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REVIEW

Sharma: Immunotherapy advances and the role of AI

Advanced immunotherapy across diseases and the role of artificial intelligence: A review

Ritika Sharma

SKAN Research Trust, Bengaluru, Karnataka, India

Correspondence to Ritika Sharma: sharma.ritika198@gmail.com

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ABSTRACT

Immunotherapy, a therapeutic strategy aimed at modulating the host immune system, has undergone rapid evolution over recent decades, particularly in oncology. Advanced methodologies, including immune checkpoint inhibition, cytokine therapy, chimeric antigen receptor T-cell therapy (CAR-T), and tumor-infiltrating lymphocyte therapies, have significantly transformed cancer treatment. This review summarizes recent advancements in immunotherapy and examines its expanding applications across a range of diseases, such as autoimmune disorders, infectious diseases, transplant rejection, and allergic conditions. A structured literature search was conducted using PubMed and Google Scholar, prioritizing studies published from 2015 to 2026. The findings underscore the efficacy of monoclonal antibodies, adoptive cell therapies, cytokine modulation, and checkpoint-targeted strategies beyond oncology. However, challenges remain, including variable patient responses, immune-related adverse events, and treatment costs. This review also explores the emerging role of artificial intelligence (AI) in enhancing personalized immunotherapy through patient stratification, biomarker identification, and predictive modeling. The integration of multi-omics data with AI presents promising opportunities for improving treatment efficacy and safety, although issues related to data quality, interpretability, regulatory frameworks, and ethical considerations must be addressed. In conclusion, immunotherapy is rapidly extending beyond cancer, and AI-supported personalized approaches offer a promising pathway to safer, more effective, and broadly applicable treatments.

Keywords: Immunotherapy, cancer immunotherapy, autoimmune disorders, infectious diseases, artificial intelligence.

INTRODUCTION

The therapeutic approach of utilizing the host's immune system for protection against a diseased state, either through the initiation, enhancement, or suppression of immune response is termed immunotherapy. The field of immunotherapy has progressed tremendously since its inception, particularly with its efficacy in the treatment of cancer. Currently, immunotherapies are being exploited for countering a variety of diseases [1].

This review attempts to highlight the progress made in immunotherapy and further focus on how these advances are currently being explored for devising superior therapeutics against diverse diseases. Further, the role of AI in conjunction with the application of immunotherapy and precision medicine has been discussed.

SEARCH METHODOLOGY

A structured literature search strategy was followed in compiling this study. Relevant studies focusing on the areas of immunotherapy, cancer immunotherapy, immunotherapy beyond cancer, AI and the intersection of AI and immunotherapy were screened. Google scholar and PubMed were the databases that were used for retrieving primary literature. The keywords and Boolean operators encompassed- "immunotherapy", "history of immunotherapy", "immunotherapy AND diverse diseases -cancer", "immunotherapy NOT cancer", "immunotherapy AND artificial intelligence", "immunotherapy AND artificial intelligence OR predictive models - cancer", "artificial intelligence AND healthcare", "explainable artificial intelligence". No strict inclusion criteria were utilized; however, to get an updated context preference was given to articles published between 2015-2026. Only articles written in English were selected. Articles were strictly excluded from the study if they were not published in a peer-reviewed, indexed journal.

HISTORICAL PERSPECTIVE

Immunotherapy has its origins dating back to 1721, when Charles Maitland intentionally infected children with low doses of smallpox to prevent them from contracting the disease [1]; [2]. Research in the mid-19th century brought infectious diseases into the limelight. However, possibility of a host defense mechanism against such invaders was not evidenced at that point. Later, the discovery of phagocytic cells

and antibodies proved the existence of an inherent host defense mechanism [3]. These discoveries led to the advent of immunology as a distinct discipline [4] (**Figure 1**).

The dawn of cancer immunotherapy came in the late 19th century, when Busch, Fehleisen and Coley independently observed tumors to regress in patients post infection with erysipelas. However, their observations were not paid much attention at that time [2]; [1]. Cancer immunotherapy regained attention around the mid-20th century as evidence for the existence of tumor associated antigens was first presented [5]; [6]; [7]. This was followed by proposition of the immunological surveillance theory that claimed lymphocytes played a key role in identifying and eliminating malignant cells [8]; [9]; [10]. The search for antibodies with binding specificity to malignant cells also began. In 1975, the advent of hybridoma technology spearheaded therapeutic antibody research and eventually led to the development of rituximab as the first Food and Drug Administration (FDA) approved monoclonal antibody against cancer (non-Hodgkin's lymphoma) [11]. A remarkable breakthrough in cancer immunotherapy came with the discovery of T-cell antigen receptor [12] and Cytotoxic T-lymphocyte associated protein-4 (CTLA-4) [13]. These discoveries set the stage for further investigations and ultimately resolved the debate on the feasibility of utilizing the immune system to fight cancer [14]. Additionally, the discovery of interferon (IFN) and interleukin-2 (IL-2), led to the development of cytokine-based immunotherapies [15]. In 1986, IFN-α2 was granted approval by the FDA for treating hairy cell leukemia, marking the first approval for an immunotherapeutic drug [2].

The 20th century also saw advances in the field of allergen immunotherapy. In 1911, Leonard Noon recognized grass pollen as the causative agent behind hay fever and observed the protective effects of its crude extract preparations. Drawing insights from this work, William Frankland conducted the first randomized, double-blind, placebo-controlled immunotherapy trial, showcasing the therapeutic efficacy of subcutaneous grass pollen injection therapy. In the years that followed, allergy shots became the standard treatment for allergies [16].

BASIC TO ADVANCED IMMUNOTHERAPY

Immunotherapy can have different forms depending on the disease condition (**Figure 2**). Immunotherapeutics are primarily categorized as immunostimulants e.g. vaccines, and immunosuppressants e.g. corticosteroids. Cytokine therapy and allergy immunotherapy are immunomodulating in nature.

Cancer immunotherapy is the most popular form of immunotherapy; it has been in the forefront of most advances made in this medicinal field. Most clinically approved, advanced cancer immunotherapies utilize T cell functions and can be broadly categorized into two types: modulators of endogenous T cell responses and cellular therapies [17]. Immune checkpoint inhibitor (ICI) therapy, cytokine therapy, cancer vaccines and oncolytic virus therapy fall under modulators of endogenous T cell responses category, while chimeric antigen receptor T-cell (CAR-T) therapy and tumor infiltrating lymphocytes (TIL) therapy comprise the principal forms of cellular therapies [18].

Checkpoint inhibitor therapies

Cancerous cells employ cell-surface, immunoregulatory proteins termed checkpoint molecules to evade the immune system; these proteins inhibit T-cell function. CTLA-4 and programmed cell death-1 (PD-1) were the first immune checkpoint molecules to be discovered, leading to the development of anti-cancer therapeutic monoclonal antibodies (mAbs) called checkpoint inhibitors [19]. mAbs such as anti-CTLA-4, anti-PD-1 or anti-PD-L1, impede the activity of these immune checkpoints. In 2011, an anti-CTLA-4 mAb Ipilimumab, became the first FDA approved ICI therapeutic against advanced melanoma. Since then, over 6 checkpoint inhibitors have been approved by the FDA as neoadjuvant and/or adjuvant therapies against different malignancies [20]. Despite their revolutionary impact, checkpoint inhibitor therapy has some limitations that affects its wider applicability [21]; [22].

Cytokine therapy

Cytokines act as molecular coordinators among immune cells, triggering self-limited, highly specific immune responses. There are seven different types of cytokine receptors, and targeting cytokines or their receptors has been at the forefront of developing anti-cancer therapeutics [1]; [23]. The FDA has approved several cytokines for treating different malignancies including IL-2 (high dose) for metastatic melanoma, IFN-α for renal cell carcinoma [24], and IFN-α2a and IFN-α2b for patients with hairy cell leukemia [1]; [21]. Recently, the combination of BCG with an IL-15 super agonist termed N-803 received approval for treating non-muscle invasive bladder cancer [23]; [25].

Cancer vaccines

Cancer vaccines comprise formulations of whole tumor lysates (either patient's own or from another), tumor specific antigens and viral vectors, amongst others. When administered with adjuvants, these vaccines can trigger anti-tumor immune responses by activating T cells [21]. In 2010, Provenge (Sipuleucel-T) became the first FDA approved cancer vaccine for treating prostate cancer [26]. Intravesical BCG indicated for non-muscle invasive bladder cancer is another FDA approved immunotherapy [27]. Preventative vaccines against cancers caused by human papillomavirus (HPV) and hepatitis B virus (HBV) infections are also under clinical use [28]. Numerous promising vaccine candidates are under different stages of clinical evaluation [29]. Therapeutic cancer vaccines are generally safe and do not cause major side-effects; but outcomes may vary significantly among individuals [21].

Oncolytic virus therapy

Oncolytic virus therapy is an innovative immunotherapeutic approach, which utilizes genetically engineered viruses to target and destroy cancer cells. When the genetically altered viruses are administered into tumors, they cause lysis of cancer cells resulting in release of tumor antigens. These antigens can activate immune cells, which subsequently target other cancer cells expressing those antigens. This approach capitalizes on the fact that cancer cells are more prone to viral infections compared to normal cells [1]. Various viruses including adenovirus, herpes simplex virus 1, measles virus, and reovirus have been explored as agents of oncolytic virus therapy [30]. The first therapeutic oncolytic viral therapy to gain FDA approval was Talimogene laherparepvec (Imlygic) or T-Vec, which is directed against melanoma [1]. Several other candidates are currently under clinical trials, for various malignancies [1]; [30].

TIL therapy

The lymphocytic cell populations that invade tumor tissue are termed tumor infiltrating lymphocytes. TIL immunotherapy involves isolating TILs from tumors, followed by their cytokine mediated activation and expansion in culture, and finally re-administration into the patient. TIL therapy was first tested for the treatment of Melanoma in the 1980's. In recent decades the technique has been improved and extended for treating cervical cancer and other solid tumors. In case of melanoma

particularly, optimal responses have risen to 50-75% [31], [21]. This increased efficacy is attributed to patient pre-conditioning and the depletion of lymphoid tissues [21]. Lymphodepletion helps by reducing the number of regulatory T cells (Tregs) that suppress immune responses and other endogenous lymphocytes that can compete with the transferred TILs [32]. Despite the promise, TIL still faces challenges in its standardization which limits its broader applicability [21].

CAR-T therapy

A cutting-edge immunotherapy where patient derived T lymphocytes are genetically modified in-vitro to express a chimeric antigen receptor (CAR) on their surface. Post this the cells are multiplied and administered back into the patient. A CAR comprises of an extracellular, a transmembrane and an intracellular domain. The extracellular domain binds to a specific antigen on cancer cells, while the transmembrane and intracellular domains trigger T-cell activation, leading to destruction of targeted cells [21]. In 2017, FDA approved Tisagenlecleucel (Kymriah) as the first CAR-T therapy for treating B-cell leukaemia. Thereafter, 5 other CAR-T cell therapies have received regulatory approvals from FDA for treating various malignancies [33]. Design of CARs has evolved to offer enhanced activation, proliferation, and survival potential. Although later generations of CARs provide superior anti-tumor effects, they also cause various side effects. Therefore, at present the clinical landscape of this therapy is currently dominated by the second-generation of CAR-T cells that exhibit intermediate efficacy [34].

IMMUNOTHERAPY BEYOND CANCER

Surge and the success of cancer immunotherapy has led to an enhanced understanding of immune homeostasis. The techniques thus developed have equipped researchers with tools to build novel, efficient therapeutics against other diseases.

Autoimmune disorders

Conventionally, immunosuppressants are preferred for treating autoimmune diseases. Although immunosuppressants can provide long lasting remission against some autoimmune diseases, their efficiency often wears off with time [35]. Therefore, developing novel measures to modulate the immune system for treating different autoimmune diseases is needed. Technological advancements in immunotherapy, such

as checkpoint inhibitor therapy, anti-cytokine therapy, anti-T cell therapy etc., have shown promising results in treating several autoimmune diseases [1].

Anti-PD-1 and anti-CTLA-4 antibodies have been developed for treatment of autoimmune disorders. The mAb Abatacept is prescribed to treat subtypes of arthritis, it mimics the action of native CTLA-4 by interacting with co-stimulatory ligands CD80 and CD86, impeding T-cell activation and ultimately inhibiting immune response [36]. Abatacept is currently being evaluated for safety and efficacy against other autoimmune diseases as well [1]; [17]; [37]. Abatacept has been observed to have a disease modifying effect on Type 1 Diabetes Mellitus (T1DM) in research studies on individuals recently diagnosed with the disease [38]; [39]. Additionally, Abatacept has been evaluated for safety and efficacy against systemic lupus erythematosus (SLE) and multiple sclerosis (MS). However, further research is required to establish its potency as a therapeutic for these ailments [1]. Belatacept, a successor of Abatacept that exhibits superior affinity for B7 ligands is also being clinically evaluated for its therapeutic efficacy against SLE, MS and T1DM [1]; [40]. Additionally, Peresolimab a mAb designed to serve as PD-1 agonist, has shown promising results in managing Rheumatoid Arthritis (RA) in a phase 2a clinical trial [41].

Administration of specific cytokines or cytokine antagonists, either alone or in conjunction with different immunosuppressants, has demonstrated promising results in managing various autoimmune conditions [1]. The cytokine type and the therapeutic approach are specific to the pathological profile of the different auto-immune conditions. The principal cytokine or cytokine directed therapies currently in use or being investigated for treating autoimmune diseases are briefed in **Table 1**.

Targeted killing of harmful B cells using mAbs [49]; [17], and the utilization of CAR-Tregs that express high-affinity T cell receptors (TCRs) to recognize antigens responsible for triggering autoimmune responses are being tested for therapeutic efficacy against autoimmune diseases [50]; [51]; [17]. Rituximab is a mAb that binds to CD20 a cell surface protein on B lymphocytes, mediating the death of these cells through antibody dependent cell mediated cytotoxicity (ADCC) and/or complement mediated cytotoxicity. Rituximab is used to treat conditions like RA, SLE, and MS [52]. Belimumab is a mAb that inhibits the interaction between soluble B-lymphocyte

stimulator (BLyS) and B cell receptor, this obstructs the activation and survival of auto-reactive B cells. Belimumab is used to treat SLE [53].

Adoptive Treg cell transfer therapy relies on the immunosuppressive role of Tregs to accomplish beneficial effects against autoimmune disorders. Adoptive Treg cell transfer involves isolation of Tregs from patients, their in-vitro expansion and finally autologous transplantation back to patients. Expansion of Tregs involves transducing them with an appropriate auto-antigen specific, high-affinity TCR or a CAR. These engineered, antigen specific Tregs can deliver local immunosuppressive effects upon being transferred back to the host [54]. This immunotherapeutic approach has shown promising therapeutic results in several pre-clinical studies against autoimmune diseases such as MS [55]; [56], SLE [57]; [58] and T1DM [59]; [60]; [61]. Currently, ~54 clinical trials are evaluating the therapeutic efficacy of adoptive Treg cell transfer for different ailments attributed to dysregulated immune responses [54].

Transplant rejection

Immunosuppressive drugs have long been utilized to avert the problem of graft rejection. However, the use of such immunosuppressants is reported to cause significant side effects. To avoid these side effects and to curb the low-grade immune responses that result in delayed allograft loss, there is a need for the development of novel therapeutics. To this end, a promising approach has been targeting immune checkpoint pathways involving the cell surface costimulatory molecules. Different co-stimulatory signaling molecules such as, CTLA-4, CD40, ICOS, OX40, TIM family and LFA-1 have been examined for efficacy in preventing allograft rejections in pre-clinical studies. Several leads are currently being tested for clinical efficacy [62]; [63]; [64]. In 2011, Belatacept (CTLA-4-Ig) received FDA approval for usage as an immunosuppressant for adult, kidney transplant patients [40].

Infectious diseases

mAb based therapies, checkpoint inhibition, manipulation of cytokine levels and T-cell-based therapies are being explored as alternatives to the conventionally utilized medications against infectious diseases [63].

Infectious viruses such as Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Epstein-Barr virus are being targeted using CAR-T therapy. Research on anti-HIV CAR-T cell therapy has seen steady progress

since its inception in the 1990's. Three generations of anti-HIV CAR-T cells have completed safety and efficacy evaluations in clinical trials [66], [67], [65] [68]. The next generation of anti-HIV CAR-T cells have shown promising results in animal model studies [68] and have recently entered clinical trials (NCT03240328, NCT03617198). **Figure 3** highlights main features of the different generations of anti-HIV CAR-T cells. As for the other viral and fungal pathogens, CAR-T therapy development is still at pre-clinical testing stages [66].

When compared to cancer and autoimmune diseases, development of therapeutic antibodies against infectious diseases has progressed rather slowly [69]. However, COVID-19 prompted scientific community to achieve extraordinary accomplishments in the development, utilization and approval of mAbs against SARS-CoV-2 virus [70]. Many neutralizing mAbs against SARS-CoV-2 were developed using memory B cells obtained from infected or recovered patients. These designed mAbs target the spike protein of the virus, which facilitates the virus's entry into the host cells via binding to angiotensin converting enzyme-2 (ACE2) receptor [69]. Several of these received emergency use authorization (EUA) and proved to be crucial in treating COVID-19. However, the emergence of new COVID-19 variants dampened their efficacy. Laboratory evaluations revealed that some variants could avoid neutralization by mAbs. Subsequently, FDA ended the EUA and placed limitations on the use of several existing anti-SARS-CoV-2 mAbs and/or their combinations [71].

Previously, the FDA has approved the use of mAb therapy against ebolavirus disease (EVD) [72], HIV-1 [73]. The mAbs Nirsevimab and Palivizumab are used as prophylactics against Respiratory Syncytial Virus (RSV) [74]. Additionally, several candidate antibodies against EVD, HIV, Influenza, HCV, HBV, Zika and Dengue are currently under investigation for safety and efficacy [75]; [76]; [69]; [65]. Most of these anti-viral antibodies are receptor targeted and disrupt the binding and entry of viruses into host cells. In recent times, broadly neutralizing antibodies (bNAbs) are gathering significant attention due to their enhanced anti-viral potency against genetically diverse strains of HIV and Influenza.

The FDA has also approved mAbs for treating bacterial infections, **Table 2**. Several new candidates have recently entered clinical trials, and others are at pre-clinical levels of development [77]; [78]. The main targets of these anti-bacterial mAb's are-

neutralizing toxins, membrane proteins, surface glycans or glycoconjugates and biofilm components.

mAb therapy is also being evaluated for efficacy against parasitic infections such as malaria, trypanosomiasis, schistosomiasis and leishmaniasis, amongst others [81]. Several candidate mAbs for the treatment of malaria are currently being reviewed for their safety and efficacy. CIS43LS, a mAb against *Plasmodium falciparum* has demonstrated promising results in phase I clinical trials [82]; [83]. Another mAb against malaria, termed as TB31F acts by binding the *P. falciparum* gamete surface protein Pfs48/45, thus impeding parasite progression and subsequent transmission. TB31F has been evaluated in a phase I clinical trial and proved to be safe and efficacious as a *P. falciparum* transmission blocking mAb (NCT04238689) [84].

Checkpoint molecules are vital for upholding self-tolerance in healthy individuals, but they often turn rogue under diseased conditions. Upregulated expression of immune checkpoint molecules results in T cell exhaustion, evidenced in chronic infectious diseases such as HIV, malaria, hepatitis and tuberculosis. This has led to an interest in exploring the efficacy of checkpoint inhibitor therapy as a safeguard against such infectious diseases [85].

Several pre-clinical studies report inhibition of checkpoint signaling results in elevated T cell responses against HIV [86]; [87]; [18]. In recent years, clinical studies have corroborated the same, through the utilization of anti-cancer mAbs for mediating immune checkpoint blockade [85]; [88]. A phase I trial (NCT02028403) involving HIV patients on suppressive ART, inspected the effects of anti-PD-L1 antibody BMS-936559. It found HIV-specific CD8 T cell responses to be boosted in subjects receiving the treatment, also no severe immune-related adverse events (irAEs) were reported. However, BMS-936559 did not impact the viral load, but was observed to be safe with no severe immune-related adverse events (irAEs) reported. This could be attributed to the single, low dose administration mode followed in this study [89]. Further evaluations with an optimized dosing regimen would be necessary for determining BMS-936559's therapeutic role. Additionally, another PD-1 receptor blocking mAb Budigalimab was found to be protective against HIV, in recently completed clinical trials (NCT04223804, NCT04799353). Budigalimab was

efficacious in delaying HIV rebound in participants with interrupted ART; detailed results from this clinical trial are yet to be published.

Blockade of checkpoint molecules is also reported to augment CD8 T and CD4 T cell responses against HBV [85]. In separate clinical studies, the PD-1 directed mAb, Nivolumab was efficacious in decreasing HCV and HBV load in infected individuals [90]; [91]. A recent clinical trial with dual checkpoint blockade of PD-1 (Nivolumab) and CTLA-4 (Ipilimumab), in patients with advanced hepatocellular carcinoma (with/without hepatitis B or C) observed no significant difference in overall survival amongst patients. However, the incidence of adverse events was observed to be higher than that formerly associated with nivolumab monotherapy [92]. Another clinical trial examining the effect of Ipilimumab treatment in advanced melanoma patients positive for HBV and/or HCV infection has recently been completed and results from the same are awaited (NCT02402699). Overall, currently available evidence points to Nivolumab being safe against chronic HBV/HCV infection. However, more clinical studies are required to validate the efficacy of immune checkpoint blockers like Nivolumab in inducing HBV/HCV remission.

Examination of immune checkpoint blockade therapy against tuberculosis has yielded varied results, depending on the checkpoint molecule being targeted. *Mycobacterium tuberculosis* infected PD-1 knockout mice are significantly prone to developing elevated mycobacterial loads and overall fatality [93]; [94]. Reportedly, cancer patients undergoing anti-PD-1/PD-L1 blockade immunotherapy develop atypical *M. tuberculosis* infections [93]; [95]. However, contrasting results have been obtained in animal studies where TIM3 and LAG3 checkpoint function was blocked. Blockade of TIM3 in mice with chronic *M. tuberculosis* infection, was found to enhance T-cell function and significantly control bacterial growth [96]. Likewise, silencing LAG3 expression in a co-culture model comprising CD4 T cells and differentiated macaque macrophages infected with *M. tuberculosis*, triggered T-cell activation and revoked regulatory T-cells induced suppressive activity [97]. This disparity is likely a consequence of the baseline immune status of the host as evidenced in pre-clinical research and clinical studies on cancer patients being treated with ICIs [98]. In seriously immunocompromised hosts, immune checkpoint inhibition successfully counters mycobacterial infection. Whereas application of ICI therapy in immunocompetent hosts results in a hyperinflammatory state and worsening control

over bacterial levels [99]. These findings demand testing for a more personalized immunotherapy approach against tuberculosis infection.

Checkpoint blockade has also been investigated as a therapeutic strategy against protist infections, albeit only in animal models. *Leishmania amazonensis* infected mice treated with anti-PD-1 and anti-PD-L1 presented remarkably lower levels of parasite; however, blockade of PD-L2 did not deliver the same results [100]. This is likely to be a consequence of the varied mechanisms by which PD-L1 and PD-L2 control immune responses during infection with *Leishmania sp*. [101]. Being a chronic infection, leishmaniasis has numerous immunoregulatory features in common with cancer. Like a one size fits all approach does not work in cancer and specific combinations of ICI's are required for obtaining an optimal response; similarly, fine-tuning of different checkpoint inhibitory pathways is suggested to offer better outcomes against Leishmaniasis [102].

The possibility of using ICI therapy against malaria has been tested in several animal model studies. Currently, the case made for efficacy is not considerable enough to neglect the safety concerns posed, as summarized below. Butler et al. observed mAb mediated dual checkpoint blockade of PD-L1 and LAG3 to increase the clearance of *Plasmodium yoelii* via enhanced CD4 T cell function and humoral immune response in C57BL/6 mice [103]. Likewise, Hou et al. observed that lymphocyte activity is reinstated upon blocking TIM3-signalling in cultured PBMC's isolated from patients infected with *P. falciparum*. Furthermore, they observed increased clearance of *P. berghei*, in infected C57BL/6 mice [104]. In contrast, blockade of PD-L1/ CTLA-4 checkpoint pathways in BALB/c mice had no effect on parasitaemia and led to enhanced T cell activation and IFNγ levels which made the mice vulnerable to develop cerebral malaria [105]. Future investigations are required to understand whether these varied findings stem from differences in the checkpoint pathway targeted, the animal model used in experimentations and/or species level differences.

Allergies

The last few decades have witnessed an increased prevalence of allergic diseases, a consequence of the changing environment as well as socio-economic status [106]. This has presented a significant public health burden, and it demands devising novel

therapeutics. To this end, advances made in immunotherapy are being explored for their safety and efficacy [107].

Allergic reactions are the aftermath of a predominant T helper type 2 (Th2) immune response, arising due to the disrupted balance of Th1, Th2, and Th17 immune functions. Th2 immune responses are steered by IL-4 and IL-13 cytokines, which makes them attractive therapeutic targets against such diseases [108]. Consequently, antagonists of these cytokines such as the synthetic peptide Pitrakinra have been developed and tested for their efficacy. However, Pitrakinra demonstrated only limited efficacy in Phase2b clinical evaluations in patients with allergic asthma and did not proceed to further stages of drug development [109]. The focus has since shifted towards developing alternative antagonists of IL-4/IL-13 such as mAbs, and CAR-T cell therapy [108].

mAb therapy for alleviating allergic reactions involves disruption of cytokine signaling or targeting of soluble or membrane bound IgE, the key mediators of an allergic response [110]. Several mAbs against allergic reactions are currently available for use [107].

Omalizumab is an FDA approved humanized anti-IgE mAb utilized for treating moderate to severe allergic asthma. Additionally, Omalizumab has shown positive influence against other diseases like seasonal allergic rhinitis and chronic urticaria [110]. Recently, it became the first FDA approved medicine for treating IgE mediated food allergies [111]. Ligelizumab is another IgE directed mAb, which proved to be more efficacious than Omalizumab in the management of symptoms associated with asthma as well as spontaneous urticaria [112]. Recently, phase III evaluations (NCT03580356) of Ligelizumab for the treatment of moderate-to-severe chronic spontaneous urticaria concluded that it was less efficacious than Omalizumab in managing the disease [113]. UB-221 is another IgE directed mAb candidate that has demonstrated promising results in relieving symptoms associated with chronic spontaneous urticaria [114].

Dupilumab is an IL4-Rα directed mAb that functions by disrupting IL-4/IL-13 signaling. It has been approved by FDA for the treatment of moderate to severe atopic dermatitis in adults and also as an adjunct therapeutic in asthmatic patients above 6 years of age [115]; [116]. Furthermore, Dupilumab has delivered promising results

against chronic rhinosinusitis with nasal polyposis and allergic rhinitis [110]. Tralokinumab is the first FDA authorized IL-13 directed mAb, used for treating atopic dermatitis in adults [117].

In recent times, CAR-T therapy has been tested in several pre-clinical studies for the management of allergic asthma by targeting dysregulated Tregs. This mechanism is responsible for the predominant Th2 immune responses that drive allergic diseases. In mice, directing Tregs towards the inflamed airways proved efficacious in the management of allergic asthma [118]. T cells Redirected for Universal Cytokine-mediated Killing (TRUCKs), represent the fourth generation of CAR-T cells that secrete specific cytokines. Using asthma specific biomarkers, TRUCKs can be directed to inflammatory sites where they can secrete cytokines like IL-12 that promote the proliferation of Th1 cells while suppressing Th2 immune responses [119]. Additionally, the approach of targeting IgE producing cells has been explored. This can result in long-term suppression of IgE levels and likely improve treatment outcomes for patients with severe allergic diseases. The transmembrane form of IgE (mIgE) expressed by all IgE producing cells, serves as a suitable target for recognition. Recently, Ward et al. generated CARs expressing the extracellular domain of FcεRIα (a high affinity IgE receptor) for mIgE recognition. These CAR-T cells specifically detected the immune cells expressing mIgE and excluded those that captured secreted IgE (mast cells, basophils, and eosinophils) [120]. FcεRIα-based CAR-T cells that additionally express the co-stimulatory domains 4-1BB and/or CD28 are a promising prospect for developing adoptive T-cell therapy for allergic diseases [119].

Type 2 innate lymphoid cells (ILC2s) play crucial roles in the development of Th2 immune response, these cells produce cytokines in a non-allergen specific manner [106]. ILC2s are activated by allergen induced, epithelial-derived cytokines such as IL-33 and thymic stromal lymphopoietin, and interactions with lymphocytes and dendritic cells [121]. Relative to T and B-cells facilitated allergic response, ILC2-mediated response is rapid and independent of antigen stimulation. Reversing the blockade of certain immune checkpoint molecules on ILC2S is being explored for potential therapeutic efficacy against allergic diseases. Recently, strategies like cross-linking immune checkpoint molecules [121], or using agonists of checkpoint molecules such as PD-1 for activating inhibitory pathways [122], [106] have been

reported in pre-clinical studies to suppress the process of allergic inflammation. These can be further investigated for their safety and efficacy in humans.

OVERCOMING IMMUNOTHERAPY ROADBLOCKS THROUGH AI-DRIVEN PERSONALIZED APPROACHES

Immunotherapy is not uniformly efficacious in alleviating the diseased state, in all patients [123]; [124]. Another common complication is the development of irAEs [125]. irAEs are the result of enhanced activation of immune system, mostly inflammatory in nature. irAEs are usually treated with steroids; however, in some cases irAEs take a more aggressive form [17]. As interest in implementation of advanced immunotherapeutic approaches grows, there is a compelling need to identify patients that will benefit the most from immunotherapy without developing untreatable irAEs and thus avoiding unnecessary health care costs [1].

The therapeutic efficacy of immunotherapy is determined by a complex interplay of factors, or a patient's immune landscape [126]; [127]; [128]; [129] and our understanding of these is still in initial stages. Techniques such as- epigenetic profiling, proteomics, single-cell transcriptomics, T cell receptor (TCR) repertoire analysis, and high-dimensional imaging of immune cells, amongst others are being utilized to develop insights into the intricate nature of this immune landscape [17]. In this way identification of specific signatures or biomarkers can aid the clinicians in anticipating immunotherapy outcomes.

In case of cancer, the immune landscape is primarily shaped by the expression of checkpoint molecules, tumor immunogenicity (mutational burden and antigen presentation) and tumor microenvironment [126]; [130]; [131]; [132]. Additionally, genetics, epigenetic modifications and gut-microbiome have also been observed to influence immunotherapy outcomes especially in case of ICI therapy [130].

Research on identification and validation of potential biomarkers for predicting sensitivity to cancer immunotherapy has remained largely focused on application of ICI therapy. Currently, the FDA has approved three biomarkers- microsatellite instability, PD-L1 expression and tumor mutational burden (TMB) for predicting response to ICI therapy [133]. However, in diverse clinical settings neither of these biomarkers have been observed to persistently correlate with treatment efficacy. This is primarily attributed to factors such as tumor heterogeneity and temporal variability

[134]. In comparison, research on predictive biomarkers for irAEs is still in its early stages and at present there are none that are widely accepted or validated for use under clinical settings [135].

Research on predictive biomarkers against autoimmune diseases such as RA, MS and allergies has also advanced. Presently, there are no biomarkers that are authorized for routine use in a clinical set-up [136]; [137]; [138]. However, several lead biomarker candidates have emerged **Table 3.**

It is increasingly becoming evident that a single biomarker is unlikely to yield an accurate estimate of the response to immunotherapy [130]. Tailored treatments specific towards a patient's characteristics and immune status can yield better outcomes and prevent unnecessary risks. Advancements in genomic sequencing and immune profiling techniques have endorsed personalized approaches to immunotherapy. These approaches aim to predict patient responses to immunotherapies like checkpoint inhibitors; identifying neo-antigens and developing novel antibodies [158]; [159]. The successful integration of sequencing information and AI in predicting immunotherapy outcomes in cancer patients has been witnessed through several research studies.

Analyzing somatic mutations such as base substitutions, rearrangements, insertions and deletions (indels) in combination with AI techniques demonstrated potential in predicting PD-1 ICI outcomes [160]; [161]. Likewise, transcriptomics or RNA sequencing data in conjunction with machine learning (ML) has facilitated the identification of responders from non-responders and elucidating the mechanisms employed by tumors in developing resistance to immunotherapy, against diverse types of cancer [162]; [163]. A deep learning model developed on specific TCR repertoire sequences in combination with Human leukocyte antigen (HLA) typing enabled patient stratification and predicting response towards ICI therapy in melanoma patients [164].

Currently, multi-omics profiling of tumor and/or tumor microenvironment (TME) is receiving significant interest for identification of novel biomarkers for cancer immunotherapy [124]; [134]. Complexity of the data being obtained makes it implausible to capture intricate signals across these data sets by human experts; however, AI encapsulates this information remarkably [124]. Following a multi

modular approach with AI models built and trained on multi-omics datasets can provide a more comprehensive, accurate, and clinically useful framework for prognostic modelling in immunotherapy [159].

Table 4 summarizes some research studies focused on developing predictive AI models for examining the success of immunotherapy across different diseases. As is evident omic datasets are widely utilized in model construction either alone or in combination with other biological information. Prognostic AI models built on routine clinical information that is relatively easy to access and cost effective to obtain, have also been observed to perform at par with multi-omics-based AI models. However, for gaining an in-depth explanation or basis for the predictions made reliance on sequencing information is perceived [165]. Moreover, the performance of models built using a multi-modular approach is observed to be more reliable. Therefore, for efficient predictions and user adoption of predictive AI models, utilization of omics as well as real world clinical data for model construction is important. Currently ICI therapy remains at the forefront of most multi-omics ML models developed for predicting immunotherapy outcomes against cancer. However, much recently there has been interest in exploring the power of ML and multi-omics for interpreting the TME in the context of CAR-T cell therapy for treating solid tumors [181].

Based on their explainability, AI-ML algorithms can be broadly demarcated into transparent or opaque categories. Transparent algorithms offer end-to-end interpretation but are not as adept as opaque algorithms in handling complex tasks with greater accuracy. K-Nearest Neighbors, Naive-Bayes, Logistic Regression (LR) and Decision Trees are some examples of transparent algorithms; while Random Forests (RFs), Support Vector Machines (SVMs) and Deep Learning (DL) methods such as Convolution Neural Networks (CNNs) and Multilayer Perceptron (MLP) represent some opaque algorithms [201].

Wider user adoption of AI-ML prognostic tools necessitates gaining the trust of clinicians, for which AI decision systems need to be thoroughly validated and made understandable. Achieving superior prediction ability requires simultaneous assessment of multiple biological parameters, which demands the utilization of complex or ensemble ML methods. This makes the tools opaquer and their decision-

making process unclear. Achieving the balance between explainability and accuracy of AI systems is therefore essential [201].

Now, while clinicians do not always need to fathom the complete algorithm, they must understand how biological underpinnings drive the decision-making process. Several methods have been developed for making ML models more interpretable which are briefly discussed here. One approach for making ML models explainable is performing post-hoc analysis, where information is extracted without precisely focusing on internal processing. In this approach, most methods are model-agonistic, implying they are applicable for a variety of models and do not essentially access the internal model structure. There are also methods that are model-specific, catering only to particular ML algorithms; these yield more precise interpretations. Additionally, ML explanation methods can be classified based on whether they yield explanations for individual samples (local), or for the working of the model at an abstract level (global interpretation) [202]. Shapley Additive Explanations (SHAP) and Local Interpretable Model-Agnostic Explanations (LIME) are widely used interpretability methods in the healthcare-AI sector, they have also been utilized for developing explainable AI models for immunotherapy outcome prediction [168, 169, 165, 203, 204].

CHALLENGES AND OPPORTUNITIES

Advances in immunotherapy and the expanding accessibility of AI and ML algorithms are transforming treatment scenarios for a range of diseases and facilitating precision medicine. However, the synergy of these fields is currently in the stages of infancy, with its wider implementation facing challenges such as data privacy and security, algorithmic bias and integration into clinical workflows.

Data quality and quantity

Data bias can be problematic in arriving at a generalized AI model. The development of robust ML models requires large cohort sizes and thorough profiling of patients; this demands huge financial investments and collaborative efforts [189]. Currently, most AI models are limited in accuracy due to the unavailability of larger comprehensive datasets and/or lack of validation in large clinical trials [189]; [159]. Recent studies aim to address these challenges by using training data from several

centres and deployment of transfer learning algorithms. Nevertheless, biases in funding, resource allocation, ethnic disparity etc. can persist [190]; [191]; [192].

Model interpretability

The "black-box nature" of AI models wherein explanations for the internal analytical processes are not understandable, presents a significant hurdle to their wider adoption [159]. This is especially true in healthcare where decision-making is risk-intensive, and patient's consent is impacted by knowledge of the operable inherent mechanisms [193]. As outlined above, response to immunotherapy depends on several interconnected and varying parameters making the data non-linear and complex. This multidimensional information is interpreted using ML and DL algorithms such as CNN's and the nuances involved are not always comprehensible, especially to non-experts. Moreover, it is challenging to deliver explanations for model workflow in a manner that is understandable, without relinquishing the accuracy factor [194]. An understanding of the decision-making process is likely to facilitate wider adoption of such predictive models in clinical practice [192]. To this end, a promising solution can be implementation of explainable AI (XAI) approaches wherein every step of the ML process is traceable with explanations [159]. However, the debate on explainable AI as a solution to the "black-box problem" is still not settled. This is mainly because of the varied concerns this issue presents to the different stakeholders involved in the process, namely developers, clinicians, patients and regulatory authorities (193), (194).

Regulatory framework and ethical aspects

As of now, regulations governing the usage of AI in healthcare are still at a nascent stage of development. Currently, AI applications in healthcare are majorly being governed under regulations of the software as a medical device (SaMD) criterion, put forth by the international medical device regulators forum (IMDRF) and the FDA [195]. Recently, principles for good machine learning practice (GMLP) have also been released by IMDRF. These can serve as a foundation for further advancing GMLP standards through co-operation amongst different international standards and regulatory organizations.

Additionally, there is the recently enacted European Union (EU) AI Act, which is the world's first thorough legal framework on AI. EU AI act is likely to drive changes in the AI based healthcare technology sector at an international level, as it establishes

benchmarks for the development and utilization of AI. This act is significant to the healthcare sector as it specifically covers medical AI technologies, unlike other existing regulations [196]. According to provisions of this act, prognostic AI models such as those for predicting immunotherapy outcomes, are classified as "high risk". This obligates developers to present model interpretability reports and longitudinal safety data to assess their clinical feasibility [196], [197].

AI tools face serious accountability issues due to their "black-box nature" and propensity to be built on biased inputs, which can result in biased outputs [198]. In scenarios where AI assistance results in unintentional harm to patients, onus should not lie solely with the clinicians but also with the manufacturers of the AI tool, the clinician's organization and the healthcare system at large. To address the unforeseen challenges posed by the application of AI in healthcare, it is important that current healthcare ethical guidelines are revaluated [199].

Another major ethical concern is that of data confidentiality and security. AI tools are trained on extensive and sensitive patient information, un-intended and un-authorized access to this data can potentially favour certain stakeholders and impact patient interests. It is imperative that patient interests are protected by reinforcing robust security measures and adherence to regulatory laws [192].

CONCLUSION

The term immunotherapy is often associated with cancer; but it is now rapidly being explored to treat several other diseases such as asthma, MS, arthritis, HIV and tuberculosis etc. Although the overall results from such explorations have been encouraging, the setbacks identified from the clinical application of novel immunotherapeutics in treating cancer must be considered, along with the associated high cost. To ensure immunotherapy is safe, efficacious, and ultimately successful in its application across the wide spectrum of diseases, following a personalized approach is essential. Personalized immunotherapy is being supported by advances in omic profiling, biomarker identification and development of prognostic models, the latter two of which are enabled by AI. Concerningly, the pace of advances happening in AI is not at par with the establishment of regulatory frameworks. This imbalance along with issues such as interpretability, quality (data bias), and ethics poses a formidable barrier to the application of AI across healthcare. Overcoming these

barriers would require collaborative efforts from clinicians, research scientists, developers, regulatory agencies and policy makers.

In sum, this article presents a broad overview of how immunotherapy is being utilized or examined for treating ailments other than just cancer. It further dwells on how AI can assist the wider implementation of immunotherapy and the challenges associated with it. However, the article has limitations due to its narrative nature and the lack of a standardized methodology or quality appraisal process followed in its framework.

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REFERENCES

1. Kulwal V, Sawarkar S. Immunotherapy: A concept. JIANFOMT. 2021:1–19. https://doi.org/10.1007/978-981-15-9038-2_1
2. Eno JJ. Immunotherapy through the years. JOTAPIO. 2017;8(7):747. https://doi.org/10.6004/jadpro.2017.8.7.8
3. Araki K, Maeda R. A brief chronicle of antibody research and technological advances. Antibodies. 2024;13(4):90. https://doi.org/10.3390/antib13040090
4. Kaufmann SH. Immunology's coming of age. FII. 2019;10:453189. https://doi.org/10.3389/fimmu.2019.00684
5. Gross L. Intradermal immunization of C3H mice against a sarcoma that originated in an animal of the same line. Cancer Res. 1943;3(5):326–33.
6. Foley EJ. Antigenic properties of methylcholanthrene-induced tumors in mice of the strain of origin. Cancer Res. 1953;13(12):835–7.
7. Prehn RT, Main JM. Immunity to methylcholanthrene-induced sarcomas. J Natl Cancer Inst. 1957;18(6):769–78.
8. Thomas L, Lawrence H. Cellular and humoral aspects of the hypersensitive states. NYH-H. 1959:529–32.
9. Burnet M. Cancer—a biological approach: III. Viruses associated with neoplastic conditions. IV. Practical applications. BMJ. 1957;1(5023):841. https://doi.org/10.1136/bmj.1.5023.841
10. Burnet F. The concept of immunological surveillance. Immunology (Acta/Ann). 1970;13:1–27. https://doi.org/10.1159/000386035
11. Allison J. A brief history of immunotherapy. JTO. 2014;3.
12. Allison JP, McIntyre BW, Bloch D. Tumor-specific antigen of murine T-lymphoma defined with monoclonal antibody. J Immunol. 1982;129(5):2293–300. https://doi.org/10.4049/jimmunol.129.5.2293
13. Shi Y, Strasser A, Green DR, Latz E, Mantovani A, Melino G, et al. Legacy of the discovery of the T-cell receptor: 40 years of shaping basic immunology and translational work to develop novel therapies. Cell. 2024;21(7):790–7. https://doi.org/10.1038/s41423-024-01168-4

14. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T-cell basic science to clinical practice. Nat Rev Immunol. 2020;20(11):651–68. https://doi.org/10.1038/s41577-020-0306-5
15. Dobosz P, Dzieciątkowski T. The intriguing history of cancer immunotherapy. FII. 2019;10:496087. https://doi.org/10.3389/fimmu.2019.02965
16. Durham SR, Shamji MH. Allergen immunotherapy: past, present and future. Nat Rev Immunol. 2023;23(5):317–28. https://doi.org/10.1038/s41577-022-00786-1
17. Bucktrout SL, Bluestone JA, Ramsdell F. Recent advances in immunotherapies: from infection and autoimmunity, to cancer, and back again. Genome Med. 2018;10(1):79. https://doi.org/10.1186/s13073-018-0588-4
18. Naran K, Nundalall T, Chetty S, Barth S. Principles of immunotherapy: implications for treatment strategies in cancer and infectious diseases. Front Microbiol. 2018;9:405758. https://doi.org/10.3389/fmicb.2018.03158
19. Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. Nat Rev Drug Discov. 2015;14(8):561–84. https://doi.org/10.1038/nrd4591
20. Ma W, Xue R, Zhu Z, Farrukh H, Song W, Li T, et al. Increasing cure rates of solid tumors by immune checkpoint inhibitors. Signal Transduct Target Ther. 2023;12(1):10. https://doi.org/10.1186/s40164-023-00372-8
21. Varadé J, Magadán S, González-Fernández Á. Human immunology and immunotherapy: main achievements and challenges. CMI. 2021;18(4):805–28. https://doi.org/10.1038/s41423-020-00530-6
22. Sun Q, Hong Z, Zhang C, Wang L, Han Z, Ma D, et al. Immune checkpoint therapy for solid tumours: clinical dilemmas and future trends. Sig Transduct Target Ther. 2023;8(1):320. https://doi.org/10.1038/s41392-023-01522-4
23. Propper DJ, Balkwill FR. Harnessing cytokines and chemokines for cancer therapy. Nat Rev Clin Oncol. 2022;19(4):237–53. https://doi.org/10.1038/s41571-021-00588-9

24. MRCRCC Trial (Lancet). Interferon-α and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Lancet. 1999;353(9146):14–7. https://doi.org/10.1016/S0140-6736(98)03544-2
25. Chamie K, Chang SS, Kramolowsky E, Gonzalgo ML, Agarwal PK, Bassett JC, et al. IL-15 superagonist NAI in BCG-unresponsive non-muscle-invasive bladder cancer. NEJM Evidence. 2022;2(1):EVIDoa2200167. https://doi.org/10.1056/EVIDoa2200167
26. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411–22. https://doi.org/10.1056/NEJMoa1001294
27. Pallerla S, Abdul AuRM, Comeau J, Jois S. Cancer vaccines, treatment of the future: with emphasis on HER2-positive breast cancer. Int J Mol Sci. 2021;22(2):779. https://doi.org/10.3390/ijms22020779
28. Ejaz M, Syed MA. Therapeutic cancer vaccines; past, present, and future aspects. HOC Immunology. Springer. 2022:1–21. https://doi.org/10.1007/978-3-030-80962-1_207-1
29. Lin MJ, Svensson-Arvelund J, Lubitz GS, Marabelle A, Melero I, Brown BD, et al. Cancer vaccines: the next immunotherapy frontier. Nat Cancer. 2022;3(8):911–26. https://doi.org/10.1038/s43018-022-00418-6
30. Lovatt C, Parker AL. Oncolytic viruses and immune checkpoint inhibitors: the "hot" new power couple. Cancers. 2023;15(16):4178. https://doi.org/10.3390/cancers15164178
31. Zhao Y, Deng J, Rao S, Guo S, Shen J, Du F, et al. Tumor-infiltrating lymphocyte (TIL) therapy for solid tumor treatment: progressions and challenges. Cancers. 2022;14(17):4160. https://doi.org/10.3390/cancers14174160
32. Rohaan MW, van den Berg JH, Kvistborg P, Haanen J. Adoptive transfer of tumor-infiltrating lymphocytes in melanoma: a viable treatment option. J Immunother Cancer. 2018;6(1):102. https://doi.org/10.1186/s40425-018-0391-1

33. Thirumalaisamy R, Vasuki S, Sindhu S, Mothilal T, Srimathi V, Poornima B, et al. FDA-approved chimeric antigen receptor (CAR)-T cell therapy for different cancers—a recent perspective. Mol Biotechnol. 2025;67(2):469–83. https://doi.org/10.1007/s12033-024-01090-0
34. Zheng Z, Li S, Liu M, Chen C, Zhang L, Zhou D. Fine-tuning through generations: advances in structure and production of CAR-T therapy. Cancers. 2023;15(13):3476. https://doi.org/10.3390/cancers15133476
35. Chandrashekara S. The treatment strategies of autoimmune disease may need a different approach from conventional protocol: a review. Indian J Pharmacol. 2012;44(6):665–71. https://doi.org/10.4103/0253-7613.103235
36. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372(9636):383–91. https://doi.org/10.1016/S0140-6736(08)60998-8
37. Rachid O, Osman A, Abdi R, Haik Y. CTLA4-Ig (abatacept): a promising investigational drug for use in type 1 diabetes. Expert Opin Investig Drugs. 2020;29(3):221–36. https://doi.org/10.1080/13543784.2020.1727885
38. Orban T, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, et al. Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;378(9789):412–19. https://doi.org/10.1016/S0140-6736(11)60886-6
39. Russell WE, Bundy BN, Anderson MS, Cooney LA, Gitelman SE, Goland RS, et al. Abatacept for delay of type 1 diabetes progression in stage 1 relatives at risk: a randomized, double-masked, controlled trial. Diabetes Care. 2023;46(5):1005–13. https://doi.org/10.2337/dci23-0050
40. Siddiqui Z, Tedesco-Silva H, Riella LV. Belatacept in kidney transplantation—past and future perspectives. Braz J Nephrol. 2017;39:205–12. https://doi.org/10.5935/0101-2800.20170035
41. Tuttle J, Drescher E, Simón-Campos JA, Emery P, Greenwald M, Kivitz A, et al. A phase 2 trial of peresolimab for adults with rheumatoid arthritis. New England

Journal of Medicine. 2023;388(20):1853–62.
https://doi.org/10.1056/NEJMoa2209856

42. Klatzmann D, Abbas AK. The promise of low-dose interleukin-2 therapy for autoimmune and inflammatory diseases. Nature Reviews Immunology. 2015;15(5):283–94.
https://doi.org/10.1038/nri3823
43. Harris F, Berdugo YA, Tree T. IL-2-based approaches to Treg enhancement. Clinical and Experimental Immunology. 2023;211(2):149–63.
https://doi.org/10.1093/cei/uxac105
44. Filipi M, Jack S. Interferons in the treatment of multiple sclerosis: a clinical efficacy, safety, and tolerability update. International Journal of MS Care. 2020;22(4):165–72.
https://doi.org/10.7224/1537-2073.2018-063
45. Postal M, Vivaldo JF, Fernandez-Ruiz R, Paredes JL, Appenzeller S, Niewold TB. Type I interferon in the pathogenesis of systemic lupus erythematosus. Current Opinion in Immunology. 2020;67:87–94.
https://doi.org/10.1016/j.coi.2020.10.014
46. Burki TK. FDA approval for anifrolumab in patients with lupus. The Lancet Rheumatology. 2021;3(10):e689.
https://doi.org/10.1016/S2665-9913(21)00291-5
47. Jung SM, Kim W-U. Targeted immunotherapy for autoimmune disease. Immune Network. 2022;22(1):e9.
https://doi.org/10.4110/in.2022.22.e9
48. Marinho A, Delgado Alves J, Fortuna J, Faria R, Almeida I, Alves G, et al. Biological therapy in systemic lupus erythematosus, antiphospholipid syndrome, and Sjögren's syndrome: Evidence- and practice-based guidance. Frontiers in Immunology. 2023;14:1117699.
https://doi.org/10.3389/fimmu.2023.1117699
49. Ellebrecht CT, Bhoj VG, Nace A, Choi EJ, Mao X, Cho MJ, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. Science. 2016;353(6295):179–84.
https://doi.org/10.1126/science.aaf6756

50. Li Y-R, Lyu Z, Chen Y, Fang Y, Yang L. Frontiers in CAR-T cell therapy for autoimmune diseases. Trends in Pharmacological Sciences. 2024. https://doi.org/10.1016/j.tips.2024.07.005
51. Yeh W-I, Seay HR, Newby B, Posgai AL, Moniz FB, Michels A, et al. Avidity and bystander suppressive capacity of human regulatory T cells expressing de novo autoreactive T-cell receptors in type 1 diabetes. Frontiers in Immunology. 2017;8:1313. https://doi.org/10.3389/fimmu.2017.01313
52. Randall KL. Rituximab in autoimmune diseases. Australian Prescriber. 2016;39(4):131. https://doi.org/10.18773/austprescr.2016.053
53. Blair HA, Duggan ST. Belimumab: a review in systemic lupus erythematosus. Drugs. 2018;78:355–66. https://doi.org/10.1007/s40265-018-0872-z
54. Fiyouzi T, Pelaez-Prestel HF, Reyes-Manzanas R, Lafuente EM, Reche PA. Enhancing regulatory T cells to treat inflammatory and autoimmune diseases. International Journal of Molecular Sciences. 2023;24(9):7797. https://doi.org/10.3390/ijms24097797
55. Kohm AP, Carpentier PA, Anger HA, Miller SD. Cutting edge: CD4+ CD25+ regulatory T cells suppress antigen-specific autoreactive immune responses and central nervous system inflammation during active experimental autoimmune encephalomyelitis. Journal of Immunology. 2002;169(9):4712–6. https://doi.org/10.4049/jimmunol.169.9.4712
56. Fransson M, Piras E, Burman J, Nilsson B, Essand M, Lu B, et al. CAR/FoxP3-engineered T regulatory cells target the CNS and suppress EAE upon intranasal delivery. Journal of Neuroinflammation. 2012;9:1–12. https://doi.org/10.1186/1742-2094-9-112
57. Scalapino KJ, Tang Q, Bluestone JA, Bonyhadi ML, Daikh DI. Suppression of disease in New Zealand Black/New Zealand White lupus-prone mice by adoptive transfer of ex vivo expanded regulatory T cells. Journal of Immunology. 2006;177(3):1451–9. https://doi.org/10.4049/jimmunol.177.3.1451
58. Weigert O, von Spee C, Undeutsch R, Kloke L, Humrich JY, Riemekasten G, et al. CD4+ Foxp3+ regulatory T cells prolong drug-induced disease remission in

(NZBxNZW) F1 lupus mice. Arthritis Research & Therapy. 2013;15:1–11. https://doi.org/10.1186/ar4188

59. Tang Q, Henriksen KJ, Bi M, Finger EB, Szot G, Ye J, et al. In vitro-expanded antigen-specific regulatory T cells suppress autoimmune diabetes. Journal of Experimental Medicine. 2004;199(11):1455–65. https://doi.org/10.1084/jem.20040139
60. Zhang L, Sosinowski T, Cox AR, Cepeda JR, Sekhar NS, Hartig SM, et al. Chimeric antigen receptor (CAR) T cells targeting a pathogenic MHC class II: peptide complex modulate the progression of autoimmune diabetes. Journal of Autoimmunity. 2019;96:50–8. https://doi.org/10.1016/j.jaut.2018.08.004
61. Tenspolde M, Zimmermann K, Weber LC, Hapke M, Lieber M, Dywicki J, et al. Regulatory T cells engineered with a novel insulin-specific chimeric antigen receptor as a candidate immunotherapy for type 1 diabetes. Journal of Autoimmunity. 2019;103:102289. https://doi.org/10.1016/j.jaut.2019.05.017
62. Kinnear G, Jones ND, Wood KJ. Costimulation blockade: current perspectives and implications for therapy. Transplantation. 2013;95(4):527–35. https://doi.org/10.1097/TP.0b013e31826d4672
63. Ding M, He Y, Zhang S, Guo W. Recent advances in costimulatory blockade to induce immune tolerance in liver transplantation. Frontiers in Immunology. 2021;12:537079. https://doi.org/10.3389/fimmu.2021.537079
64. Kitchens WH, Larsen CP, Badell IR. Costimulatory blockade and solid organ transplantation: the past, present and future. Kidney International Reports. 2023. https://doi.org/10.1016/j.ekir.2023.08.037
65. Ramamurthy D, Nundalall T, Cingo S, Mungra N, Karaan M, Naran K, et al. Recent advances in immunotherapies against infectious diseases. Immunotherapy Advances. 2021;1(1):ltaa007. https://doi.org/10.1093/immadv/ltaa007
66. Seif M, Einsele H, Löffler J. CAR T cells beyond cancer: hope for immunomodulatory therapy of infectious diseases. Frontiers in Immunology. 2019;10:498743. https://doi.org/10.3389/fimmu.2019.02711

67. Leibman RS, Richardson MW, Ellebrecht CT, Maldini CR, Glover JA, Secreto AJ, et al. Supraphysiologic control over HIV-1 replication mediated by CD8 T cells expressing a re-engineered CD4-based chimeric antigen receptor. PLOS Pathogens. 2017;13(10):e1006613. https://doi.org/10.1371/journal.ppat.1006613
68. Wang X, Liu J, Hao F, Ajavavarakula T, Shi X. CAR-T therapy in HIV: pioneering advances and navigating challenges. Infectious Diseases & Immunity. 2024;4(04):194–205. https://doi.org/10.1097/ID9.0000000000000129
69. Otsubo R, Yasui T. Monoclonal antibody therapeutics for infectious diseases: beyond normal human immunoglobulin. Pharmacology & Therapeutics. 2022;240:108233. https://doi.org/10.1016/j.pharmthera.2022.108233
70. Miljanovic D, Cirkovic A, Lazarevic I, Knezevic A, Cupic M, Banko A, et al. Clinical efficacy of anti-SARS-CoV-2 monoclonal antibodies in preventing hospitalisation and mortality among patients infected with Omicron variants: a systematic review and meta-analysis. Reviews in Medical Virology. 2023;33(4):e2439. https://doi.org/10.1002/rmv.2439
71. Cox M, Peacock TP, Harvey WT, Hughes J, Wright DW, Willett BJ, et al. SARS-CoV-2 variant evasion of monoclonal antibodies based on in vitro studies. Nature Reviews Microbiology. 2023;21(2):112–24. https://doi.org/10.1038/s41579-022-00809-7
72. Fausther-Bovendo H, Kobinger G. The road to effective and accessible antibody therapies against Ebola virus. Current Opinion in Virology. 2022;54:101210. https://doi.org/10.1016/j.coviro.2022.101210
73. Promsote W, DeMouth ME, Almasri CG, Pegu A. Anti-HIV-1 antibodies: an update. BioDrugs. 2020;34(2):121–32. https://doi.org/10.1007/s40259-020-00413-2
74. Walter EB, Munoz FM. New approaches to respiratory syncytial virus prevention and treatment. Annual Review of Medicine. 2025;76. https://doi.org/10.1146/annurev-med-061323-073934

75. Rijal P, Donnellan FR. A review of broadly protective monoclonal antibodies to treat Ebola virus disease. Current Opinion in Virology. 2023;61:101339. https://doi.org/10.1016/j.coviro.2023.101339
76. Wang C-Y, Wong W-W, Tsai H-C, Chen Y-H, Kuo B-S, Lynn S, et al. Effect of anti-CD4 antibody UB-421 on HIV-1 rebound after treatment interruption. New England Journal of Medicine. 2019;380(16):1535–45. https://doi.org/10.1056/NEJMoa1802264
77. Verma V. Leveraging monoclonal antibodies as therapeutics to address antimicrobial resistance in bacteria. Journal of Applied Biology & Biotechnology. 2023;11(3):53–60. https://doi.org/10.7324/JABB.2023.90087
78. Kharga K, Kumar L, Patel SKS, Lazarevic I, Knezevic A, Cupic M, et al. Recent advances in monoclonal antibody-based approaches in the management of bacterial sepsis. Biomedicines. 2023;11(3):765. https://doi.org/10.3390/biomedicines11030765
79. Hesse EM, Godfred-Cato S, Bower WA. Antitoxin use in the prevention and treatment of anthrax disease: a systematic review. Clinical Infectious Diseases. 2022;75(Supplement_3):S432–S40. https://doi.org/10.1093/cid/ciac532
80. Mohamed MF, Ward C, Beran A, Abdallah MA, Asemota J, Kelly CR. Efficacy, safety, and cost-effectiveness of bezlotoxumab in preventing recurrent Clostridioides difficile infection: systematic review and meta-analysis. Journal of Clinical Gastroenterology. 2024;58(4):389–401. https://doi.org/10.1097/MCG.0000000000001875
81. Laustsen AH. How can monoclonal antibodies be harnessed against neglected tropical diseases and other infectious diseases? Expert Opinion on Drug Discovery. 2019;14(11):1103–12. https://doi.org/10.1080/17460441.2019.1646723
82. Aleshnick M, Florez-Cuadros M, Martinson T, Wilder BK. Monoclonal antibodies for malaria prevention. Molecular Therapy. 2022;30(5):1810–21. https://doi.org/10.1016/j.ymthe.2022.04.001
83. Lyke KE, Berry AA, Mason K, Idris AH, O'Callahan M, Happe M, et al. Low-dose intravenous and subcutaneous CIS43LS monoclonal antibody for protection

against malaria (VRC 612 Part C): a phase 1, adaptive trial. The Lancet Infectious Diseases. 2023;23(5):578–88.

84. van der Boor SC, Smit MJ, van Beek SW, Ramjith J, Teelen K, van de Vegte-Bolmer M, et al. Safety, tolerability, and Plasmodium falciparum transmission-reducing activity of monoclonal antibody TB31F: a single-centre, open-label, first-in-human, dose-escalation, phase 1 trial in healthy malaria-naive adults. The Lancet Infectious Diseases. 2022;22(11):1596–605. https://doi.org/10.1016/S1473-3099(22)00428-5
85. Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. Nature Reviews Immunology. 2018;18(2):91–104. https://doi.org/10.1038/nri.2017.112
86. Porichis F, Kwon DS, Zupkosky J, Tighe DP, McMullen A, Brockman MA, et al. Responsiveness of HIV-specific CD4 T cells to PD-1 blockade. Blood. 2011;118(4):965–74. https://doi.org/10.1182/blood-2010-12-328070
87. Chew GM, Fujita T, Webb GM, Burwitz BJ, Wu HL, Reed JS, et al. TIGIT marks exhausted T cells, correlates with disease progression, and serves as a target for immune restoration in HIV and SIV infection. PLOS Pathogens. 2016;12(1):e1005349. https://doi.org/10.1371/journal.ppat.1005349
88. Rasmussen TA, McMahon J, Chang JJ, Symons J, Roche M, Dantanarayana A, et al. Impact of alemtuzumab on HIV persistence in an HIV-infected individual on antiretroviral therapy with Sezary syndrome. AIDS. 2017;31(13):1839–45. https://doi.org/10.1097/QAD.0000000000001540
89. Gay CL, Bosch RJ, Ritz J, Hataye JM, Aga E, Tressler RL, et al. Clinical trial of the anti-PD-L1 antibody BMS-936559 in HIV-1 infected participants on suppressive antiretroviral therapy. Journal of Infectious Diseases. 2017;215(11):1725–33. https://doi.org/10.1093/infdis/jix191
90. Gardiner D, Lalezari J, Lawitz E, DiMicco M, Ghalib R, Reddy KR, et al. A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C virus infection. PLOS ONE. 2013;8(5):e63818. https://doi.org/10.1371/journal.pone.0063818

91. Gane E, Gaggar A, Nguyen A, Subramanian G, McHutchison J, Schwabe C, et al. A phase 1 study evaluating anti-PD-1 treatment with or without GS-4774 in HBeAg-negative chronic hepatitis B patients. Journal of Hepatology. 2017;66(S1):S26–S7. https://doi.org/10.1016/S0168-8278(17)30315-X
92. Yau T, Kang Y-K, Kim T-Y, El-Khoueiry AB, Santoro A, Sangro B, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. JAMA Oncology. 2020;6(11):e204564–e. https://doi.org/10.1001/jamaoncol.2020.4564
93. Barber DL, Sakai S, Kudchadkar RR, Fling SP, Day TA, Vergara JA, et al. Tuberculosis following PD-1 blockade for cancer immunotherapy. Science Translational Medicine. 2019;11(475):eaat2702. https://doi.org/10.1126/scitranslmed.aat2702
94. Lázár-Molnár E, Chen B, Sweeney KA, Wang EJ, Liu W, Lin J, et al. Programmed death-1 (PD-1)-deficient mice are extraordinarily sensitive to tuberculosis. Proceedings of the National Academy of Sciences of the USA. 2010;107(30):13402–7. https://doi.org/10.1073/pnas.1007394107
95. Anand K, Sahu G, Burns E, Ensor A, Ensor J, Pingali SR, et al. Mycobacterial infections due to PD-1 and PD-L1 checkpoint inhibitors. ESMO Open. 2020;5(4):e000866. https://doi.org/10.1136/esmoopen-2020-000866
96. Jayaraman P, Jacques MK, Zhu C, Steblenko KM, Stowell BL, Madi A, et al. TIM3 mediates T cell exhaustion during Mycobacterium tuberculosis infection. PLOS Pathogens. 2016;12(3):e1005490. https://doi.org/10.1371/journal.ppat.1005490
97. Phillips BL, Gautam US, Bucsan AN, Foreman TW, Golden NA, Niu T, et al. LAG-3 potentiates the survival of Mycobacterium tuberculosis in host phagocytes by modulating mitochondrial signaling in an in-vitro granuloma model. PLOS ONE. 2017;12(9):e0180413. https://doi.org/10.1371/journal.pone.0180413
98. Vaddi A, Hulsebus HJ, O'Neill EL, Knight V, Chan ED. A narrative review of the controversy on the risk of mycobacterial infections with immune checkpoint

inhibitor use: does Goldilocks have the answer? Journal of Thoracic Disease. 2024;16(2):1601.
https://doi.org/10.21037/jtd-23-1395

99. Lyu J, Narum DE, Baldwin SL, Larsen SE, Bai X, Griffith DE, et al. Understanding the development of tuberculous granulomas: insights into host protection and pathogenesis, a review in humans and animals. Frontiers in Immunology. 2024;15:1427559.
https://doi.org/10.3389/fimmu.2024.1427559

100. da Fonseca-Martins AM, Ramos TD, Pratti JE, Firmino-Cruz L, Gomes DCO, Soong L, et al. Immunotherapy using anti-PD-1 and anti-PD-L1 in Leishmania amazonensis-infected BALB/c mice reduce parasite load. Scientific Reports. 2019;9(1):20275.
https://doi.org/10.1038/s41598-019-56336-8

101. Liang SC, Greenwald RJ, Latchman YE, Rosas L, Satoskar A, Freeman GJ, et al. PD-L1 and PD-L2 have distinct roles in regulating host immunity to cutaneous leishmaniasis. European Journal of Immunology. 2006;36(1):58–64.
https://doi.org/10.1002/eji.200535458

102. Kumar R, Chauhan SB, Ng SS, Sundar S, Engwerda CR. Immune checkpoint targets for host-directed therapy to prevent and treat leishmaniasis. Frontiers in Immunology. 2017;8:1492.
https://doi.org/10.3389/fimmu.2017.01492

103. Butler NS, Moebius J, Pewe LL, Traore B, Doumbo OK, Tygrett LT, et al. Therapeutic blockade of PD-L1 and LAG-3 rapidly clears established blood-stage Plasmodium infection. Nature Immunology. 2012;13(2):188–95.
https://doi.org/10.1038/ni.2180

104. Hou N, Zou Y, Piao X, Liu S, Wang L, Li S, et al. T-cell immunoglobulin- and mucin-domain-containing molecule 3 signaling blockade improves cell-mediated immunity against malaria. Journal of Infectious Diseases. 2016;214(10):1547–56.
https://doi.org/10.1093/infdis/jiw428

105. Hafalla JCR, Claser C, Couper KN, Grau GE, Renia L, de Souza JB, et al. The CTLA-4 and PD-1/PD-L1 inhibitory pathways independently regulate host resistance to Plasmodium-induced acute immune pathology. PLOS Pathogens. 2012;8(2):e1002504.
https://doi.org/10.1371/journal.ppat.1002504

106. Zheng H, Zhang Y, Pan J, Liu N, Qin Y, Qiu L, et al. The role of type 2 innate lymphoid cells in allergic diseases. Frontiers in Immunology. 2021;12:586078. https://doi.org/10.3389/fimmu.2021.586078
107. Pengo N, Wuillemin N, Bieli D, Gasser P. Anti-allergen monoclonal antibodies for the treatment of allergies. Allergo Journal International. 2023;32(7):289–95. https://doi.org/10.1007/s40629-023-00263-8
108. Bernstein ZJ, Shenoy A, Chen A, Heller NM, Spangler JB. Engineering the IL-4/IL-13 axis for targeted immune modulation. Immunological Reviews. 2023;320(1):29–57. https://doi.org/10.1111/imr.13230
109. Slager RE, Otulana BA, Hawkins GA, Yen YP, Peters SP, Wenzel SE, et al. IL-4 receptor polymorphisms predict reduction in asthma exacerbations during response to an anti-IL-4 receptor α antagonist. Journal of Allergy and Clinical Immunology. 2012;130(2):516–22.e4. https://doi.org/10.1016/j.jaci.2012.03.030
110. Chen Y, Wang W, Yuan H, Li Y, Lv Z, Cui Y, et al. Current state of monoclonal antibody therapy for allergic diseases. Engineering. 2021;7(11):1552–6. https://doi.org/10.1016/j.eng.2020.06.029
111. Ali T, Jawed I, Maqsood B, Khan I, Haque MA. Xolair (omalizumab) breakthrough: FDA's first approval to combat allergic reactions to multiple foods. JIGH. 2025;e00554. https://doi.org/10.1097/GH9.0000000000000554
112. Gauvreau GM, Arm JP, Boulet L-P, Leigh R, Cockcroft DW, Davis BE, et al. Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses. Journal of Allergy and Clinical Immunology. 2016;138(4):1051–9. https://doi.org/10.1016/j.jaci.2016.02.027
113. Maurer M, Ensina LF, Gimenez-Arnau AM, Sussman G, Hide M, Saini S, et al. Efficacy and safety of ligelizumab in adults and adolescents with chronic spontaneous urticaria: results of two phase 3 randomised controlled trials. The Lancet. 2024;403(10422):147–59.
114. Kuo B-S, Li C-H, Chen J-B, Shiung Y-Y, Chu C-Y, Lee C-H, et al. IgE-neutralizing UB-221 mAb, distinct from omalizumab and ligelizumab, exhibits CD23-mediated IgE downregulation and relieves urticaria symptoms. Journal of

Clinical Investigation. 2023;132(15). https://doi.org/10.1172/JCI157765

115. Strowd LC, Feldman SR. Dupilumab for atopic dermatitis. The Lancet. 2017;389(10086):2265–6. https://doi.org/10.1016/S0140-6736(17)31192-3

116. Napolitano M, Fabbrocini G, Neri I, Stingeni L, Boccaletti V, Piccolo V, et al. Dupilumab treatment in children aged 6–11 years with atopic dermatitis: a multicentre, real-life study. Paediatric Drugs. 2022;24(6):671–8. https://doi.org/10.1007/s40272-022-00531-0

117. Dodson J, Lio PA. Biologics and small molecule inhibitors: an update in therapies for allergic and immunologic skin diseases. Current Allergy and Asthma Reports. 2022;22(12):183–93. https://doi.org/10.1007/s11882-022-01047-w

118. Skuljec J, Chmielewski M, Happle C, Habener A, Busse M, Abken H, et al. Chimeric antigen receptor-redirected regulatory T cells suppress experimental allergic airway inflammation, a model of asthma. Frontiers in Immunology. 2017;8:247521. https://doi.org/10.3389/fimmu.2017.01125

119. Esmaeilzadeh A, Tahmasebi S, Athari SS. Chimeric antigen receptor-T cell therapy: applications and challenges in treatment of allergy and asthma. Biomedicine & Pharmacotherapy. 2020;123:109685. https://doi.org/10.1016/j.biopha.2019.109685

120. Ward DE, Fay BL, Adejuwon A, Han H, Ma Z. Chimeric antigen receptors based on low affinity mutants of FcεRI re-direct T cell specificity to cells expressing membrane IgE. Frontiers in Immunology. 2018;9:2231. https://doi.org/10.3389/fimmu.2018.02231

121. Morita H, Saito H, Matsumoto K. Immune checkpoint molecules on ILC2s as potential therapeutic targets for allergic diseases. Journal of Allergy and Clinical Immunology. 2022;149(1):60–2. https://doi.org/10.1016/j.jaci.2021.10.021

122. Helou DG, Shafiei-Jahani P, Lo R, Howard E, Hurrell BP, Galle-Treger L, et al. PD-1 pathway regulates ILC2 metabolism and PD-1 agonist treatment ameliorates airway hyperreactivity. Nature Communications. 2020;11(1):3998. https://doi.org/10.1038/s41467-020-17813-1

123. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. JAMA Network Open. 2019;2(5):e192535–e. https://doi.org/10.1001/jamanetworkopen.2019.2535

124. Wang R, Xiong K, Wang Z, Wu D, Hu B, Ruan J, et al. Immunodiagnosis—the promise of personalized immunotherapy. Frontiers in Immunology. 2023;14:1216901. https://doi.org/10.3389/fimmu.2023.1216901

125. Okwundu N, Grossman D, Hu-Lieskovan S, Grossmann KF, Swami U. The dark side of immunotherapy. Annals of Translational Medicine. 2021;9(12). https://doi.org/10.21037/atm-20-4750

126. Nixon AB, Schalper KA, Jacobs I, Potluri S, Wang I-M, Fleener C. Peripheral immune-based biomarkers in cancer immunotherapy: can we realize their predictive potential? Journal for ImmunoTherapy of Cancer. 2019;7:1–14. https://doi.org/10.1186/s40425-019-0799-2

127. Feldmann M, Steinman L. Design of effective immunotherapy for human autoimmunity. Nature. 2005;435(7042):612–9. https://doi.org/10.1038/nature03727

128. Jesenak M, Brndiarova M, Urbancikova I, Rennerova Z, Vojtkova J, Bobcakova A, et al. Immune parameters and COVID-19 infection—associations with clinical severity and disease prognosis. Frontiers in Cellular and Infection Microbiology. 2020;10:364. https://doi.org/10.3389/fcimb.2020.00364

129. Obeagu EI, Obeagu GU. Utilization of immunological ratios in HIV: implications for monitoring and therapeutic strategies. Medicine. 2024;103(9):e37354. https://doi.org/10.1097/MD.0000000000037354

130. Pilard C, Ancion M, Delvenne P, Jerusalem G, Hubert P, Herfs M. Cancer immunotherapy: it's time to better predict patients' response. British Journal of Cancer. 2021;125(7):927–38. https://doi.org/10.1038/s41416-021-01413-x

131. Nelde A, Rammensee H-G, Walz JS. The peptide vaccine of the future. Molecular & Cellular Proteomics. 2021;20:100022. https://doi.org/10.1074/mcp.R120.002309

132. Fernández VA, Martínez PB, Granhøj JS, Borch TH, Donia M, Svane IM. Biomarkers for response to TIL therapy: a comprehensive review. Journal for ImmunoTherapy of Cancer. 2024;12(3):e008640. https://doi.org/10.1136/jitc-2023-008640
133. Catalano M, Iannone LF, Nesi G, Nobili S, Mini E, Roviello G. Immunotherapy-related biomarkers: confirmations and uncertainties. Critical Reviews in Oncology/Hematology. 2023;192:104135. https://doi.org/10.1016/j.critrevonc.2023.104135
134. Butterfield LH, Najjar YG. Immunotherapy combination approaches: mechanisms, biomarkers and clinical observations. Nature Reviews Immunology. 2024;24(6):399–416. https://doi.org/10.1038/s41577-023-00973-8
135. Miao Y-D, Quan W-X, Tang X-L, Shi W-W, Li Q, Li RJ, et al. Uncovering the flip side of immune checkpoint inhibitors: a comprehensive review of immune-related adverse events and predictive biomarkers. International Journal of Biological Sciences. 2024;20(2):621. https://doi.org/10.7150/ijbs.89376
136. Pachner AJ. The brave new world of early treatment of multiple sclerosis: using the molecular biomarkers CXCL13 and neurofilament light to optimize immunotherapy. Biomedicines. 2022;10(9):2099. https://doi.org/10.3390/biomedicines10092099
137. Ling SF, Yap CF, Nair N, Bluett J, Morgan AW, Isaacs JD, et al. A proteomics study of rheumatoid arthritis patients on etanercept identifies putative biomarkers associated with clinical outcome measures. Rheumatology. 2024;63(4):1015–21. https://doi.org/10.1093/rheumatology/kead321
138. Layhadi JA, Lalioti A, Palmer E, van Zelm MC, Wambre E, Shamji MH, et al. Mechanisms and predictive biomarkers of allergen immunotherapy in the clinic. Journal of Allergy and Clinical Immunology: In Practice. 2024;12(1):59–66. https://doi.org/10.1016/j.jaip.2023.11.027
139. Takeuchi T, Miyasaka N, Inui T, Yano T, Yoshinari T, Abe T, et al. High titers of both rheumatoid factor and anti-CCP antibodies at baseline in patients with rheumatoid arthritis are associated with increased circulating baseline TNF level, low drug levels, and reduced clinical responses: a post hoc analysis of the

RISING study. Arthritis Research & Therapy. 2017;19:1–11. https://doi.org/10.1186/s13075-017-1401-2

140. Harrold LR, Bryson J, Lehman T, Zhuo J, Gao S, Han X, et al. Association between baseline anti-cyclic citrullinated peptide antibodies and 6-month clinical response following abatacept or TNF inhibitor treatment: a real-world analysis of biologic-experienced patients with RA. Rheumatology and Therapy. 2021;8(2):937–53. https://doi.org/10.1007/s40744-021-00310-2

141. Julià A, López-Lasanta M, Blanco F, Gómez A, Haro I, Mas AJ, et al. Interactions between rheumatoid arthritis antibodies are associated with the response to anti-tumor necrosis factor therapy. BMC Musculoskeletal Disorders. 2021;22:1–7. https://doi.org/10.1186/s12891-021-04248-y

142. Lend K, Lampa J, Padyukov L, Hetland ML, Heiberg MS, Nordström DC, et al. Association of rheumatoid factor, anti-citrullinated protein antibodies and shared epitope with clinical response to initial treatment in patients with early rheumatoid arthritis: data from a randomised controlled trial. Annals of the Rheumatic Diseases. 2024;83(12):1657–65. https://doi.org/10.1136/ard-2024-226024

143. Inoue M, Nagafuchi Y, Ota M, Tsuchiya H, Tateishi S, Kanda H, et al. Carriers of HLA-DRB1*04:05 have a better clinical response to abatacept in rheumatoid arthritis. Scientific Reports. 2023;13(1):15250. https://doi.org/10.1038/s41598-023-42324-6

144. Cha S, Bang S-Y, Joo YB, Cho S-K, Choi C-B, Sung Y-K, et al. Association of HLA-DRB1 locus with treatment response to abatacept or TNF inhibitors in patients with seropositive rheumatoid arthritis. Scientific Reports. 2024;14(1):6763. https://doi.org/10.1038/s41598-024-56987-2

145. Delcoigne B, Manouchehrinia A, Barro C, Benkert P, Michalak Z, Kappos L, et al. Blood neurofilament light levels segregate treatment effects in multiple sclerosis. Neurology. 2020;94(11):e1201–12. https://doi.org/10.1212/WNL.0000000000009097

146. Sormani MP, Haering DA, Kropshofer H, Leppert D, Kundu U, Barro C, et al. Blood neurofilament light as a potential endpoint in phase 2 studies in MS.

Annals of Clinical and Translational Neurology. 2019;6(6):1081–9. https://doi.org/10.1002/acn3.795

147. Dalla Costa G, Martinelli V, Moiola L, Sangalli F, Colombo B, Finardi A, et al. Serum neurofilaments increase at progressive multifocal leukoencephalopathy onset in natalizumab-treated multiple sclerosis patients. Annals of Neurology. 2019;85(4):606–10. https://doi.org/10.1002/ana.25437

148. Fissolo N, Pignolet B, Rio J, Vermersch P, Ruet A, Desèze J, et al. Serum neurofilament levels and PML risk in patients with multiple sclerosis treated with natalizumab. Neurology: Neuroimmunology & Neuroinflammation. 2021;8(4):e1003. https://doi.org/10.1212/NXI.0000000000001003

149. Abdelhak A, Antweiler K, Kowarik MC, Senel M, Havla J, Zettl UK, et al. Serum glial fibrillary acidic protein and disability progression in progressive multiple sclerosis. Annals of Clinical and Translational Neurology. 2024;11(2):477–85. https://doi.org/10.1002/acn3.51969

150. Talaat F, Abdelatty S, Ragaie C, Dahshan A. Chitinase-3-like 1 protein in CSF: a novel biomarker for progression in patients with multiple sclerosis. Neurological Sciences. 2023;44(9):3243–52. https://doi.org/10.1007/s10072-023-06764-2

151. Bordas-Le Floch V, Berjont N, Batard T, Varese N, O'Hehir RE, Canonica WG, et al. Coordinated IgG2 and IgE responses as a marker of allergen immunotherapy efficacy. Allergy. 2022;77(4):1263–73. https://doi.org/10.1111/all.15107

152. Ortega HG, Yancey SW, Mayer B, Gunsoy NB, Keene ON, Bleecker ER, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. The Lancet Respiratory Medicine. 2016;4(7):549–56. https://doi.org/10.1016/S2213-2600(16)30031-5

153. Celis-Preciado CA, Lachapelle P, Couillard S. Blood eosinophils take centre stage in predicting the response to sublingual immunotherapy (SLIT): a familiar twist. Thorax. 2024;79(5):297–8. https://doi.org/10.1136/thorax-2023-221274

154. Katz LE, Gleich GJ, Hartley BF, Yancey SW, Ortega HG. Blood eosinophil count is a useful biomarker to identify patients with severe eosinophilic asthma. Annals of the American Thoracic Society. 2014;11(4):531–6. https://doi.org/10.1513/AnnalsATS.201310-354OC

155. Ogulur I, Pat Y, Ardicli O, Barletta E, Cevhertas L, Fernandez-Santamaria R, et al. Advances and highlights in biomarkers of allergic diseases. Allergy. 2021;76(12):3659–86. https://doi.org/10.1111/all.15089

156. Pavord ID, Deniz Y, Corren J, Casale TB, FitzGerald JM, Izuhara K, et al. Baseline FeNO independently predicts the dupilumab response in patients with moderate-to-severe asthma. Journal of Allergy and Clinical Immunology: In Practice. 2023;11(4):1213–20.e2. https://doi.org/10.1016/j.jaip.2022.11.043

157. Hoshino M, Akitsu K, Kubota K, Ohtawa J. Association between biomarkers and house dust mite sublingual immunotherapy in allergic asthma. Clinical and Experimental Allergy. 2020;50(9):1035–43. https://doi.org/10.1111/cea.13686

158. Li T, Li Y, Zhu X, He Y, Wu Y, Ying T, et al., editors. Artificial intelligence in cancer immunotherapy: applications in neoantigen recognition, antibody design and immunotherapy response prediction. Seminars in Cancer Biology. 2023.

159. Li Y, Wu X, Fang D, Luo Y. Informing immunotherapy with multi-omics driven machine learning. npj Digital Medicine. 2024;7(1):67. https://doi.org/10.1038/s41746-024-01043-6

160. Peng J, Zhang J, Zou D, Xiao L, Ma H, Zhang X, et al. Deep learning to estimate durable clinical benefit and prognosis from patients with non-small cell lung cancer treated with PD-1/PD-L1 blockade. Frontiers in Immunology. 2022;13:960459. https://doi.org/10.3389/fimmu.2022.960459

161. Wang Y, Chen L, Ju L, Xiao Y, Wang X. Tumor mutational burden related classifier is predictive of response to PD-L1 blockade in locally advanced and metastatic urothelial carcinoma. International Immunopharmacology. 2020;87:106818. https://doi.org/10.1016/j.intimp.2020.106818

162. Liu R, Dollinger E, Nie Q. Machine learning of single cell transcriptomic data from anti-PD-1 responders and non-responders reveals distinct resistance mechanisms in skin cancers and PDAC. Frontiers in Genetics. 2022;12:806457. https://doi.org/10.3389/fgene.2021.806457
163. Kang Y, Vijay S, Gujral TS. Deep neural network modeling identifies biomarkers of response to immune-checkpoint therapy. iScience. 2022;25(5):104228. https://doi.org/10.1016/j.isci.2022.104228
164. Sidhom J-W, Ross-Macdonald P, Wind-Rotolo M, Pardoll A, Baras A. Deep learning reveals predictive sequence concepts within immune repertoires to immunotherapy. Journal for ImmunoTherapy of Cancer. 2021;9(Suppl):A832. https://doi.org/10.1136/jitc-2021-SITC2021.832
165. Yoo S-K, Fitzgerald CW, Cho BA, Fitzgerald BG, Han C, Koh ES, et al. Prediction of checkpoint inhibitor immunotherapy efficacy for cancer using routine blood tests and clinical data. 2025:1–12.
166. Li X, Dowling EK, Yan G, Dereli Z, Bozorgui B, Imanirad P, et al. Precision combination therapies based on recurrent oncogenic coalterations. Cancer Discovery. 2022;12(6):1542–59. https://doi.org/10.1158/2159-8290.CD-21-0832
167. Yin J, Xu L, Wang S, Zhang L, Zhang Y, Zhai Z, et al. Integrating immune multi-omics and machine learning to improve prognosis, immune landscape, and sensitivity to first- and second-line treatments for head and neck squamous cell carcinoma. Scientific Reports. 2024;14(1):31454. https://doi.org/10.1038/s41598-024-83184-y
168. Gschwind A, Ossowski S. AI model for predicting anti-PD1 response in melanoma using multi-omics biomarkers. Cancers. 2025;17(5):714. https://doi.org/10.3390/cancers17050714
169. Tao W, Concepcion AN, Vianen M, Marijnissen AC, Lafeber FP, Radstake TR, et al. Multiomics and machine learning accurately predict clinical response to adalimumab and etanercept therapy in patients with rheumatoid arthritis. Arthritis & Rheumatology. 2021;73(2):212–22. https://doi.org/10.1002/art.41516
170. Edner NM, Heuts F, Thomas N, Wang CJ, Petersone L, Kenefeck R, et al. Follicular helper T cell profiles predict response to costimulation blockade in

type 1 diabetes. Nature Immunology. 2020;21(10):1244–55. https://doi.org/10.1038/s41590-020-0744-z

171. Wang D, Lv Q, Yao H, Chen Y, Yu J, Jin X, et al. The efficacy prediction of subcutaneous immunotherapy for pediatric allergic rhinitis: application of machine learning methods. Biomedical Signal Processing and Control. 2026;112:108704. https://doi.org/10.1016/j.bspc.2025.108704

172. Yao H, Wang L, Zhou X, Jia X, Xiang Q, Zhang W, et al. Predicting the therapeutic efficacy of AIT for asthma using clinical characteristics, serum allergen detection metrics, and machine learning techniques. Computers in Biology and Medicine. 2023;166:107544. https://doi.org/10.1016/j.compbiomed.2023.107544

173. Salehi F, Zarifi S, Bayat S, Habibpour M, Asemanrafat A, Kleyer A, et al. Predicting Disease Activity Score in rheumatoid arthritis patients treated with biologic disease-modifying antirheumatic drugs using machine learning models. Technologies. 2025;13(8):350. https://doi.org/10.3390/technologies13080350

174. Suárez-Fariñas M, Suprun M, Chang HL, Gimenez G, Grishina G, Getts R, et al. Predicting development of sustained unresponsiveness to milk oral immunotherapy using epitope-specific antibody binding profiles. Journal of Allergy and Clinical Immunology. 2019;143(3):1038–46. https://doi.org/10.1016/j.jaci.2018.10.028

175. Liu R, Rizzo S, Wang L, Chaudhary N, Maund S, Garmhausen MR, et al. Characterizing mutation-treatment effects using clinico-genomics data of 78,287 patients with 20 types of cancers. Nature Communications. 2024;15(1):10884. https://doi.org/10.1038/s41467-024-55251-5

176. Jee J, Fong C, Pichotta K, Tran TN, Luthra A, Waters M, et al. Automated real-world data integration improves cancer outcome prediction. 2024:1–9.

177. Yang Y, Yang J, Shen L, Chen J, Xia L, Ni B, et al. A multi-omics-based serial deep learning approach to predict clinical outcomes of single-agent anti-PD-1/PD-L1 immunotherapy in advanced stage non-small-cell lung cancer. 2021;13(2):743.

178. Wang N, Song J, Sun SR, Zhu KZ, Li JX, Wang ZC, et al. Immune signatures predict response to house dust mite subcutaneous immunotherapy in patients with

allergic rhinitis. Allergy. 2024;79(5):1230–41. https://doi.org/10.1111/all.16068

179. Ferrè L, Clarelli F, Pignolet B, Mascia E, Frasca M, Santoro S, et al. Combining clinical and genetic data to predict response to fingolimod treatment in relapsing remitting multiple sclerosis patients: a precision medicine approach. Journal of Personalized Medicine. 2023;13(1):122. https://doi.org/10.3390/jpm13010122

180. Bouget V, Duquesne J, Hassler S, Cournède P-H, Fautrel B, Guillemin F, et al. Machine learning predicts response to TNF inhibitors in rheumatoid arthritis: results on the ESPOIR and ABIRISK cohorts. RMD Open. 2022;8(2):e002442. https://doi.org/10.1136/rmdopen-2022-002442

181. Zhou Z, Wang J, Wang J, Yang S, Wang R, Zhang G, et al. Deciphering the tumor immune microenvironment from a multidimensional omics perspective: insight into next-generation CAR-T cell immunotherapy and beyond. Molecular Cancer. 2024;23(1):131. https://doi.org/10.1186/s12943-024-02047-2

182. MacMath D, Chen M, Khoury P. Artificial intelligence: exploring the future of innovation in allergy immunology. Current Allergy and Asthma Reports. 2023;23(6):351–62. https://doi.org/10.1007/s11882-023-01084-z

183. Yoosuf N, Maciejewski M, Ziemek D, Jelinsky SA, Folkersen L, Müller M, et al. Early prediction of clinical response to anti-TNF treatment using multi-omics and machine learning in rheumatoid arthritis. Rheumatology. 2022;61(4):1680–9. https://doi.org/10.1093/rheumatology/keab521

184. Fousteri G, Rodrigues EM, Giamporcaro GM, Falcone M. A machine learning approach to predict response to immunotherapy in type 1 diabetes. Cellular & Molecular Immunology. 2021;18(3):515–7. https://doi.org/10.1038/s41423-020-00594-4

185. Gautier T, Ziegler LB, Gerber MS, Campos-Náñez E, Patek SD. Artificial intelligence and diabetes technology: a review. Metabolism. 2021;124:154872. https://doi.org/10.1016/j.metabol.2021.154872

186. Chitnis T, Prat A. A roadmap to precision medicine for multiple sclerosis. Multiple Sclerosis Journal. 2020;26(5):522–32. https://doi.org/10.1177/1352458519881558

187. Engel S, Zipp F. Preventing disease progression in multiple sclerosis—insights from large real-world cohorts. Genome Medicine. 2022;14(1):41. https://doi.org/10.1186/s13073-022-01044-8

188. Engelhardt B, Comabella M, Chan A. Multiple sclerosis: immunopathological heterogeneity and its implications. European Journal of Immunology. 2022;52(6):869–81. https://doi.org/10.1002/eji.202149757

189. Masina R, Caldas C. Precision cancer medicine 2.0—oncology in the postgenomic era. Molecular Oncology. 2024;18(9):2065–9. https://doi.org/10.1002/1878-0261.13707

190. Celi LA, Cellini J, Charpignon M-L, Dee EC, Dernoncourt F, Eber R, et al. Sources of bias in artificial intelligence that perpetuate healthcare disparities—a global review. PLOS Digital Health. 2022;1(3):e0000022. https://doi.org/10.1371/journal.pdig.0000022

191. Zou J, Schiebinger L. AI can be sexist and racist—it's time to make it fair. Nature. 2018;559:324–6. https://doi.org/10.1038/d41586-018-05707-8

192. Wang J, Zeng Z, Li Z, Liu G, Zhang S, Luo C, et al. The clinical application of artificial intelligence in cancer precision treatment. Journal of Translational Medicine. 2025;23(1):120. https://doi.org/10.1186/s12967-025-06139-5

193. Wadden JJ. Defining the undefinable: the black box problem in healthcare artificial intelligence. Journal of Medical Ethics. 2022;48(10):764–8. https://doi.org/10.1136/medethics-2021-107529

194. Gerlings J, Jensen MS, Shollo A. Explainable AI, but explainable to whom? An exploratory case study of xAI in healthcare. In: Handbook of Artificial Intelligence in Healthcare. Vol 2: Practicalities and Prospects. Springer; 2021. p. 169–98. https://doi.org/10.1007/978-3-030-83620-7_7

195. Palaniappan K, Lin EYT, Vogel S, editors. Global regulatory frameworks for the use of artificial intelligence (AI) in the healthcare services sector. Healthcare. 2024;12(5):562. https://doi.org/10.3390/healthcare12050562

196. Van Kolfschooten H, Van Oirschot J. The EU Artificial Intelligence Act (2024): implications for healthcare. Health Policy. 2024;149:105152. https://doi.org/10.1016/j.healthpol.2024.105152
197. Han L, Chen Y, Wang L, Zong X. Discussion on the regulatory test of artificial intelligence-enabled medical devices and their technical potential in tumor immunity. Technology in Cancer Research & Treatment. 2025;24(3):1–14. https://doi.org/10.54963/ti.v9i3.1217
198. Yang C, Chen Y, Qian C, Shi F, Guo Y. The data-intensive research paradigm: challenges and responses in clinical professional graduate education. Frontiers in Medicine. 2025;12:1461863. https://doi.org/10.3389/fmed.2025.1461863
199. Maliha G, Gerke S, Cohen IG, Parikh RB. Artificial intelligence and liability in medicine: balancing safety and innovation. Milbank Quarterly. 2021;99(3):629–67. https://doi.org/10.1111/1468-0009.12504
200. Pachner AR, Pike SC, Smith AD, Gilli F. The CXCL13 index biomarker predicts success or failure of moderate-efficacy disease-modifying therapies in multiple sclerosis: a real-world study. Multiple Sclerosis and Related Disorders. 2025;95:106303. https://doi.org/10.1016/j.msard.2025.106303
201. Assis A, Dantas J, Andrade E. The performance–interpretability trade-off: a comparative study of machine learning models. Journal of Reliable Intelligent Environments. 2025;11(1):1–14. https://doi.org/10.1007/s40860-024-00240-0
202. Abdullah TA, Zahid MSM, Ali W. A review of interpretable ML in healthcare: taxonomy, applications, challenges, and future directions. Symmetry. 2021;13(12):2439. https://doi.org/10.3390/sym13122439
203. Prelaj A, Galli EG, Miskovic V, Pesenti M, Viscardi G, Pedica B, et al. Real-world data to build explainable trustworthy artificial intelligence models for prediction of immunotherapy efficacy in NSCLC patients. Frontiers in Oncology. 2023;12:1078822. https://doi.org/10.3389/fonc.2022.1078822

204. Hounye AH, Xiong L, Hou M. Integrated explainable machine learning and multi-omics analysis for survival prediction in cancer with immunotherapy response. Apoptosis. 2025;30(1):364–88. https://doi.org/10.1007/s10495-024-02050-4

TABLES AND FIGURES WITH LEGENDS

Table 1. Cytokine therapy and cytokine-directed therapy for autoimmune diseases

S. No.	Cytokine therapy/ targeted cytokine	Autoimmune condition	Mechanism of action	Clinical status	References
1	Low Dose IL-2 therapy	GvHD, SLE, T1DM	confer Tregs with a competitive advantage leading to high Treg:Teff ratios.	Under investigation	[42]; [17]; [43]
2	IFN-β therapy	MS	upregulation of Th2 anti-inflammatory response while dampening the pro-inflammatory Th1/Th17 response	Approved	[44]
3	IFN inhibition (Anifrolumab)	SLE	complete blockade of type I IFN pathway leading to reduced inflammatory damage	Approved	[45]; [46]
4	TNF-α inhibition	Psoriasis and	blocking the pro-	Approved	[47]

		different forms of arthritis	inflammatory action of TNF-α		
5	IL-1 inhibition (Anakinra, Canakinumab)	RA and Juvenile idiopathic arthritis (JIA)	binds to IL-1 receptor thus inhibiting the activity of inflammatory IL-1 α and β cytokines	Approved	[47]
6	IL-6 inhibition (Tocilizumab, Sarilumab)	RA, JIA, SLE	binds to IL-6 receptor/ IL-6 thus inhibiting the inflammatory action of this cytokine	Approved (RA, JIA); under investigation (Tocilizumab for SLE)	[47]; [1]; [48]
7	IL-17 inhibition (Ixekizumab, Secukinumab, Brodalumab)	Psoriasis, Psoriatic arthritis, ankylosing spondylitis, SLE	binds to IL-17/ IL-17 receptor thus inhibiting the inflammatory action of this cytokine	Approved (Psoriasis, Psoriatic arthritis, ankylosing spondylitis); under investigation (Secukinumab for SLE)	[47]
8	IL-23 inhibition (Ustekinumab, Guselkumab, Risankizumab,	Psoriasis	binds to IL-23 leading to disruption of its inflammatory signalling pathway	Approved	[47]

	Tildrakizumab)				

Abbreviations: GvHD: Graft-versus-host disease; SLE: Systemic lupus erythematosus; T1DM: Type 1 diabetes mellitus; Treg: Regulatory T cell; Teff: Effector T cell; IFN: Interferon; IFN-β: Interferon-beta; MS: Multiple sclerosis; Th1: T helper 1 cell; Th2: T helper 2 cell; Th17: T helper 17 cell; TNF-α: Tumor necrosis factor-alpha; RA: Rheumatoid arthritis; JIA: Juvenile idiopathic arthritis.

Table 2. Monoclonal antibodies developed as therapeutics for infectious diseases

S. No.	Pathogen	mAb	Regulatory status	Reference
1	**Virus**			
	SARS-CoV-2	Bamlanivimab, Bamlanivimab and Etesevimab, Casirivimab and Imdevimab, Sotrovimab	Received EUA which was later revoked by FDA	[70]
	Ebola Virus	Ansuvimab (mAb114), Inmazeb	FDA-approved	[72]
	RSV	Nirsevimab, Palivizumab	FDA-approved	[74]
	HIV-1	Ibalizumab	FDA- approved	[73]
2	**Bacteria**			
	Bacillus anthracis	Raxibacumab, Obiltoxaximab	FDA Approved	[79]
	Clostridium difficile	Obiltoxaximab	FDA Approved	[80]

Abbreviations: mAb: Monoclonal antibody; EUA: Emergency use authorization; FDA: Food and Drug Administration; RSV: Respiratory syncytial virus; HIV-1: Human immunodeficiency virus type 1.

Table 3. Candidate biomarkers for predicting immunotherapy outcomes in autoimmune diseases

S. No	Disease	Candidate biomarker	Biomarker type	Biomarker relevance	Clinical implementation	Reference
1	RA	Anti-CCP and RF	Protein	Diagnostic and Prognostic	Clinically utilized diagnostic biomarker; Investigational prognostic biomarker (tested in small/moderate sized cohorts)	[139]; [140]; [141]; [142]
2	RA	HLA-DRB1*01, HLA-DRB1*04, HLADRB1*10 and HLA-DRB1*14:02.	Genetic	Prognostic	Investigational (tested in small cohorts)	[143]; [144]; [142]
3	MS	NFL	Protein	Prognostic	Investigational (tested in large and small cohorts)	[145]; [146]; [147]; [148]

4	MS	GFAP	Protein	Prognostic	Investigational (tested in small cohorts)	[149]
5	MS	CXCL13	Protein (Chemokine)	Predictive and Prognostic	Investigational (tested in small cohorts)	[200]
6	MS	CHI3L1	Protein	Prognostic	Investigational (tested in small cohorts)	[150]
7	Asthma	IgE	Humoral	Diagnostic, Prognostic and Predictive	Clinically utilized diagnostic biomarker; Investigational prognostic biomarker (tested in small/medium cohorts)	[138]; [151]
8	Asthma	Eosinophil count	Cellular	Diagnostic, Prognostic and Predictive	Clinically utilized diagnostic biomarker; Investigational prognostic biomarker (tested in small and large cohorts)	[152]; [153]; [154]; [155]
9	Asthma	FeNO	Metabolic	Diagnostic, Prognostic and Predictive	Clinically utilized diagnostic biomarker; Investigational prognostic and predictive biomarker	[156]; [157]; [155]

					(tested in large cohort)	

Abbreviations: RA: Rheumatoid arthritis; Anti-CCP: Anti-cyclic citrullinated peptide; RF: Rheumatoid factor; HLA-DRB1: Human leukocyte antigen DR beta 1; MS: Multiple sclerosis; NFL: Neurofilament light chain; GFAP: Glial fibrillary acidic protein; CXCL13: C-X-C motif chemokine ligand 13; CHI3L1: Chitinase-3-like protein 1; IgE: Immunoglobulin E; FeNO: Fractional exhaled nitric oxide.

Table 4. Representative prognostic AI models for predicting immunotherapy outcomes in cancer and autoimmune diseases, along with their key features

Input dataset	Outcome	AI model	Validation	Performance metric	Model interpretability	Disease				
						Cancer	Allergy	RA	T1DM	MS
Omics	Distinguishes responders from non-responders for anti-PD-1 therapy against skin cancer	10 Different models; multilayer perceptron neural network and AdaBoost were observed to be most accurate	Internal	96.7% testing accuracy for basal cell carcinoma and 60.7% testing accuracy for melanoma	Moderate	[162]				

	Predicts success of anti PD/PD-L1 therapy in NSCLC patients	Convolutional neural network (CNN), logistic regression, support vector machine (SVM), and random forest (RF) models	External cohort	Area under the curve (AUC) in the range of 0.959-0.965 for the different models	Moderate	[160]				
	Predicts success of anti PD/PD-L1 therapy	9 Different models; Least Absolute Shrinkage and Selection Operator (LASSO) offered the highest prediction performance	Internal	AUC of 0.93	High	[161]				

	Distinguishes Responders from Non-Responders for ICI therapy	SVM, XGBoost and Deep Neural Networking	External cohort (leave-one-out cross validation)	Accuracy of 100%	Moderate	[163]				
	Enables patient stratification and predicts success of ICI Therapy	CNN, variational autoencoders, and multi-instance learning algorithm	External cohort	AUC of 0.86	Moderate	[164]				
Multi-omics	Enables a consistently effective therapeutic strategy	REFLECT: combination of sparse hierarchical clustering and LASSO algorithm	In-vitro cell lines, patient-derived xenografts and clinical trial data	Average concordance of 83%	High	[166]				

	Predicts the efficacy of different anti-cancer therapeutic regimens	StepCox (forward) + Ridge algorithm	Multiple external datasets and previously published models	AUC >0.65	High	[167]				
	Predicts success of anti-PD-1 therapy	LASSO regression	Internal	AUC in the range of 0.62-0.64 for the different models	High	[168]				
	Predicts response to Adalimumab and Etanercept in RA patients	RF-ML Model	Internal	Models displayed accuracy in the range of 72-88%	Moderate			[169]		
Immune cell profiling	Enables stratification of T1D patients into responders/non-	Gradient boosting model	Internal and External	AUC of 0.81	Moderate				[170]	

	responders w.r.t Abatacept treatment									
Clinical Parameters	Predicts outcome of subcutaneous immunotherapy in paediatric allergic rhinitis patients	Binary improved sine cosine algorithm (birSCA)-SVM algorithm	Internal	Accuracy of 88.99%	Moderate		[171]			
	Predicts the efficacy of mite subcutaneous immunotherapy in asthma	Disperse Foraging Strategy Salp Swarm Algorithm-Kernel Extreme Learning Machine (DFSSSA-KELM)	Internal	Accuracy of 87.18%	Moderate		[172]			

	Predicts a disease activity score for RA patients undergoing immunotherapy	8 Regression models; Ridge regression model was observed to be most accurate	Internal and External	Mean absolute error values for the different models ranged between 0.633-0.857	High			[173]		
Immunoassays	Predicts sustained unresponsiveness to milk oral immunotherapy	Elastic Net algorithm (logistic regression method)	Internal	Average accuracy of 92%- 95%	High		[174]			
Multi-Dimensional	Provides a risk score for response to immunotherapeutic agents	Random Survival Forest (RSF) Algorithm	Internal	Not listed	High	[175]				

	Predicting overall survival and success of ICI therapy	Deep Learning-Natural Language Processing and RSF	Internal and External	AUC >0.95	Low	[176]				
	Differentiates responders from non-responders and enables patient stratification into high and low-risk groups for anti-PD-1/PD-L1 therapy	SimTA: deep learning model with temporal attention module assembled using multi layer perceptron	Internal	SimTA60d-AUC of 0.77 and SimTA90-AUC of 0.80	Low	[177]				

	Predicts patient's survival post ICI-therapy	SCORPIO: ensemle of ridge logistic regression, SVM and RF with soft voting algorithm	Internal and External-test sets and cohorts	Internal: median pan-cancer AUC's of 0.759 and 0.641 for overall survival and clinical benefit respectively. External test set: median pan-cancer AUC of 0.725 for overall survival	High	[165]				
	Predicts response to SCIT	RF Modelling-ML Algorithm	Internal and External cohort	Internal: AUC of 0.899 and External:	Moderate		[178]			

				AUC of 0.893						
	Predicts clinical response to Adalimumab and Etanercept therapy in RA patients	RF Algorithm	Internal	Accuracy of the different models ranged between 79%-88%	Moderate			[169]		
	Predicts response to Fingolimod therapy in MS patients	RF Algorithm	External test set	AUC of 0.71	Moderate.					[179]
	Predicts response to TNF inhibitor therapy in RA patients	Linear Regression, RF, XGBoost and CatBoost	External cohort	AUC values of 0.7 and 0.71	Moderate			[180]		

Abbreviations: AI: Artificial intelligence; anti-PD-1: Anti–programmed cell death protein 1; PD-L1: Programmed death-ligand 1; NSCLC: Non-small cell lung cancer; CNN: Convolutional neural network; SVM: Support vector machine; RF: Random forest; RF-ML: Random forest–based machine learning; ML: Machine learning; AUC: Area under the curve; ICI: Immune checkpoint inhibitor; RA:

Rheumatoid arthritis; T1D: Type 1 diabetes; T1DM: Type 1 diabetes mellitus; MS: Multiple sclerosis; LASSO: Least absolute shrinkage and selection operator; XGBoost: Extreme gradient boosting; CatBoost: Categorical boosting algorithm; REFLECT: Name of an AI framework combining sparse hierarchical clustering and LASSO; StepCox: Stepwise Cox proportional hazards regression; w.r.t.: With respect to; birSCA: Binary improved sine cosine algorithm; DFSSSA: Disperse Foraging Strategy Salp Swarm Algorithm; KELM: Kernel Extreme Learning Machine; DFSSSA-KELM: Disperse Foraging Strategy Salp Swarm Algorithm–Kernel Extreme Learning Machine; RSF: Random survival forest; DL: Deep learning; NLP: Natural language processing; SimTA: Deep learning model with temporal attention module; SCIT: Subcutaneous immunotherapy; TNF: Tumor necrosis factor; SCORPIO: Ensemble prognostic model (ridge logistic regression, SVM and RF with soft voting).

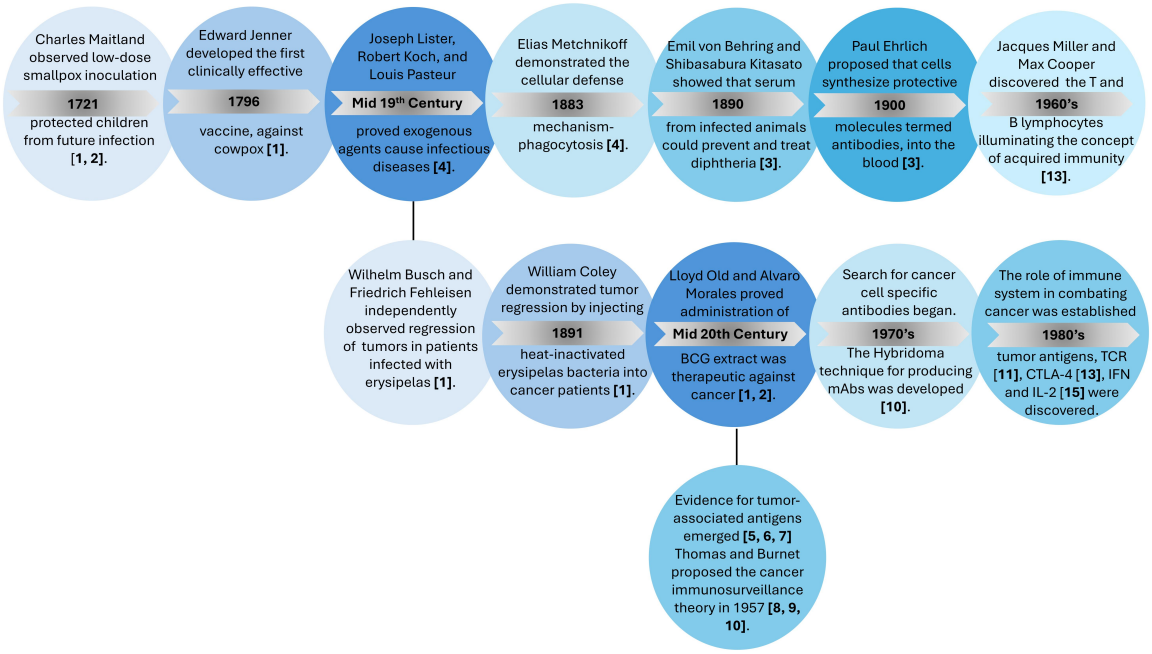

Figure 1. Chronological overview of landmark discoveries that shaped modern immunology and immunotherapy. The upper panels trace the recognition of infectious diseases and host defence mechanisms—from early variolation and Jenner's smallpox vaccination, through the germ theory of disease, discovery of phagocytosis, antibodies and serum therapy, to the identification of T and B lymphocytes. The lower panels highlight pivotal advances in cancer immunotherapy, including observations of infection-induced tumour regression, the therapeutic use of BCG, the description of tumour-associated antigens and cancer immunosurveillance, the advent of hybridoma technology and monoclonal antibodies, and the discovery of TCR, CTLA-4 and key cytokines that enabled modern immune-based therapies. Dates indicate the approximate time of each discovery; bracketed numbers correspond to the primary references cited in the Historical Perspective section. *Figure created by the authors from cited sources.* Abbreviations: BCG: Bacillus Calmette–Guérin; TCR: T-cell receptor; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4.

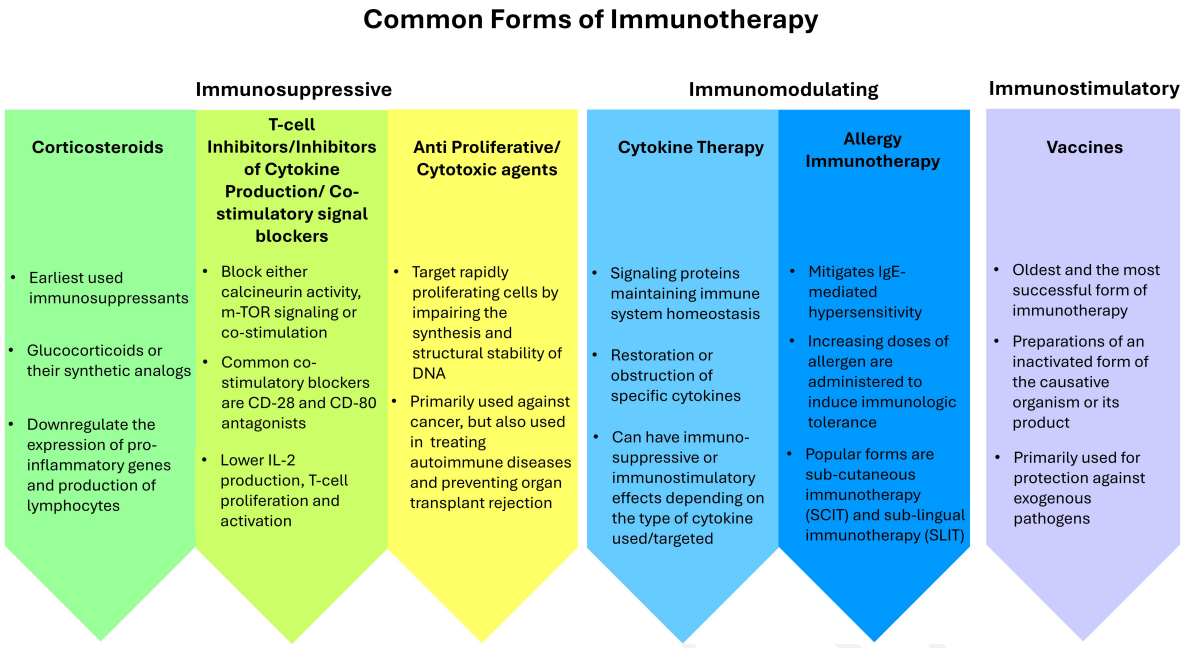

Figure 2. Schematic overview of common forms of basic immunotherapy, grouped according to their predominant effect on the immune system. Immunosuppressive approaches include corticosteroids, T-cell inhibitors that block calcineurin, mTOR signalling or co-stimulation (CD28/CD80 antagonists), and anti-proliferative/cytotoxic agents used in cancer, autoimmune disease and prevention of allograft rejection. Immunomodulating approaches comprise cytokine therapy, which restores or blocks specific signalling proteins to re-establish immune homeostasis, and allergen immunotherapy, which gradually increases allergen exposure (e.g. via SCIT or SLIT) to induce long-term tolerance and reduce IgE-mediated hypersensitivity. Immunostimulatory approaches are exemplified by vaccines, in which inactivated or attenuated pathogens or their components are administered to elicit durable protective immunity against subsequent infections. *Figure created by the authors from cited sources.* Abbreviations: IgE: Immunoglobulin E; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy; mTOR: Mechanistic target of rapamycin.

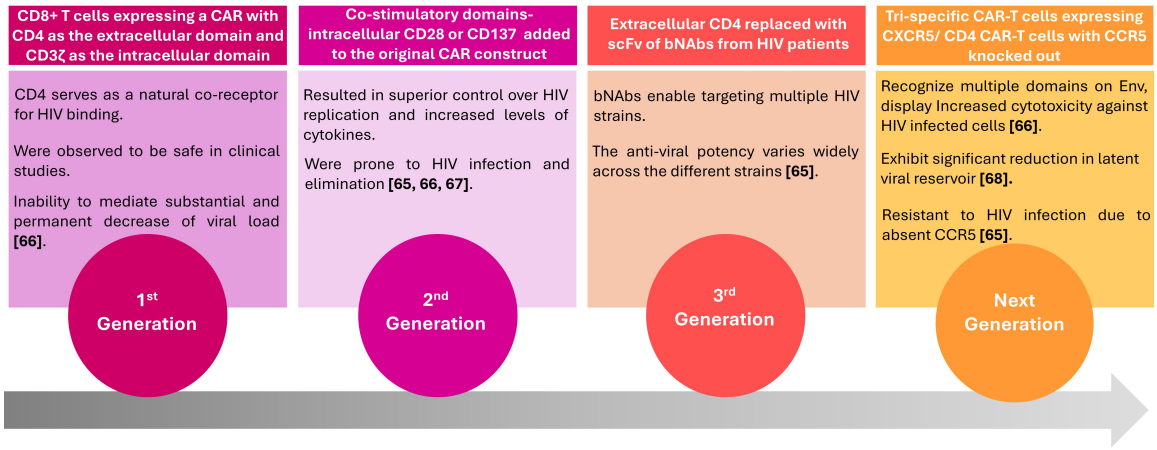

Figure 3. Evolution of anti-HIV CAR-T cell designs and their clinical development status. First-generation products comprised $CD8^+$ T cells expressing a CD4-based CAR, in which the CD4 extracellular domain was linked to an intracellular signalling module derived from the native T-cell receptor complex. These constructs were safe in early trials but failed to induce substantial, durable reductions in viral load. Second-generation CAR-T cells incorporated an additional intracellular co-stimulatory domain (CD28 or CD137) into this backbone, resulting in superior control of HIV replication and increased cytokine secretion, but the cells remained susceptible to HIV infection and elimination. Third-generation constructs replaced extracellular CD4 with single-chain variable fragments from bNAbs, enabling recognition of multiple HIV strains, although antiviral potency varied between specific bNAbs. "Next-generation" strategies, currently in pre-clinical and early clinical evaluation, include trispecific CAR-T cells and $CXCR5^+$ CAR-T cells with CCR5 knocked out, designed to recognise multiple epitopes on Env, home to lymphoid HIV reservoirs, enhance cytotoxicity against infected cells and resist de novo HIV infection. *Figure created by the authors from cited sources.* Abbreviations: CAR-T: Chimeric antigen receptor T cell; HIV: Human immunodeficiency virus; bNAb: Broadly neutralizing antibody; scFv: Single-chain variable fragment; Env: Viral envelope glycoprotein; CXCR5: C-X-C chemokine receptor type 5; CCR5: C-C chemokine receptor type 5.