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Review article

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Sequential immunotherapy: towards cures for autoimmunity

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Abstract

Despite major progress in the treatment of autoimmune diseases in the past two decades, most therapies do not cure disease and can be associated with increased risk of infection through broad suppression of the immune system. However, advances in understanding the causes of autoimmune disease and clinical data from novel therapeutic modalities such as chimeric antigen receptor T cell therapies provide evidence that it may be possible to re-establish immune homeostasis and, potentially, prolong remission or even cure autoimmune diseases. Here, we propose a 'sequential immunotherapy' framework for immune system modulation to help achieve this ambitious goal. This framework encompasses three steps: controlling inflammation; resetting the immune system through elimination of pathogenic immune memory cells; and promoting and maintaining immune homeostasis via immune regulatory agents and tissue repair. We discuss existing drugs and those in development for each of the three steps. We also highlight the importance of causal human biology in identifying and prioritizing novel immunotherapeutic strategies as well as informing their application in specific patient subsets, enabling precision medicine approaches that have the potential to transform clinical care.

Sections

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Introduction

The past 25 years have seen remarkable improvements in the treatment of patients with autoimmune diseases[1]. A major breakthrough came in 1998 with the approval of infliximab, a monoclonal antibody against the key pro-inflammatory cytokine tumour necrosis factor (TNF), for the treatment of Crohn's disease[2]. This was followed by the expansion of the use of infliximab to treat other autoimmune diseases and the approval of a range of novel biologics that target TNF, other cytokines and integrins, and small molecules that inhibit key immune cell signalling mediators such as Janus kinases (JAKs)[1]. However, although these therapies are effective at controlling symptoms, none cure the underlying disease[1]. Moreover, their broad immunosuppressive mechanisms of action are typically associated with negative effects, such as an increased risk of infection[1]. Thus, a major need remains for novel therapeutic approaches that control, prevent or cure autoimmune diseases in ways that minimize risk.

To address this unmet need, here we propose a three-step 'sequential immunotherapy' framework based on advances in understanding of human biology and the growing potential to guide treatment using the specific clinical and molecular profile of each patient. Step 1 is controlling inflammation through targeted immune suppression, step 2 is resetting the immune system by eliminating pathogenic immune memory cells and step 3 is promoting immune homeostasis via immune regulatory agents and tissue repair (Fig. 1). Although future therapies or combinations may achieve multiple steps simultaneously, we present them in a sequential framework to highlight gaps in available treatments. Most approved and in-development therapies are categorized into step 1. Therapies in development for steps 2 and 3 are, or will often be, based on new science and will require novel clinical trial designs and clinical or biomarker end-points to establish proof of concept. Although the effectiveness of a therapeutic approach in a particular autoimmune disease or patient subset may depend on the underlying mechanisms, we believe that administering medicines that achieve the goals of the three steps in the right sequence or the right combinations to the right patients has the potential to shift the paradigm from the current approach of chronic immune suppression in unselected patients to immune modulation and one-time treatments in patient subsets in the future.

In this Review, we first highlight evidence supporting the potential to achieve long-term remissions and, potentially, even cure autoimmune diseases. We then discuss each step of our sequential immunotherapy framework, highlighting progress with the range of therapies that are relevant for each step and considering the challenges in their development. Finally, we review how growing evidence grounded in causal human biology can help in identifying appropriate therapeutic strategies and diseases as well as subsets of patients in whom to apply these treatments most effectively.

The potential to cure autoimmune diseases

Autoimmune diseases are characterized by chronic aberrant immune responses against normal host constituents[3] (Box 1). Current treatments for autoimmune diseases that target aspects of these immune responses (Fig. 1) can result in improvement and even remission for some patients, but treatment cessation is usually followed by disease recurrence or flare.

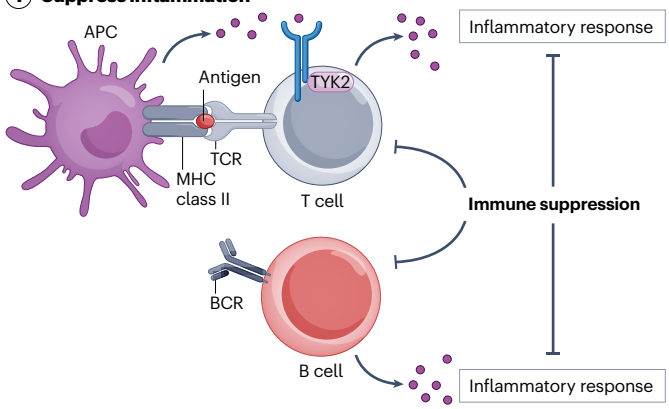
However, experiments of nature suggest that long-term remission, and even cure, may be achievable. For instance, in patients with multiple sclerosis or rheumatoid arthritis, reduction in relapses and improvements in disease activity, respectively, are sometimes seen during pregnancy, but are frequently followed by flares in the postpartum period[4,5]. These observations suggest that, even without a change in autoantigen load, a state of autoantigen tolerance can be induced physiologically. A second supportive observation is that autoimmune manifestations improve and frequently resolve after surgical removal or treatment of the underlying malignancy in patients with malignancy-triggered autoantibody-mediated diseases, such as paraneoplastic dermatomyositis, paraneoplastic pemphigus and paraneoplastic Lambert–Eaton myasthenic syndrome[6–8].

Support for curative potential is also provided by the sustained therapeutic benefit observed with autologous haematopoietic stem cell transplantation (aHSCT). For example, in a case series and in phase II and III studies in patients with multiple sclerosis, aHSCT resulted in profound and sustained reductions in disease activity and formation of new lesions on magnetic resonance imaging[9,10]. Likewise, aHSCT was found to be superior to cyclophosphamide in patients with systemic sclerosis, with improvements in skin scores, decreased incidence of pulmonary arterial hypertension and improved event-free survival[11]. Although refractory lupus has been less systematically investigated, reports also suggest a potential long-term benefit of aHSCT in these patients[12,13]. Although incipient toxicities, the need for careful patient selection and reliance on qualified medical centres may limit widespread aHSCT use in autoimmune disease[14], it appears that resetting the immune system to induce long-term disease control is realistically attainable.

Further evidence of the potential for a lasting reset of the immune system comes from the field of organ transplantation, where induction of immunological tolerance remains the 'holy grail' for protection of allografts[15]. Liver transplant in particular reveals

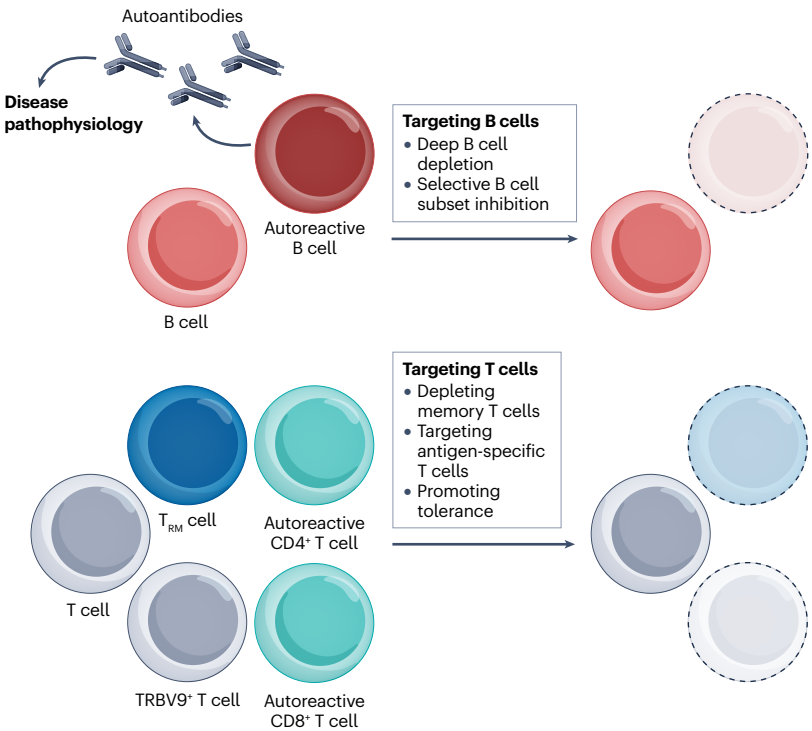
Fig. 1 | The sequential immunotherapy framework for immune modulation. The proposed framework provides a basis for approaches to precisely reset the human immune system in a way that is both safe and effective, ultimately leading to durable remissions and, potentially, even cures in immunologically mediated diseases. The three steps of this framework are shown from top to bottom, and currently approved therapeutic strategies and future opportunities for each step of the framework discussed in the main text are highlighted on the right; these lists are not exhaustive. Step 1 involves controlling inflammation; for example, by targeting inflammatory cytokines such as tumour necrosis factor (TNF) or downstream mediators of cytokine signalling such as tyrosine kinase 2 (TYK2). Step 2 involves resetting the immune system through modulation of pathogenic cells, such as B cells (for example, through deep B cell depletion using chimeric antigen receptor (CAR) T cells targeted at CD19, as shown in Fig. 2) and T cells (for example, through depletion of T cell subsets enriched for pathogenic cells such as TRBV9$^+$ T cells, specific deletion of tissue-resident memory T cells (T_{RM} cells), or the induction of T cell tolerance or exhaustion). Step 3 involves promoting and maintaining immune homeostasis through manipulation of regulatory T cells (T_{reg} cells) and tissue repair pathways. Application of this framework will need to take into account the context of particular patient subsets. APC, antigen-presenting cell; BCR, B cell receptor; cGAS, cyclic GMP–AMP synthase; IL, interleukin; JAK, Janus kinase; KLK5, kallikrein-related peptidase 5; MHC, major histocompatibility complex; NLRC4, NLR family caspase recruitment domain-containing protein 4; PAD4, peptidylarginine deiminase 4; STING, stimulator of interferon genes; TCR, T cell receptor; TL1A, tumour necrosis factor-like ligand 1A; TLR, toll-like receptor; TNFR, TNF receptor.

1 Suppress inflammation



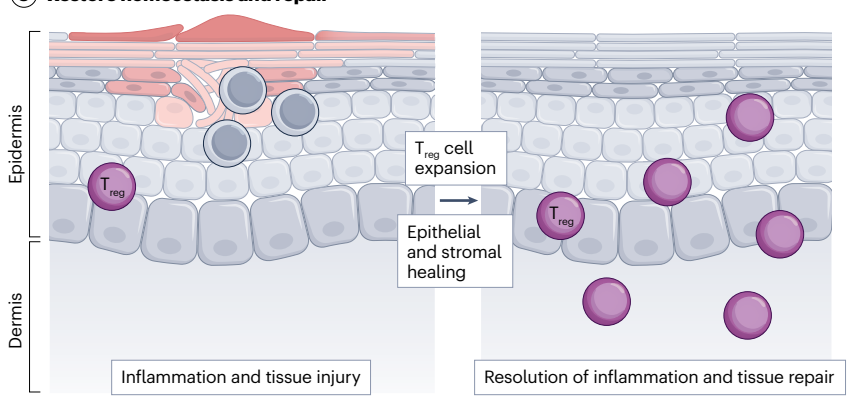
Approved therapeutic strategies	Future therapeutic strategies
• Targeting cytokines (anti-TNF, anti-IL-6/IL-6R, anti-IL-17/IL-17R, anti-IL-23, anti-IL-12/IL-23, anti-IL-1, anti-IL-4R/IL-13) • Targeting the complement pathway (C5 inhibition, C3 inhibition, factor B inhibition) • Targeting downstream mediators (JAK inhibition, TYK2 inhibition) • Classical anti-inflammatory drugs (corticosteroids, antimetabolites, hydroxychloroquine, sulfasalazine, azathioprine) • Depleting B cells (anti-CD20)	• Anti-CD40/CD40L • Anti-IL-18/IL-18R • Anti-TL1A • Inflammasome inhibition (for example, NLRC4) • Inhibition of nucleic acid sensing (for example, TLR inhibitors, cGAS/STING inhibitors) • Pyroptosis inhibition • Immunoproteasome inhibition • Precision medicine (for example, targeted to patient subsets) • Rational combinations

2 Reset the immune system



Approved therapeutic strategies	Future therapeutic strategies
None for immune reset	• CAR T cells that deplete B cells • T cell engagers • Natural killer cell engagers • Optimized B cell-depleting antibodies • Antigen-specific B cell depletion • Modulation of B cell stage-specific survival factors (for example, BAFF, APRIL)
None for immune reset	• Anti-IL-7/IL-7R • Anti-IL-15/IL-15R • Checkpoint agonists • Tolerogenic vaccines • mRNA delivery for cellular reprogramming • Reduction of autoantigens (for example, PAD4 inhibition) • Subset-specific T cell depletion

3 Restore homeostasis and repair



Approved therapeutic strategies	Future therapeutic strategies
None	• IL-2R agonists • TNFR2 agonists • Targeting IL-33/ST2 signalling • Adoptive polyclonal T_{reg} cell transfer • Engineered T_{reg} cells • Modulation of neuroimmune axis • Modulation of epithelial integrity (for example, via targeting filaggrin, KLK5)

Box 1

A brief primer on autoimmunity

Autoimmune diseases are the consequence of genetic predisposition and environmental triggers[3]. For example, many autoimmune diseases are driven by the loss of tolerance to specific self-antigens[3]. When these autoantigens have been clearly identified (such as myelin antigens in multiple sclerosis[300]), it may be possible to re-tolerize by presenting these antigens to the immune system in a non-inflammatory and tolerogenic environment.

Another key axis involved is the interface between the innate and adaptive immune systems[301,302]. In systemic lupus erythematosus (SLE), activation of the innate immune system is a driver of pathogenesis through release of cellular by-products by stressed and dying cells and subsequent recognition by pattern recognition receptors such as Toll-like receptors (TLRs) and cyclic GMP–AMP synthase (cGAS) (DNA by-products), as well as by autoantibodies that form immune complexes[74,301]. In response, type 1 interferons are released by plasmacytoid dendritic cells, which then activate B cells and T cells[303].

Support for the disease relevance of these pathways from the discovery of associated variants in human genes is available for SLE and primary immune deficiency disorders, including defective cellular clearance (*DNASE1L3*), nucleic acid sensing (for example, *TREX1* and *IFIH1*), immune complex sensing (for example, *FCGR2A*, and *FCGR2B*), intracellular signalling molecules activating type 1 interferons (for example, *IRF5* and tumour necrosis factor-induced protein 3 (*TNFAIP3*)) and intracellular signalling molecules transducing signals from type 1 interferons (for example, Janus kinase (JAK)/STAT family members)[304–310]. Pattern recognition receptors also trigger an inflammatory cascade in inflammatory bowel disease (IBD), culminating in the release of interleukin (IL)-1β, IL-18 and other inflammatory cytokines[311]. The role of NLR family caspase recruitment domain-containing protein 4 (NLRC4) and the IL-18 pathway in IBD also have support from human genetics[312].

Other mechanisms centre around specific immune cell populations, such as T cells and B cells. T cell function is thought to play a central role across many autoimmune diseases[313–316]. T cell subsets and T cell-derived cytokines are involved in IBD and SLE pathogenesis, as demonstrated by the effects of drugs in humans (for example, anti-IL-12/23 in IBD) and human genetics (for example, disease-associated variants in *IL2RA*, *PTPN22*, *STAT4* and *TNFSF4*)[317–320].

B cells and autoantibodies are also involved, with B cells driving autoimmune disease pathophysiology, such as in SLE and rheumatoid arthritis, and autoantibodies as a hallmark of and disease activity marker (for example, anti-double-stranded DNA antibodies) in SLE[321–323]. The role of these cells in SLE is also supported by the effects of drugs such as anti-BAFF monoclonal antibodies in humans and disease-associated variants in genes such as *BAFF*, *BANK1* and *BLK*[109,324,325]. However, targeting B cells with BTK inhibitors has failed to show clinical benefit in broad SLE populations[113]. It is possible that B cells and related pathways are drivers in a subset of patients or that current B cell-targeted treatments incompletely deplete and reset autoantibody-producing B cell memory. Alternatively, B cells and autoantibodies may be only part of the problem in SLE, with therapeutic intervention potentially requiring either upstream targets of immune dysregulation or combination therapy.

In rheumatoid arthritis, dysregulated protein citrullination appears to play a role in development[326]. Antibodies to citrullinated peptide antigens (ACPAs) contribute to the formation of pathogenic immune complexes and are uniquely found in most patients[326]. Peptidylarginine deiminase 4 (PAD4) has also been implicated in rheumatoid arthritis, with activating anti-PAD4 autoantibodies found in some patients[327,328]. Emerging data suggest that certain citrullination modifications can lead to detrimental effects on protein function[326]. Many diseases also involve autoantibodies to specific self-antigens that may be driven by autoreactive B cells residing in different lineages (for example, central memory B cells and long-lived plasma cells) or tissue compartments (for example, peripheral blood, germinal centres and bone marrow)[323].

immunoregulatory effects, with liver allografts typically exhibiting a lower immunosuppression requirement than other organs; complete immunosuppression withdrawal can be achieved in a subset of individuals[15]. Intriguingly, immunosuppression withdrawal appears to be most successful in patients with long-standing allografts[16], suggesting that immune tolerance can develop over time. Moreover, these results point to potential pathways that could be exploited for tolerance induction in other settings.

Based on such observations, we believe there is potential to achieve long-term remissions and cures in patients with autoimmune disease. Although our three-step framework for achieving this goal is presented below in discrete sequential fashion for ease of categorization, it is likely that therapeutic interventions could occur in parallel, and some novel targets or treatments may be relevant at more than one step. The need for each step will probably also be indication-dependent, as targets in individual steps may be sufficient for effective treatment in some diseases. For instance, interleukin (IL)-23 blockade, which we categorize in step 1, is a highly effective treatment for the signs and symptoms of psoriasis and may provide a high response rate and improve quality of life. However, psoriasis relapses upon cessation of treatment, clearly demonstrating that an immune reset does not occur and chronic treatment is required to maintain efficacy. Thus, controlling inflammation alone appears unlikely to lead to long-term remissions or cures in many autoimmune diseases.

Step 1: control inflammation

The first step in the framework is to control inflammation, and therefore treat symptoms, in patients with active disease. This category comprises the majority of approved therapies for autoimmune diseases, including corticosteroids, which have widespread suppressive effects on the immune system and have been a mainstay of treatment for around 75 years[17]. Most newer therapies also act primarily by

suppressing immune function to control inflammation, although they may be more selective; for example, monoclonal antibodies against specific cytokines such as TNF[18]. Some of these therapies reduce specific populations of immune cells, such as monoclonal antibodies that can deplete B cells[19]. Unfortunately, relapses upon discontinuation of the CD20-targeted antibody rituximab and other established agents for B cell depletion are common, suggesting that these therapies do not eliminate autoreactive B cell memory (see below).

Despite the many approved therapies controlling inflammation, opportunities remain to target emerging areas of biology to develop clinically differentiated therapies. Our focus for step 1 therapies is to target pathogenic cell types and pathways defined by causal human biology (for example, human genetics, as discussed later), to identify subsets of patients in whom the disease is driven by a particular axis and to propose rational combinations to increase efficacy while preserving safety. Although not exhaustive, here we highlight a few examples of areas ripe for continued innovation.

Targeting pathogenic cells and pathways

A key consideration for novel immunosuppressive mechanisms in step 1 is targeting only pathological pathways while sparing protective mechanisms, thereby avoiding broad immunosuppression. Is this ambitious goal realistic? Clinical experience with drugs such as anti-IL-17 and anti-IL-23 antibodies for psoriasis suggests that both efficacy and relative preservation of broad immune function are possible[20]. Importantly, human genetic data also suggest that less suppressive, yet effective immunomodulation is possible. For instance, inhibition of tyrosine kinase 2 (TYK2), an intracellular signalling molecule downstream of cytokines such as type I interferon and IL-23, offers a case study[21]. *TYK2* deficiency from a homozygous mutation is associated with immunodeficiency in humans[22]; however, a common coding allele (P1104A) reduces TYK2 function and offers protection from several autoimmune diseases, including psoriasis, systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD)[21,23,24]. Importantly, although the P1104A loss-of-function allele may be associated with some susceptibility to viral infection and active tuberculosis, the latter specifically in homozygous carriers, it is not associated with broad infection risk or other negative health consequences[23,25]. These human data informed the level of TYK2 inhibition needed to achieve efficacy while avoiding systemic immunosuppression, as well as the disease indications most likely to respond to TYK2 inhibition. Indeed, the TYK2 inhibitor deucravacitinib was efficacious in patients with moderate to severe plaque psoriasis and received US Food and Drug Administration (FDA) approval[26–28]. More recently, deucravacitinib has also demonstrated efficacy in phase II studies for psoriatic arthritis and SLE, without evidence of increased opportunistic infections[29,30].

In addition to individual cytokines or kinases involved in cytokine signalling and production, increasing the understanding of cellular and molecular pathways involved in disease pathophysiology will enable novel target discovery. An example is modulating interactions between CD40 and CD40L, which are critical for T cell-mediated B cell activation, class switching and germinal centre formation[31,32]. Additionally, CD40 polymorphisms influence the risk of rheumatoid arthritis, SLE and Graves' disease, thus offering genetic support for targeting the CD40 pathway[33–35]. Although early versions of CD40L-targeting antibodies were discontinued due to thromboembolic effects, these effects later appeared to be related to the potential for platelets to upregulate CD40L, coupled with the CD32a-binding activity of these early antibodies[36,37]. More recently, anti-CD40 or modified anti-CD40L molecules lacking fragment crystallizable (Fc) activity have progressed in the clinic and continue to be investigated in SLE, Sjögren's disease and Graves' disease[38–40].

Studies of monogenic autoinflammatory diseases such as familial Mediterranean fever have enabled the identification of inflammasomes, the inflammatory cell death process of pyroptosis and IL-1 cytokines as drivers of inflammatory disease[41]. Aside from these monogenic disorders, therapeutic intervention may also be beneficial in other, more common polygenic inflammatory disorders. An example for the potential use of rare, monogenic diseases to inform on more common polygenic disorders is NLR family caspase recruitment domain-containing protein 4 (*NLRC4*) inflammasome gain-of-function mutations in children with enterocolitis and macrophage activating syndrome[42,43]. In these children, *NLRC4* gain-of-function mutations were accompanied by large increases in levels of IL-18; in a case report, blockade of IL-18, but not of IL-1β or other anti-inflammatory agents, was efficacious in relieving enterocolitis and other inflammatory symptoms[42,44]. Furthermore, common variants at the *NLRC4* locus are associated with variation in IL-18 levels, and Mendelian randomization has indicated that genetically predicted elevations in IL-18 are associated with an increased risk of IBD[45]. Together, these observations point to modulation of *NLRC4*, pyroptosis or IL-18 as potential therapeutic strategies in subsets of patients with IBD.

Other monogenic syndromes highlight the importance of the ubiquitylation machinery in immune function. Mutations in enzymes involved in ubiquitin activation, ligation and deubiquitylation, as well as the proteasome, have been identified in patients with autoinflammatory syndromes[46]. An example is TNF-induced protein 3 (TNFAIP3; also known as A20), an enzyme with ligase and deubiquitylating activity that modulates NF-κB signalling; rare mutations lead to A20 haploinsufficiency and are associated with an autoinflammatory disease with highly variable clinical manifestations, one of which resembles Behcet's disease[47]. Independently, common variants at the *TNFAIP3* locus are associated with autoimmune diseases such as SLE, ulcerative colitis, rheumatoid arthritis and psoriasis[48–51]. Common *TNFAIP3* polymorphisms may also be prognostic markers for treatment response to anti-TNF drugs[52,53]. The recent description of VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, an adult-onset autoinflammatory disorder, and the identification of causal somatic mutations in UBA1 (a ubiquitin-activating enzyme) indicate that not only germ-line but also somatic mutations in ubiquitylation components may be associated with inflammatory disease[54]. The protean manifestations of this syndrome, which overlap with inflammatory syndromes such as relapsing polychondritis, polyarteritis nodosa, giant cell arteritis and Sweet syndrome[54], suggest that ubiquitylation modulation could be important even in more common autoimmune and inflammatory diseases.

Although it has historically been seen as a key player in innate responses to pathogens, the complement cascade is now understood to play broader roles in immune surveillance, tissue homeostasis, modulation of adaptive responses and beyond[55]. When dysregulated, it can lead to harmful inflammation and tissue damage, and several promising approaches to inhibit complement are in development[55]. For instance, inhibitors of C5 and C3 in the cascade (such as eculizumab and pegcetacoplan) have been approved for diseases such as paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome[55–57]. Genetic deficiency of complement components can also be harmful by leading to primary immunodeficiencies, including

infections with encapsulated bacteria in deficiencies of the early classical complement pathway and increased risk of *Neisseria* infections with deficiencies of the late common pathway, suggesting that broad complement system inhibition is undesirable[58]. Therefore, more-selective avenues of complement pathway modulation are also being investigated. For instance, small-molecule inhibitors of factor B, more specific to the alternative complement pathway, are showing potential in preclinical studies and clinical trials, and one, iptacopan, is now approved for paroxysmal nocturnal haemoglobinuria[59–61]. Additional approaches that might also provide safer and more effective therapies include local modulation of complement to inhibit solely at the site of inflammation without systemic inhibition[62].

Targeting patient subsets

Although drugs with targets in step 1 are useful for treating various autoimmune and inflammatory diseases, not all patients benefit equally, potentially reflecting heterogeneity in disease biology. In this light, it is critical to identify not only targets based on causal human biology but also patient subsets most likely to benefit from modulation of these targets. Recent drug approvals and clinical trial data suggest that patient stratification and the development and implementation of prognostic biomarkers are indeed possible. For example, asthma and chronic obstructive pulmonary disease (COPD) have been recognized as heterogeneous diseases, and novel treatments have been elusive[63–65]. In some patients, type 2 inflammation, as identified by increased eosinophil counts, may drive disease persistence or exacerbations[63,66]. Indeed, the IL-4 receptor α-subunit (IL-4Rα)-blocking monoclonal antibody dupilumab demonstrated efficacy in patients with moderate to severe COPD or asthma with an eosinophilic phenotype; it is now approved for the treatment of patients with moderate to severe asthma with high levels of eosinophils and is under regulatory review specifically for patients with moderate to severe COPD with an eosinophilic phenotype[67–70].

In addition to clinical features, laboratory values and circulating blood biomarkers, genetic analyses are increasingly being used to implicate pathway relevance and identify patient subsets. One example is the development of tumour necrosis factor-like ligand 1A (TL1A)-blocking antibodies in IBD; the stratification of treatment response by polygenic risk score has some preliminary evidence in ulcerative colitis and is being studied in Crohn's disease[71,72]. Another example is the response to anti-CD40 intervention (described above), which may be related to a polymorphism resulting in increased CD40 mRNA levels in some patients with Graves' disease[73]. Although these results were obtained from a small study, it will be important to examine whether CD40 haplotypes permit patient stratification in other indications.

As noted above, innate immunity also plays critical roles in autoinflammatory and autoimmune diseases. In this regard, targeting various components of type I interferon production and signalling (such as the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway) may be beneficial in diseases such as SLE and amenable to precision medicine. For instance, some patients with SLE have elevated levels of 2′,3′-cyclic GMP–AMP, a second messenger produced upon cGAS activation, in serum or in apoptosis-derived microvesicles, suggesting that inhibition of cGAS/STING could be particularly beneficial in a segmented population[74,75]. We anticipate that precision medicine approaches, enabled by novel biomarkers such as digital biomarkers, polygenic risk scores and imaging, will improve treatment responses in defined patient segments and enable rational combinations, as outlined below.

Rational combinations

In contrast to the advances in the treatment in psoriasis, in which blockade of individual cytokines such as IL-17 and IL-23 has shown remarkable efficacy and relative preservation of immune function, narrow pathway modulation has been less broadly effective in other indications such as IBD, pointing to both complexity and heterogeneity in autoimmune diseases. It may thus be necessary to selectively modulate multiple pathways to achieve deeper responses in many autoimmune indications. For example, omics analyses of tissue from patients with IBD and mouse colitis models supported the hypothesis of a synergistic effect of the combination of anti-TNF and anti-IL-23 blockade in IBD[76]. This hypothesis was validated in a proof-of-concept study in which the combination of golimumab (anti-TNF) and guselkumab (anti-IL-23) demonstrated higher efficacy than either therapy alone[77]. Building on these types of approaches, we predict that a drug discovery strategy rooted in causal human biology will identify targets and pathways involved in residual inflammation that are incompletely targeted by existing therapies[78]. This work will provide a framework for rational combinations, including those that involve novel targets, that can be advanced with higher likelihood than monotherapies of breaking the efficacy ceiling while avoiding deep immunosuppression.

Step 2: reset the immune system

A central feature of the immune system is its ability to generate protective immunity from subsequent exposure to the same antigen. This immunological memory prevents reinfections with the same pathogen and is also the basis for the efficacy of vaccines and the control of maladaptive states, including cancer; however, it can also have deleterious effects[79]. Indeed, when central and peripheral tolerance mechanisms fail to prevent immune responses to self-antigens or innocuous antigens, immune memory plays a key role in the persistence of inflammation and presents a barrier to long-term remissions and cures in allergy and autoimmunity[80]. Therapeutic approaches that manipulate immunological memory to eliminate pathological reactivity to and memory of autoantigens while maintaining beneficial primary and recall immune responses are a critical unmet need in the road to resetting the immune system.

Adaptive immunological memory resides in subsets of B cells and T cells, which play distinct but sometimes overlapping and even sequential roles in the pathophysiology of autoimmune diseases. As such, approaches to reset the immune system vary depending on the contribution of these cell types.

Targeting B cells

Autoantibodies are central to the pathophysiology of various autoimmune diseases (Box 1); therefore, deletion of their source holds promise for treatment. To achieve this goal, a comprehensive understanding of antibody production is needed.

A striking example of immunological memory is the formation of long-lived plasma cells. In response to infections and other triggers, B cell activation culminates in their differentiation into antibody-secreting cells, which in some cases can provide lasting and even lifelong immunity. However, not all B cell responses result in the formation of long-lived memory plasma cells or maintenance of antibody production. For instance, in response to mumps virus infection or vaccination, anti-mumps virus immunoglobulin G (IgG) can be detected in individuals for 20 years[81]; conversely, ~40% of individuals recovering from asymptomatic or mild-to-moderate COVID-19 disease lose SARS-CoV-2 antibodies[82]. In this light, the source of autoantibodies in humoral autoimmunity and the life cycle of antibody-producing cells have therapeutic implications.

Given the complexity of B cell activation and differentiation (Box 2), the optimal B cell memory population to target may vary in different autoimmune settings. This notion is validated by clinical experience with various B cell depletion or modulation approaches in autoimmune diseases. Enthusiasm for the potential of B cell depletion in the treatment of autoimmunity emerged with rituximab, an anti-CD20 pan-B cell-depleting antibody that was efficacious in rheumatoid arthritis and demonstrated improvement in SLE[83]. However, randomized controlled trials have failed to confirm efficacy in broad lupus populations[83,84]. Nevertheless, rituximab is prescribed off-label for the treatment of some patients with lupus[85]. Alternative anti-CD20-depleting antibodies with improved B cell depletion mechanisms, such as ocrelizumab, obinutuzumab and ofatumumab, have advanced in clinical trials, with ocrelizumab and ofatumumab being approved for multiple sclerosis[83,86,87]. In a study in lupus nephritis that was terminated due to an imbalance in severe infections, ocrelizumab

Box 2

B cell activation and differentiation

B cell activation (see the figure) predominantly takes place in secondary lymphoid tissues (spleen, lymph nodes and Peyer's patches)[153]. Specialized cells in these sites capture antigens from blood, lymph or mucosal contents for display to trafficking naive B cells[153]. Upon antigen encounter, B cell receptor (BCR) triggering may result in T cell-dependent or T cell-independent B cell activation[153]. Strong BCR signals (such as multivalent antigens) or strong co-stimulation via co-receptors (such as Toll-like receptors (TLRs)) result in T cell-independent B cell responses[153]. Alternatively, BCR binding may result in antigen internalization and presentation via major histocompatibility complex (MHC) class II, thereby both activating T cells and acquiring T cell help[153]. Depending on the nature of activation, B cells may enter germinal centres, where additional T cell influence promotes class switch, affinity maturation and formation of plasmablasts, and ultimately terminal differentiation into long-lived memory plasma cells[32]. Conversely, some B cell responses result in extrafollicular (that is, outside germinal centres) B cell proliferation and differentiation into short-lived plasma cells or plasmablasts[323]. In addition to plasma cell formation, B cell activation may also generate memory B cells, quiescent B cells capable of rapid activation, immunoglobulin production and differentiation into plasmablasts or plasma cells upon antigen encounter[153]. Thus, antibody secretion during an immune response may occur in various cell types (B cells, plasmablasts and plasma cells), with different degrees of persistence and recall capacity.

During activation and differentiation, B cells undergo epigenetic and transcriptional reprogramming, rely on lineage-specific receptors for maintenance and proliferation, and express distinct cell-surface markers. For instance, CD19 is expressed during the stages from immature B cell to plasmablast, CD20 is more narrowly expressed in mature B cells and some plasmablasts but not in plasma cells, and CD38 is expressed predominantly by plasma cells[329]. Likewise, distinct tumour necrosis factor receptor (TNFR) family members function as important survival and regulatory factors at different stages of B cell lineage differentiation. For instance, BAFF-R plays a role in survival and maturation of B cells, TACI plays a role in class-switch recombination and B cell maturation antigen (BCMA) is expressed predominantly in plasmablasts and plasma cells and promotes their survival[109].

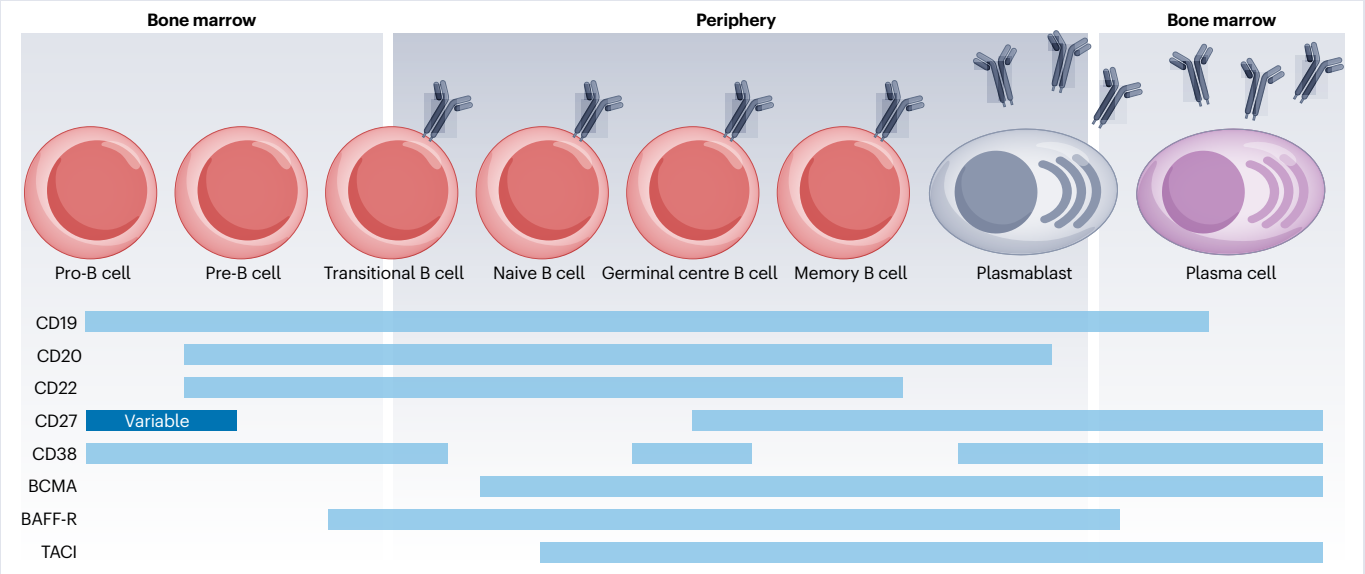


Figure adapted with permission from Crickx et al.[330], Elsevier.

treatment for >32 weeks resulted in numerical but not statistically significant differences in renal response compared with placebo[88]. Non-depleting approaches to inhibit selective B cell subsets, such as anti-CD19 (obexelimab) and anti-CD22 (epratuzumab) antibodies, did not achieve the primary end-point in SLE studies[89,90] but could, potentially, be effective in other indications or, perhaps, in patient subsets.

These conflicting data suggest that deeper B cell depletion, including in various tissue compartments (for example, lymph nodes and ectopic lymphoid follicles) or specific B cell subsets, may be required for broader efficacy and B cell immune reset in diseases such as SLE. On this note, B cells are efficiently depleted by rituximab in peripheral blood, but less so in lymphoid tissues[91,92]. The recent demonstration that B cell depletion using CD19-targeted chimeric antigen receptor (CAR) T cells can result in long-term remission (with discontinuation of all immunosuppression, including systemic steroids) and decreased autoantibodies in patients with refractory SLE (including patients with relapse following other B cell depletion treatments), as well as potential benefit in several other autoimmune diseases, gives credence to the notion that B cell memory resetting could lead to long-standing remissions[93–96]. Importantly, CD19-CAR T cell treatment in SLE has resulted in a marked shift in phenotype and heavy-chain usage in the emerging B cells, again suggestive of a potential reset of the B cell repertoire[94]. Although early, these exciting data have supported the clinical investigation of cell therapy approaches for B cell depletion across multiple indications with promising results[97]. For this novel modality, it will be important to establish long-term risks and benefits, including the potential for neurotoxicity and cytokine release syndrome (CRS), which appear manageable in the ongoing clinical studies to date[97] (see Fig. 2 for CAR T cell approaches).

Whether the early evidence for a 'B cell reset' is due to deeper depletion enabled by CAR T cells relative to other conventional depletion approaches or to specific depletion of pathogenic $CD19^+$ B cell populations remains a key question. In this regard, it is important to consider the choice of both the target on B cells and the effector-depleting mechanisms. As shown in the figure in Box 2, targets such as CD20 and CD19 identify different B cell populations, which may be differentially involved in distinct autoimmune diseases. Indeed, the early data from CD19-CAR T cell treatments suggest that the autoreactive antibody-producing cells in SLE and myasthenia gravis may reside in $CD19^+$ B cell and plasmablast populations, rather than in long-lived plasma cells that are CD19-negative (and which would not be expected to be depleted by CD19-targeted CAR T cells)[98]. Considering effector mechanisms, depleting antibodies activate mechanisms such as complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity (in which natural killer cells and other cell types kill target cells), antibody-dependent cell-mediated phagocytosis and direct programmed cell death. Next-generation antibodies incorporate Fc modifications to improve effector function[99]. A newer depleting technology first tested in oncology is the use of bispecific or multispecific biologics to directly engage T cell or natural killer cell effector cells to target cells such as B cells[100]. T cell engagers have entered early clinical studies in SLE, rheumatoid arthritis and other autoimmune indications[101–103]. Conversely, engineered CAR T cells are the effectors in the cell therapy approach.

The potential of any of these depletion approaches to induce a B cell reset thus depends on both the B cell target and the effector cell localization, frequency, functionality and ability to traffic and kill target B cells in all relevant compartments. It will be interesting to compare not only efficacy but also safety and ability to promote a B cell reset and off-drug remission across CAR T cell, conventional and engager B cell depletion approaches in the same indications. On this note, CD19-CAR T cell therapies and the CD19-depleting antibody inebilizumab are currently under clinical investigation in scleroderma and myasthenia gravis[104–107].

B cell targeting via modulation of stage-specific survival factors or signalling pathways is also an area of active investigation. BAFF, a survival factor that signals via BAFF-R, TACI and B cell maturation antigen (BCMA), is the target of the monoclonal antibody belimumab, which has been approved for SLE and lupus nephritis, and is in development for other autoantibody-driven diseases[108–110]. In phase II studies, the BAFF-R-blocking and depleting antibody ianalumab has shown encouraging efficacy in primary Sjögren's syndrome and SLE[111,112]. Finally, small-molecule inhibitors of BTK — which, among other functions, transmit signals downstream of the B cell receptor (BCR) during B cell development, differentiation and activation — have shown promise in autoimmune indications such as multiple sclerosis, immune thrombocytopenia (ITP) and chronic spontaneous urticaria but have not shown efficacy in SLE[113]. Whether more complete BTK inhibition is necessary for broad efficacy, or whether a BTK inhibitor has the potential to be efficacious in subpopulations of patients with SLE, remains unanswered. As BTK also signals downstream of RANK and Fc receptors, the efficacy of BTK inhibition in some indications and patient subpopulations may also be related to non-B cell-mediated mechanisms[113].

Targeting plasma cells

Clinical experience with B cell depletion and modulation across multiple autoimmune indications has been helpful to generate novel data-driven therapeutic hypotheses. For instance, the finding that CD20 depletion and BTK inhibition result in reduction in various B cell subsets in SLE with incomplete autoantibody reduction and disappointing efficacy suggests that subsets of plasmablasts and/or long-lived memory plasma cells not depleted by these approaches may be critical for autoantibody production in SLE. These observations led to investigating plasma cell targeting as a novel strategy in autoantibody-mediated diseases to deplete plasmablasts and plasma cells not targeted by anti-CD20 or other B cell depletion approaches and to promote faster remission by reducing autoantibody titres more rapidly.

How and where long-lived plasma cells gain access to survival factors, such as the BCMA ligands APRIL and BAFF, is not completely understood. Plasma cells are thought to migrate to plasma cell survival niches in the bone marrow and gut, in which they maintain access to these survival factors. A potential approach for depletion of long-lived plasma cells is modulating their survival niches and access to survival factors. However, the cellular organization and critical components of this putative niche are not well defined because multiple cell types (including osteoclasts and myeloid cells) are known to secrete APRIL. Furthermore, APRIL and BAFF play roles in B cell activation as well as plasma cell survival; thus, it is not currently clear whether blockade of APRIL and BAFF may result in plasma cell reduction directly or indirectly. In this context, the TACI–Fc fusion protein telitacicept, which binds to and neutralizes both APRIL and BAFF, has demonstrated encouraging efficacy in phase II studies in SLE[114]. CXCL12 and its receptor CXCR4 are part of a key chemotactic axis that promotes plasma cell migration to the bone marrow and, presumably, their survival niche. Indeed, the CXCR4 antagonist plerixafor reduced long-lived plasma cells in the bone marrow and prolonged survival in a lupus mouse model[115]. This finding suggests that modulating access to survival

factors in the plasma cell niche may be a viable therapeutic approach to reduce autoantibody-producing long-lived plasma cells.

Approaches to treat multiple myeloma have informed the concept of plasma cell depletion in autoimmune diseases. The approved proteasome inhibitor bortezomib resulted in accumulation of misfolded proteins in the endoplasmic reticulum leading to endoplasmic reticulum stress and death of cells with high extracellular protein production, such as plasma cells[116,117]. In case reports, case series and small clinical trials in SLE, autoimmune haemolytic anaemia and other autoantibody-mediated diseases, bortezomib demonstrated on-treatment efficacy, with notable reduction in blood and bone marrow plasmablasts and plasma cells, as well as rapid reduction in autoantibody titres[118]. Daratumumab, another drug approved for multiple myeloma, binds to CD38 and induces elimination of CD38-expressing cells via antibody-dependent cellular toxicity and complement-dependent cytotoxicity. Daratumumab has shown rapid autoantibody reduction and clinical efficacy in two patients with SLE refractory to other treatments as well as in a case study of anti-phospholipid syndrome[119–121].

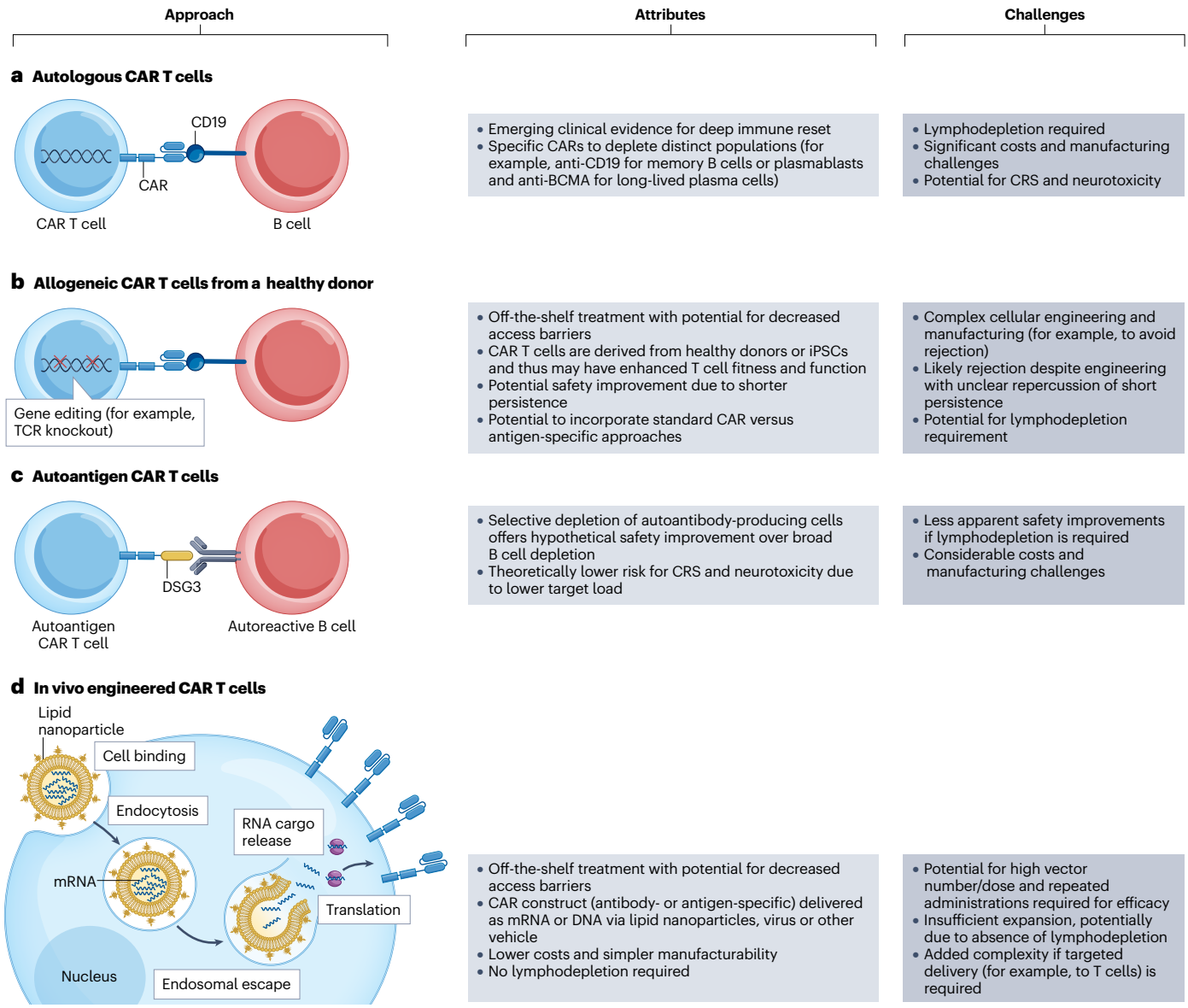


Fig. 2 | CAR T cell approaches to resetting humoral immunity. a, Autologous chimeric antigen receptor (CAR) T cells derived from the patients themselves, targeting antigens on B cells such as CD19. **b**, Allogeneic CAR T cells derived from healthy donors or induced pluripotent stem cells (iPSCs) also target antigens such as CD19, but are additionally engineered (for example, to knockout expression of the endogenous T cell receptor (TCR) and major histocompatibility complex (MHC)) to reduce the risk of issues such as graft-versus-host disease and avoid rejection. **c**, T cells engineered to express an autoantigen CAR (such as desmoglein 3 (DSG3)) to recognize and bind to target autoantibodies expressed as B cell receptors (BCRs) on autoreactive B cells. **d**, Engineered CAR T cells produced in vivo through expression of a CAR construct encoded by an mRNA encapsulated in a lipid nanoparticle for delivery. The attributes and challenges for each of the approaches are highlighted on the right[291–296]. BCMA, B cell maturation antigen; CRS, cytokine release syndrome.

Given the success of BCMA-directed depleting therapies in multiple myeloma, it is tempting to speculate whether these approaches could also add to the armamentarium against antibody-mediated autoimmunity. Indeed, BCMA-directed CAR T cells are currently under investigation for the treatment of generalized myasthenia gravis[122]. Given the limited expression of BCMA on plasmablasts and long-lived plasma cells and the lack of or limited expression on memory B cell populations, in contrast to the broader expression of CD19 (see the figure in Box 2), targeting BCMA-positive populations may not result in a complete immune reset in diseases in which memory B cells contribute to formation of antibody-secreting cells. Intriguingly, in a case report, a patient with coexisting SLE and diffuse large B cell lymphoma had improvement in SLE and malignancy, including remission, despite receiving no additional immunosuppressive or chemo/radiotherapy for ≥23 months, with a dual CD19/BCMA-targeting CAR T cell therapy that would be expected to deplete memory B cells as well as plasmablasts and plasma cells[123]. Despite not knowing the contribution of the conditioning regimen or the safety, durability and generalizability for other patients, this case further suggests that humoral system reset could be beneficial in autoantibody-mediated diseases such as SLE. Given the early success of CD19-only CAR T cell therapy in SLE, idiopathic inflammatory myositis and systemic sclerosis[97], BCMA-mediated depletion may not be necessary in conditions driven by memory B cells and plasmablasts, and may introduce additional risk factors, such as reduction of vaccine memory. Conversely, indications that are driven by CD19^{lo}/negative long-lived plasma cells (for example, light chain amyloidosis) may respond better to BCMA-mediated depletion and not CD19-mediated depletion.

In the plasma cell depletion examples mentioned previously, bortezomib and daratumumab resulted in rapid reduction in autoantibodies, which appeared to increase upon drug discontinuation. This increase may be the result of antigen-driven reactivation of autoreactive B cells, which are probably not effectively eliminated by these modalities. Thus, achieving rapid and prolonged remission in autoantibody-mediated diseases might necessitate plasma cell depletion followed by autoreactive B cell modulation to prevent recurrence, or a more complete B cell and plasma cell reset using modalities targeting a broader B cell population (for example, dual CD19/BCMA CAR T cell therapy), with the caveats mentioned above. Although tantalizing, this approach may also result in an undesirable immunosuppression risk. In this light, more precise approaches to autoreactive B cell depletion are warranted.

Targeting autoreactive B cells

A significant advance in resetting the immune system would be selective depletion of autoantigen-specific cells while sparing other immune cells; this effect may be within reach for depletion of autoantibody-producing cells. When the antigen recognized by autoantibodies is known, it is, in principle, possible to design baits to recognize autoreactive B cells, taking advantage of the fact that the autoantibody is also expressed on the B cell surface as the BCR. Preclinical proof of concept was obtained in a mouse model of pemphigus vulgaris, in which an infusion of T cells engineered to express desmoglein 3 (DSG3) as a chimeric autoantibody receptor showed selective killing of DSG3-autoreactive B cells and improved the autoantibody-provoked acantholysis and blister formation[124]. This exciting approach has now advanced to clinical trials in patients with mucosal pemphigus vulgaris[125]. A similar approach is being investigated preclinically in MuSK myasthenia gravis and NMDAR encephalitis and clinically in MuSK autoantibody-positive myasthenia gravis[126–128]. Considering that plasmablasts and plasma cells downregulate cell-surface immunoglobulin (that is, the BCR), the chimeric autoantibody receptor approach could be limited in diseases primarily driven by plasmablasts/plasma cells.

A nascent strategy to selectively deplete or modulate autoreactive B cells has evolved from antibody–drug conjugates. Administration of a known autoantigen conjugated with dexamethasone in an experimental autoimmune encephalomyelitis (EAE) model ameliorated clinical scores[129]. Although these preliminary data are intriguing, additional and more-detailed mechanistic studies are needed to determine the potential of this technology.

The clinical data from B cell-targeting and plasma cell-targeting modalities suggest that whereas many approaches demonstrate some efficacy in autoimmune indications, not all achieve a true B cell memory immune reset (and, as a corollary, they may not lead to long-term off-drug remissions). In addition to antibody generation, B cells participate in immune responses via cytokine production and antigen presentation, and partial depletion of B cells with conventional approaches may be efficacious, at least in part, through partial inhibition of antibody-independent processes rather than through resetting the B cell compartment[19]. Conversely, the encouraging data from CAR T cells and optimized biologics suggest that novel modalities may be nearing this exciting and elusive goal.

Targeting T cell tolerance and memory

Diverse memory T cell populations play important roles in defence from infection and cancer, as well as chronicity of autoimmune diseases (Box 3). However, an important corollary of these functions is that existing treatments do not appear to completely modify tissue autoimmune memory, thereby leading to disease recurrence when treatment is discontinued. A telling example is the response to treatment in vitiligo, a depigmenting disease marked by immune-mediated destruction of melanocytes in the skin. Although treatment with JAK inhibitors or topical calcineurin inhibitors was efficacious in arresting vitiligo, clinical studies demonstrated rapid relapse upon treatment cessation[130,131]. JAK inhibitors were similarly efficacious in a murine model of vitiligo; however, they did not reduce the frequency of tissue-resident memory T cells (T_{RM} cells) in affected skin[132]. Similar observations have been reported in psoriasis[133]. Therefore, although solely targeting effector T cells driving inflammation may result in short-term responses, long-term disease modification and cure are likely to require editing or control of tissue-resident autoimmune memory responses.

Several approaches to modify T cell memory have advanced to clinical studies, including depletion through cell-surface markers and taking advantage of differentiation and survival factors and transcriptional programmes.

Depleting memory T cells. In murine models of autoimmunity, including IBD and vitiligo, specific deletion of T_{RM} cells was effective at preventing or reversing disease[134,135], suggesting that T_{RM} cell depletion may be efficacious in achieving autoimmune disease modification. Selective depletion of memory subsets necessitates identification of cell-surface markers, transcription factors or other memory-specific features. An early indication of the potential to selectively modulate memory T cell populations was noted with the CD2-blocking LFA3–IgG fusion protein, alefacept, which was approved by the FDA as a psoriasis treatment in 2003 (ref. 136). CD2 is a co-stimulatory protein in T cells and subsets of other lymphocytes that is upregulated in certain memory T cell subsets. In clinical studies, alefacept preferentially depleted effector T_{RM} cells

Box 3

Memory T cells and autoimmune disease

T cells are critical repositories of immune memory and develop in the thymus where they undergo T cell receptor rearrangement and positive (for major histocompatibility complex (MHC) binding) and negative (for self-antigen binding) selection[331,332]. Naive T cells that emerge from the thymus and encounter antigen in the context of MHC presented by antigen-presenting cells (APCs) become activated and expand[331]. During resolution of an immune response, activated T cell clones contract, with some remaining as long-lived memory T cells capable of rapid reactivation to a subsequent challenge with the same antigen[333].

Several subsets of memory T cells have been described based on phenotype and function[334]. Migratory effector memory T cells survey the circulation and can quickly migrate to inflamed tissues, whereas central memory T cells express lymph-node homing surface proteins and survey secondary lymphoid organs[334–336]. Conversely, tissue-resident memory T cells (T_{RM} cells) are non-circulating memory T cells that protect tissues such as the lung, skin and gut[337]. Although these diverse memory T cell populations play important roles in defence against infection and cancer, autoreactive memory T cells participate in the chronicity of autoimmune diseases. For instance, peripheral helper T cells are a subset of memory $CD4^+$ T cells that have been observed to expand in several autoantibody-mediated diseases, such as rheumatoid arthritis, systemic lupus erythematosus and coeliac disease[338–340]. These pathogenic peripheral helper T cells can stimulate autoreactive B cells and promote plasmablast formation, thereby augmenting autoantibody production[341]. In barriers such as the gut and skin, T_{RM} cells differentiate in the tissue and are locally maintained to provide a first line of defence against recurrent pathogen exposure[334]. However, T_{RM} cells have also been recognized to expand and produce inflammatory cytokines in diseases such as psoriasis, vitiligo and inflammatory bowel disease. Indeed, their local presence may explain the clinical observation that psoriasis and vitiligo skin lesions tend to recur in the same location[147,342]. Recurrent site-specific inflammation is also a feature in rheumatoid arthritis, and, recently, an expanded population of T_{RM} cells capable of inducing flares of disease were described in a murine model of rheumatoid arthritis[343]. T_{RM} cells were also found to be expanded in the joints of patients with rheumatoid arthritis[343].

while preserving central memory T cells and not substantially reducing naive T cell counts[137–139]. Intriguingly, most patients with psoriasis who were clear or almost clear after treatment also manifested prolonged remission from disease[137]. Of note, alefacept was withdrawn from the market in 2011 as more broadly effective treatments emerged. Another example is mogamulizumab, a CCR4-depleting antibody that depletes central T_{RM} cells, despite its development to deplete CCR4-expressing regulatory T cells (T_{reg} cells)[140].

Other memory T cell-surface markers have been described, such as CD103 (α_E integrin) on T_{RM} cells, which associates with β_7 integrin, binds to E-cadherin expressed by epithelial cells and may have a role in retention in the skin and gut[141,142]. Therefore, CD103-mediated depletion is a potential approach to resetting tissue-resident memory (Fig. 3a). In a murine model of pancreatic islet allograft rejection, an anti-CD103 antibody conjugated to saporin or maleimidocaproyl-monomethyl auristatin F resulted in T_{RM} cell depletion and islet allograft survival[143,144]. A limitation of these approaches is the potential lack of selectivity, given that these cell-surface markers are expressed by other cell types.

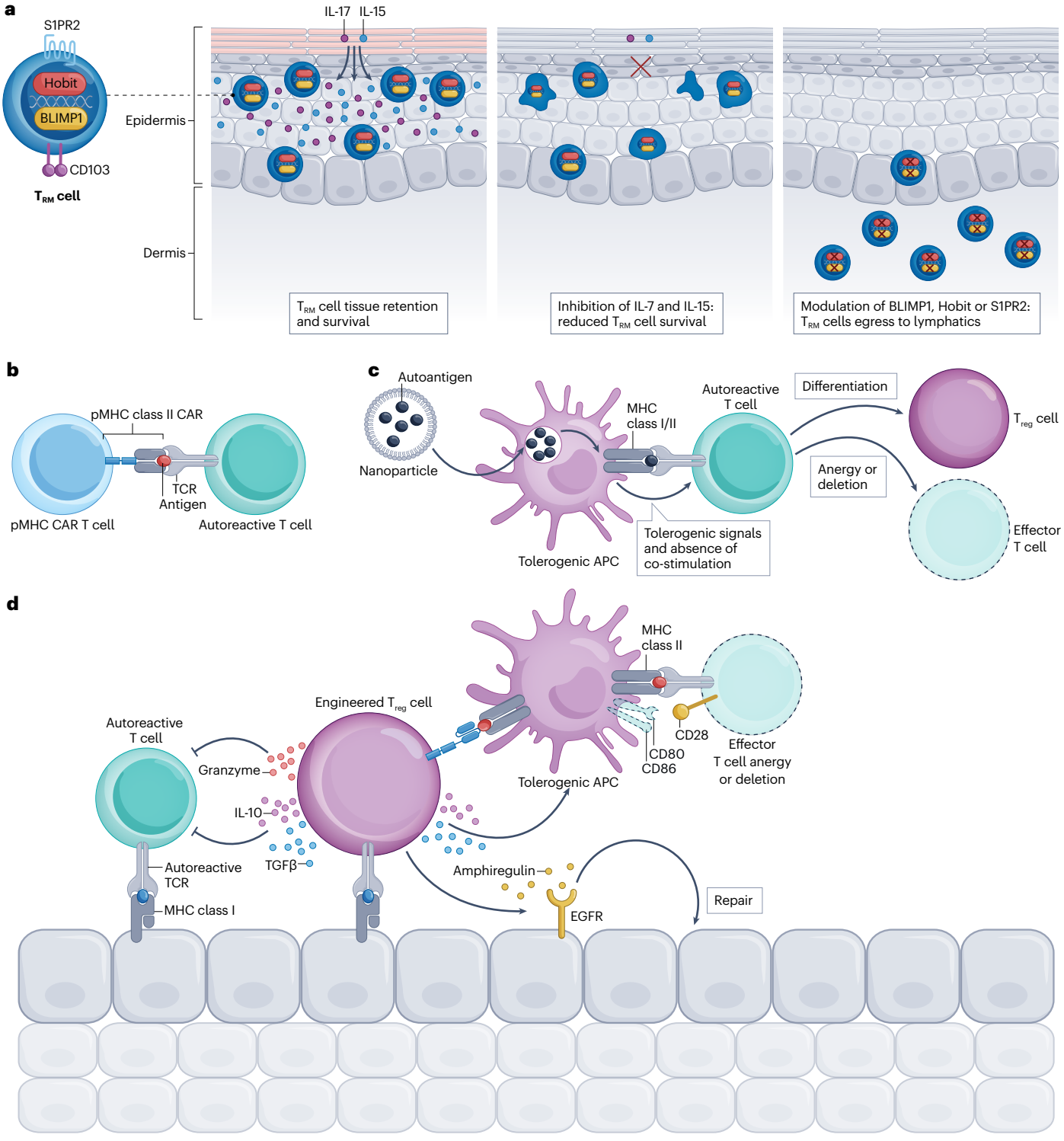
Inhibiting memory T cell differentiation and maintenance. Memory T cells express IL-7Rα and IL-15Rα and depend on IL-7 and IL-15 signalling for maintenance and survival[145]. In patients with type 1 diabetes (T1D), an anti-IL-7Rα blocking antibody reduced T_{RM} cells and, to a lesser extent, naive T cell counts, but relatively spared T_{reg} cells, consistent with their low IL-7Rα expression[146]. Although this approach is intriguing and may result in resetting T cell memory, IL-7 signalling plays important roles in lymphocyte development and homeostasis, and extensive blockade of this pathway may result in substantial immunosuppression.

A related approach is IL-15Rα blockade because IL-15 is necessary for T_{RM} cell differentiation and may be *trans*-presented by keratinocytes and other cells to maintain T_{RM} cells[147]. In a mouse model of vitiligo, IL-15 signalling inhibition reduced T_{RM} cells and resulted in long-lasting skin repigmentation[148]. Additionally, mice lacking IL-15 had reduced, but not abolished, naive T cell populations, whereas IL-7-deficient animals were severely immunodeficient[145]. Therefore, blockade of IL-15 *trans*-presentation may represent a more-selective approach than IL-7 blockade for certain memory T cell populations (Fig. 3a). A caveat with this approach is that the relevance of IL-15 to T_{RM} cell maintenance in human tissues remains unconfirmed, with at least one clinical study of an anti-IL-15 therapy in patients with coeliac disease failing to meet the primary objective[149]. Clinical investigation of IL-15-blocking antibodies in vitiligo is ongoing[150].

Memory T cell populations express unique transcriptional programmes for their differentiation and maintenance. For instance, T_{RM} cells depend on the transcription factors Hobit and BLIMP1 for development and tissue retention[151]. Furthermore, chemoattractant and chemorepulsive receptors such as the sphingosine 1-phosphate receptor 1 (S1PR1) and S1PR2 axis control tissue-resident cell egress[152]. It is tempting to speculate that selective inhibition or degradation of retention factors utilizing proteolysis-targeting chimeras or other tools may result in resetting of tissue immune memory (Fig. 3a). However, even this approach may result in the reduction of multiple cell types, because other tissue-homing innate cells may also use these transcriptional and migratory networks[151]. Thus, a more complete understanding of selective cell-surface markers and transcriptional programmes will be needed to develop more-selective depletion approaches for memory T cell populations.

Targeting antigen-specific T cells

Although a T cell memory reset appears feasible based on the approaches described previously, unselected and complete T cell memory depletion



may result in increased risk of infection or malignancies. For instance, cases of Epstein–Barr virus reactivation (including symptomatic active infection) were observed in a clinical study of an IL-7Rα-blocking antibody[146]. Furthermore, higher-dose anti-IL-7Rα-blocking antibody reduced recall response to tetanus toxoid vaccine, highlighting the potential for loss of immunity to previously encountered pathogens and vaccinations[146]. Thus, more-selective depletion or modulation of autoreactive memory T cells would be desirable.

At first glance, it appears that depletion of antigen-specific T cells should be possible, as with the antigen-specific B cell depletion blueprint described previously. However, the mode of T cell antigen recognition represents a challenge for this approach. Whereas B cell

Fig. 3 | Approaches to reset T cell memory and restore homeostasis. **a**, Inhibition of trophic factors for tissue-resident memory T cells (T_{RM} cells) and drivers of T_{RM} cell tissue residence[152,297]. Interleukin (IL)-7 and IL-15 are critical trophic factors for T_{RM} cells. Inhibition of IL-7 and IL-15, either directly or through their cognate receptors, and/or modulation of the factors that promote tissue residence of T_{RM} cells (for example, BLIMP1, Hobit and sphingosine 1-phosphate receptor 2 (S1PR2)) are potential approaches to reset tissue immune memory. Alternatively, T_{RM} cells could be depleted via tissue-resident cell-surface markers (for example, CD103) (not shown). **b**, Peptide major histocompatibility complex (pMHC) constructs[298]. If an autoimmune state is driven by a single or a few immunodominant antigens, pMHC constructs could be used to selectively deplete autoreactive T cells, such as pMHC chimeric antigen receptor (CAR) T cells. Alternatively, pMHC constructs could be used to induce autoreactive T cell death via fragment crystallizable (Fc) function or delivery of toxins or inhibitors (not shown). **c**, Tolerance induction[189]. Tolerogenic antigen-presenting cells (APCs) may employ various mechanisms to enforce peripheral tolerance, such as mediating the differentiation of T cells to peripheral regulatory T cells (T_{reg} cells) and promoting T cell anergy or deletion. Approaches that have reached the clinic include delivering antigens conjugated to glycopolymers to target tolerogenic cells in the liver and spleen, as well as nanoparticle delivery, which mimics apoptotic bodies for silent antigen presentation. Autoantigens could theoretically be delivered as proteins, peptides or mRNA and could include additional components to enforce tolerance (for example, cytokines such as IL-10 or mTOR inhibitors). **d**, Engineered T_{reg} cells[299]. T_{reg} cells can be engineered to express an anti-pMHC CAR, promoting tolerogenic APCs and leading to anergy or deletion of autoreactive effector T cells. Another approach is to express autoreactive T cell receptors (TCRs), leading to bystander suppression of effector T cells via direct killing through granzyme production or expression of inhibitory cytokines such as IL-10 and transforming growth factor-β (TGFβ), as well as through competition for trophic factors (not shown). Engineered T_{reg} cells also promote homeostasis through repair mechanisms such as production of amphiregulin and other growth factors. Panel **c** is adapted from ref. 189, Springer Nature Limited.

receptors recognize antigens directly, T cells recognize peptide antigens presented in the context of major histocompatibility complexes (MHCs) expressed by other cells[153]. $CD4^+$ helper T cells recognize peptide MHC (pMHC) class II complexes, whereas $CD8^+$ cytotoxic T cells recognize pMHC class I complexes. MHCs are also polygenic and highly polymorphic, and different antigen epitopes may be immunodominant in different individuals. MHC allelic diversity and pMHC complexity makes the production of agents to selectively deplete autoantigen-specific T cells more difficult because multiple pMHCs may be required to recognize and remove all antigen-specific T cells, and these pools of pMHCs may need to be distinct in different patients. Nevertheless, disease amelioration has been demonstrated through depletion of antigen-specific T cells in a mouse model of T1D using toxin-coupled pMHC class I tetramers[154].

Advances have been made in the identification and production of pMHCs for delivery of payloads such as toxins or for expression on CAR T cells, suggesting that, although challenging, antigen-specific T cell depletion could be feasible in the clinical setting (see Fig. 3b for the CAR T cell approach)[155,156]. A potentially more feasible approach may be to deplete specific T cell subsets enriched for autoreactive cells. As an example of this strategy, depletion of $TRBV9^+$ T cells, subsets of which are expanded in patients with ankylosing spondylitis, has been associated with clinical response in a case study and is currently under clinical investigation[157–160]. As with B cell memory reset, the optimal approach to achieve a long-standing and safe T cell memory reset remains to be elucidated.

Promoting peripheral tolerance

The remarkable features of self-tolerance are governed at various stages of T cell development and maturation. Central tolerance refers to the negative selection (deletion) of potentially autoreactive T cells as they develop and mature in the thymus. This process is not failure-proof, and T cells that recognize self-antigen can and do migrate to the periphery[161–163]. As even a single T cell can become activated and rapidly expand upon encounter with antigen, why is autoimmunity not more common? In addition to central regulation, multiple checkpoints and controls (T cell intrinsic and T cell extrinsic) can restrain peripheral self-reactive T cell fate. Only when both central tolerance and peripheral tolerance fail does autoimmunity ensue. Although much remains to be understood about these checkpoints, the emerging biology suggests potential areas of intervention to reset peripheral tolerance.

T cells that emerge from the thymus are initially naive in phenotype. One mechanism that appears to lower the potential for self-reactivity is quiescence, an active process that limits activation and expansion when antigen (including self-antigen) is encountered in the absence of inflammatory signals[164,165]. A recently recognized driver of naive T cell quiescence is V-type immunoglobulin domain-containing suppressor of T cell activation (VISTA), with its agonism resulting in T cell deletion and tolerance[165]. These results suggest that modulation of VISTA or other quiescence modulators may be a promising point of intervention for maintaining or re-establishing peripheral tolerance.

Upon T cell receptor (TCR)-mediated activation, additional checkpoints govern T cell fate. For instance, if the initial TCR stimulation occurs in the absence of co-stimulatory signals, naive T cells may become anergic[166]. A key co-stimulatory pathway already being exploited clinically is the CD28 pathway[167]. Antigen-presenting cells (APCs) present peptide in the context of MHC to the TCR on the surface of T cells, and then activated APCs simultaneously provide co-stimulation via CD80 and CD86, which bind to CD28 expressed on T cells[167]. As T cells become activated, they express CTLA4, a second ligand for CD80 and CD86 that has higher affinity than CD28 but also negatively modulates T cell activation[168]. Given the higher affinity of CTLA4 for the co-stimulatory ligands, a CTLA4–immunoglobulin fusion protein was developed to prevent T cell activation and promote anergy[168,169]. Two CTLA4–immunoglobulin biologics are in clinical use: abatacept, approved for rheumatoid arthritis, psoriatic arthritis and polyarticular juvenile idiopathic arthritis; and belatacept, approved for prevention of kidney transplant rejection[170,171]. Although a primary mechanism of co-stimulatory blockade is to prevent T cell activation and expansion, anergy induction probably also plays a role[172,173]. Furthermore, CD28 blockade has also been used to promote anergy in donor T cells ex vivo to reduce the risk of graft-versus-host disease (GVHD) after unrelated donor bone marrow transplantation[174]. Emerging data from trials of short-term use of abatacept in individuals at risk for rheumatoid arthritis development (positive for antibodies to citrullinated peptide antigens (ACPA) with evidence of inflammation by magnetic resonance imaging, but no overt arthritis) suggest that rheumatoid arthritis development may be curtailed or at least delayed through co-stimulatory blockade and anergy induction, and thus point to the potential for resetting the immune system to achieve long-term remission[175,176].

If peripheral T cells successfully become activated and expand, mechanisms such as exhaustion and clonal deletion can further limit the response. T cell exhaustion, a state of dysfunction associated with persistent antigen exposure, was first observed in chronic viral infections[177] but is best understood in the context of immuno-oncology, with checkpoint blockade reversing T cell dysfunction and increasing antitumour immunity[178,179]. Multiple lines of evidence point to T cell exhaustion as an active pathway limiting autoimmunity. Immune-checkpoint treatment is associated with immune adverse events, such as vitiligo, dermatitis and colitis. A $CD8^+$ T cell exhaustion signature is also associated with good prognosis (for example, fewer flares) in autoimmune diseases such as SLE, anti-neutrophil cytoplasmic antibody-associated vasculitis and IBD[180]. In patients with T1D, evidence of T cell exhaustion in islet-specific T cells had a slower progressing phenotype compared with those without this signature[181]. Furthermore, the anti-CD3 antibody teplizumab, which is efficacious in preventing or delaying T1D development in patients at risk, induced a T cell exhaustion-like phenotype in patients with clinical response[182]. These observations suggest that checkpoint agonists, at least in part by inducing an exhaustion phenotype, may be useful in resetting peripheral tolerance. Indeed, several agonists of T cell immune checkpoints classically associated with T cell exhaustion, such as PD1, B lymphocyte and T lymphocyte attenuator (BTLA) and lymphocyte-activation gene 3 (LAG3), are currently in preclinical or clinical development, with encouraging results in early-phase studies[183–185].

During thymic differentiation, medullary thymic epithelial cells express peripheral-tissue antigens that lead to clonal deletion of highly responsive T cell receptors (negative selection leading to central tolerance), with autoimmune regulator being the transcription factor responsible for this expression[186]. Clonal deletion may also be important in the periphery; for instance, dendritic cells may promote apoptosis of effector T cells via Fas and Fas ligand (FasL) interactions[187]. Indeed, tolerogenic dendritic cells — which may be inherently tolerogenic (termed natural tolerogenic dendritic cells) or induced by specific contexts such as exposure to apoptotic debris without inflammation — may employ various mechanisms to enforce peripheral tolerance[188] (Fig. 3c). Tolerogenic dendritic cells (and other tolerizing APCs) may deplete T cells, as mentioned previously, but also promote T cell anergy and actively induce exhaustion or inhibition via expression of checkpoint agonists and anti-inflammatory cytokines such as IL-10. Additionally, tolerogenic APCs may mediate the conversion of effector T cells to peripheral T_{reg} cells, further enhancing antigen-specific tolerance[189]. For example, a population of $ROR\gamma t^+$ cells in intestinal lymph nodes have recently been identified and described as tolerogenic APCs that promote differentiation and expansion of peripheral T_{reg} cells with important roles in tolerance to gut microbiota in mice[190–192]. Although T_{reg} cells clearly play a role in peripheral tolerance, we discuss their therapeutic potential more fully in step 3 of our sequential immunotherapy approach.

Several mechanisms used by tolerogenic dendritic cells to imprint tolerance are already being exploited for therapeutic purposes, such as CTLA4–immunoglobulin and checkpoint agonists. As tolerogenic APCs become better understood, manipulation and reprogramming of dendritic cells or other APCs to promote tolerance become possible. In EAE murine models, a non-inflammatory vaccine using myelin oligodendrocyte glycoprotein (MOG) mRNA-containing nanoparticles led to MOG antigen expression in splenic dendritic cells, which elicited tolerance as evidenced by improved clinical signs, reduction of antigen-specific effector T cells, increases in exhaustion markers in remaining antigen-specific T cells and the induction of T_{reg} cells, which also elicited bystander suppression of unrelated, EAE-relevant effector T cell responses[193]. Several approaches to deliver peptides in a tolerogenic fashion have been developed and achieved proof of concept in preclinical models, and some have advanced into clinical testing[194,195]. Targeting of gluten peptides via nanoparticles or through conjugation to glycopolymers, which are recognized by scavenger receptors to tolerogenic APCs in the spleen or liver, has resulted in evidence of immunological tolerance induction in clinical trials of patients with coeliac disease undergoing a gluten challenge[196,197]. Alternative approaches using nanoparticle-based delivery of peptides while, simultaneously, enforcing a tolerogenic environment are also promising. For instance, nanoliposomes loaded with MOG antigens and a ligand for aryl hydrocarbon receptor, which promotes tolerogenic dendritic cell function, ameliorated EAE in mice[198]. Clinical proof of concept for this approach to tolerance induction is also emerging. Pegadricase, a promising therapy for gout that frequently elicits anti-drug antibodies, exhibited reduced anti-drug antibodies and maintained uricase activity in patients with hyperuricaemia when co-administered with rapamycin-containing nanoparticles compared with those treated with pegadricase alone[199]. Although the clinical studies previously explored tolerization to exogenous proteins, they nonetheless offer tantalizing evidence that tolerance induction may be within reach.

Tolerance through manipulation of autoantigens

T cell memory and B cell memory maintain chronicity of autoimmune responses. These memory populations rely on continuous exposure to self-antigens for activation and differentiation. Would it then be possible to circumvent this chronic activation and memory formation by reducing the antigenic load? In rheumatoid arthritis, patients develop autoantibodies to post-translationally modified proteins, particularly citrullinated proteins, and appearance of ACPA may precede the onset of frank inflammatory arthritis[200]. Post-translational citrullination is mediated by the peptidylarginine deiminase (PAD) family, with PAD2 and PAD4 primarily implicated in rheumatoid arthritis pathogenesis, including genetic, cellular and translational evidence[201]. In addition, some patients with erosive rheumatoid arthritis develop activating anti-PAD4 antibodies[202]. In murine models, repeated exposure to one modified autoantigen led to autoantibody responses to multiple post-translationally modified antigens[203]. These observations supported the attractive hypothesis that reduction of citrullinated neoantigens in pre-rheumatoid arthritis or early rheumatoid arthritis could limit the formation of autoreactive T cell and B cell memory and antibodies to post-translationally modified proteins, and delay or prevent rheumatoid arthritis. Indeed, PAD inhibition demonstrated efficacy in murine models of rheumatoid arthritis[204,205]. Whether such an approach to modulating the antigenic environment would be useful in other autoimmune diseases is less clear, but T cell reactivity or autoantibodies with specificities to post-translationally modified neoantigens have been described in SLE, T1D and other autoimmune diseases[206,207].

Anti-double-stranded DNA antibodies and an impaired ability to degrade DNA characterize patients with SLE[208]. Indeed, deficiencies in several DNAses, such as DNAse1, DNAse1L3, DNase II and TREX1, have been linked to monogenic lupus[209], and autoantibodies to DNAse1L3 and the load of microparticles containing cell-free DNA (cfDNA) were correlated with disease activity in some patients with sporadic SLE[210]. One source of cfDNA is neutrophil extracellular traps (NETs) of decondensed chromatin expelled by activated neutrophils. Dysregulated NET formation (NETosis) has been linked to various autoimmune

diseases, including SLE[211]. Reduction of cfDNA may therefore be a useful approach to limiting autoantigen load. Of note, NETosis is modulated through citrullination of histones by the PAD4 enzyme[211], suggesting that PAD inhibition may reduce antigenic load both through reduction of neoantigens as well as through reduction of NETosis and cfDNA.

Step 3: homeostasis and tissue repair

The third and final step in the sequential immunotherapy approach is promoting and maintaining homeostasis and tissue repair. This is an important step for achieving durable responses because it is likely that patients with autoimmunity will be enriched for risk factors that predispose to autoimmune disease. Once active disease is controlled and immune memory is reset, is it possible to prevent new autoreactive cells from emerging? We believe that, by exploiting long-lived regulatory mechanisms, the answer is yes.

Targeting regulatory T cells

T_{reg} cells are key drivers of immune tolerance and homeostasis, and patients with mutations in the T_{reg} cell-expressed *FOXP3* gene develop immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome[212–214]. Moreover, the contribution of T_{reg} cell reduction and/or dysfunction to the pathophysiology of autoimmunity is an active area of research[214]. In murine models, adoptive T_{reg} cell transfer prevented autoimmunity and transplant rejection, suggesting that T_{reg} cell manipulation could be exploited therapeutically[215]. Indeed, ex vivo T_{reg} cell expansion and transfer has been tested in several clinical studies of GVHD prophylaxis, with some encouraging results[216]. Given their immunomodulatory potential, T_{reg} cells and their therapeutic application are under active investigation[214] and are briefly reviewed in Box 4.

Although T_{reg} cell functions may fit within steps 1 and 2 of the sequential immunotherapy paradigm, we believe that expansion and activation of T_{reg} cells will promote long-term immune homeostasis by generating tolerogenic memory and are, therefore, a key pillar within step 3. Although the optimal intervention for T_{reg} cell modulation remains to be established, several methods are being investigated clinically.

IL-2R agonists. IL-2 is a critical growth factor for all T cells and is an approved treatment for melanoma and renal cell carcinoma[217]. At high doses, IL-2 can expand conventional T cells and generate antitumor responses. T_{reg} cells express higher levels of the IL-2Rα subunit than conventional T cells, and are therefore activated and expanded at lower IL-2 concentrations. This observation led to the hypothesis that low doses of IL-2 could be used to bias the expansion of T cells to the T_{reg} cell compartment. In small, early clinical studies, low-dose IL-2 expanded T_{reg} cells and showed clinical efficacy in several autoimmune conditions, such as GVHD and SLE[218].

Although exciting, this low-dose IL-2 approach is limited by the short half-life of the cytokine[218,219]. Modified IL-2-based agents with improved pharmacokinetics and ease of administration, as well as increased selectivity for T_{reg} cells, are under development[220–222]. Several of these approaches modify the affinity of the agents for IL-2R subunits to further enhance IL-2R agonism in T_{reg} cells, including pegylated IL-2 molecules with increased half-life and reduced IL-2Rβ binding as well as IL-2 muteins fused to Fc or other carriers that decrease binding to IL-2Rβ while improving the half-life[220–223]. These approaches are currently under clinical evaluation[224,225]. An alternative to IL-2R binding modification is improving T_{reg} cell IL-2R agonism selectivity through optimized pharmacokinetics[226]. A long-lived IL-2–CD25 fusion inactive dimer protein was shown to slowly dissociate into an active monomer and led to selective T_{reg} cell expansion and efficacy in animal models of autoimmunity, including SLE, and this agent is also being tested clinically[226–228].

Whereas these novel biased IL-2R agonists are encouraging with regard to improved T_{reg} cell selectivity, evidence of eosinophil increases has been observed with both wild-type IL-2 and modified IL-2 (possibly indirectly via ILC2-mediated IL-5 production)[223]. The eosinophil increases seen to date do not appear to be limiting[223]. In addition to ILC2s, a subset of natural killer cells ($CD56^{bright}$ natural killer cells) are activated by low-dose IL-2, which has also been described for some of the IL-2R-biased approaches[223,229]. Future studies will determine whether current IL-2R agonists have sufficient selectivity or whether new, more-selective IL-2R-mediated approaches can be developed.

Although the early data from low-dose IL-2 were encouraging, enthusiasm for this approach has decreased recently as several clinical studies failed to show benefit in several indications[224,225,230]. One hypothesis for the lacklustre clinical efficacy despite robust T_{reg} cell expansion is that even biased IL-2R signalling agonists may activate subsets of inflammatory cells in addition to T_{reg} cells. Alternatively, T_{reg} cell activation may not be sufficient to control inflammation but, rather, may promote homeostasis and tissue healing only after an inflammatory insult has waned. In this scenario, we predict that, as our sequential immunotherapy approach suggests, T_{reg} cell expansion will be efficacious in preventing relapses after inflammation is controlled as part of sequential treatment.

Box 4

Regulatory T cells and their functions

Regulatory T cells (T_{reg} cells) express the lineage-defining transcription factor FOXP3 and high levels of the IL-2 receptor α-subunit (IL-2Rα; also known as CD25) and participate in both central and peripheral tolerance[344,345]. During negative and positive selection in the thymus, T cells expressing T cell receptors (TCRs) with intermediate affinity for peptide major histocompatibility complexes (pMHCs) differentiate into T_{reg} cells[345]. Peripherally, tolerogenic dendritic cells may promote the conversion of conventional T cells to T_{reg} cells[189]. Mechanistically, T_{reg} cells employ multiple contact-dependent and contact-independent processes to suppress effector responses, including consumption of IL-2, production of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGFβ), conventional T cell and antigen-presenting cell (APC) killing via granzyme production, depletion of co-stimulatory molecules on APCs and the transfer of inhibitory factors such as cAMP[344].

Critically, T_{reg} cells contribute to bystander suppression — that is, the inhibition not only of cognate antigen responses but also of unrelated but co-localized antigens[346]. In addition to participating in the resolution of inflammation, T_{reg} cells promote tissue repair and maintenance through production of growth factors such as amphiregulin[347].

Alternative T_{reg} cell targets. Other T_{reg} cell targets are also under investigation, such as TNF receptor 2 (TNFR2) agonism. TNF mediates its pleotropic functions via binding to two distinct receptors, TNFR1 and TNFR2 (ref. 231). TNFR1 predominantly mediates pro-inflammatory effects of TNF signalling across many cell types, whereas TNFR2 has been associated with immunomodulatory activity and has a more restricted expression pattern including expression in T_{reg} cells[231]. TNFR2-selective agonism, in vitro and in vivo, promoted T_{reg} cell expansion in models of GVHD and experimental arthritis[232,233]. Furthermore, a TNFR2-agonist antibody expanded a population of human T_{reg} cells in vitro[234].

Although these data are encouraging, TNFR2 is expressed in multiple cell types, including effector T cells and myeloid cells[231,235], and the effect of selective stimulation across cell types remains to be understood. Other receptors expressed by T_{reg} cells have been targeted, such as ST2, a receptor for the alarmin cytokine IL-33 that promotes the proliferation of T_{reg} cells in tissues[236–238]. ST2 expression also appeared to increase in tumour-infiltrating T_{reg} cells, suggesting that $ST2^{+}$ T_{reg} cells are potently suppressive[239].

T_{reg} cell therapy

Initial evidence has suggested the therapeutic potential of adoptive transfer of ex vivo-expanded polyclonal T_{reg} cells for autoimmune indications[215]. Although these results are encouraging, at least regarding the feasibility, safety and tolerability of the approach, efficacy remains to be evaluated in large, well-controlled studies[215,240]. Concurrently, animal models have also demonstrated that, in comparison with polyclonal T_{reg} populations, antigen-specific T_{reg} cells have an improved capacity to control autoimmunity, in part because of specific homing to the relevant affected tissues where the cognate antigen is presented[241,242]. These preclinical data have fuelled an interest in developing antigen-specific T_{reg} therapies. Although exciting, this approach is limited by the rarity of these cells in circulation, which necessitates complex isolation and expansion methods[241,243].

Alternatively, antigen-specific engineered T_{reg} cells have been developed to facilitate production and utility (Fig. 3d). One approach is the generation of CAR T_{reg} cells such as those recognizing HLA-A2 for the prevention of $HLA\text{-}A2^{+}$ organ transplant rejection[244–247]. T_{reg} cells can also be generated with TCRs with known specificity or CARs specific for disease-relevant pMHCs, such as for the treatment of multiple sclerosis or T1D (refs. 248–250). A key question for engineered T_{reg} cell technologies is the durability and stability of the T_{reg} cell phenotype. To address these issues, additional engineering steps have included 'locking' the T_{reg} cell phenotype, such as through enforced FOXP3 expression and cytokine support through expression of artificial cytokine receptors that can be modulated[243,251].

Additional mechanisms

In epithelial tissues such as the skin and gut, barrier disruption or failure to repair following an injury may trigger inflammation and break of tolerance. A case study is the filaggrin gene; individuals with mutations in this epidermal protein are at increased risk of not only atopic dermatitis but also asthma and food and other environmental allergies[252]. Likewise, individuals with loss-of-function mutations in *SPINK5*, which encodes the serine protease inhibitor LEKTI in keratinocytes, display an abnormal skin barrier that results in Netherton syndrome[253]. In patients with IBD, underlying defects in the intestines associated with epithelial repair were identified, such as *PTGER4*, *ERRFI1* and *HNF4A* risk alleles that may act through loss of tolerance to luminal contents[254]. Additionally, decreased expression of epithelial junction proteins indicating compromised integrity of the oral mucosa barrier was observed in patients with coeliac disease[255]. These complex traits located downstream of epithelial defects point to the important role of barrier biology in the pathophysiology of autoimmune and inflammatory diseases. Maintaining homeostasis once inflammation is controlled and autoimmunity is reset is likely to necessitate restoration and preservation of the barrier; thus, epithelial biology is likely to be ripe for identification of novel targets to promote epithelial integrity.

In addition to epithelial–immune interactions, hyperactivated stromal cells such as fibroblasts are a fundamental feature of immune-mediated inflammatory diseases[256]. Fibrosis has been identified as a complication in IBD, particularly in Crohn's disease, in which fibrosis can lead to strictures that may require surgical interventions[257]. Mesenchymal cells, especially myofibroblasts, play a pathogenic role in promoting inflammation and fibrosis[258]. Therapies targeting fibrosis in autoimmune disease, such as modulation of transforming growth factor-β (TGFβ) pathways via ALK5 inhibition, are currently under clinical investigation[258,259].

The pathogenesis of several inflammatory disorders may also be associated with defects in efferocytosis (the clearance of apoptotic cells by phagocytes), suggesting that this process could be a therapeutic target[260]. Efferocytosis is important for tissue repair, inflammation resolution and the modulation of immune balance during homeostasis, with deficits leading to apoptotic-cell accumulation and, subsequently, necrosis, cytolysis and the generation of intracellular components that initiate tissue damage[260]. cAMP and the secreted protein endothelial locus 1 (DEL1) have been shown to stimulate macrophage efferocytosis, with data also suggesting that DEL1 facilitates homeostatic functions in the setting of inflammation[261,262]. T_{reg} cells can also induce macrophage efferocytosis via IL-13 secretion and subsequent stimulation of IL-10 production in macrophages[263].

In addition to deficits in the clearance of apoptotic cells, necroptosis (a non-apoptotic and pro-inflammatory form of cell death triggered by TNF) has been implicated in disease chronicity and tissue injury through induction of an uncontrolled inflammatory response[264]. Preclinical models suggest that modulation of necroptosis may be beneficial to decrease inflammation-associated barrier dysfunction in IBD and other diseases[265,266]. However, blocking necroptosis via RIPK1 inhibition has shown mixed success in clinical trials of rheumatoid arthritis and psoriasis[267,268], suggesting that necroptosis as a target in inflammation still needs further exploration.

Finally, the nervous system has also shown involvement in autoimmune diseases and neuroinflammatory conditions through its interaction with the immune system[269]. Emerging evidence indicates that neuroimmune interactions (that is, those between the innate and adaptive immune systems and neurons) are critical for effective immunity, tissue homeostasis and tissue repair. A key example of these neuroimmune interactions is the itch amplification and chronicity in atopic dermatitis, which may also help explain the rapid relief of pruritus afforded by IL-4Rα and downstream signalling inhibition in clinical settings[270,271]. Another example is the well-documented link between psychological stress and symptoms in IBD, which appears to be mediated by the enteric nervous system[272]. However, these neuroimmune interactions can promote or inhibit immunity, depending on the tissue microenvironment and immune response mediator[273]. For instance, in the intestinal tract, vasoactive intestinal polypeptide derived from enteric neurons stimulates the production of IL-22, which affects non-lymphoid cells such as epithelial cells, and is critical for

the maintenance of homeostasis in the gut barrier[274]. These lines of evidence suggest that the neuroimmune axis will likely be a source of targets to promote homeostasis and barrier tissue integrity.

Unlocking causal human biology

Rapid technological progress in molecular profiling of the immune system, combined with increases in computational power, now allows the relationship between millions of molecular features and clinical outcomes to be interrogated in large sample sizes. These data hold tremendous promise to guide the identification of new drug targets that will control residual inflammation not addressed by current drugs, reset the immune system and restore homeostasis. We approach the vast amount of data generated by these novel immune-profiling technologies with guidance from the concept of causal human biology (Box 5). In this framework, therapeutic hypotheses are formed based on causal inference methods applied to observations made in tissue samples from patients and healthy donors that describe molecular processes dysregulated in disease. Although we use model organisms and human cell culture for preclinical experimentation, our decision-making remains rooted in our understanding of human biology.

New immunotherapies from human genetics

Human genetics is a core component of our causal human biology strategy because it provides convincing causal inference and a broad view of human disease biology. Genome-wide scans can distinguish targets with more-selective roles in autoimmune disease from those with broadly immunosuppressive consequences. For example, key insights into the relative impact of different potential targets on the immune system and infectious disease risk have been gleaned from rare mutations in approximately 350 genes that cause various forms of primary immunodeficiencies[275]. Similarly, monogenic autoinflammatory diseases with well-known mechanisms can point to new therapeutic mechanisms for both targeted immunosuppression and restoration of homeostasis in more common indications. For instance,

Box 5

Causal human biology

We use the concept of causal human biology to guide our efforts to discover novel therapies and achieve the goals of sequential immunotherapy. New technologies that facilitate deep immune profiling, including single-cell omics, B cell receptor (BCR) and T cell receptor (TCR) sequencing, profiling of the peptide major histocompatibility complex (pMHC) multimers and other innovations, are dramatically increasing the resolution at which observational studies can describe dysregulated processes in patients with autoimmune and inflammatory diseases. However, molecular features associated with disease do not necessarily represent effective targets. For example, Somineni et al. demonstrated that the vast majority of DNA methylation changes in blood from patients with active Crohn's disease were a reaction to, rather than drivers of, inflammation[348]. As such, a key component of causal human biology is highlighting the molecular processes for which intervention would alter the probability of a clinical improvement.

Randomized controlled clinical trials are the generally recognized gold standard of causal inference. Unfortunately, the data available from completed trials provide a narrow window into human disease biology and are limited by the set of therapies and related pathways that have been tested, as well as by the disease characteristics, comorbidities and co-medications of the patients enrolled. Human genetics is a core component of our strategy for identifying causal human biology because it provides a broad view of human disease biology. Germ-line genetic variants provide experiments of nature in which the genotype is determined at birth through a well-defined process dependent on the parental genotype and the random segregation of chromosomes; such natural experiments can be used to perform causal inference about molecular processes driving disease through Mendelian randomization[349]. Indeed, retrospective studies have shown that successfully approved drugs have genetically supported targets, likely reflecting their impact on causal pathways in human disease[350,351].

Although existing genetic studies give us a broad view of genes involved in disease pathobiology, we seek more quantitative estimates of potential efficacy and safety profiles for targets of interest, well ahead of drug discovery and initiation of randomized clinical trials. This goal can be accomplished through the construction of genetic dose–response curves (see an expanded discussion of this concept by Plenge et al.[78,352]). Importantly, these efforts require very large sample sizes and/or targeted recruitment to capture genetic variants with large loss-of-function and gain-of-function effects, which tend to be found at very low frequencies in the general population, as shown by initial analyses of UK Biobank whole-exome sequencing data[353,354]. Biobanks that reflect global diversity and capture as wide a set of informative alleles as possible will be critical to generating informative genetic dose–response curves.

Although we focus on therapeutic hypotheses directly supported by evidence of causal human biology from randomized clinical trials or human genetics, we acknowledge that these methods leave some gaps in our understanding of human disease biology. For example, a substantial number of genes lack loss-of-function alleles, likely due to negative selection, and include known targets for safe and effective therapies[355]. As such, we also consider a broader set of data sources for clues on disease biology and potential interventions. A key example of this concept is a well-controlled prospective longitudinal study that demonstrated that Epstein–Barr virus can cause multiple sclerosis by showing a strong predictive ability and directly addressing the risk of confounding through comparison with similar viruses that do not cause multiple sclerosis[356]. Similar considerations exist for real-world evidence from pharmacological interventions (for example, off-label use) or natural interventions (for example, autoantibodies or somatic mutations), which involve an in vivo intervention experiment in humans but which we approach with caution because randomization has not been used to remove the threat of confounding.

sequencing of monogenic forms of IBD with very early onset have revealed mutations across genes involved in broad immune dysregulation, as well as more-specific defects in T_{reg} cells or epithelial barrier function[276]. Genome-wide association studies have also mapped loci directly associated with multiple autoimmune diseases, mostly driven by non-coding polymorphisms that influence gene regulation, and subsequent causal inference methods have implicated hundreds of genes in these diseases[277].

Deeper immune profiling will be needed to identify mechanisms that move beyond immune suppression to reset the immune system and restore homeostasis, and human genetics can be used to distinguish molecular features (for example, cell types or circulating protein levels) that reflect causal versus reactive processes. One of the most mature examples is the use of Mendelian randomization to implicate circulating proteins in autoimmune diseases[278,279]. A 2018 proteo-genomics study found that alleles that increased plasma levels of proteinase 3 (PR3) protein in healthy individuals also increased the risk of $PR3^+$ anti-neutrophil cytoplasmic antibody-associated vasculitis, suggesting an increased tendency to break tolerance in individuals with higher antigen levels[280]. Many additional insights will likely emerge from even larger studies of the genetic basis of variation in immune-related protein levels[281] and other molecular measurements.

Immunotherapy at single-cell resolution

Single-cell omics has been used to generate atlases of characteristic cell types and transcriptional states across many autoimmune and other diseases[282]. Combined with genetics-based causal inference, these information repositories can be used to identify components of a dysregulated immune system that may need to be reset (for example, autoreactive cells) and key features of homeostasis that may be missing or disrupted in disease. The nature of immune cell populations that mediate genetic risk for immune diseases has often been unclear. Recent studies have made progress by combining single-cell omics with genetics to associate specific cells and candidate causal genes with immune-mediated diseases, including cells that could be targeted according to step 2, such as memory B cells expressing CD27 (refs. 283–285).

Similar approaches can also provide insights into the interaction between immune, epithelial and stromal cells that may perpetuate inflammation. For example, a cross-disease integrative analysis of single-cell RNA sequencing data identified fibroblast cell populations that co-occur with infiltrating immune cell counts and active inflammation across rheumatoid arthritis, ulcerative colitis, interstitial lung disease and Sjögren's disease[286]. Together with clinical data, single-cell RNA sequencing also enables precision medicine by providing a direct link between potential targets and relevant patient populations with unmet needs. Friedrich et al. used this approach to define expression patterns associated with non-response to anti-TNF drugs in patients with IBD and ascribed these patterns to changes in specific gut neutrophil and fibroblast populations[287]. Cross-analysis with human genetics could reveal novel step 3 targets through insights into epithelial and stromal cells, such as the role of M cells as potential mediators of genetic signals in *FERMT1* and other IBD-associated loci[283–285].

Models of causal human biology

Another key tool in causal inference is the ability to perform experiments using human-derived in vitro model systems that directly recapitulate or resolve disease in humans. These approaches could help define the next generation of targets, guided by observations in humans. For example, clustered regularly interspaced short palindromic repeats (CRISPR)-based screens in vitro can be used to identify genes that modulate T_{reg} cell expansion, as has been accomplished in murine cells and could be performed directly in human cells, and can shed light on novel therapeutic approaches that enhance T_{reg} cell numbers and/or function to promote immune tolerance and homeostasis[288]. Gene editing can also be used to reproduce human disease mutations in models, such as atopic dermatitis-causing *FLG* variants[289], and to screen for upstream modifiers.

Enabling sequential immunotherapy

To modulate pathophysiological drivers of disease identified via a causal human biology approach, novel tools and technologies may be required. Fortunately, recently emerged technologies can unlock previously undruggable biology. For instance, small-molecule allosteric modulators (for which artificial intelligence tools have accelerated design) can enable unprecedented target selectivity[290]; complex biologics such as antibody–drug conjugates and multispecific constructs can achieve selective modulation of cellular populations; and cell therapies have the potential to result in immune reset via deep, specific cell depletion. Proximity-based approaches such as ligand-dependent degradation allow modulation of transcription factors, scaffold proteins and other proteins not amenable to typical small-molecule inhibitors. Nucleic acid technologies coupled with selective delivery mechanisms — including gene therapy, small interfering RNA, mRNA and CRISPR — now enable editing, silencing and replacement of genes and gene products, and even in vivo cell engineering and reprogramming. Used appropriately, these technologies will unleash the potential of sequential immunotherapy.

Aside from scientific and technological advances, we acknowledge that realizing the potential revolution in treating autoimmune disorders through sequential immunotherapy requires a path to clinical proof of concept. This path will include translational medicine, clinical development and regulatory innovation. Typical clinical trials in autoimmune indications favour testing of step 1 targets, usually as monotherapy. In our view, the most innovative novel approaches to change the autoimmunity treatment paradigm are targets in steps 2 and 3. However, generating evidence for an immune reset and maintenance of homeostasis may require novel predictive biomarkers to test hypotheses efficiently. Targets in step 3 may demonstrate superior efficacy to standard of care only when used in true sequence or combination approaches. For instance, a drug that enhances barrier repair or promotes regulatory function may only demonstrate efficacy after appropriate inflammatory modulation and immune reset. As mentioned earlier, patients with autoimmunity may continue to break tolerance even after achieving an immune reset if underlying barrier defects are not also addressed. Partnership with and feedback from clinicians and health authorities will be necessary to establish approaches to test these ideas in ways that could lead to drug approvals and guidelines in a new era of precision medicine.

Conclusions

We believe that the possibility of achieving long-term remissions and cures in the treatment of autoimmune and inflammatory diseases is within reach. This ambitious goal is bolstered by promising emerging clinical data from CD19-targeted CAR T cell therapy for diseases such as SLE, rational combinations of drugs such as anti-IL-23 and anti-TNF therapies that are breaking efficacy ceilings in the treatment of IBD,

and the emergence of precision-based approaches such as anti-IL-4Rα therapies in the subset of patients with COPD and type 2 inflammation.

The sequential immunotherapy framework proposed here is guiding our drug discovery portfolio. Our approach is also rooted in the identification of targets based on causal human biology and is facilitated by novel technologies that match the modality to the mechanism, allowing us to address disease drivers that previously could not be targeted. Coupled with identification of specific clinical or molecular patient subsets and a pathway to establishing clinical proof of concept through translational biomarkers, clinical trials and regulatory advances, sequential immunotherapy offers the promise to transform the treatment of immunological disorders.

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