promise of being safer and more efficacious treatments for autoimmune diseases [53,54]

A. Monoclonal Antibodies

Monoclonal antibodies are currently one of the most beneficial and extensively used biologics worldwide. About 42% of monoclonal antibodies targeting a wide variety of cytokines and receptors are being investigated to treat autoimmune and inflammatory diseases [55]. The expansive use of monoclonal antibodies against hematological malignancies or solid tumors has uncovered the collateral benefit of treating severe autoimmune disorders such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), and psoriasis [56]. Humanized monoclonal antibodies against CTLA-4, IL-6, IL-17, IL-12/23, IL-23, and B-cell activating factor (BAFF) are currently in clinical use. Other monoclonal antibodies (anti-CD4, CD19, anti–JAK-1, -2) that target T lymphocytes, dendritic cells, or other immune cells are in various stages of clinical development against autoimmune diseases [57].

Following the enormous success of monoclonal antibodies as immune-checkpoint inhibitors in oncotherapy, their use against autoimmune diseases not responding to conventional immunosuppression is drawing attention. Preclinical studies demonstrated the efficacy of monoclonal antibodies targeting PD-1, PD-L1, or CTLA-4 in animal models of SLE, RA, Sjögren's syndrome, and MS. Fortunately, there have been reports of anecdotal efficacy and unwanted autoimmune side effects in responsive patients [58]. Anti-TNF therapy has been efficacious in combinatorial treatments against advanced skin cancer but rendered the patient with psoriatic-like psoriasis. In failed combinatorial anti–PD-1/CTLA-4 immunotherapy contra advanced melanoma, acquired vitiligo is common [59].

Following CD-20 mAb therapy against multiple sclerosis, there is a risk of reactivated autoimmune demyelinating neuropathy. Following modern monoclonal therapies, reinvigorated autoimmune diseases and autoimmune side effects are being increasingly reported [60].

B. Checkpoint Inhibitors

Checkpoint Inhibitors that Target PD-1/PD-L1

Further investigation focused on availability of PD-L1 in both human skin and skin from the pd-1/ pd-l1 pgtk mouse model by formalin-fixing the skin and staining it for PD-L1. PD-L1 can be found at the epidermal/ dermal junction within the skin of healthy human and pgtk skin tissues [61]. Unlike healthy human skin or normal skin from the pgtk mouse, skin pyrosequencing found a greater amount of PD-L1 in the psoriatic skin of immunocompetent hosts following introduction of the pGTK tumor compared with the control hosts. In vivo pgtk tumor growth was robust in allogeneic mice following ADT as well as in wild-type mice receiving anti-PD-1 [62]. Mouse skin from anti-PD-1 treated mice exhibited an inflammatory environment with increased keratinocyte proliferation and infiltration of CD4+ T lymphocytes. Analysis of CD4 T lymphocytes recovered from the pgtk tumor microenvironment by GeneSET enrichment analysis showed a decreased Th2 cell signature in the anti-PD-1 treated tumors [63]. Furthermore, autoantibodies and IL-6 were present in lymph node samples taken from mice with regressing pGTK tumors following anti-PD-1 therapy while epithelial proliferation markers were upregulated and the number of diagonal junctions between keratinocytes was increased. Uncontrolled pathogenic epidermal proliferation was associated with remission of some metastatic tumors [64].

Further investigation examined the involvement of checkpoint blockade in exacerbation of vitiligo by mice inoculated with melanoma cells. The mice were treated intraperitoneally with isotype IgG, anti-PD-1, anti-CTLA-4, or both, followed by potassium iodide. Blockade of PD-1, CTLA-4, or both enhanced ACC in melanoma-bearing mice, exacerbating vitiligo-related depigmentation [65]. Enhanced numbers of CD8+ T cells and effector T cell phenotypes were evident in the skin of treated mice. In a chemokine assay, PD-1/PD-L1 and CTLA-4 inhibitors upregulated TRAIL and RBPJ in the CD8+ T cell population. Further experimentation in CD8+ T lymphocytes introduced exogenous anti-PD-1 plus exogenous anti-CTLA-4 [66]. Dual checkpoint blockade also upregulated RBPJ and TRAIL with accentuated production of perforin and granzyme, illustrating PD-1/PD-L1 and CTLA-4 blockers enhanced TRM cells undergoing effector function. CD8+ T cells from the tumor and skin also showed reduced inhibitory pathway receptor expression following dual checkpoint blockade, displaying diminished capacity to suppress cytotoxic activity [67].

C. Cytokine Therapy

As knowledge and technology progress, there is increasing evidence that various cytokines play an important role in the pathogenesis of autoimmune and inflammatory diseases by promoting immunity and inflammation, as well as by affecting maintenance of tolerance to autoantigens. Based on this knowledge, engineering of some cytokines and cytokine receptors has been developed such that they function as antagonists [68]. More than a decade of clinical experience with these agents has provided meaningful information on their efficacy, tolerability, and safety, and continues to provide a rationale for the development of novel cytokines and cytokine inhibitors [69].

This article focuses on "new generation" cytokines that have emerged recently in rheumatology in terms of their biological history and clinical experience. New generation cytokine inhibitors in rheumatic disease include antagonists of IL-1, IL-4, IL-6, IL-10, IL-11, IL-12, IL-13, IL-15, IL-17, IL-18–20, IL-23, IL-27, TNF, agonists of IL-2, IL-10, IL-20, IL-33, systemically administered antibodies targeting local action IL-15, and receptor blockers

of receptor-based activities or fusion proteins of receptors to block cytokines (or) receptor pathways [70].

Therapeutic agents that target cytokine pathways represent a promising means of intervention that can be both preventive and curative. Many of type I anti-cytokine treatment have been developed in spite of common clinical challenge associated with effective targeting because one cytokine pathway may involve multiple subtypes of receptors and target cytokine generating mechanisms [71]. Uniquely, different cytokine-blocking agents, with different mechanisms of action and of totally different structure and size, should be in the armamentarium of inflammatory diseases, consequently, it leads to a sort of precision medicine in the treatment of chronic inflammatory diseases [72]. Much effort is needed in pathological analysis to understand vibrant and complex biology system of cytokines in a mode of personalized treatment with consideration of timing and prioritization of therapy, in alliance with concerted progress of molecular imaging on cytokines in vivo and adapted pharmacogenomics [73].

D. Cell-Based Therapies

Highly characterized effector lymphocytes can be produced by conventional stimulation protocols for adoptive T cell therapy. Natural killer, or NK cells, are innate effector lymphocytes capable of asking the question, "self," meaning "do I have a ligand for any of the countless inhibitory receptors expressed on my surface?" If the answer is no, the NK cell is poised to kill the target cell [74]. The remarkable ability of NK cells to kill target cells but nonetheless spare "self" has sparked interest in engineering this capacity to provide more powerful and selective adoptive cell therapy for cancer [75]. Although NK cells possess cytotoxicity and serve other roles in immune regulation and tolerance, there has been little consideration of whether engineered NK cells could be harnessed for adoptive therapy in the reverse context to suppress unwanted immune responses [76]. This is an area of intensive investigation, particularly in solid organ transplantation, autoimmune diseases, and other disorders driven by abnormal T cells. Development of sufficiently robust methods for researching and manipulating NK cells is providing the tools that are needed to create a tractable and predictive platform for translating this potential into the clinic [77].

A growing number of animal models have been reported to study autoimmunity including animal models of epitope targeting that provide valuable insight into the early events leading to tolerance breakdown. Although such models have been developed for both spontaneous and induced instances of autoimmunity, most animal models of these diseases replicate the characteristics of human disease only partially [78]. There is a need for animal models that are relevant for human disease, that develop in a timeline that is conducive for pre-clinical experimentation and that replicate the cardinal features expected. Allochthonous mouse strains and immune tolerance will be an integral part of improving upon existing experimental protocols [79].

Monoclonal Ab therapy is listed in guidelines for the management of many diseases yet includes high profile failures. Attachment of payloads to mAbs has transformed this class of drugs into some of the most potent chemotherapeutics. Targeting diverse cancers is only of academic interest unless mAbs can be delivered to the solid microenvironment of the tumor which typically excludes the entry of the much larger molecules [80]. Here a platform that allows rapid preparation of liposomes bearing a portion of mAb, providing a broader druggable space compared to homodimerization and polymerization approaches that utilize the mAb's Fc domain is described. It is shown that liposomes bearing mAb halves exhibit persistence in the blood, internalization to liver, and prompt redistribution to the tumor microenvironment [81].

Case Studies

Hymenoptera venom immunotherapy (VIT) is a well-established effective treatment of individuals suffering from anaphylaxis due to an allergy to Hymenoptera stings. VIT

protects against severe allergic reactions to venom re-stings and, in numerous studies, shows a long-lasting state of clinical tolerance of venom even after the treatment has been withdrawn [82]. However, detailed information on the immune mechanisms involved in the state of clinical tolerance is still lacking. Several studies have identified specific IgG avidity and long-lasting changes in T cell cytokine production as putative immunological markers of protection. However, it is presently not clear whether these are directly involved in the maintenance of clinical tolerance. Moreover, knowledge of the mechanisms involved in the acquisition and maintenance of clinical tolerance is currently limited [83].

The overall aims of the proposed project are to unravel the immunological changes that occur after Hymenoptera VIT and to relate these changes to clinical tolerance. A recombinant wasp venom protein, phospholipase A1 (PL-A, 54kDa) is used to compare immune responses pre- and post-treatment [84]. The venoms of honeybee, wasps (hornets), fire ants and yellow jackets are mixtures of a large number of different proteins which are all actively involved in anaphylaxis. Only a few have been characterized, and very few have been cloned as recombinant proteins; they constitute ideal candidate antigens for studying the chemistry of protein variation and for finding the actual allergen [85]. There is a unique challenge in studying the allergenic proteins of Hymenoptera venoms: these are the first proteins that will be dealt with in the laboratory. In the first phase of the project we will concentrate on the identify proteins in the venom of a specific species of wasp, the hornet (Vespa crabro). Unlike honeybee or yellow jacket venoms, there is very little knowledge on wasp venoms [86,87]. Subsequently, we hope to characterize their allergenic properties, develop a robust test format for diagnostic and therapy based on the recombinant allergens, and study their immune response pre- and post-VIT to gain a better understanding of the mechanisms of clinical tolerance. Progress on these successive aims is described here. In particular, recent developments on the expression of functionally active wasp venom phospholipase C and the initial characterization of its allergenic properties are detailed [88].

A. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune and inflammatory disease characterized by chronic inflammation of the synovial membrane, resulting in irreversible joint destruction and extra-articular manifestations. Understanding the underlying mechanisms of initiation and chronicity is mandatory, especially with respect to predictive factors of treatment response to enhance the treatment efficacy of disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs [89]. Recently, there have been rapid advances in biotechnology and molecular imaging modalities for ligands, biomarkers, and imaging probes. Development of excellent delivery systems of biomaterials and controlled release of drugs would help to enhance the treatment efficacy while minimizing the side effects of drugs [90]. Better understanding of the roles of immune cells such as myeloid-derived suppressor cells (MDSCs), innate lymphoid cells (ILCs), and B regulatory cells (Bregs) in the initiation and progression of RA would open new avenues for treatment. Generation of novel animal models for preclinical studies such as humanized mouse models would help to evaluate the interactions between the immune system and the target organs as well as the effects of the newly developed drugs [91,92].

Recent advances in our understanding of the pathophysiology of RA have identified new molecular targets for therapy. Major advances, utilizing potent inhibition of aberrantly activated mediators of autoimmunity and inflammation, have occurred over the last decade in the field of RA pathophysiology [93]. Despite the introduction and fast-fail approaches of several biologics, unequivocal efficacy for RA targeting new pathways is still unavailable. Systematic one-drug-one-target approaches inhibiting aberrantly activated signaling pathways of RA pathophysiology and state-of-the-art immunization approaches in animal models are anticipated to provide new therapeutic drugs, delay efficacy testing, and improve the success rate of drug development [94].

B. Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune disease that gradually destroys the central nervous system (CNS), resulting in progressive and widespread behavioral impairments in patients. In MS, attacks by the peripheral immune system induce inflammation, particularly by T helper 1 (Th1) and Th17 cells [94]. MS occurs in two clinical forms, relapsing-remitting (RR) and secondary-progressive (SP), which may develop from RRMS due to neurodegeneration. The cellular sources of MS are not well understood, nor is how to prevent the onset of RRMS or halt the conversion to MS [95]. Before symptoms appear, individuals are classified as having pre-clinical or radiologically isolated syndrome (RIS). Current disease-modifying therapies (DMTs) target inflammation or neuroprotection and are initiated after diagnosis, though they have limited efficacy [96]. However, a preventive and immunotherapeutic paradigm aims to intervene before lesions arise and is being actively explored in clinical trials. Such strategies achieve preventative DMT by removing or reducing pathogenic and quiescent T cell specificities linked to MS and RIS, respectively [97,98].

MS is the commonest inflammatory autoimmune disorder of the central nervous system (CNS), progressively leading to demyelination, neurodegeneration, and neuronal disability. Despite the availability of a large arsenal of putative therapeutic approaches, numerous studies in animal model systems, and clinical trials, MS is still non-curable [99]. Inflammatory lesions at the CNS, generated by autoreactive lymphocytes, are suggested to underlie the pathophysiology of the disease, which results in neuronal demyelination and damage. Genetic and environmental factors influence MS susceptibility: Family history, single nucleotide polymorphisms, infection, smoking, obesity, and vitamin D shortage are associated with MS development. Patients experience relapsing-remitting phases of the disease, which are followed by a progressive phase, accompanied by neurodegeneration [100]. MS symptomatology largely varies among patients, including sensory disturbances, cognitive defects, loss of vision, weakness, bladder dysfunction and neurological disability among others. Therapeutic strategies against MS have been mainly relied on immune function suppressors, such as glucocorticoids, methotrexate, and antihistamines, which non-specifically reduce immune activity [101,102].

C. Lupus Erythematosus

Systemic lupus erythematosus (SLE, lupus) is a highly complex and heterogeneous autoimmune disease characterized by specific circulating self-reactive antibodies [103]. Most commonly, these antibodies are against double-stranded DNA (anti-dsDNA) but can also be against ribonucleoproteins (anti-RNP), phospholipids (anti-phopholipids (aPL)), and Smith epitopes (anti-Sm). SLE most often afflicts women in their child-bearing years, with a 10:1 female-to-male ratio [104]. Children as young as 6 months old to individuals over 88 years of age have been diagnosed with SLE, emphasizing its profound complexity and heterogeneity. Children and adult-onset SLE differ in many respects: frequency of skin rash, anemia, glomerulonephritis, serositis, discoid lupus, and anti-RNP antibodies [105]. The risk of SLE is also influenced by ethnicity and environmental exposure. Newer therapies impacting the retinoic acid-induced gene1, the activation of aPL, ligation of TLRs and IL-6, and anti-IL-1 probably also normalizes abnormal humoral and pro-inflammatory responses in populations but await clinical outcome confirmation. Approved medications impact humoral immune responses and disease flares. There is nevertheless a large population of patients who are not optimally managed or remain treatment-resistant despite a creative array of therapeutic options [106].

The current treatments of SLE are palliative at best and severe dose-limiting toxicities limit their clinical utility. New medicines for the treatment of SLE are thus urgently needed. Such a new medicine should preferably target a mechanism theoretically associated with the etiology of the disease rather than a downstream inflammatory manifestation [107]. SLE is an extreme of immune pathology. While most autoimmune

diseases are characterized by pathological adaptive immune responses, there is a growing body of evidence that a primary causative component of SLE lies with the innate immune system and associated inflammation. It has been a time of incredible new technologies and discoveries in immunology, particularly in understanding the innate immune system [108]. In SLE, some of these new paradigms have led to the identification of new players in the initiation and perpetuation of systemic autoimmunity and pro-inflammatory responses and events that are specific to SLE and might be suitable therapeutic targets [109].

D. Inflammatory Bowel Disease

Historically, difficult cases of inflammatory bowel disease (IBD) were treated with surgical resection or diversion. The lesion was appreciated as intractable although pathologically reversible. However, evolution of understanding of the mechanism of hosts' resistance and hold on mucosal immunity has brought newer approaches directed at healing lesions instead of removing [110]. The approach is now led by monoclonal antibodies against adhesion molecules and proinflammatory cytokines. In addition researchers are currently seeking to develop biological agents besides monoclonal antibodies to interfere with adherence of leukocytes. Topical administration routes to deliver these agents directly to the site of inflammation while eliminating systemic side effects are now available [111]. During chronic inflammatory processes, focal inflammation occurs and it is sustained by the ectopic and aberrant lymphocyte trafficking from the lamina propria into the epithelium. So far the stepwise approach of inhibiting interactions between adhesion molecules on the endothelium and on the inflammatory cells has been explored to block leukocyte infiltration and to halt PSA IDB [112]. One such pilot study evaluating efficacy and safety of an anti-α4-integrin monoclonal antibody, natalizumab (NR) prompted a large scale clinic trial of this agent now ongoing. CD and ulcerative colitis (UC) are apparently diseases affecting different segments of the gut occurring with different predilection. Accumulating evidence are indicating however that these are but the results of shared genetically based mechanisms that nevertheless would suffice for the establishment of disparate inflammation [113]. The efficacy of five antibodies in treating mucosal inflammation (TNF-α, IL12, ICAM1, α-LFA1) (via TNF receptors) has been demonstrated but efficacy of these antibodies in treating extraintestinal manifestations (EIM) requires further study. Their safety profile appears to be satisfactory as well and there have been no instances of opportunistic infections or DIL [114]. The generalization of TNF-α blockers has led to the need for stricter supervision and monitoring or supporting data as well as regulatory risks. Cancer risks associated with blocking TNF-a require further pharmacovigilance [115].

Challenges in Immunotherapy

The impressive effectiveness of cancer immunotherapy has been tempered by heightened sensitivity to immune-related adverse events, in light of autoimmunity in normal tissues. Statistically significant proof highlights the link between the degree of autoimmunity and tumour response to immune therapy [116]. Recently, there has been awakening interest in the potential application of immunomodulatory agents for autoimmune disorders. A wider understanding of the trait of the immune system in individuals with autoimmune diseases has opened the door for innovative therapeutic targeting methods [117].

Although immunotherapy is being developed to treat autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and diabetes mellitus [118], and inflammatory diseases such as inflammatory bowel diseases, asthma, and eczema, many barriers remain, including toxin pathology, early primary toxicity in treated agents, inclusion selection bias, and the differentiation of pathophysiologic targets in smarter therapies [119]. While the physiological outcome of all immune targets is a reduced inflammatory immune response, that context may lead to expanded helper or

regulatory T cells in treated recipients, resulting in decreased cell-mediated immunity against tumours in cancer immunotherapy [120].

The restriction of immunotherapy currently limits its use for diseases diagnosed during hyperinflammation and/or multiple autoimmunity responses. During the 2021 area-wide pandemic immunization, unexpected immune pathology was noted in the safety profile of the Pfizer–BioNtech vaccine [121]. Developing and establishing on-target toxicities triggered by new therapeutic drugs are also problems needing new considerations. Key needed pathophysiological and testing information must be implemented before adopting programmable materials as imbued agents for targeted therapy [122].

A. Adverse Effects

Immune checkpoint inhibitors have demonstrated durable antitumor effects in a range of cancers. The objective of this study was to determine adverse effects due to check point blockade therapy with an emphasis on those requiring hospitalization. The primary adverse effects were renal dysfunction, pneumonitis, hepatitis, endocrinopathies, infusion reactions and skin rashes and pruritus [123]. These checkpoint inhibitors have revolutionized the treatment paradigm of various malignancies. Checkpoint blockade agents are usually well tolerated by patients, yet the potential off-target and unpredictable immune responses may lead to toxicities in other organs of the body beyond the intended area of treatment. The mechanisms of toxicity extend from infusion-related reactions due to the immune activation followed by immune-related adverse reactions (iRAEs) to immunosuppression [124]. Development of interstitial lung disease (ILD) was the most common presentation noted in the patients, and was broadly classified as pneumonitis, diffuse lung disease, hypersensitivity pneumonitis and cryptogenic organizing pneumonia. ILD was mostly observed after the first few rounds of PD-1 inhibitor treatment [125]. Chemotherapy agents were blamed in several cases; however, keeping in mind the timing of development of symptoms, the suspicion of PD-1 inhibitors was high, particularly as the cTLA-4 inhibitor was started merely 8 days prior to analysis. The mechanisms of toxicity are very diverse [126]. It encompasses non-specific interstitial pneumonia, organizing pneumonia, diffuse alveolar damage and acute fibrinous organizing pneumonia. Management of these iRAEs is generally based on expert opinion and data extrapolated from various diseases. Presentation of nephrotoxicity due to checkpoint blockade therapy seen in this cohort was unique compared to existing literature [127]. The most common side effect of renal dysfunction was acute interstitial nephritis (AIN), which was noted in all cases. AIN was found to be dose dependent, with 3 mg/kg doses showing minimal toxicity. Renal dysfunction due to checkpoint blockade therapy also improves significantly with treatment with steroids and discontinuation of the drugs [128].

B. Treatment Resistance

AIDC are very heterogeneous and vary in severity even in individual patients. Most patients with AID may only experience mild or moderate symptoms and many non-steroidal anti-inflammatory drugs can be taken to avoid more aggressive treatment. Some patients, however, develop severe symptoms that can necessitate aggressive treatment. Despite the advances brought by the new immunotherapies, resistance to treatment can be a limiting factor [129]. Only a subset of patients can benefit from every anti-cytokine monoclonal antibody (mAbs) successfully brought to the market [130]. The most advanced and best results to date are with anti-TNFα mAbs in patients with IBD, RA and AS. Some patients, however, experience a rapid relapse to therapy with the mAb, or started showing a partial response to treatment. Many of these patients were effectively treated with a different anti-cytokine mAbs. It would appear thus that treatment resistance with monoclonal antibodies in AIDC is not due to the fact that patients had been previously treated with the same drug but by the different mode of action [131]. Even patients that

had demonstrated a efficacy to a first anti-cytokine mAbs can then show evidence of resistance to a second mAb directed against another cytokine. Resistance to a second treatment may also be in part due to the development of antibodies rapidly neutralizing the treatment mAb [132]. Treatment resistance in AIDC is thus multifactorial and may include pre-existing differences in the anatomy, baseline innate immune response, effector T and B cell tolerance to the attacking antigen, and the hemostatic plasma cascade. Such resistance does not preclude the chances of developing successful treatments in other pathways [133].

C. Cost and Accessibility

The promises of newer and increasingly less toxic immunotherapy agents — including checkpoint inhibitors, antibodies against CTLA-4, PD-1, PD-L1, IDO1, and small molecule inhibitors of relevant signaling pathways — have begun to transform the treatment of numerous cancer types. Historically, it has been recognized that conditioning chemotherapy [134], high-dose interleukin-2 (IL-2), and some other therapeutics could produce unusual long-term responses for a small number of patients. However, these approaches have been limited in their targets and modes of action, with side effects capable of causing considerable morbidity and mortality [135]. Most notably, the U.S. Food and Drug Administration (FDA) has shown considerable elation regarding the recent advent of checkpoint inhibitors, including monoclonal antibodies against CTLA-4, PD-1, and PD-L1 [136]. PD-1 blockers have been licensed for advanced melanoma and non-small cell lung carcinoma; PD-L1 blockers have been approved for breast and bladder cancer, numerous lymphomas, and several other malignancies. The next generation of T cell agonists is reported in current trials and includes FDA-licensed 4-1BB antibody [137], DART-fusion protein combining anti-4-1BB with anti-PDL1, and antibodies against OX40, GITR, and CD137. These are being tested in multiple malignancies, particularly those with a propensity to respond to PD-1/L1 inhibitors (melanoma, lung, breast, uterine, etc.) [138]. While response rates with most agents remain low, the irreversibility of some responses is striking, suggesting the ability of some tumors to co-opt the immune system with Tregs, tumor-associated macrophages (TAMs), and upregulation of PDL1 expression [139]. Delineating the complex biology of immune tolerance and tumor-induced immune suppression will no doubt stimulate the development of exciting novel therapeutics to attack cancer and regulate the immune system with greater precision and effectiveness [140].

Future Directions

Over the last decade or so, impressive advances have been made in bridging the gap between academic and clinical research for autoimmune diseases. The emergence of innovative monoclonal antibodies modulating cell interactions like co-stimulation, T cell or B cell migration, and mainly the action of mediators of inflammation, paved the way for new treatments for Rheumatoid arthritis, Psoriatic arthritis, and inflammatory bowel diseases, among others [141]. During the same period of time, an enormous body of work has refined our knowledge of the precise pathophysiology of the different autoimmune diseases. These basic discoveries together with the means of manipulating the disease have impacted on the design of immunotherapies for autoimmune diseases in numerous ways [142]. First, histologically identifiable lesions like the rheumatoid nodules or the inflamed plaques of skin psoriasis now serve as the starting point. Biopsy material obtained from these lesions is used to refine the understanding of the pathogenically relevant autoantigens and their T and B cell determinants [143]. These can subsequently be synthesized on a large scale for eventual employ in clinical testing. Secondly, these same pathologically-relevant antigens can be used at the level of cell suspensions obtained from the patients, to isolate or expand, ex vivo, Treg/Tr1 or regulatory B cell populations with beneficial properties. Their mechanistic mode of action could involve downregulation of other T cell populations [144]. Freshly obtained or cultured cells could then be applied into

the patients by various modes of delivery. These recent advances in immunotherapy are very promising for the near future. It is hoped that the combination of treatment of the autoimmunity with carefully designed immunotherapies plus the instrumentation of the mechanism of action could lead to the eventual understanding of the intricacies of autoimmune disease [145].

A. Personalized Medicine

A Pioneering Concept in Medicine

The term "personalized medicine" describes a new concept in medicine that initiates a radical revolution in conducting standard medical care by adjusting therapies and prevention strategies to the individual patient and, thereby, increasing the quality of life of patients [146]. Personalized medicine also includes the use of biomarkers as prognostic, predictive, or response markers, in order to prevent adverse drug reactions as well as maximize efficacy. Personalized medicine was a further major boost to research and drug development in pharma [147]. Today, the concept of personalized medicine typically involves the tailoring of drug doses and combinations to individuals, especially in the area of cancer care where targeted therapies and respective companion diagnostics have been implemented. The notion of personalized medicine in industry and academic research has grown to promising momentum in recent years [148].

Recently, in cancer care, alone in the US, more than 400 biomarkers (more than 750 worldwide) are currently clinically employed in personalized cancer care across all cancer types. Personalized cancer treatments, particularly those with predictive biomarkers, are now standard practice and have led to major survival benefits for cancer patients. In addition, in some cases, the gain has been up to 20 years of higher quality of life without cancer recurrence or delay in death [149]. While these "standard applications" of personalized medicine are now well established in cancer care, it is an important challenge for researchers and medical practitioners striving to reach the same success in other therapeutic areas currently lacking biomarkers-based personalized medicine [150]. Examples include adequate prevention measures and tailored treatments of neurodegeneration, autoimmune diseases including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and other inflammatory disorders requiring personalized prevention strategies and therapy. Similar efforts to tailor medication are being made for drug abuse and addiction. Innovative medication approaches, initiated hypotheses or empirical observations need to be validated by other studies but with a similar new approach: more individualized and other study designs than before [151].

B. Combination Therapies

New targets have emerged in the immunotherapy landscape promoting the early diagnosis, prevention and treatment of autoimmune diseases and conditions. The past two decades of research have established the relevance of pathogenic T cell effector subsets secreting distinct cytokines controlling the immune balance [152]. By discovering key cytokine axes controlling these users, it was possible to achieve the vision of a tailored immunotherapy which improved the fascinating but sometimes dreadful specific activity of vaccine-based therapies [152]. It was recognized that in a somewhat naive task to design the panacea of a highly immuno-stimulating immune catalyst, the design of highly selective anti-cytokine monoclonal antibodies (mAbs) could promote the decrement of overactive T cell populations with minimal off-target effects [153]. Of those, the IL-17 family giving rise to 5 unique members and a plethora of combinatorial possibilities designed to be centered around the same selectively in pro-inflammatory responses were the earliest resolution on mAb design [154].

The pathophysiological nature of chronic AID had been presumed to reside in a reactivity against putative self-antigens which could favor the emergence of pre-pathogenic T-cells primed in highly variant ways . However, it was realized that most AID could share or be exclusively of Th17 origin. That prompted the need for new treatment

options targeting the emerging Th17 pathway [155]. The basic concept of a mAb-blocking specifically Th17 cytokines participation in pathology and offering a future of more selective treatments for many AID like RA, axial spondyloarthritis, psoriasis or uveitis was hence born. The redundancy of p19/p40-bearing cytokines in more prominent Th1 and Th2 pathology made them less attractive targets for systemic or gut-acting interventions. It was hypothesized that daily mAb was needed for mAbs targeting p19 providing a drop-off safety net for Th17-like pathology [156].

A major step in the journey was the design of p16/p19 mutant mice. The most advanced immunotherapeutic in clinical trials was the IL-17A specific mAb Secukinumab, originally aimed to be a treatment for RA. It subsequently emerged as a game changer first in the treatment of psoriasis, then psoriatic arthritis, and later ankylosing spondylitis. It was tested and proved to be highly efficacious in Pso [157]. Subsequent trials with IL-17 and IL-23 specific mAbs have illuminated in detail the relevance of IL-17A blockade in AID. Since its commercialization, no severe drug induced adverse events have been reported. The composite of clinical, animal and in vitro data with anti-IL-17A therapy indicate a low risk for mycobacterial infection such as that observed with anti-TNF and anti-IL-2R therapies [158].

C. Research and Development Trends

Over the last decade, the gross market revenues on autoimmune diseases have reached unprecedented levels mainly due to the advent of the new therapies. As a global $100 billion market segment now, substantial growth is expected in this field fueled by R&D investments in other disruptive technologies like monoclonal antibody drugs (mAbs), small molecules, peptides, and even biopolymer-based therapies [159]. Apart from the three historically dominant pharmaceutical companies in the segment over the last 10 years, now there are new-lever players like Regeneron Pharmaceuticals, GSK, and Eli Lilly joining the contest. It is expected that this trend will even increase in the near future as there are still unmet medical needs in terms of patient segments, disease types, and regulatory environments[160].

Disruptive technologies that promise huge potential also risk by drawing excessive competition if not maintained properly. This proved to be true for the mAb drugs that lost their charm years after being introduced. To sustainably maintain their positions in a long-run arm wrestle with other kinetic players, sponsors of all desperate and commonly perceived potential breakthroughs need to formulate and communicate their advantages better [161, 162]. The challenge is therefore how to convince investors, physicians, health care providers, and most importantly, the prospective patients that their molecules will make a difference in an indomitable array of alternatives. highlight such an emerging trend as the development of tolerogenic immunotherapy as a transformative option for curing autoimmune and inflammatory diseases while not inducing broad immunosuppression [163, 164].

Compared to the earlier generations of therapies, these new treatments hold the potential of huge clinical and commercial advantages. However, the challenge for developers now is how best to conceive and promote the potency of these therapies so that the proposed advantages resonate the needs of patients, regulators, and health care budgets, so as to capture their slice of the highly lucrative autoimmune market. The difficult question is moreover how far enhanced efficacy and safety can be attained without undue immunogen restrictions of the protein drugs [165].

4. Conclusion

Historically, immunopathogenetic mechanisms led to the development of various therapeutic protocols for autoimmune and inflammatory diseases. Anti-inflammatory medications have been classified into several categories based on their mechanism of action: non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate (MTX),

glucocorticoids (GCs), and disease-modifying antirheumatic drugs (DMARDs). Initial studies of various anti-inflammatory agents demonstrated that they generally have a limited efficacy, sometimes taking weeks or months before a significant response was achieved. Moreover, they have been associated with multiple adverse effects leading to a lack of safety and patient adherence to therapies. Consequently, there is an increasing demand for a more detailed understanding of the molecular bases of these diseases in order to induce a more potent, yet safer, response to autoimmunity. Over the years, substantial effort has been dedicated to developing targeted immunotherapies with the goal of fully silencing the pathogenic mechanisms associated with autoimmune diseases without inducing immunosuppression. These treatments have provided long-term clinical benefits and associated refinement in the underlying pathophysiology, although studies have raised warnings as to potentially lethal adverse effects. Advances in understanding the immunopathogenesis provided insights to design other novel therapeutic paradigms aimed at resetting autoimmunity. Loading the human immune system with the correct set of autoantigens is not only predicted to halt the ongoing attack against self-tissues, but also to provide a curatively sustained effect. nSuch a treatment is compatible with the new trend in medicine that anticipates the preemptive management of an emerging pathology rather than treating it restrictively after the onset of symptoms. The discovery of new immunological checkpoints has led to a paradigm change in the treatments of cancerous pathology. The latest trend in the field is to employ similar pharmacological agents not to dash upon the immune system, but to restore its capacity to peacefully coexist with various pre-cancerous or autoimmune lesions.

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