Haematological malignancies: at the forefront of immunotherapeutic innovation

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Abstract | The recent successes of cancer immunotherapies have stimulated interest in the potential widespread application of these approaches; haematological malignancies have provided both initial proofs of concept and an informative testing ground for various immune-based therapeutics. The immune-cell origin of many of the blood malignancies provides a unique opportunity both to understand the mechanisms of cancer immune responsiveness and immune evasion, and to exploit these mechanisms for therapeutic purposes.

Professional antigen-presenting cells (Professional APCs). Professional APCs comprise three major types of immune cells: dendritic cells, macrophages and B cells. Although all nucleated cell types can present intracellularly derived peptides on the ubiquitously expressed major histocompatibility complex (MHC) class I molecule, these three can additionally present antigens derived from the extracellular space, binding them to MHC class II molecules.

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doi:10.1038/nrc3907
Published online 19 March 2015

Haematological malignancies provided the earliest effective application of antitumour immunotherapeutic approaches, ranging from adoptive cellular therapy (ACT) and antibody-based therapies to active cancer vaccination. The blood malignancies possess several salient characteristics that facilitated important laboratory and clinical investigation with immunotherapy, including their close apposition and relationship to sites of immune origin and the ease of isolation and manipulation of cancer cells. Altogether, their study has elucidated the complexity of antitumour responses and the tumour microenvironments within which they operate. These trailblazing investigations into monoclonal antibodies (mAbs) and ACT have long provided beacons of hope that immunotherapeutic approaches could be broadly applicable across neoplasms. Recently, immune checkpoint inhibitors, which were pioneered in various solid tumours[1], have also shown considerable promise in the treatment of blood cancers. The efficacy of so many distinct immunotherapeutics highlights the blood malignancies as a unique therapeutic arena to tackle the full complement of independent but inter-related vulnerabilities in the cancer–immune relationship.

Enabling features of haematological malignancies

A key clinical feature of the blood malignancies is their immune responsiveness. Parallelling the early successes of chemotherapy for the treatment of blood malignancies were the spontaneous tumour regressions in lymphomas[2,3] and durable remissions of leukaemias after allogeneic haematopoietic stem cell transplantation (allo-HSCT). Indeed, the efficacy of allo-HSCT is largely derived from the graft-versus-leukaemia (GVL) effect: an eradication of malignant cells by the donor's immune cells (BOX 1). Studies exploring the GVL effect have highlighted the ability of the human immune system to specifically and effectively eliminate cancer.

These studies consequently provided a clinically relevant background for elucidating the essential elements of effective antitumour immunity. Several key features of the blood malignancies enabled these studies. First, in addition to their immune responsiveness, the relative ease of tumour and normal-tissue sampling facilitated the extensive characterization of cellular surface markers that define the normal haematopoietic lineage. This unique delineation of the cellular hierarchy could discriminate normal from malignant immune cells and furnish potential therapeutic targets, such as CD20 (REF. 4). Second, the clinical use of allo-HSCT and donor lymphocyte infusion (DLI) led to well-defined immune-based anticancer responses in humans. The ability to directly sample relevant tissues before and after immunotherapy, in turn, has aided the identification and interrogation of critical antitumour immune components, such as cellular effectors and expression of specific tumour antigens.

Finally, the cellular and immune sites of origin of haematological malignancies are uniquely related to host immunity. For many blood malignancies, their cellular origins as professional antigen-presenting cells (professional APCs) may endow a distinct tolerogenic or immunostimulatory capacity, as discussed below. Moreover, the ability to elicit and subsequently evade an immune response may be entwined with blood malignancies arising from and remodelling the niches of various

High mobility group box 1 (HMGB1). A DNA-binding protein that, when released by dead or damaged cells, stimulates a robust pro-inflammatory response through the binding of Toll-like receptor 4 on dendritic cells, enhancing tumour antigen presentation and driving chemotherapeutic efficacy.

Nurse-like cells (NLCs). Stromal-like adherent cells that develop *in vitro* from peripheral blood mononuclear cells of patients with chronic lymphocytic leukaemia (CLL). They are tightly surrounded by CLL cells and promote their survival.

T helper 1 cell (T_H1 cell). A pro-inflammatory subset of $CD4^+$ T cells defined by interleukin-2 and interferon-γ production, which leads to promotion of cellular immunity through $CD8^+$ cytotoxic T cells, macrophages and natural killer cells.

immune populations. Indeed, the marrow, spleen and lymph nodes serve as primary, endogenous sources of T and B cell priming and immune memory generation[5]. Hence, the direct apposition of leukaemic or lymphoma cells to immune cells at these immune-priming sites creates unique tumour–immune interactions that have the potential either to incite effective antitumour cellular immunity or, as discussed below, to co-opt these responses for malignant growth.

Subversion of physiological immune programmes

As corruptions of normal haematopoiesis, myeloid and lymphoid neoplasms harbour the ability to co-opt the normal physiological circuitry of immune cells. Blood malignancies can subvert these normal homeostatic signals to drive tumour growth (BOX 2; FIG. 1a,b) and/or to manipulate endogenous immune responses. Understanding these strategies may illuminate key pathways for therapeutic modulation.

FIGURE 1 depicts several modes by which malignant blood cells may manipulate conventional antitumour immune mechanisms to induce a growth-promoting tumour microenvironment. Antigen presentation, the induction of immunogenic cell death and an inflammatory microenvironment are all crucial components for generating an effective antitumour immune response, which is subverted in the process of blood cancer growth.

Box 1 | **Allo-HSCT: the first cancer immunotherapy**

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) comprises a rare combination of immune, stem cell and personalized therapies that can eliminate otherwise incurable haematological malignancies[183]. Developed more than 50 years ago, allo-HSCT allows the delivery of high doses of radiation and chemotherapy, enabling higher tumour kill at the expense of permanent bone marrow suppression. Donor HSCs were infused to engraft and repopulate all elements of the haematopoietic system. Over the past three decades, a large body of evidence from clinical experience and laboratory studies has demonstrated that recipient immune reconstitution by donor immune cells has a critical role in the elimination of recipient tumour cells (the graft-versus-leukaemia (GVL) effect) through both cellular and antigenic determinants. Engraftment permits non-tolerant immune cells to reject recipient tumour tissue; and major and minor histocompatibility antigens (in addition to tumour-associated antigens) distinguish recipient from donor tissue, further driving the GVL effect (and in many patients, graft-versus-host disease (GVHD)). The earliest direct evidence for the potency of the GVL effect stemmed from the post allo-HSCT setting in which donor lymphocyte infusions (DLIs) alone, in the absence of chemotherapy or radiation, induced dramatic responses and enduring remissions of relapsed haematological malignancies, particularly chronic myeloid leukaemia[184].

Separating the GVL effect from GVHD

A challenging complication of both DLI and allo-HSCT is GVHD, wherein donor lymphocytes recognize allo-antigens expressed on normal host tissue (for example, skin, gastrointestinal tract or liver tissues), leading to organ damage and dysfunction. Efforts to identify the cellular and antigenic determinants that divorce the GVL effect from GVHD have driven much of the progress in HSCTs by highlighting the central roles of various T cell subsets, natural killer cells and B cells as well as identifying tumour-specific antigens such as Wilms tumour protein (WT1), proteinase 3 (PRTN3) and BCR–ABL. Moreover, these advances in understanding the GVL effect have informed the rationale for current immunotherapeutic approaches such as adoptive cellular therapy and chimeric antigen receptor T cells[185] (see the main text). Future directions of investigation in allo-HSCT include identifying antigens and cellular effectors that exclusively drive the GVL effect. Finally, the immediate post-transplantation state provides an effective clinical and immunological setting to examine novel vaccine approaches (see the main text).

As corrupted professional APCs, many blood malignancies may recapitulate the peripheral tolerance mechanisms of their physiological counterparts (FIG. 1c). Professional APCs promote, or 'license', antigen-specific T cell proliferation and activation in the presence of co-stimulatory molecules, and tolerance or anergy in their absence. Indeed, studies have shown that low-level expression of co-stimulatory molecules by pre-B cell acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) cells induces antigen-specific T cell tolerance[6–8]. However, adherence to this paradigm varies among blood malignancies. For example, many B cell lymphomas have divested themselves entirely of their self-antigen presentation machinery, either through recurrent mutations in the gene encoding β2 microglobulin (an important subunit of major histocompatibility complex (MHC) class I molecules) or through deletions of MHC class II genes on chromosome 6 (REFS 9,10).

Along with manipulation of antigen-presentation pathways, blood malignancies may also co-opt mechanisms that are normally associated with immunogenic cell death (FIG. 1d). A successful chemotherapeutic response partly derives from induction of novel, or reactivation of pre-existing, antitumour immune responses to 'danger' signals emitted by cancer cells during drug-induced apoptosis[11]. One such danger signal is high mobility group box 1 (HMGB1)[12]. However, in chronic lymphocytic leukaemia (CLL), leukaemia cells seem to co-opt the immunostimulatory activity of secreted HMGB1 to create a protective microenvironment. The plasma concentration of HMGB1 positively correlates with absolute lymphocyte count, reflecting CLL burden. CLL-released HMGB1 directly induces *in vitro* differentiation of monocytes into nurse-like cells (NLCs), which are vital for CLL survival *in vitro* and *in vivo*[13,14], illustrating the adaptation of a mechanism of immunogenic cell death into one of tumour promotion.

A T helper 1 cell (T_H1 cell)-generated inflammatory tumour microenvironment, which is typically associated with effective anticancer immunity[15], may actually promote neoplastic expansion in haematological malignancies (FIG. 1e). Many B cell lymphomas exemplify this paradigm by their exquisite dependence on inflammatory signals within a microenvironment comprising various immune populations, including $CD68^+$ NLCs, T cells and stromal cells. Numerous *in vitro* studies have indicated the dependence of CLL on NLCs for recruiting T cells, and promoting CLL cell survival and chemotherapeutic resistance[16,17]. Similarly, *in vivo* survival and proliferation of cells in xenograft models derived from patients with CLL uniquely require robust expansion of autologous $CD4^+$ T cells[13,18]. Likewise, in classical Hodgkin lymphoma (cHL), an activated, proliferative and inflammatory T cell infiltrate with a T_H1 cell phenotype has been identified[19]. Both follicular lymphoma and gastric mucosa-associated lymphoid tissue lymphoma cells depend on T cell contact for proliferation[20,21], and multiple studies have also illustrated the ability of follicular lymphoma to remodel and 're-educate' the lymph node microenvironment by inducing changes in T cell gene expression profiles[22], polarizing monocytes into

Box 2 | **Driving tumour growth through subversion of homeostatic pathways**

Proliferation of T and B lymphocytes is a normal response of the adaptive immune system to antigen encounter and stimulation that can be driven by both antigen-dependent and -independent mechanisms, largely through cytokine exposure. Consistent with its key role in T cell growth, the interleukin-7 (IL-7) signalling pathway crucially contributes to the progression and chemotherapeutic resistance of human T cell acute lymphoblastic leukaemia (T-ALL)[186] (FIG. 1a). In fact, somatic gain-of-function mutations in multiple components of this pathway have been found in both paediatric and adult T-ALL, suggesting the perversion by T-ALL of the homeostatic regulator of its normal counterpart (that is, normal T cells)[187]. Numerous studies have further suggested a similar growth-promoting role for this pathway in multiple B cell malignancies[188]. Intriguingly, although inhibition of the IL-7-driven PI3K–AKT–mTOR signalling pathway attenuates proliferation of both T-ALL and healthy T cells, only T-ALL cells undergo apoptosis[189,190]; this provides a new therapeutic opportunity based on understanding the hijacking of a physiological immune programme[186].

As another illustration of how the malignant process can subvert normal physiological immune responses, certain mature B cell malignancies have evolved to constitutively activate B cell receptor (BCR) signalling even in the absence of its cognate antigen[191] (FIG. 1b). Chronically active BCR signalling further drives the pathobiology of the activated B cell-like subset of diffuse large B cell lymphoma (DLBCL), which is evidenced by somatic gain-of-function mutations in the BCR signalling pathway[192]. The recent reports of marked responses in DLBCL, chronic lymphocytic leukaemia and mantle cell lymphoma to pharmaceutical inhibition of Bruton's tyrosine kinase, which is critical for BCR activation, further clearly demonstrate the potency of targeting these homeostatic subversions[193,194].

tumour-associated macrophages[23] and recruiting follicular dendritic cells[24]. This critical heterogeneity of the B cell lymphoma microenvironment has recently been reviewed[25]. Multiple myeloma further typifies this paradigm: primarily housed within the bone marrow, multiple myeloma cells therefore reside within a protective network of extracellular matrix proteins, adhesion molecules, stromal cells, osteoclasts and other immune cells[26]. As in CLL, macrophages provide support to multiple myeloma cells through inflammatory cytokines such as interleukin-6 (IL-6)[27] that are essential for multiple myeloma cell survival and proliferation[28]. Multiple myeloma cells also hijack the CD28 T cell co-stimulatory receptor to bind to CD80 and CD86 on dendritic cells, inducing autocrine pro-survival signals, production of IL-6 by dendritic cells and dendritic cell-mediated protection against chemotherapy-induced apoptosis *in vivo*[29,30]. Moreover, T_H17 cells contribute directly to multiple myeloma cell growth and indirectly to a growth-promoting microenvironment[31,32].

The active recruitment by so many haematological malignancies of the components of an inflammatory microenvironment may explain the unexpectedly positive prognostic benefit ascribed to infiltrating regulatory T cells (T_{Reg} cells). Although tumour infiltration by T_{Reg} cells is strongly associated with worse clinical outcomes in many solid tumour malignancies[33,34], studies in follicular lymphoma, cHL and T cell neoplasms have, conversely, identified a clinical benefit[35–38]. How are T_{Reg} cells fostering tumour development in one context and impeding its growth in another? Although no definitive answers exist, T_{Reg} cells may suppress lymphoid cancer cells either directly, or indirectly through the inhibition of tumour-promoting inflammatory responses in the microenvironment. Consistent with this scenario, increased expression of immune-inhibitory programmed cell death protein 1 (PD1; also known as CD279) by follicular lymphoma-infiltrating lymphocytes favourably affects clinical outcomes[39]. Together, these observations suggest that haematological malignancies recruit an inflammatory microenvironment that enhances growth and dissemination.

T_H17 cells
(T_H17 cells). An inflammatory interleukin-17-producing subset of $CD4^+$ T cells that is implicated in many autoimmune diseases.

Regulatory T cells
(T_{Reg} cells). A $CD4^+CD25^{hi}$ T cell subset known to effectively suppress T cell effector functions as well as proliferation and activation of various immune cells, including antigen-presenting cells, B cells and natural killer cells. T_{Reg} cell infiltration has been implicated in multiple disease states, ranging from neoplastic growth to autoimmune dysfunction.

Programmed cell death protein 1
(PD1). An immune-checkpoint receptor expressed on activated T cells, as well as other immune subsets, that primarily functions in peripheral tissues. Binding to its ligands, PDL1 or PDL2, which are expressed on tumour and stromal cells, induces T cell exhaustion.

Four major nodes of cancer immunotherapy

The historically close relationship between cancer immunity and haematological malignancies has, over decades, motivated the development of a varied landscape of clinically relevant cancer immunotherapeutics that target each of four major nodes of vulnerability in the cancer–immune relationship. These are: direct targeting of surface tumour antigens; boosting of numbers and functioning of immune effectors; activating tumour antigen-specific immunity; and overcoming inhibitory immune suppression. This broad scope strongly suggests an exceptional opportunity to use blood cancers to simultaneously understand and therapeutically leverage multiple components of the antitumour immune response (FIG. 2; TABLE 1).

Direct targeting of surface tumour antigens

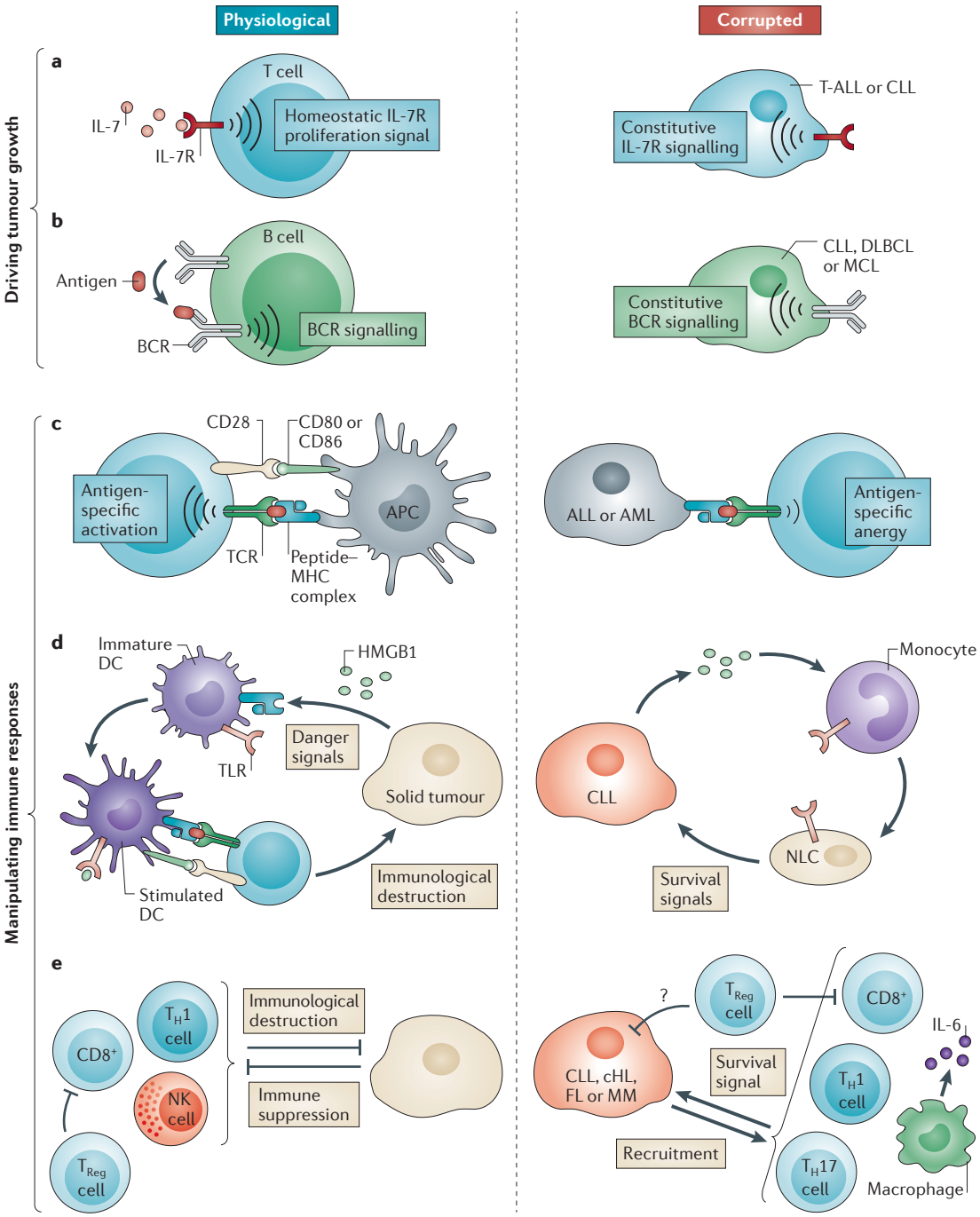
The ability to define lineage markers in the haematopoietic tissue hierarchy enabled the isolation of blood cell subsets and, in turn, the identification of subpopulation-specific surface antigens (FIG. 2, purple boxes). The B cell marker CD20 is an archetypal example of a clinically feasible target, as it led to the development of the chimeric CD20-specific mAb rituximab, which is now a standard component in the clinical management of B cell malignancies, increasing cure rates with minimal toxicity[40,41]. By providing proof of concept that simply targeting a surface tumour antigen is sufficient for cancer cell elimination, its success has fuelled the development of other tumour-targeting mAbs and bispecific antibodies.

Monoclonal antibodies. The specificity of humoral immunity has long been recognized as therapeutically advantageous and led to the development of mouse mAbs. However, this approach was broadly successful only once the barrier of xenogeneically derived immunogenicity was overcome through humanization of murine antibodies by grafting murine-complementary determining regions onto a recombinant human immunoglobulin[42–44]. In addition to direct cytotoxicity, mAbs seem to elicit tumour destruction

Natural killer cells
(NK cells). Lacking the antigen-recognition diversity of T and B cell receptors, NK cells function instead through an array of inhibitory and activating cell surface receptors, of which killer-cell immunoglobulin-like receptors have a prominent role.

through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADP) and/or complement-dependent cytotoxicity (CDC) mediated through engagement of Fcγ or complement receptors on natural killer cells (NK cells), macrophages and neutrophils. Adaptive immunity is also induced, primarily through Fcγ receptor pathway dendritic cell-mediated enhancement of antigen presentation[45–47].

CD20-specific mAbs can be divided into two groups based on *in vitro* mechanisms of action. Type I antibodies (for example, rituximab and ofatumumab) redistribute CD20 into large lipid rafts in the cell membrane and exhibit increased CDC and ADCC, whereas the more recently developed type II mAbs (for example, obinutuzumab) neither affect CD20 redistribution nor use CDC[48]. Instead, type II mAbs are glyco-engineered to have enhanced ADCC and mediate increased direct cell killing; new CD20-specific mAbs of both types have recently proved to be highly effective[48]. Based on single-agent efficacy in relapsed or refractory CLL, ofatumumab was approved for the treatment of advanced CLL and is undergoing Phase III trials for other leukaemias[49,50]. Recently, obinutuzumab was approved for newly diagnosed CLL because of its superiority to a standard rituximab-containing regimen in a randomized controlled trial[51].



Hodgkin Reed–Sternberg cells
(HRS cells). Neoplastic cells of B cell origin that serve as hallmarks of classical Hodgkin lymphoma. These cells have unusual morphology and a unique immunophenotype that does not resemble any normal cell in the body.

Bispecific T cell engagers
(BiTEs). Fusion proteins that are composed of two single-chain variable fragments, which are derived from a T cell-specific CD3-specific antibody and a tumour-targeting antibody, respectively.

Granzyme- and perforin-mediated tumour cytotoxicity
The principal mode of targeted cell killing by cytotoxic T cells (after antigen recognition on the surface of the target cell), whereby intracellular cytotoxic granules within T cells release their stores of perforin and granzymes to trigger apoptosis of the target cell.

Beyond CD20, other antigens unique to or over-expressed on malignant B cells have been targeted. CD52 is a surface antigen that is also expressed on T cells and monocytes. A humanized antibody targeting this antigen (alemtuzumab) was originally approved as a single agent for the treatment of fludarabine-refractory B cell CLL and then explored as a broadly immunosuppressive agent in non-myeloablative allo-HSCT conditioning regimens[52]. Another example is CD30 (also known as TNFRSF8), a surface antigen expressed by Hodgkin Reed–Sternberg cells (HRS cells) and by cells of other lymphoma subtypes, such as anaplastic large-cell lymphoma. In healthy individuals, its expression is restricted to activated T and B cells. Notwithstanding a long history of targeted strategies against CD30, potent clinical efficacy and favourable toxicity profiles were achieved only recently with the introduction of an antibody–drug conjugate, brentuximab vedotin[53,54].

Heretofore, mAbs have had no clinical impact in the treatment of multiple myeloma. However, two promising candidates have recently emerged. Elotuzumab is a humanized immunoglobulin G1 (IgG1) mAb that targets signalling lymphocytic activation molecule F7 (SLAMF7; also known as CS1), a surface glycoprotein that shows nearly universal expression in normal plasma and multiple myeloma cells and lower expression in NK cells[55]. Despite a Phase I study showing no objective responses to elotuzumab as a monotherapy[56], a long-term Phase I/II clinical trial reported a better outcome when it was used with a common combination regimen of the pleiotropic immunodulatory agents lenalidomide (BOX 3) and dexamethasone[57]: namely, >80% partial response rates and a prolonged progression-free survival benefit of 33 months in relapsed or refractory multiple myeloma. This combination is now under investigation in Phase III studies[57,58]. Daratumumab is a humanized mAb that targets CD38, another cell surface glycoprotein that is expressed in a range of haematological malignancies and has shown promising results in a Phase Ib/II dose-escalation study in heavily, previously treated patients with multiple myeloma. High response rates were observed above the pharmacokinetic effective dose, with no median progression-free survival reached at 6 months, thereby earning daratumumab a breakthrough-therapy designation from the US Food and Drug Administration (FDA)[58,59]. These encouraging single-agent data have stimulated multiple ongoing Phase II studies for the treatment of multiple myeloma, testing this agent both alone and in combination with other chemotherapeutics[58].

◀ Figure 1 | **Strategies of co-opting physiological immune programmes.** This figure summarizes the mechanisms observed in blood cancers of hijacking the physiological circuitry of their normal counterpart cells (left column) to drive tumour growth and manipulate endogenous immune responses (right column). Example malignancies are listed in the right column for each mechanism (row). **a** | An interleukin-7 (IL-7)-mediated signalling pathway drives physiological homeostatic proliferation of T cells via the IL-7 receptor (IL-7R). By contrast, by acquiring somatic mutations at one or more points throughout this pathway, blood cancers such as T cell acute lymphoblastic leukaemia (T-ALL) can drive autonomous signalling. **b** | A similar phenomenon occurs via the B cell receptor (BCR) signalling pathway, which is activated by multiple B cell malignancies through acquired somatic mutations in the gene encoding the BCR itself as well as by downstream components. **c** | The typical antigen-specific activation of T cells, which is mediated by peptide–major histocompatibility complex (MHC) complexes on professional antigen-presenting cells (APCs) in the physiological setting, contrasts with the lack of co-stimulation during antigen presentation by malignant cells, which can induce T cell anergy. **d** | The conventional role of high mobility group box 1 (HMGB1) as a 'danger' signal emitted by dying solid tumour cells that stimulates and attracts antitumour T cells is reversed in chronic lymphocytic leukaemia (CLL), in which HMGB1 may promote differentiation of monocytes into nurse-like cells (NLCs) to promote CLL cell survival *in vivo*. **e** | The duality of T helper 1 (T_H1) cell-led inflammation is shown in solid tumours. $CD8^+$, $CD4^+$ T and NK cells have tumour-destructive roles and are therefore often inhibited by mechanisms of tumour-induced immune suppression; regulatory T (T_{Reg}) cells have tumour-promoting activities. By contrast, in CLL, classical Hodgkin lymphoma (cHL), follicular lymphoma (FL) and multiple myeloma (MM), $CD4^+$ T_H1 and T_H17 cells, and macrophages are actively recruited by tumour cells and produce tumour-survival signals (such as IL-6); here, T_{Reg} cells have a potential antitumour influence. AML, acute myeloid leukaemia; DC, dendritic cell; DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; TCR, T cell receptor; TLR, Toll-like receptor.

Bispecific T cell engagers. Bispecific T cell engagers (BiTEs) may overcome the limitations of an immunosuppressive tumour microenvironment by directly linking cytotoxic T lymphocytes (CTLs) and their tumoricidal activity with the targeting platform of a mAb. Comprising dual specificities to a tumour surface antigen and to the CD3 signalling complex on T cells, BiTEs physically couple tumours and T cells, inducing T cell activation and proliferation along with granzyme- and perforin-mediated tumour cytotoxicity[60]. Thus, antitumour efficacy relies on passive recruitment of cytotoxic T cells to the tumour milieu and subsequent tumour eradication. Activation of a polyclonal CTL population can occur, as there is no requirement for MHC expression.

A quintessential example of this class is blinatumomab, a bispecific antibody that recognizes CD3 and the B cell-specific marker CD19 (REF. 60). Very encouraging clinical potency has been reported in Phase II studies in patients with B cell ALL (B-ALL) who are in haematological remission but with persistent minimal residual disease[61] and in patients with morphologically relapsed or refractory disease[62,63] (TABLE 1). As a result, the FDA has recently granted accelerated approval for blinatumomab for relapsed or refractory Philadelphia chromosome-negative B-ALL. Preliminary evidence suggests its efficacy in additional B cell malignancies[64], and further BiTE antibodies targeting CD3 and CD33 are awaiting clinical investigation in AML[65].

Boosting immune effector number and function

Direct expansion and availability of an increased number of functionally competent antitumour immune effectors represent an intuitively desirable therapeutic concept. Early evidence of the effectiveness of this strategy emerged from two clinical scenarios related to the post allo-HSCT setting (FIG. 2, blue boxes): DLI (BOX 1) for leukaemic relapse, and viral antigen-specific CTLs (BOX 4) for Epstein–Barr virus (EBV)-associated lymphoproliferative malignancies linked to impaired immune reconstitution and prolonged use of immunosuppressive medications. The successes in these arenas

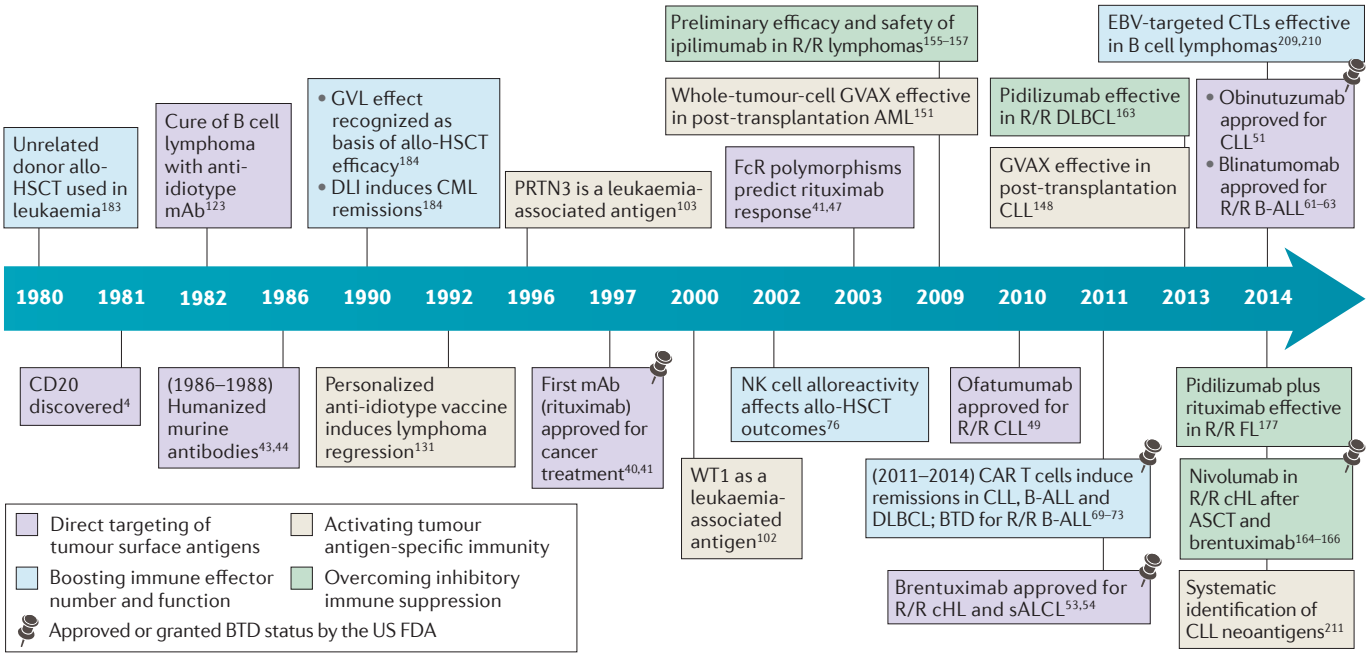


Figure 2 | **Timeline of major immunotherapeutic advances in haematological malignancies.** The figure depicts four areas of potential vulnerability in the tumour–immune relationship and the historical development of corresponding immunotherapies. Events in purple boxes emphasize the potency of immunological targeting of tumour surface antigens, primarily through monoclonal antibodies (mAbs). Events in blue boxes highlight the long-standing influence of boosting immune effectors on immunotherapy via donor lymphocyte infusion (DLI) and now encapsulated by chimeric antigen receptor (CAR) T cells. Events in beige boxes relate to the importance of activating tumour antigen-specific immunity. Events in green boxes underscore the potency of overcoming inhibitory immune suppression in the tumour microenvironment. Combining elements from these four separate nodes of cancer immunotherapy should yield promising therapeutic combinations. Allo-HSCT, allogeneic haematopoietic stem cell transplantation; AML, acute myeloid leukaemia; ASCT, autologous stem cell transplantation; B-ALL, B cell acute lymphoblastic leukaemia; BTD, breakthrough therapy designation; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CTLs, cytotoxic T lymphocytes; DLBCL, diffuse large B cell lymphoma; EBV, Epstein–Barr virus; FcR, Fc receptor; FDA, Food and Drug Administration; FL, follicular lymphoma; GVAX, vaccine comprised of cancer cells genetically modified to secrete granulocyte–macrophage colony-stimulating factor; GVL, graft-versus-leukaemia; NK cell, natural killer cell; PRTN3, proteinase 3; R/R, relapsed or refractory; sALCL, systemic anaplastic large-cell lymphoma; WT1, Wilms tumour protein.

have directly inspired and informed the growing field of ACT, and this is dramatically illustrated by chimeric antigen receptor T cells (CAR T cells). Other promising avenues that exploit this node include NK cell alloreactivity and stimulation of immune effector function by agonistic mAbs.

CAR T cells. ACT involves *ex vivo* manipulation of either naturally occurring or genetically engineered tumour-specific T cells that are subsequently infused into the patient. Two features are paramount to the success of ACT. First, insights gleaned from the study of the post-transplant immune milieu revealed that a preparative lymphodepleting regimen created 'space' for homeostatic expansion of the infused T cells. Mounting evidence from allo-HSCT and autologous stem cell transplantation (ASCT) preparative regimens suggests that increased levels of homeostatic cytokines (that is, IL-2, IL-15, IL-21 and IL-7) during the lymphopenic state accelerate the expansion of infused T cells[66] and promote an activated phenotype with enhanced effector functions[66,67]. Second, the selection of an antigen against which the infused T cells will be targeted is essential for direct, tumour-specific T cell-mediated killing: for example, virus antigens may be exclusively displayed on viral-associated malignant tissue as opposed to normal tissue (BOX 4).

CAR T cells, which have recently been shown to be clinically active, exploit synthetically engineered CARs to bridge the nodes of targeting tumour surface antigens and the boosting of effector functions. The specificity of these CAR T cells for a tumour surface molecule renders them independent of MHC restriction, enabling them to overcome tumour escape mechanisms such as disruption of antigen-presentation machinery.

The disappointing clinical efficacy of first-generation CARs led to the development of a second generation, which added intracellular signalling domains from co-stimulatory molecules — either CD137 (also known as TNFRSF9) or CD28 — to a CD19-targeting moiety[68]. In patients with relapsed or refractory CLL, infusion of low numbers of these second-generation CD19-targeted CAR T cells led to massive *in vivo* expansion, tumour killing and B cell aplasia. The long-term toxicity of B cell aplasia is an expected on-target, off-tissue result of the CD19-targeted CAR; currently, patients are supplemented with probably life-long intravenous immunoglobulin. Importantly, durable remissions over 2 years

Philadelphia chromosome
The defining translocation in chronic myeloid leukaemia between two genes on the long arms of chromosome 22 (*BCR*) and chromosome 9 (*ABL*), resulting in a novel fusion protein (BCR–ABL) that can be targeted by ABL kinase inhibitors, such as imatinib.

Chimeric antigen receptor
(CAR). A synthetically engineered receptor composed of a single-chain antibody fragment, to confer tumour recognition, coupled with intracellular signalling domains derived from the T cell receptor and a co-stimulatory molecule, most commonly either CD28 or CD137.

Table 1 | **Promising clinical immunotherapeutics for haematological malignancies**

Therapeutic class	Agents	Study	Patients	Comments	Clinical approval	Refs
Monoclonal antibody	Obinutuzumab	Phase III	Untreated CLL ($n = 781$)	Combination with chlorambucil, compared with combination with rituximab, increased PFS and showed MRD$^-$	In combination with chlorambucil for untreated CLL	51
	Daratumumab	Phase I/II	Relapsed or refractory MM ($n = 32$)	• 31% ORR in all patients • 67% ORR at target PK dose	FDA breakthrough therapy designation for relapsed or refractory MM	59
Bispecific T cell engager	Blinatumomab	Phase II	MRD$^+$ B-ALL ($n = 21$)	80% MRD$^-$	Relapsed or refractory Ph$^-$ B-ALL	61–63
			Relapsed B-ALL ($n = 36$)	69% CR or CRh		
			Relapsed or refractory B-ALL ($n = 189$)	43% CR or CRh		
Adoptive cellular therapy	CAR T cells	Phase I	Relapsed or refractory NHL ($n = 15$)	53% CR; 27% PR	FDA breakthrough therapy designation for relapsed or refractory B-ALL	69–73
			Relapsed or refractory B-ALL or T-ALL* ($n = 30$)	90% CR; 78% OS at 6 months		
			Relapsed or refractory B-ALL ($n = 16$)	88% CR or CRh		
	EBV-targeted CTLs	Phase II	High-risk disease ($n = 29$)	97% with NED at 3 years	Not approved	195, 196
			Relapsed or refractory EBV$^+$ NHL or HL ($n = 21$)	62% ORR; 52% CR		
In situ vaccination	Intratumoural TLR9 agonist and low-dose RT	Phase I/II	Indolent NHL ($n = 15$)	1 CR; 3 PR; 2 SD (but continually regressing)	Not approved	146
Multi-epitope vaccination	Whole-tumour-cell plus GM-CSF vaccination post RIC allo-HSCT	Phase I	High-risk MDS or AML ($n = 28$)	9 out of 15 in CR at 2 years	Not approved	148, 151
			Advanced CLL ($n = 22$)	88% OS at 2 years (for evaluable patients)		
Immune checkpoint blockade	Pidilizumab	Phase II	Relapsed or refractory DLBCL status post ASCT ($n = 66$)	51% ORR; 34% CR	FDA breakthrough therapy designation for relapsed or refractory HL status post ASCT and brentuximab (for nivolumab)	163
	Pidilizumab with rituximab	Phase II	Relapsed or refractory FL ($n = 32$)	52% CR		177
	Nivolumab	Phase I	Relapsed or refractory cHL status post ASCT ($n = 23$)	87% ORR; 17% CR		164

Allo-HSCT, allogeneic haematopoietic stem cell transplantation; AML, acute myeloid leukaemia; ASCT, autologous stem cell transplantation; B-ALL, B cell acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; CR, complete remission; CRh, complete remission with incomplete or partial haematological recovery; CTL, cytotoxic T lymphocyte; DLBCL, diffuse large B cell lymphoma; EBV, Epstein–Barr virus; FDA, US Food and Drug Administration; FL, follicular lymphoma; GM-CSF, granulocyte–macrophage colony-stimulating factor; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MRD, minimal residual disease; NED, no evidence of disease; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Ph, Philadelphia chromosome; PK, pharmacokinetics; PR, partial remission; RIC, reduced-intensity conditioning; RT, radiotherapy; SD, stable disease; T-ALL, T cell acute lymphoblastic leukaemia; TLR9, Toll-like receptor 9. *One patient had relapsed CD19$^+$ T-ALL.

were observed[69,70]. Multiple groups have reported similarly impressive clinical activities in other diseases: for example, B-ALL seems to be even more sensitive than CLL, with an 80% response rate across various CAR designs, clinical trials and institutions[68–71]. Very recently, CAR T cells using the CD137 co-stimulatory domain were shown to induce complete remissions in 90% of both adult and paediatric patients with relapsed or refractory ALL, with durable remissions in over two-thirds of patients[72]. Another group, using the CD28 co-stimulatory domain, demonstrated similarly impressive response rates, although the CAR T cell product was short-lived compared with the CD137-containing version[73]. Although these cells were insufficient for curative intent, the achieved complete remissions nevertheless enabled many patients to transition to allo-HSCT, the only potentially curative treatment. Finally, third-generation CARs that include two co-stimulatory molecules are currently being developed and tested[68].

The question of whether persistent engraftment *in vivo* is needed to prevent tumour relapse and the management of acute and long-term toxicities are two remaining key issues. Collectively, second-generation CAR T cells incorporating either CD28 or CD137 signalling domains persist *in vivo* for several months after adoptive cell transfer[68,70]. Studies comparing these two molecules in CAR designs are ongoing. The development of tumour lysis syndrome and cytokine release syndrome in most cases underlines the rapid kinetics of T cell expansion and tumour elimination; however, the severity of both can be lethal, and the precise role of anti-inflammatory agents such as corticosteroids and

CAR T cells
(Chimeric antigen receptor T cells). T cells that are isolated from patients' peripheral blood, genetically modified with CARs, and then activated and expanded *ex vivo* and subsequently infused back into the patient a few days after a lymphodepleting chemotherapeutic regimen.

Killer-cell immunoglobulin-like receptor
(KIR). Expressed on natural killer cells, this receptor recognizes self-major histocompatibility complex class I molecules and may be activating or inhibitory; as a result, natural killer cells preferentially kill target cells that lack self-MHC class I molecules (that is, KIR ligands).

tocilizumab (an IL-6-specific antibody) in treatment needs to be clarified[69]. Whether CARs can be modified to disappear after tumour elimination, thereby allowing B cell recovery, is under study. Finally, the expansion of CD19-negative tumour cells as a mechanism for relapse highlights the importance of considering multiple therapeutic targets on a tumour cell[72].

NK cell alloreactivity. In addition to T cells, NK cells have long been appreciated as contributors in the eradication of leukaemias and lymphomas[74]. Potent NK cell-mediated human antileukaemia activity emerged from studies that identified a remarkably low risk of relapse in a specific patient subgroup receiving allo-HSCT with T cell-depleted grafts. This subgroup consisted of patients with AML who exhibited mismatching of killer-cell immunoglobulin-like receptor (KIR) ligands with their donors (that is, in which donor NK cells failed to recognize recipient MHC class I molecules owing to mismatch) and hence benefited from donor NK cell alloreactivity, which killed recipient-derived leukaemic cells[75,76]. Another large study demonstrated distinct clinical outcomes associated with specific KIR genes, suggesting the relevance of prospective genotyping of activating, in addition to inhibitory, KIRs to improve outcomes after allo-HSCT[77]. Across studies, the benefit of KIR genotyping has been observed in AML, myelodysplastic syndrome and paediatric ALL — but interestingly not in adult ALL or chronic myeloid leukaemia (CML)[77–79], owing perhaps to differences in activating KIR ligand expression and/or whether T cells were depleted in the infused graft[80,81]. The safety, feasibility and engraftment of adoptively transferred allogeneic, IL-2-activated NK cells after a preparative lymphodepleting regimen have also been demonstrated, with encouraging results in a small group of patients with high-risk AML[82,83].

Agonist stimulation of immune effector function. The example of NK cells and KIRs highlights the clinical potency of modulating immune effector function through co-stimulatory and co-inhibitory receptors on the cell surface. In T cells, strong stimulation is delivered by surface CD28 binding to B7 family molecules, such as CD80 and CD86, both of which are expressed by APCs. However, therapeutic targeting of this interaction by 'super-agonistic' antibodies against CD28 sounded a dramatic alarm after the first-in-human clinical trial in healthy volunteers resulted in a cytokine storm and multisystem organ failure in some patients[84]. All patients survived; but clearly, manipulation of T cell co-stimulatory pathways requires clinical caution to avoid non-specific T cell activation.

Nevertheless, direct stimulation of immune effector function to promote tumour killing remains an attractive option. Agonist antibodies against CD40, CD137 and others have been tested in patients and did not show life-threatening toxicity, apart from severe hepatotoxicity noted with agonist antibodies against CD137, necessitating dose reduction and less-intense dosing regimens[85,86]. Thus far, few studies have examined the activity of agonistic mAbs in haematological malignancies. CD40-specific mAbs have notably shown promising efficacy and safety, although without a clear understanding of their antitumour mechanism, which may include tumour-specific T cell priming and activation[87,88], direct tumour cytotoxicity and macrophage activation[89,90]. CD137 is expressed in most haematopoietic cells and is an intriguing target that has critical T cell-independent activity. Agonistic mAbs targeting CD137 directly stimulated NK cell-mediated ADCC against lymphoma cells, synergizing with rituximab activity[91]. Phase I trials testing CD137-specific agonists with rituximab in non-Hodgkin lymphoma (NHL) are ongoing (ClinicalTrials.gov identifiers: NCT01307267 and NCT01775631).

Activating tumour antigen-specific immunity

Although surface antigens can serve as targets for antibody-based therapeutics, most cancer-associated or cancer-specific antigens are derived from intracellular proteins. The ability to specifically recognize the aberrant features of malignant cells and subsequently eliminate them while sparing normal host tissue is an attractive property of CTLs that is exploited by various cancer vaccination strategies. Together, the choice of antigen source, vaccine formulation, delivery system, adjuvant, immunomodulation, treatment schedule and treatment

Box 3 | **Immunological effects of non-immunotherapies**

Many therapies used to disable a tumour cell-intrinsic circuit that is crucial for proliferation have unexpectedly shown profound immunomodulatory function, falling into one of two main mechanistic categories: revoking oncogene-driven immune evasion, or 'off-tissue' effects of unintentionally modulating a tumour-associated pathway in immune cells. Both categories have been thoroughly reviewed[195], and hence we focus on examples relevant to haematological malignancies. The revoking of oncogene-driven immune evasion is illustrated in preclinical studies establishing the importance of antitumour immunity in oncogene addiction for many oncogenes, such as *MYC* in T cell acute lymphoblastic leukaemia[196], *BCR–ABL* in Philadelphia chromosome-positive B cell acute lymphoblastic leukaemia[196], *BRAF* in melanoma[197] and epidermal growth factor receptor (*EGFR*) in non-small cell lung cancer[198]. In chronic myeloid leukaemia, the combination of interferon-α2a and imatinib significantly increased the rate of molecular responses compared with each alone[199], and imatinib also synergized with donor lymphocyte infusion therapy to induce molecular remissions even in bulky, relapsed disease[200].

Therapies that unintentionally modulate a tumour-associated pathway in immune cells include a diverse group of immunomodulatory, targeted and cytotoxic agents. A classic example is thalidomide, a drug infamous for causing limb deformations and other birth defects when used during pregnancy. Although it was initially developed as an anti-angiogenic drug[201], thalidomide and more so its better-tolerated derivative lenalidomide have displayed highly potent activity in multiple myeloma, mantle cell lymphoma, chronic lymphocytic leukaemia (CLL) and myelodysplastic syndrome[202]. The immunomodulatory effects, in addition to the anti-angiogenic and cytotoxic effects, of this class of agents have long been suspected. However, these agents have only recently been shown to enhance E3 ubiquitin ligase degradation of Ikaros 1 and Ikaros 3, the former of which directly represses interleukin-2 (IL-2) transcription and production — ultimately leading to T cell and natural killer cell activation[203]. Moreover, lenalidomide antagonizes regulatory T cell function and repairs T cell synapse formation with CLL cells[204–206]. The PI3Kδ inhibitor idelalisib and the Bruton's tyrosine kinase inhibitor ibrutinib inhibit B cell receptor signalling (BOX 2) and are two examples of targeted therapies with unforeseen immunological effects. Idelalisib impairs a vital component of regulatory T cell suppressor function[207], and ibrutinib seems to inhibit several other kinases, including IL-2-inducible T cell kinase (ITK), which is essential for $CD4^+$ T helper 2 cells. ITK inhibition by ibrutinib seems to favour T helper 1 cell skewing and promote antitumour immunity[208].

Box 4 | **Targeting pathogens and cancer neoantigens**

Pathogens

The immune system effectively uses genetic variability, evolutionary selection and rapid population expansion to defend against the onslaught of viral and bacterial pathogens; tumour immunologists have long sought to harness this ability to attack malignant cells. Tumour antigens derived from foreign pathogens have historically provided the quintessential example of this concept. Post-transplantation lymphoproliferative disease (PTLD), Hodgkin lymphoma and non-Hodgkin lymphoma are strongly associated with Epstein–Barr virus (EBV) infection and therefore express unique EBV-derived antigens. The generation of cytotoxic T lymphocytes (CTLs) against EBV proteins has been highly feasible for PTLDs in haematopoietic stem cell transplantation recipients, with 80% response rates in refractory disease and complete prevention in high-risk individuals[209]. Autologous gene-modified antigen-presenting cells have also been impressively efficacious in stimulating CTLs against additional EBV antigens that share expression among most EBV-associated lymphomas (although an important exception is Burkitt lymphoma), with an 82% event-free survival rate at 2 years in the adjuvant setting for high-risk individuals and a 62% response rate in the relapsed or refractory setting, including many complete remissions[210]. Of note, therapeutic success seemed to elicit epitope spreading, as this phenomenon was completely lacking in those who failed to respond. That this procedure required minimal patient tissue (only 120 mL of peripheral blood) highlights its potential as a feasible immunotherapy.

Cancer neoantigens

The diversity of mutations in each tumour provides an even broader source of tumour-specific antigens. These neoantigens are novel immunogenic epitopes that are uniquely expressed by the malignant cells and arise from genetic alterations of protein-coding regions within the tumour. This antigen class may be targeted efficiently (that is, lack of central tolerance) and safely (that is, no risk of autoimmunity induction) by immunotherapy. The development of next-generation sequencing technologies that enable rapid identification of the complete repertoire of non-synonymous mutations within a tumour has brought a breath of fresh air to this promise, and a pipeline for designing personalized vaccines was recently developed for the treatment of chronic lymphocytic leukaemia[211]. Indeed, a patient-specific multi-epitope cancer vaccine is a highly attractive direction for cancer immunotherapy, serving to focus immunity against truly tumour-restricted epitopes that may be predicted by advanced human leukocyte antigen class I peptide-binding prediction algorithms[212]. Two clinical trials have been initiated to assess the concept of personalized neoantigen vaccines in patients with melanoma (ClinicalTrials.gov identifiers: NCT01970358 and NCT02035956), and additional trials across other cancers, including in the blood malignancies, are planned.

setting shape the quality and strength of a cancer vaccine-induced T cell response[92,93]. Three features unique to the haematological malignancies afford opportunities to effectively investigate novel vaccination strategies (FIG. 2, beige boxes): the discovery of multiple blood malignancy antigens; the ability of tumour cells to serve as both APCs and a source of antigens; and the reconstitution of immune-competent T cells in the post-HSCT lymphopenic milieu.

The targeting of individual tumour antigens selective to the blood malignancies. In haematological malignancies, many examples of prominent tumour-selective antigens have been clinically assessed: Wilms tumour protein (WT1), which is present in $CD34^+$ haematopoietic progenitor cells and many acute leukaemias[94,95]; the azurophilic granule protein proteinase 3 (PRTN3; also known as myeloblastin), which is overexpressed in myeloid leukaemia blasts[96]; and the receptor for hyaluronic acid-mediated motility, which is differentially expressed in various leukaemias and lymphomas[97,98]. Evidence for their immunogenicity came both from the identification of spontaneous T cell responses against antigen-specific epitopes that preferentially killed leukaemic cells and from their association with longer overall survival or disease remission after allo-HSCT or other therapies[99–103]. These observations suggested that boosting these pre-existing immune responses was feasible through active immunotherapy.

Early promising studies using peptide vaccination demonstrated that functional leukaemia-reactive CTL responses directed against single antigens could contribute to the control of leukaemic blasts in some patients and were associated with clinical benefit[104–108]. The detection of antigen-specific T cell responses early after a single vaccine dose indicated the expansion of pre-existing leukaemia-reactive memory $CD8^+$ T cells[109–111]. Subsequent efforts to generate a more sustained immune response led to studies combining human leukocyte antigen (HLA) class I- and/or class II-restricted WT1 and PR1 (a specific PRTN3-derived peptide) epitopes as immunogens[111–114] to potentiate $CD4^+$ T_H cells. These efforts revealed the transient, dysfunctional nature of high-avidity peptide-specific $CD8^+$ T cell responses generated by vaccination — possibly explaining the lack of correlation between immune and clinical responses observed in several recent follow-up trials[111–113]. Although peripheral tolerance mechanisms could have impaired the function and *in vivo* expansion of high-avidity T cells[96,107,113], suboptimal presentation of immune-dominant epitopes by APCs could also have contributed[115]. Various vaccination studies focusing on WT1 have thus used direct antigen loading of autologous dendritic cells to activate them *ex vivo*; these studies have reported promising clinical data alongside biological activity[116,117].

As an alternative to tumour-selective antigens, vaccination against tumour-specific neoantigens arising from malignancy-defining genetic alterations (BOX 2) has been pioneered in the blood malignancies. This idea was extensively tested in CML using breakpoint junction-derived peptides from the BCR–ABL fusion oncoprotein; although Phase I/II studies demonstrated

Idiotype vaccine
A cancer vaccine that targets the unique antigenic determinant located in the variable region of the B or T cell receptor that is expressed by clonally expanded malignant B or T cells, respectively.

induction of peptide-specific immune responses as well as reductions in *BCR–ABL* transcripts, they failed to prove a clear clinical benefit for vaccinated patients over other treatments[118–121]. Indeed, recently, the immunogenicity of BCR–ABL breakpoint-derived peptides was called into question[122]. Concurrently, inspired by a case report of complete remission of a B cell lymphoma after infusion of a monoclonal anti-idiotype antibody[123], a personalized vaccination approach directed against this prototypic lymphoma neoantigen — the idiotypic determinant of malignant B cell-derived immunoglobulin, or idiotype vaccine — revealed highly encouraging results in Phase I/II trials[124–127]. However, only one of three Phase III trials[128–130] demonstrated prolonged disease-free survival[129] (but this trial failed to achieve its primary clinical end points). The observed failures have been attributed to flaws in trial design, such as imbalances in standard prognostic scores between treated and control arms as well as enrolment of patients lacking sustained partial or complete remissions. Thus, the value of idiotype vaccines in conjunction with current rituximab-containing regimens remains to be determined[131,132].

Whole tumour cells as APCs and a source of antigens. As the normal cellular counterpart of several blood malignancies is an APC, some clinical vaccination trials have leveraged the antigen-presentation capacity of the tumour cell to stimulate tumour-specific immunity. For example, in CML and AML, *in vitro* differentiation of myeloid leukaemic blasts into leukaemia-derived dendritic cells results in preservation of the expression of some relevant cancer antigens that could stimulate leukaemia-specific T cell populations[133–136]. Another whole-tumour-cell-based approach exploits the unique capability of activated B cell lymphoma cells to present their own tumour antigens via HLA class I and II molecules in the presence of co-stimulatory molecules. Specifically, malignant B cells can be activated through ligation of CD40 by its ligand CD40L (also known as CD154), which can be provided either by *ex vivo* admixture with CD40L-expressing cells[137,138] or by engineering lymphoma cells themselves to express CD40L[139,140].

In general, inducing broader polyclonal antitumour immune responses against multiple cancer antigens may be more effective than targeting a single antigen. Autologous tumours are a ready source of personal tumour antigens and have been tested as immunogens using formulations such as autologous dendritic cells pulsed with tumour lysate[141,142] or apoptotic tumours[143], and tumour cell–dendritic cell hybrids (that is, multiple myeloma cells chemically fused with autologous dendritic cells)[144,145]. These dendritic cell-based vaccines have demonstrated potent cellular tumour-specific responses and objective clinical outcomes[141–145]. However, obstacles such as high cost, labour-intensive processes and the difficulty of optimizing protocols for dendritic cell maturation and administration limit the development of these vaccination strategies[115].

Recruitment of APCs and their ensuing capture of tumour antigens in the tumour bed are vital for subsequent successful T cell priming in draining lymph nodes. One approach for intratumoural activation of APCs in patients with accessible tumour sites is *in situ* tumour vaccination. Intratumoural injection of a Toll-like receptor 9 agonist in combination with low-dose radiotherapy in patients with relapsed B cell lymphoma led to impressive clinical outcomes[146,147]. Still other whole-tumour-cell vaccination approaches have incorporated adjuvant cytokines, particularly granulocyte–macrophage colony-stimulating factor (GM-CSF), to recruit APCs to the vaccination site. An 'off-the-shelf' allogeneic whole-tumour-cell vaccine, derived from the HLA-negative K562 human cell line that was engineered to secrete GM-CSF (GM-K562 vaccine)[148,149], expresses several CML-associated antigens[150]. Treatment of patients with CML — who had measurable disease despite continued therapy with the tyrosine kinase inhibitor imatinib — with the GM-K562 vaccine led to a decline in *BCR–ABL* transcript levels in all patients and in disease burden in 13 out of 19 participants[150]. Finally, administration of lethally irradiated autologous whole tumour cells that were genetically modified to secrete GM-CSF, or admixed with GM-CSF-secreting bystander cells, has achieved significant immunological and clinical responses in both AML and CLL[148,150,151]. Overall, these highly encouraging results suggest the superiority of a multi-epitope vaccination strategy over the use of single tumour antigens in improving immunological treatment of haematological malignancies, but this notion requires further investigation in larger randomized trials.

The post-HSCT setting as a platform for vaccination. The increased frequencies of CTLs targeting WT1, PRTN3, BCR–ABL or recipient minor histocompatibility antigens after allo-HSCT suggested that the post-transplantation period could 'reset' cancer–immune relations, enhancing the GVL effect and marking an ideal setting for cancer vaccination. In addition to lymphopenia and associated growth-promoting cytokines, vaccine responses may be aided by T_{Reg} cell depletion and minimal residual disease states that diminish tumour-induced immune suppression[152]. Equally important is reconstitution of immune-competent donor T cells not previously tolerized to the recipient's leukaemia. Indeed, administration of an autologous GM-CSF-secreting vaccine in the early post-HSCT period resulted in a statistically significant 2-year survival advantage compared with historical controls in patients with AML or myelodysplastic syndrome[151]. Notably, in patients with advanced CLL, co-injection of irradiated autologous tumour cells and the GM-K562 vaccine in the early post-HSCT period led to a rise in circulating CLL-specific (rather than alloreactive) $CD8^+$ T cells as well as favourable clinical activity[148]. These observations affirm the strategic therapeutic scenario of the post-transplantation immunological milieu.

Regulatory B cells
(B_{Reg} cells). A newly described subpopulation of B cells that remains incompletely defined in humans. B_{Reg} cells have been suggested to functionally resemble chronic lymphocytic leukaemia cells in humans and contribute to rituximab resistance in preclinical models.

Myeloid-derived suppressor cells
(MDSCs). A highly heterogeneous population of tolerogenic myeloid-derived cells often described in either granulocytic or monocytic subtypes. MDSCs have been strongly implicated in the pathogenesis of many blood malignancies, including multiple myeloma, chronic myeloid leukaemia and myelodysplasia.

CTL-associated antigen 4
(Cytotoxic T lymphocyte-associated antigen 4). CTLA4 is exclusively expressed on the surface of activated T cells, where it counteracts CD28 both by outcompeting it for its ligands, CD80 and CD86, on antigen-presenting cells and by triggering intracellular inhibitory pathways. It has an important role in maintaining immune homeostasis.

Smouldering multiple myeloma
Early-stage multiple myeloma preceding the active, clinically symptomatic phase.

Overcoming inhibitory immune suppression

The tumour immunology field has recently been reinvigorated by the development of reagents that relieve inhibitory immune suppression within the microenvironment (FIG. 2, green boxes). The impressive activity of immune checkpoint inhibitors across many types of malignancies has underscored the crucial immune-dampening roles of multiple immunosuppressive elements within the tumour milieu, including co-inhibitory molecules, T_{Reg} cells, regulatory B cells (B_{Reg} cells) and myeloid-derived suppressor cells (MDSCs).

Co-inhibitory molecules. Immune effector activity is finely tuned by the net output of activating and inhibitory signals known as immune checkpoints. To date, the most clinically well-studied immune checkpoints are two co-inhibitory receptors: CTL-associated antigen 4 (CTLA4; also known as CD152) and PD1 (extensively reviewed in REFS 1,153). Both receptors function predominantly to inhibit T cell responses and dampen T cell activation.

CTLA4 was the first co-inhibitory molecule to be clinically targeted. In haematological malignancies, ipilimumab, a CTLA4-specific mAb with FDA approval for treatment of metastatic melanoma[154], has been studied to a limited extent. Phase I studies have demonstrated its antitumour activity in relapsed and refractory B cell lymphoma after chemotherapy or after allo-HSCT[155,156]. Interestingly, although three clinical responses and multiple incidents of organ-specific adverse immune events were noted in the allo-HSCT trial, no graft-versus-host disease (GVHD) was observed in any of the patients. This large therapeutic window may be attributed to the relatively prolonged time between the last donor cell infusion and ipilimumab administration, suggesting an opportunity for immunomodulation in the post-transplantation setting[156]. Very recent preliminary data from a similar Phase I study of ipilimumab after allo-HSCT have also suggested both efficacy and tolerability in this patient population[157].

PD1 is an immunoinhibitory receptor that induces T cell suppression through a unique state of T cell dysfunction termed 'exhaustion' on ligand binding. First described in chronic viral infections, T cell exhaustion has been increasingly recognized as an important immune-evasive strategy in many haematological malignancies[158–161]. Antibodies targeting the PD1–PD1 ligand 1 (PDL1) interaction have evoked impressive antitumour activity in various types of solid tumours[1,162]. A growing body of clinical evidence also strongly supports anti-PD1 activity in haematological malignancies. A highly promising Phase II trial testing the role of pidilizumab, a humanized IgG1 PD1-specific mAb, in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after ASCT reported a response rate of 51% in those patients with residual disease after ASCT and a complete remission rate of 34%[163]. As in previous Phase I trials of this antibody, toxicity was minimal. Nivolumab, a humanized IgG4 PD1-specific mAb, recently demonstrated significant response rates in relapsed or refractory cHL, with close to 90% of patients responding to therapy[164]; similar preliminary results were seen with another PD1-specific antibody, pembrolizumab[165]. Preliminary results from a study of nivolumab in multiple relapsed or refractory lymphoid (B and T cell) malignancies indicated response rates across the range of lymphomas, with more than one-third of patients with DLBCL and follicular lymphoma responding to therapy[166]. As a result, nivolumab was granted breakthrough therapy status by the FDA as a treatment for Hodgkin lymphoma after failure of ASCT and brentuximab therapy. Altogether, these data highlight the impressive therapeutic opportunity for modulation of T cell co-inhibitory molecules in haematological malignancies and suggest that targeting of additional co-inhibitory T cell receptors, such as the T cell immunoglobulin and mucin domain 3 (TIM3; also known as HAVCR2) and lymphocyte activation gene 3 protein (LAG3), could also be clinically effective[153,167]. The recent combined blockade of both PD1 and CTLA4 has resulted in impressive clinical response rates in melanoma, further driving excitement for combinations in this therapeutic class[168].

KIRs are another promising set of inhibitory molecules; as described above, they function as inhibitory receptors to guide NK cell activity away from self-MHC-expressing cells. Lirilumab is an IgG4 mAb that specifically binds to a common set of inhibitory KIRs expressed on half of the total NK cell population; a first-in-human study in elderly patients with AML in first complete remission showed that lirilumab was safely tolerated. Moreover, the observation of a significantly increased overall survival rate in patients treated at higher doses indicated a potential dose–response effect[169]. In multiple myeloma, a Phase I trial confirmed safety and disease stabilization for one-third of patients; however, a recent Phase II study in smouldering multiple myeloma closed early owing to a lack of any clinical efficacy[170,171]. Nevertheless, given compelling clinical data in allo-HSCT and a generous safety window, KIR-specific antibodies will probably play a part in stimulating antitumour NK activity within haematological malignancies.

T_{Reg} cells, B_{Reg} cells and MDSCs. In addition to co-inhibitory molecules, cellular elements within the tumour microenvironment, particularly T_{Reg} cells, B_{Reg} cells[172] and MDSCs, mediate local immune suppression. Currently, few effective agents specifically target these cell types. Denileukin diftitox is a chimeric immunotoxin that is formed by conjugating a diphtheria toxin fusion protein to IL-2 and targets the IL-2 receptor (CD25), which is highly, but not selectively, expressed on T_{Reg} cells. Although approved by the FDA for cutaneous T cell lymphoma, with objective response rates ranging from 30 to 44%, its precise mechanism of action remains poorly understood, and its parent company has ceased production[173,174]. Ipilimumab may also function by intratumoural T_{Reg} depletion, but this mechanism has yet to be formally demonstrated in patients[175,176]. Finally, T_{Reg} cell depletion *ex vivo* from adoptive cellular infusions is discussed below in the context of targeting multiple immunotherapeutic nodes. Immunomodulation of T_{Reg} cell, B_{Reg} cell and MDSC function is therefore a potent therapeutic opportunity in haematological malignancies.

NK T cells
(Natural killer T cells). A specialized subset of innate-like T cells that recognize lipid-based antigens presented by the CD1 family of major histocompatibility complex-like molecules and rapidly produce very large amounts of various cytokines without clonally expanding like 'classical' T cells.

Combinations, timing and future directions

Each of these four immunotherapeutic nodes constitutes a critical aspect of the tumour–immune relationship and is thus an exciting therapeutic opportunity for intervention. However, the essential feature of the immune system — that distinct immune effectors act in a coordinated manner to diminish, amplify and/or focus a response — naturally suggests a multi-pronged approach. In fact, these strategies have been pursued with preliminary success. For example, a Phase II trial in patients with relapsed follicular lymphoma treated with the combination of rituximab and pidilizumab found a high complete response (CR) rate of 52%, comparing favourably with historical data suggesting CR rates near 11%[177,178]. Importantly, this combination was very well tolerated. Similarly, T_{Reg} cell depletion before NK cell infusion improved median duration of CR in patients with high-risk AML compared with historical controls who received NK cell infusions without T_{Reg} cell depletions[179].

Another opportunity for immune intervention is the targeting of 'early' neoplastic lesions. Because increasing genomic complexity and tumour burden facilitate immune escape and immunotherapeutic resistance, exploiting early immune recognition may have a substantial therapeutic impact. Multiple myeloma is a model example: in patients with monoclonal gammopathy of undetermined significance (a multiple myeloma precursor lesion), T cells specific to a stem cell-associated antigen expressed on myeloma progenitor cells were enriched in the bone marrow and strongly predicted reduced risk of progression to multiple myeloma[180]. Furthermore, in a small patient cohort, a combination of lenalidomide (BOX 3) and an activating ligand for NK T cells elicited activation of multiple immune subsets and durable tumour regression in patients with smouldering multiple myeloma[181]. Thus, careful study of immune interactions with precursor lesions may uncover novel therapeutic avenues.

The growing arsenal of immune therapies, with increasing awareness of the immunological consequences of non-immunotherapies (BOX 3), can be further complemented by the discovery and implementation of biomarker strategies. Haematological malignancies, which have been at the forefront of immunotherapeutic innovation for decades, again offer ample opportunity to study well-characterized immune interventions with easily accessible tissue from malignant and infiltrating immune cells. Indeed, recent interrogation of gene expression profiles within marrow-infiltrating T cells before and after DLI in patients treated for relapsed leukaemia after allo-HSCT suggested T cell exhaustion as a potential marker and mechanism of DLI responses[182]. Similar studies with newer agents could unlock molecular signatures predicting response and thereby pair patients with the correct choice (or choices) of immunotherapy. Indeed, the advent of next-generation sequencing technologies offers a more intelligent approach. Molecular signatures generated from both tumour and infiltrating immune cells may identify patient-specific tumour-induced immune defects. Judicious application of these signatures can thus enable the tantalizing possibility of accurately individualizing cancer immunotherapies for patients.

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Acknowledgements
P.B. was supported by the US National Cancer Institute under award number T32CA009172. U.E.B. acknowledges support from the German Research Foundation (Deutsche Forschungsgemeinschaft; BU 3028/1-1). C.J.W. is supported in parts by grants NHGRI (U54HG003067), NCI (1RO1CA155010-02) and NHLBI (5R01HL103532-03); the Blavatinik Family Foundation; and the Leukaemia and Lymphoma Translational Research Program. C.J.W. is a recipient of an Innovative Research Grant for Stand Up to Cancer/AACR. The authors thank E. Fritsch, J. Ritz, R. Soiffer and P. Ott for valuable feedback on and discussion of this manuscript.

Competing interests statement
The authors declare competing interests: see Web version for details.

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