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Hematologic malignancies: at the forefront of immunotherapeutic innovation

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Abstract

The recent successes of cancer immunotherapy have stimulated interest for the potential widespread application of these approaches; hematologic malignancies have provided both initial proofs-of-concept and an informative testing ground for a variety of immune-based therapeutics. The immune-cell origin of many of the blood malignancies provides a unique opportunity to both understand the mechanisms of human immune-responsiveness and immune-evasion as well as to exploit the unique therapeutic opportunities they provide.

Introduction

Hematologic malignancies provided the earliest effective application of antitumor immunotherapeutic approaches – ranging from adoptive cellular transfer 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 anti-tumor responses and the tumor microenvironments within which they operate. These trailblazing investigations in monoclonal antibodies and adoptive cellular transfer have long provided beacons of hope that immunotherapeutic approaches could be broadly applicable across neoplasms. Recently, checkpoint blockade inhibitors, pioneered within various solid tumors¹, have also shown considerable promise in 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 interrelated vulnerabilities in the cancer-immune relationship.

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Enabling features of hematologic malignancies

A key clinical feature of the blood malignancies is their immune responsiveness. Paralleling the early successes of chemotherapy for the treatment of blood malignancies were the spontaneous tumor regressions within lymphomas^{2, 3} and durable remissions of leukemias following allogeneic hematopoietic stem cell transplantation (allo-HSCT). Indeed, the efficacy of allo-HSCT derives largely from the graft-versus-leukemia effect (GvL), a donor-derived immune eradication of malignant cells (see BOX 1). Studies exploring the GvL effect have highlighted the dramatic ability of the human immune system to specifically and effectively eliminate cancer.

Box 1

Allo-HSCT: The first cancer immune therapy

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) comprises a rare combination of immune, stem cell and personalized therapies that can eliminate otherwise incurable hematologic malignancies¹⁸². Developed more than 50 years ago, allo-HSCT allowed the delivery of high doses of radiation and chemotherapy, enabling higher tumor kill at the expense of permanent bone marrow suppression. Donor HSCs were infused to engraft and repopulate all elements of the hematopoietic system. Over the past three decades, a large body of clinical experience and laboratory studies has demonstrated that reconstitution of donor immune cells plays a critical role in the elimination of recipient tumor cells (the GvL effect) through both *cellular* and *antigenic* determinants: 1) engraftment permits nontolerant immune cells to reject recipient tumor and 2) major and minor histocompatibility antigens (in addition to tumor-associated antigens) distinguish recipient from donor, further driving GvL (and in many patients graft-vs-host disease or GvHD). The earliest direct evidence for the potency of the GvL effect stemmed from the post allo-HSCT setting in which donor lymphocyte infusions (DLI) alone, in the absence of chemotherapy or radiation, induced dramatic responses and enduring remissions of relapsed hematologic malignancies, particularly chronic myelogenous leukemia (CML)¹⁸³.

Separating GvL from GvHD

A challenging complication of both DLI and allo-HSCT is GvHD wherein donor lymphocytes recognize alloantigens expressed on normal host tissue (e.g. skin, gastrointestinal tract, liver) leading to organ damage and dysfunction. Efforts to identify the cellular and antigenic determinants that divorce GvL from GvHD have driven much of the progress in HSCT by highlighting the central role of various T cell subsets, natural killer cells, and B cells as well as identifying tumor-specific antigens such as WT1, PR3, and BCR-ABL. Moreover, these advances in understanding the GvL effect have informed a founding rationale for current immunotherapeutic approaches such as adoptive cellular therapy and chimeric-antigen receptor T cells¹⁸⁴ (see text). Future directions of investigation within allo-HSCT include identifying antigens and cellular effectors that exclusively drive GvL and not GvHD. Finally, the immediate

posttransplantation state provides an effective clinical and immunologic setting for interrogating novel vaccine approaches (see text).

Over time, these experiences provided a clinically relevant backdrop to dissect and test the essential ingredients of effective anti-tumor immunity. Several key features of the blood malignancies enabled these studies. First, in addition to their immune-responsiveness, the relative ease of tumor and normal tissue sampling facilitated the extensive characterization of cellular surface markers defining the normal hematopoietic lineage. This unique delineation of cellular hierarchy could discriminate normal from malignant immune cells and furnish potential therapeutic targets, such as CD20⁴. Second, the clinical use of allo-HSCT and donor lymphocyte infusion (DLI) led to well-defined immune-based anti-cancer responses in humans. The ability to directly sample relevant tissues before and after immunotherapy, in turn, have aided the identification and interrogation of critical anti-tumor immune components, such as cellular effectors and expression of specific tumor antigens.

Finally, a feature inherent to hematologic malignancies is their cellular and immune sites of origin. For many blood malignancies, their cellular origins as **professional antigen-presenting cells (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 remodeling the sites of residence and natural nurturing grounds of various 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 leukemic or lymphoma cells to immune cells at these immune-priming sites creates unique tumor-immune interactions with the potential for either inciting effective anti-tumor cellular immunity or, as discussed in Section II, co-opting these responses for malignant growth.

Subversion of physiologic immune programs

As corruptions of normal hematopoiesis, myeloid and lymphoid neoplasms harbor the ability to co-opt the normal physiologic circuitry of immune cells. Blood malignancies can subvert these normal homeostatic signals to (i) drive tumor growth (BOX 2; Fig 1A,B) and/or (ii) manipulate endogenous immune responses. Understanding these strategies may illuminate key pathways for therapeutic modulation.

Box 2

Driving tumor growth through subversion of homeostatic pathways

T and B lymphocyte proliferation 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)** signaling pathway critically contributes to the progression and chemotherapeutic resistance of human T-cell acute lymphoblastic leukemia (T-ALL) (see Fig 1A).¹⁸⁵ In fact, somatic gain-of-function mutations in multiple components of this pathway have been found in both pediatric and adult T-ALL, suggesting the perversion by T-ALL of its normal counterpart's homeostatic regulator¹⁸⁶.

Numerous studies have further suggested a similar growth-promoting role for this pathway in multiple B-cell malignancies¹⁸⁷. Intriguingly, while inhibition of the IL-7-driven PI3K/Akt/mTOR signaling pathway attenuates proliferation in both T-ALL and healthy T cells, only T-ALL cells undergo apoptosis^{188, 189} – suggesting a new therapeutic opportunity based on understanding the hijacking of a physiologic immune program¹⁸⁵.

As another illustration of how the malignant process can subvert normal physiologic immune responses, certain mature B cell malignancies have evolved to constitutively activate B-cell receptor (BCR) signaling even in the absence of cognate antigen (see Fig 1B)¹⁹⁰. Chronically active BCR signaling further drives the pathobiology of the activated B-cell-like (ABC) subset of diffuse large B-cell lymphoma (DLBCL), evidenced by somatic gain-of-function mutations within the BCR signaling pathway¹⁹¹. The recent reports of dramatic responses in DLBCL, CLL and mantle cell lymphoma to pharmaceutical inhibition of Bruton's tyrosine kinase (BTK), a kinase critical for BCR activation, further clearly demonstrate the potency of targeting these homeostatic subversions^{192, 193}.

Figure 1 depicts several modes by which malignant blood cells may manipulate conventional anti-tumor immune mechanisms to induce a pro-growth tumor microenvironment. Antigen presentation, the induction of immunogenic cell death, and an inflammatory microenvironment each constitute crucial components for generating an effective anti-tumor immune response that is subverted in the process of blood cancer growth. As corrupted professional APCs, many blood malignancies may recapitulate the peripheral tolerance mechanisms of their physiologic counterparts (Fig 1C). Professional APCs promote, or “license,” antigen-specific T cell proliferation and activation in the presence of costimulatory molecules and tolerance or anergy in their absence. Indeed, studies have shown that low level expression of costimulatory molecules by pre-B ALL and acute myeloid leukemia (AML) cells induces antigen-specific T cell tolerance^{6–8}. Utilization of this paradigm, however, varies among blood malignancies. For example, many B-cell lymphomas have divested themselves entirely of their self-antigen presentation machinery through recurrent mutations in b2-microglobulin, an important subunit of major histocompatibility complex (MHC) class I molecules, or deletions of MHC class II genes on chromosome 6^{9, 10}.

Along with manipulation of antigen-presentation pathways, blood malignancies may also co-opt mechanisms normally associated with immunogenic cell death (Fig 1D). Successful chemotherapeutic response derives partly from induction of novel, or reactivation of pre-existing, antitumor immune responses recruited by ‘danger’ signals emitted by cancer cells during drug-induced apoptosis¹¹. One such danger signal is **high mobility group box 1 (HMGB1)**¹². In chronic lymphocytic leukemia (CLL), however, leukemia cells appear to co-opt the immunostimulatory activity of secreted HMGB1 to create a protective microenvironment. HMGB1 plasma concentration 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 a tumor-promoting activity.

A Th1-led, inflammatory tumor microenvironment, typically (though not always) associated with effective anti-cancer immunity¹⁵, may actually promote neoplastic expansion within hematologic malignancies (Fig 1E). Many B cell lymphomas exemplify this paradigm via 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 in CLL patient-derived xenograft models uniquely require robust expansion of autologous CD4+ T cells.^{13, 18} Likewise, in classical Hodgkin's lymphoma (cHL), an activated, proliferative and inflammatory T cell infiltrate with a Th1 phenotype has been identified¹⁹. Both follicular lymphoma (FL) and gastric MALT lymphoma cells depend on T cell contact for proliferation^{20, 21}, and multiple studies have also illustrated the ability of FL to remodel and 're-educate' the lymph node microenvironment by inducing changes in T cell gene expression profiles²², polarizing monocytes into tumor-associated macrophages²³, and recruiting follicular dendritic cells²⁴. This critical heterogeneity of the B cell lymphoma microenvironment has been recently reviewed²⁵. Multiple myeloma (MM) further typifies this paradigm; primarily housed within bone marrow, MM cells have a protective network of extracellular matrix proteins, adhesion molecules, stromal cells, osteoclasts, and other immune cells²⁶. As in CLL, macrophages provide support to MM cells through inflammatory cytokines such as interleukin-6 (IL-6)²⁷ that are essential for MM survival and proliferation²⁸. MM cells also hijack the CD28 T cell co-stimulatory receptor to bind CD80/86 on dendritic cells (DCs), inducing autocrine pro-survival signals, DC production of IL-6, and DC-mediated protection against chemotherapy-induced apoptosis *in vivo*^{29, 30}. Moreover, Th17 T cells significantly contribute directly to MM cell growth and indirectly to a permissive microenvironment^{31, 32}.

The active recruitment of an inflammatory microenvironment by so many hematologic malignancies may explain the unexpectedly positive prognostic benefit ascribed to infiltrating **regulatory T cells (Tregs)**. While tumor infiltration by Tregs strongly associates with worse clinical outcomes in many solid tumor malignancies^{33, 34}, studies in FL, cHL and T cell neoplasms have, conversely, identified a clinical benefit^{35–38}. How are Tregs fostering tumor development in one context and impeding its growth in another? While no definitive answers exist, Tregs may suppress lymphoid cancer cells directly or indirectly by inhibiting tumor-promoting inflammatory responses in the microenvironment. Consistent with this scenario, increased immune-inhibitory PD-1 expression by FL-infiltrating lymphocytes favorably impacts clinical outcomes.³⁹ Together, these observations suggest that hematologic malignancies recruit an inflammatory microenvironment that enhances their growth and dissemination.

Four major nodes of cancer immunotherapy

The historically close relationship between cancer immunity and hematologic malignancies has motivated, over decades, a varied landscape of clinically relevant cancer

immunotherapeutics targeting each of 4 major nodes of potential vulnerability in the cancer-immune relationship: (1) direct targeting of surface tumor antigens; (2) the boosting of immune effector number and function; (3) activating tumor antigen-specific immunity; and (4) overcoming inhibitory immune suppression. This broad landscape strongly suggests the blood cancers as an exceptional opportunity to simultaneously address and leverage multiple components of the anti-tumor immune response (Figure 2) (Table 1).

Direct targeting of surface tumor antigens

The ability to define lineage markers in the hematopoietic tissue hierarchy enabled the isolation of blood cell subsets and, in turn, the identification of subpopulation-specific surface antigens (Figure 2.1). The B cell marker CD20 is an archetypal example of a clinically feasible target that led to the development of the monoclonal chimeric anti-CD20 antibody rituximab, a standard component in the clinical management of B-cell malignancies, increasing cure rates with only minimal toxicity^{40, 41}. By providing proof-of-concept that simply targeting a surface tumor antigen is sufficient for cancer cell elimination, its success has fueled the development of other tumor-targeting monoclonal and bi-specific antibodies.

Monoclonal antibodies (mAbs)

The specificity of humoral immunity was long recognized to be therapeutically advantageous and led to the development of mouse monoclonal antibodies. However, this approach was broadly successful only once the barrier of xenogeneic-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 appear to elicit tumor destruction through antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADP), and/or complement-dependent cytotoxicity (CDC) via engagement of Fcγ or complement receptors on NK cells, macrophages and neutrophils; or indirectly by inducing adaptive immunity via Fc receptor-pathway dendritic cell-mediated enhancement of antigen presentation^{45–47}.

Anti-CD20 mAbs can be divided into two groups based on *in vitro* mechanisms of action. Type I antibodies (e.g. rituximab, ofatumumab) redistribute CD20 into large lipid rafts in the cell membrane and exhibit increased CDC and ADCC activity while the more recently developed type II mAbs (e.g. obinituzumab) neither affect CD20 redistribution nor utilize CDC⁴⁸. Type II mAbs, however, are glyco-engineered to have enhanced ADCC activity and mediate increased direct cell killing; new anti-CD20 mAbs of both types have recently proven highly effective⁴⁸. Based on single-agent efficacy in the relapsed/refractory setting of CLL, ofatumumab was approved for treating advanced CLL and is undergoing testing in phase 3 trials for other leukemias^{49, 50}. Recently, obinituzumab was approved for newly diagnosed CLL because of superiority to a standard rituximab-containing regimen in a randomized controlled trial⁵¹.

Beyond CD20, other antigens unique or overexpressed in malignant B cells have been targeted. CD52 is a surface antigen 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-CLL and explored as a broadly immunosuppressive agent in nonmyeloablative allo-HSCT conditioning regimens⁵². Another example is CD30, a surface antigen expressed by **Hodgkin Reed-Sternberg (HRS) cells** and by other lymphoma subtypes such as anaplastic large cell lymphoma (ALCL). In healthy individuals, its expression is restricted to activated T and B cells. Despite a long history of targeted strategies against CD30, potent clinical efficacy and favorable toxicity profiles were achieved only recently with the introduction of an antibody drug conjugate, brentuximab vedotin^{53, 54}.

MM has heretofore remained untouched by mAbs. Two promising candidates, however, have recently emerged. Elotuzumab (ELO) is a humanized, monoclonal IgG1 Ab that targets CS1, a surface glycoprotein nearly universally expressed in normal plasma and MM cells and with lower expression in NK cells⁵⁵. Despite a phase I study lacking any objective responses as a monotherapy⁵⁶, a long-term phase I/II clinical trial reported >80% partial response (PR) rates and a prolonged progression-free survival (PFS) benefit of 33 months in relapsed/refractory MM when used with a common combination regimen of the pleiotropic, immunomodulatory agents, lenalidomide (BOX 4) and dexamethasone⁵⁷. This combination is now under investigation in phase III studies^{57, 58}. Daratumumab, a humanized mAb targeting CD38, another cell surface glycoprotein expressed on a range of hematologic malignancies, has revealed promising results in a phase Ib/II dose escalation study in heavily, previously treated MM patients. High response rates were observed above the pharmacokinetic effective dose with no median PFS reached at six months, earning a breakthrough therapy designation from the FDA^{58, 59}. This encouraging single-agent data has stimulated multiple, ongoing phase II studies in MM testing this agent alone and in combination with other chemotherapeutics⁵⁸.

Box 4

Immunologic effects of non-immune therapies

Many therapies used to disable a tumor cell-intrinsic circuit critical to proliferation have unexpectedly shown profound immunomodulatory function, falling into two main mechanistic categories: 1) revoking oncogene-driven immune evasion and/or 2) “off-tissue” effects of unintentionally modulating a tumor-associated pathway in immune cells as well. Both categories have been thoroughly reviewed¹⁹⁸, and hence we focus on examples relevant to hematologic malignancies. The former category is illustrated in preclinical studies establishing the importance of anti-tumor immunity to oncogene addiction for many oncogenes such as c-MYC in T-ALL¹⁹⁹, BCR-ABL in Ph⁺ B-ALL¹⁹⁹, B-RAF in melanoma²⁰⁰, and EGFR in non-small cell lung cancer²⁰¹. In CML, the combination of interferon alfa-2a and imatinib significantly increased the rate of molecular responses over each alone²⁰², and imatinib also synergized with DLI therapy to induce molecular remissions even in bulky, relapsed disease²⁰³.

The latter category includes 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. Though developed

initially as an anti-angiogenic drug²⁰⁴, thalidomide, and more so its better-tolerated derivative lenalidomide, have displayed highly potent activity in MM, MCL, CLL and MDS²⁰⁵. The immunomodulatory, in addition to the anti-angiogenic and cytotoxic, effects of this class have long been suspected. Only recently, however, have these agents been shown to enhance E3 ubiquitin ligase degradation of Ikaros 1 and 3, the former of which directly represses interleukin-2 transcription and production – ultimately leading to T and NK cell activation²⁰⁶. Moreover, lenalidomide antagonizes regulatory T cell function and repairs T cell synapse formation with CLL cells^{207–209}. The PI3Kd and BTK inhibitors, idelalisib and ibrutinib, respectively, inhibit BCR signaling (BOX 1) and are two examples of targeted therapies with unforeseen immunologic effects. Idelalisib impairs a vital component of Treg suppressor function²¹⁰, and ibrutinib appears to inhibit several other kinases, including interleukin-2-inducible T-cell kinase (ITK) that is essential for CD4⁺ Th2 cells. ITK inhibition by ibrutinib appears to favor Th1 skewing and promote anti-tumor immunity²¹¹.

Bi-specific T cell engagers (BiTE)

BiTEs potentially overcome the limitations of an immune-suppressive tumor microenvironment by directly linking cytotoxic T lymphocytes (CTLs) and their tumoricidal activity with the targeting platform of a mAb. Comprising dual specificities to both a tumor surface antigen and to CD3 on T cells, BiTEs physically couple tumors and T cells, inducing T cell activation, proliferation, and granzyme/perforin-mediated tumor cytotoxicity⁶⁰. Thus, anti-tumor efficacy relies on passive recruitment of cytotoxic T cells to the tumor milieu and subsequent tumor eradication. The lack of requirement for MHC expression allows for activation of a polyclonal CTL population.

A quintessential example of this class is blinatumomab, a bispecific antibody recognizing CD3 and the B cell-specific marker CD19⁶⁰. Strongly encouraging clinical potency has been reported in phase II studies in patients with B-ALL in hematologic remission but with persistent minimal residual disease⁶¹ and those with morphologically relapsed/refractory disease^{62, 63} (Table 1). As a result, the FDA has recently granted accelerated approval for blinatumomab for relapsed/refractory Philadelphia chromosome-negative B-ALL. Preliminary evidence suggests its efficacy in other B-cell malignancies as well⁶⁴, and additional BiTE antibodies targeting CD3/CD33 await clinical investigation in AML⁶⁵.

Boosting immune effector number and function

Direct expansion and availability of an increased number of functionally competent anti-tumor immune effectors represents 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 (Figure 2.2): (1) DLI (BOX 1) for leukemic relapse and (2) viral antigen-specific CTLs (BOX 3) for EBV-associated lymphoproliferative malignancies linked to the impaired immune reconstitution and prolonged use of immune suppressive medications. The successes in these arenas have directly inspired and informed the growing field of adoptive cellular therapy, illustrated dramatically by chimeric antigen receptor

(CAR)-T cells. Other promising avenues exploiting this node include NK cell alloreactivity and agonistic mAbs stimulating immune effector function.

Box 3

Targeting pathogens and cancer neoantigens

PATHOGENS

The immune system effectively utilizes genetic variability, evolutionary selection and rapid population expansion to defend against the onslaught of viral and bacterial pathogens; tumor immunologists have long sought to harness this ability to attack malignant cells. Tumor antigens derived from foreign pathogens have historically provided the quintessential example of this concept. Post-transplantation lymphoproliferative disease (PTLD), Hodgkin's lymphoma (HL), and non-Hodgkin's lymphoma (NHL) are strongly associated with Epstein-Barr virus (EBV) infection and therefore express unique EBV-derived antigens. The generation of CTLs against EBV proteins has been highly feasible for PTLDs in HSCT recipients, with 80% response rates in refractory disease and complete prevention in high-risk individuals¹⁹⁴. Autologous gene-modified APCs to stimulate CTLs against additional EBV antigens that share expression amongst most EBV-associated lymphomas (with the important exception of Burkitt's lymphoma) have also been impressively efficacious, with an 82% event-free survival at 2 years in the adjuvant setting for high-risk individuals and a 62% response rate in the relapsed/refractory setting with many complete remissions¹⁹⁵. Of note, therapeutic success appeared 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 immunotherapeutic.

CANCER NEOANTIGENS

The diversity of mutations in each tumor provides an even broader source of tumor-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 tumor. This antigen class may be targeted efficiently (i.e. lack of central tolerance) and safely (i.e. no risk of autoimmunity induction) by immunotherapy. The development of next-generation sequencing technologies enabling rapid identification of the complete repertoire of nonsynonymous mutations within a tumor has brought a breath of fresh air to this promise, and a pipeline for designing personalized vaccines was recently developed in CLL¹⁹⁶. Indeed, a patient-specific multi-epitope cancer vaccine is a highly attractive direction for cancer immunotherapy, serving to focus immunity against truly tumor-restricted epitopes that may be predicted by advanced HLA class I peptide binding prediction algorithms¹⁹⁷. Two clinical trials have now been initiated to assess the concept of personalized neoantigen vaccines in melanoma patients (NCT01970358 and NCT02035956), and additional trials across other cancers, including in the blood malignancies, are planned.

Chimeric antigen receptor (CAR) T cells

Adoptive cellular therapy (ACT) involves *ex vivo* manipulation of either naturally occurring or genetically engineered tumor-specific T cells that are subsequently infused into the patient. Two features are paramount to the success of ACT. First, insights gleaned from studying the post-transplant immune milieu revealed that a preparative lymphodepleting regimen created 'space' for homeostatic expansion of the infused T cells. Mounting evidence from HSCT preparative regimens suggests that elevated levels of homeostatic cytokines (i.e. IL-2, IL-15, IL-21 and IL-7) during the lymphopenic state accelerate the expansion of infused T cells⁶⁶ and promote an activated phenotype with enhanced effector functions^{66, 67}. Second, the selection of antigen against which the infused T cells are directed is essential for direct, tumor-specific T cell-mediated killing. Viral antigens, for example, may be exclusively displayed on viral-associated malignancies as opposed to normal tissue (BOX 3).

A very recently clinically active therapy, CAR-T cells exploit synthetically engineered **chimeric antigen receptors (CARs)** to bridge the nodes of targeting tumor-surface antigens with the boosting of effector functions. The specificity of these CAR-T cells for a tumor surface molecule renders them independent of MHC restriction, allowing them to overcome tumor escape mechanisms such as disruption of antigen presentation machinery.

The disappointing clinical efficacy from first generation CARs led to the development of a second generation that added intracellular signaling domains from either CD28 or CD137 co-stimulatory molecules to a CD19-targeting moiety⁶⁸. In patients with relapsed/refractory CLL, infusion of low numbers of CD19-targeted CAR-T cells led to massive *in vivo* expansion, tumor 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, likely lifelong, intravenous immunoglobulin. Importantly, durable remissions over two years were observed^{69, 70}. Multiple groups have reported similarly impressive clinical activities in other diseases; for example, B-ALL appears even more sensitive than CLL with an 80% response rate across various CAR designs, clinical trials and institutions^{68–70}. Very recently, CAR-T cells using the CD137 co-stimulatory domain were shown to induce complete remissions in 90% of both adult and pediatric patients with relapsed/refractory ALL, with durable remissions in over 2/3 of patients⁷¹. Another group, using a different CD28 co-stimulatory domain, also demonstrated similarly impressive response rates, though the CAR-T cell product was comparatively short-lived, insufficient for curative intent but able to serve as a bridge to allo-HSCT⁷². Finally, third generation CARs that include 2 co-stimulatory molecules are currently being developed and tested⁶⁸.

Remaining key issues are the question of whether persistent engraftment *in vivo* is needed to prevent tumor relapse and the management of acute and long-term toxicities. Collectively, second generation CAR-T cells incorporating either CD28 or CD137 signaling domains persist *in vivo* for several months following adoptive cell transfer^{68, 70}. Studies comparing these two molecules in CAR designs are ongoing. The development of tumor lysis syndrome and cytokine release syndrome in most cases underlines the rapid kinetics of T cell expansion and tumor elimination; however their severity can be lethal, and the precise role

of anti-inflammatory agents such as corticosteroids and tocilizumab (an anti-IL6 antibody) in treatment needs to be clarified⁶⁹. Whether CARs can be modified to disappear following tumor elimination and allow B cell recovery is under study. Finally, the expansion of CD19-negative tumor cells as a mechanism for relapse highlights the importance of considering multiple therapeutic targets on a tumor cell⁷¹.

NK cell alloreactivity

In addition to T cells, NK cells have long been appreciated to contribute to the eradication of leukemias and lymphomas⁷³. Potent NK-mediated human anti-leukemia 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 AML patients who exhibited **killer-cell immunoglobulin-like receptor (KIR)** ligand mismatching with their donors (i.e. in which mismatch led donor NK cells to fail to recognize recipient MHC class I molecules) and hence benefited from donor NK cell alloreactivity that killed recipient-derived leukemic cells^{74, 75}. Another large study demonstrated distinct clinical outcomes associated with specific *KIR* genes, suggesting the relevance of prospectively genotyping activating in addition to inhibitory KIR receptors to improve outcomes after HSCT.⁷⁶ Across studies, the benefit of KIR genotyping has been observed in AML, myelodysplastic syndrome (MDS), and pediatric ALL but interestingly not adult ALL or CML⁷⁶⁻⁷⁸, owing perhaps to differences in activating KIR ligand expression and/or whether T cells were depleted from the infused graft^{79, 80}. 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.^{81, 82}

Agonist stimulation of immune effector function

The example of NK cells and KIR receptors 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 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 patients⁸³. All patients survived, but clearly, manipulation of T cell costimulatory pathways requires clinical caution to avoid non-specific T cell activation.

Nevertheless, direct stimulation of immune effector function to promote tumor killing remains an attractive option. Agonist antibodies to CD40, CD137, and others have been tested in patients without excessive toxicity although severe hepatotoxicity was noted with agonist antibodies to CD137, necessitating dose reduction and less intense dosing regimens.^{84, 85} Thus far, few studies have examined the activity of agonistic mAbs in hematologic malignancies. A notable example of anti-CD40 mAbs has shown promising efficacy and safety without a clear understanding of its antitumor mechanism, which may include tumor-specific T cell priming and activation^{86, 87}, direct tumor cytotoxicity, and macrophage activation^{88,89}. CD137 is expressed in most hematopoietic cells and is an

intriguing target with critical T-cell independent activity. Agonistic mAbs targeting CD137 directly stimulated NK cell-mediated ADCC against lymphoma cells, synergizing with rituximab activity⁹⁰. Phase I trials testing anti-CD137 agonists with rituximab in NHL are ongoing (NCT01307267; NCT01775631).

Activating tumor antigen-specific immunity

While 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 to subsequently eliminate them while sparing normal host tissue is an attractive property of CTLs exploited by various cancer vaccination strategies. Together, the choice of antigen source, vaccine formulation, delivery system, adjuvant, immunomodulation, treatment schedule and treatment setting shape the quality and strength of a cancer vaccine-induced T cell response^{91, 92}. Three features unique to the hematologic malignancies afford opportunities to effectively investigate novel vaccination strategies (Figure 2.3): i) the discovery of multiple blood malignancy antigens; ii) the ability of tumor cells to serve as both APC and source of antigen; iii) and the reconstitution of immune competent T cells in the post-HSCT lymphopenic milieu.

The targeting of individual tumor antigens selective to the blood malignancies

Within hematologic malignancies, many prominent examples of tumor-selective antigens have been clinically assessed: Wilms' tumor antigen (WT-1) present in CD34+ hematopoietic progenitor cells and in many acute leukemias^{93, 94}; azurophilic granule protein Proteinase 3 (Pr3), overexpressed in myeloid leukemia blasts⁹⁵; and the receptor for hyaluronic acid-mediated motility (RHAMM), differentially expressed in various leukemias and lymphomas^{96, 97}. Evidence for their immunogenicity came from both the identification of spontaneous T cell responses against antigen-specific epitopes that preferentially killed leukemic cells as well as their association with longer overall survival or disease remission following allo-HSCT or other therapies^{98–102}. These observations suggested that boosting these pre-existing immune responses was feasible through active immunotherapy.

Early promising studies employing peptide vaccination demonstrated that functional leukemia-reactive CTL responses directed against single antigens could contribute to control of leukemic blasts in some patients and were associated with clinical benefit^{103–107}. The detection of antigen-specific T cell responses early after a single vaccine dose indicated the expansion of pre-existing leukemia-reactive memory CD8+ T cells^{108–110}. Subsequent efforts to generate more sustained immune responses led to studies combining HLA class I- and/or class II-restricted WT-1 and PR1 epitopes as immunogens^{110–113} to potentiate CD4+ helper T 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 a number of recent follow-up trials^{110–112}. While peripheral tolerance mechanisms could have impaired the function and *in vivo* expansion of high avidity T cells^{95, 106, 112}, suboptimal presentation of immune-dominant epitopes by APCs can also contribute¹¹⁴. Various vaccination studies,

focusing on WT-1, have thus employed direct antigen loading of autologous DCs, activating them *ex vivo* and reporting promising clinical data along with biological activity^{115,116}.

As an alternative to tumor-selective antigens, vaccination against *tumor-specific* neoantigens arising from malignancy-defining genetic alterations (see BOX 2), have been pioneered in the blood malignancies. This idea was tested extensively in CML using breakpoint junction-derived peptides from the BCR-ABL fusion oncoprotein. However, while phase I/II studies demonstrated 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^{117–120}. Indeed, recently, the immunogenicity of BCR-ABL breakpoint-derived peptides was called into question¹²¹. Concurrently, inspired by a case report of a B cell lymphoma complete remission after infusion of a monoclonal anti-idiotypic antibody¹²², a personalized vaccination approach directed against this prototypic lymphoma neoantigen, the idiotypic determinant of malignant B cell-derived immunoglobulin, revealed highly encouraging results in phase I/II trials^{123–126}. However, only one of three phase III trials^{127–129} demonstrated prolonged disease-free survival¹²⁸ but failed to achieve its primary clinical end points. The observed failures have been attributed to flaws in trial design, such as imbalances between standard prognostic scores between treated and control arms as well as enrollment 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^{130, 131}.

Whole tumor cells as APCs and source of antigen

Since the normal cellular counterpart of several blood malignancies is an APC, some clinical vaccination trials have leveraged the antigen-presentation capacity of the tumor cell to stimulate tumor-specific immunity. For example, in CML and AML, *in vitro* differentiation of myeloid leukemic blasts into leukemia-derived DCs retained the expression of some relevant cancer antigens and could stimulate leukemia-specific T cell populations^{132–135}. Another whole tumor cell-based approach exploits the unique capability of activated B cell lymphoma cells to present their own tumor 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 was either provided by *ex vivo* admixture with CD40L expressing cells^{136, 137} or by engineering lymphoma cells themselves to express CD40L^{138, 139}.

In general, inducing broader polyclonal antitumor immune responses against multiple cancer antigens may be more effective than targeting a single antigen. Autologous tumor is a ready source of personal tumor antigens and has been tested as an immunogen using formulations such as autologous DCs pulsed with tumor lysate^{140, 141} or apoptotic tumor¹⁴² and tumor-dendritic cell hybrids (i.e. autologous DCs chemically fused with MM cells)^{143, 144}. These DC-based vaccines have each demonstrated potent cellular tumor-specific responses and objective clinical responses^{140–144}. However, obstacles such as high cost, labor-intensive processes, and optimization of protocols for DC maturation and administration limit DC-based vaccination strategies¹¹⁴.

Recruitment of APCs and their ensuing capture of tumor antigen in the tumor bed are vital for subsequent, successful T cell priming in draining lymph nodes. One approach for intratumoral activation of APCs in patients with accessible tumor sites is *in situ* tumor vaccination. Intratumoral 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^{145, 146}. Still other whole tumor cell vaccination approaches have incorporated adjuvant cytokines, particularly granulocyte-macrophage stimulating factor (GM-CSF), to recruit APCs to the vaccination site. An ‘off-the-shelf’ allogeneic whole tumor cell vaccine, derived from the human HLA-negative K562 cell line engineered to secrete GM-CSF (K562/GM-CSF)^{147, 148}, expresses a number of CML-associated antigens¹⁴⁹. Treatment of CML patients who had measurable disease despite continued tyrosine kinase-inhibitor imatinib therapy with K562/GM-CSF led to declines in *BCR-ABL* transcript levels in all patients and in disease burden in 13 of 19 participants¹⁴⁹. Finally, administration of lethally irradiated autologous whole tumor cells genetically modified to secrete GM-CSF, or admixed with GM-CSF-secreting bystander cells, has achieved significant immunologic and clinical responses in both AML and CLL^{147, 149, 150}. Overall, these highly encouraging results suggest the superiority of a multi-epitope vaccination strategy over the use of single tumor antigens in advancing immunological destruction of hematologic malignancies, but this notion bears further investigation in larger randomized trials.

The post-HSCT setting as a platform for vaccination

The increased frequencies of CTLs targeting WT1, PR1, BCR-ABL or recipient minor histocompatibility antigens after allo-HSCT suggested that the post-transplantation period could “reset” cancer-immune relations, enhancing GvL and marking an ideal setting for cancer vaccination. In addition to lymphopenia and associated growth-promoting cytokines, vaccine responses may be aided by Treg depletion and minimal residual disease states that diminish tumor-induced immune suppression¹⁵¹. Equally important is reconstitution of immune competent donor T cells not previously tolerized to the recipient’s leukemia. Indeed, administration of autologous GM-CSF secreting vaccine in the early post-HSCT period resulted in a significant 2-year survival advantage compared to historical controls in AML and MDS patients¹⁵⁰. Notably, co-injection of irradiated autologous tumor cells with K562/GM-CSF cells in the early post-HSCT period for patients with advanced CLL led to a rise in circulating CLL-specific, rather than alloreactive, CD8+ T cells and favorable clinical activity¹⁴⁷. These observations affirm the strategic therapeutic scenario of the post-transplantation immunologic milieu.

Overcoming inhibitory immune suppression

The tumor immunology field has been recently reinvigorated by the development of reagents that relieve inhibitory immune suppression within the microenvironment (Figure 2.4). The impressive activity of checkpoint blockade inhibitors across many types of malignancies has underscored the critical immune-dampening roles of multiple immunosuppressive elements within the tumor milieu, including co-inhibitory molecules, Tregs, B regulatory cells (Bregs) 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: **cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4, also known as CD152)** and **programmed cell death protein-1 (PD-1, also known as CD279)** (previously reviewed extensively^{1, 152}). Both represent immune checkpoint receptors that function predominantly to inhibit T cell responses and dampen T cell activation.

CTLA-4 was the first co-inhibitory molecule to be clinically targeted. Within hematologic malignancies, ipilimumab, an anti-CTLA-4 mAb with FDA-approval for treatment of metastatic melanoma¹⁵³, has been studied to a limited extent. Phase I studies have demonstrated its antitumor activity in relapsed and refractory B cell lymphoma after chemotherapy or after allo-HSCT^{154, 155}. Interestingly, although three clinical responses and multiple incidents of organ-specific immune adverse events were noted in the latter trial, no GvHD was observed in any of the patients. This large therapeutic window may be attributed to the relatively prolonged time between last donor cell infusion and ipilimumab administration, suggesting an opportunity for immunomodulation in the post-transplantation setting¹⁵⁵. Very recent preliminary data from a similar phase I study of ipilimumab after allo-HSCT has also suggested both efficacy and tolerability in this patient population¹⁵⁶.

PD-1 is an immunoinhibitory receptor whose ligand binding induces T cell suppression through a unique state of T cell dysfunction termed 'exhaustion.' First described in chronic viral infections, T-cell exhaustion has been increasingly recognized as an important immune-evasive strategy in many hematologic malignancies^{157–160}. Antibodies targeting the PD-1:PD-L1 interaction have evoked impressive antitumor activity in a variety of solid tumors^{1, 161}. A growing body of clinical evidence strongly supports anti-PD-1 activity in hematologic malignancies as well. A highly promising phase II trial testing the role of pidilizumab, a humanized, IgG1 anti-PD-1 mAb, in patients with relapsed/refractory DLBCL after autologous HSCT reported a response rate of 51% in those patients with residual disease after auto-HSCT and a complete remission rate of 34%¹⁶². As in previous phase I trials of this antibody, toxicity was minimal. Recently nivolumab, a humanized IgG4, anti-PD-1 mAb, demonstrated significant response rates in relapsed/refractory cHL with close to 90% of patients responding to therapy¹⁶³; similar results were seen with another anti-PD-1 antibody, pembrolizumab¹⁶⁴. Preliminary results from a study of nivolumab in multiple relapsed/refractory lymphoid (B and T cell) malignancies indicated response rates across the spectrum of lymphomas, with more than a third of patients with DLBCL and FL responding to therapy¹⁶⁵. As a result, nivolumab has been granted breakthrough status by the FDA as a treatment for Hodgkin's lymphoma after failure of autologous stem cell transplant and brentuximab. Altogether, these data highlight the impressive therapeutic opportunity for modulation of T cell co-inhibitory molecules in hematologic malignancies and anticipate a very active role for targeting additional co-inhibitory T cell receptors such as TIM-3 and LAG-3 in this arena^{152, 166}. The recent combined blockade of both PD-1 and CTLA-4 has resulted in impressive clinical rates of

response in melanoma, further driving excitement for combinations within this therapeutic class¹⁶⁷.

KIRs are another promising set of inhibitory molecules; as described above, they serve as inhibitory receptors to guide NK cell activity away from self-MHC expressing cells. Lirilumab is an IgG4 mAb that binds specifically 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 in patients treated at higher doses indicates a potential dose-response effect¹⁶⁸. In multiple myeloma, a phase I trial confirmed safety and disease stabilization for one-third of patients; however a recent phase II study in smoldering multiple myeloma closed early owing to lack of any clinical efficacy^{169, 170}. Nevertheless, given compelling clinical data in allo-HSCT and generous safety window, anti-KIR antibodies likely will play some role in stimulating anti-tumor NK activity within hematologic malignancies.

Tregs, Bregs and MDSCs

In addition to co-inhibitory molecules, cellular elements within the tumor microenvironment, particularly Tregs, Bregs¹⁷¹, and MDSCs, also mediate local immune suppression. Currently, few effective agents specifically target these cell types. Denileukin diftitox is a chimeric immunotoxin formed by conjugating a diphtheria toxin fusion protein to IL-2, targeting the IL2 receptor (CD25), which is highly, though not selectively, expressed on Tregs. Although FDA approved for CTCL with objective response rates ranging from 30–44%, its precise mechanism of action remains poorly understood^{172, 173}. Its parent pharmaceutical company has ceased supply since 2011 though it remains available through a compassionate use program. Ipilimumab may also function by intratumoral Treg depletion though this mechanism has yet to be formally demonstrated in patients^{174, 175}. Finally, Treg depletion *ex vivo* from adoptive cellular infusions is discussed below in the context of targeting multiple immunotherapeutic nodes. Immunomodulation of Treg, Breg, and MDSC function, then, represents a potent therapeutic opportunity within hematologic malignancies.

Combinations, Timing, and Future Directions

Each of these four immunotherapeutic nodes constitutes a critical aspect of the tumor-immune relationship and thus an exciting therapeutic opportunity for intervention. However, the essential feature of the immune system – that distinct immune effectors coordinately act 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 FL treated with the combination of rituximab and pidilizumab found a high complete response (CR) rate of 52%, comparing quite favorably to historical data suggesting CR rates near 11%^{176, 177}. Importantly, this combination was very well tolerated. Similarly, Treg depletion before NK cell infusion improved median duration of CR in patients with high-risk AML compared to historical controls who received NK cell infusions without Treg depletions¹⁷⁸.

Another opportunity for immune-intervention is the targeting of ‘early’ neoplastic lesions. Because increasing genomic complexity and tumor burden facilitate immune escape and immunotherapeutic resistance, exploiting early immune recognition may have substantial impact. MM is a model example. In patients with monoclonal gammopathy of undetermined significance (MGUS), an MM 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 MM¹⁷⁹. Furthermore, in a small patient cohort, a combination of lenalidomide (BOX 4) and an activating ligand for natural killer T cells elicited activation of multiple immune subsets and durable tumor regression in patients with smoldering MM¹⁸⁰. Thus, careful study of immune-interactions with precursor lesions may uncover novel therapeutic avenues.

The growing arsenal of novel immune therapies, with increasing awareness of the immunologic consequences of non-immune therapies (BOX 4), can be further complemented by the discovery and implementation of biomarker strategies. The hematologic malignancies, 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 pre-DLI marrow-infiltrating T cells in patients treated for relapsed leukemia after allo-HSCT suggested T cell exhaustion as a potential marker and mechanism of DLI response¹⁸¹. Similar studies with newer agents could unlock molecular signatures predicting response, pairing patients with the correct choice(s) of immunotherapy. Indeed, the advent of next-generation sequencing technologies offers a more intelligent approach. Molecular signatures generated from both tumor and infiltrating immune cells may identify patient-specific tumor-induced immune defects. Judicious application of these signatures can thus enable the tantalizing possibility of accurately individualizing cancer immune therapies for patients.

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Glossary

Interleukin-7 (IL-7)

A cytokine, produced in the bone marrow, thymus and other organs, that drives T cell homeostasis and development.

Professional antigen presenting cells (APCs)

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

High mobility group box 1 (HMGB1)	A DNA-binding protein that, when released by dead or damaged cells, stimulates a robust proinflammatory response through the binding of Toll-like receptor 4 (TLR4) on dendritic cells, enhancing tumor antigen presentation and driving chemotherapeutic efficacy.
Nurse-like cells (NLCs)	Stromal-like adherent cells that develop <i>in vitro</i> from PBMCs of CLL patients and are tightly surrounded by CLL cells, promoting their survival.
T helper 1 (Th1) cells	A pro-inflammatory subset of CD4 ⁺ T cells defined by interleukin-2 and interferon- γ production leading to promotion of cellular immunity through CD8 ⁺ cytotoxic T cells, macrophages and NK cells.
Multiple Myeloma (MM)	A form of blood cancer that is characterized by the accumulation of neoplastic plasma cells within the bone marrow.
T helper 17 (Th17) cells	An inflammatory, interleukin-17-producing subset of CD4 T cells implicated in many autoimmune diseases.
Regulatory T cells (Tregs)	A CD4 ⁺ CD25 ^{hi} T cell subset known to effectively suppress T cell effector functions as well as proliferation and activation for a variety of other immune cells, including APCs, B cells and NK cells. Treg infiltration has been implicated in multiple disease states ranging from neoplastic growth to autoimmune dysfunction.
Hodgkin Reed-Sternberg (HRS) cells	Neoplastic cells of B cell origin that serve as hallmarks of classical Hodgkin's lymphoma with unusual morphology and a unique immunophenotype that does not resemble any normal cell in the body.
Bi-specific T cell engagers (BiTEs)	A fusion protein composed of two single-chain variable fragments (scFv) derived from a T cell specific anti-CD3 antibody and a tumor-targeting antibody, respectively.
Granzyme/perforin-mediated tumor cytotoxicity	The principal mode of target cell killing by cytotoxic T cells (after antigen recognition on the target cell's surface) whereby intracellular cytotoxic granules, within T cells, release their stores of perforin and granzymes to trigger apoptosis of the target cell.
Philadelphia chromosome (Ph)	The defining translocation in chronic myelogenous leukemia between two genes on the long arms of chromosome 22 (<i>BCR</i>) and 9 (<i>ABL</i>), resulting in a novel oncogenic fusion gene (<i>BCR-ABL</i>) that can be targeted by ABL kinase inhibitors, such as imatinib (Gleevec).

Chimeric antigen receptor (CAR)	Synthetic, engineered receptor composed of a single chain antibody fragment conferring tumor recognition coupled with intracellular signaling domains derived from the T cell receptor and a costimulatory molecule, most commonly either CD28 or CD137.
CAR-T cells	T cells that are isolated from patients' peripheral blood, genetically modified with CARs, then activated and expanded <i>ex vivo</i> and subsequently infused back into the patient a few days after a lymphodepleting chemotherapeutic regimen.
Natural killer (NK) cells	Lacking the antigen-recognition diversity of T- and B-cell receptors, NK cells function instead by an array of inhibitory and activating cell surface receptors, of which killer-cell immunoglobulin-like receptors (KIRs) serve a prominent role.
Killer-cell immunoglobulin-like receptors (KIRs)	KIRs, expressed on NK cells, recognize self MHC class I molecules and may be inhibitory or activating; as a result, NK cells preferentially kill target cells that are missing "self" MHC class I molecules (i.e. KIR ligands).
Idiotypic vaccine	Cancer vaccines targeting the unique antigenic determinant located in the variable region of the B cell (or T cell receptor) that is expressed by clonally expanded malignant B or T cells, respectively.
Cytotoxic-T-lymphocyte-associated antigen 4 (CTLA4 or CD152)	CTLA-4 is exclusively expressed on the surface of activated T cells where it counteracts CD28 by both outcompeting it for its ligands, CD80 and CD86, on APCs as well as triggering intracellular inhibitory pathways; plays an important role in maintaining immune homeostasis.
Programmed cell death protein 1 (PD1 or CD279)	PD-1 is an immune-checkpoint receptor expressed on activated T cells as well as other immune subsets and functions primarily in peripheral tissues. Binding to its ligands, PD-L1 or PD-L2 expressed on tumor and/or stromal cells, induces T cell exhaustion.
Smoldering multiple myeloma	Early stage multiple myeloma preceding the active, clinically symptomatic phase.
B regulatory cells (Bregs)	A newly described subpopulation of B cells that remain incompletely defined in humans, Bregs have been suggested to functionally resemble CLL 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

Natural killer T cells (NKTs)

the pathogenesis of many blood malignancies including multiple myeloma, CML, and myelodysplasia.

NKTs are a specialized subset of innate-like T cells that recognize lipid-based antigens presented by the CD1 family of MHC-like molecules. Following lipid antigen recognition, they rapidly produce very large amounts of a variety of cytokines without clonally expanding like “classical” T cells. NKT cells have been implicated in shaping immune responses in infection, autoimmunity, and cancer.

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Biographies

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Ute E. Burkhardt's career path is characterized by a strong focus on cancer immunotherapy. She received her PhD in biochemistry from Goethe-University Frankfurt, Germany, for studies which focused on optimizing cancer vaccine design using murine models. In her current postdoctoral work, at the Dana-Farber Cancer Institute in Boston, MA, USA, she developed innovative approaches to dissect the global and clonal dynamics of T cell responses underlying promising graft-versus-leukemia activity in chronic leukemia patients following post-transplant personalized vaccination.

Mohini Rajasagi received her PhD from the German Cancer Research Center (Heidelberg, Germany) in 2008, where she worked on allogeneic bone marrow transplantation in hematological malignancies to overcome GvHD without eliminating GvL. Her postdoctoral training was in the laboratory of Dr. Catherine J. Wu at Dana-Farber Cancer Institute (Boston, Massachusetts, USA), where she spearheaded the project on systematic identification of tumor-specific neoantigens to develop personalized multi-epitope cancer vaccines. Currently, she is a Research investigator in the Oncology Department at Bristol-Myers Squibb (Princeton, New Jersey, USA), where she continues to pursue her interests in developing new cancer immunotherapy drugs.

Catherine J. Wu, MD is an Associate Professor in Medicine at the Dana-Farber Cancer Institute (DFCI), Boston. She received her M.D. from Stanford University School of Medicine and completed her clinical training at the Brigham and Women's Hospital and DFCI in Boston. At DFCI, she has initiated an integrated program of research and clinical activities that focuses on dissecting the mechanisms underlying the pathobiology of chronic lymphocytic leukemia to more rationally generate effective therapies, including immune-based approaches. A major priority of her studies is the development of personalized tumor vaccines through the targeting of tumor-specific antigens, discovered through genomics-based approaches.

KEY POINTS

- The impressive potency of novel cancer immune therapies has refocused attention on this class of agents across the spectrum of cancers, and the robust experience of immunotherapeutic efforts specifically within hematologic malignancies offers insights germane to the future development of these strategies.
- From adoptive cellular transfer and antibody-based therapies to active cancer vaccination, early investigations within the blood malignancies provided both initial proofs-of-principles and informative testing grounds for agents such as allogeneic hematopoietic stem cell transplantation (allo-HSCT), donor lymphocyte infusion (DLI), and rituximab.
- Unique features of hematologic malignancies enabling the development of immunotherapies include their historic immune-responsiveness, ease of tissue sampling to distinguish malignant from normal cells by surface marker expression, the ability to directly examine immune-based anti-tumor responses following allo-HSCT and DLI, and their shared sites of origin with normal immune counterparts.
- Lymphoid and myeloid malignant cells subvert physiologic immune programs to both directly drive cancer growth as well as indirectly recruit an inflammatory, immune-supportive infiltrate.
- Clinical and laboratory investigations within hematologic malignancies have suggested 4 major nodes of potential vulnerability in the cancer-immune relationship: (1) direct targeting of surface tumor antigens; (2) boosting immune effector number and function; (3) activating tumor antigen-specific immunity; and (4) overcoming inhibitory immune suppression.
- An appreciation of the coordination among distinct cells during an effective immune response suggests a multi-pronged combinatorial strategy for inducing potent anti-tumor immunity; indeed, recent clinical evidence within hematologic malignancies supports this paradigm. Moreover, it is becoming increasingly evident that evaluation of both leukemic *and* infiltrating immune cells at the site of disease is important to identify biomarkers of immunotherapeutic response and resistance, which in turn allow for selection of appropriate treatment options.

Figure 1. Strategies of co-opting physiologic immune programs

This figure summarizes the mechanisms observed in blood cancers of hijacking the physiologic circuitry of their normal counterparts (left column) to drive tumor growth and manipulate endogenous immune responses (right column). Example malignancies are listed centrally for each mechanism (row). **A**, on the left panel, illustrates an IL-7-mediated signaling pathway that drives physiologic homeostatic proliferation of T cells. In contrast, the right-sided panel shows that, by acquiring somatic mutations throughout this pathway (indicated by black color), blood cancers such as T-ALL can drive autonomous signaling. **B** highlights a similar phenomenon via the BCR signalling pathway that is activated by multiple B cell malignancies through acquired somatic mutations of the BCR itself as well as downstream components (indicated by black color). **C** depicts the typical antigen-specific activation of T cells mediated by professional antigen presenting cells (APCs) in the physiologic setting (left); in contrast, the lack of co-stimulation during antigen (Ag) presentation by malignant cells can induce T cell anergy (right). In **D**, the conventional role of HMGB1 as a “danger” signal emitted by dying cancer cells that stimulates and attracts anti-tumor T cells (left panel) is reversed in CLL in which (right panel) HMGB1 may promote differentiation of monocytes into nurse-like cells (NLCs) to promote CLL cell survival *in vivo*. Finally, **E** portrays the duality of Th1-led inflammation, with the left panel attributing tumor-destructive roles to CD8+ T cells and macrophages and tumor-promoting activities to regulatory T cells (Tregs); the right panel ascribes tumor-survival signals to

CD4⁺ Th1 cells and a potential anti-tumor influence to Tregs as seen in CLL, cHL, FL and MM.

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Figure 2. Timeline of major immunotherapeutic advances within hematologic malignancies

The figure depicts four areas of potential vulnerability in the tumor-immune relationship and the historical development of corresponding immune therapies. **1** emphasizes the potency of immunologic *targeting of tumor surface antigens*, primarily illustrated through mAbs. **2** highlights the long-standing influence of *boosting immune effectors* on immune therapy via DLI and now encapsulated by CAR-T cells. **3** recognizes the importance of *activating tumor antigen-specific immunity*. **4** underscores the potency of *overcoming inhibitory immune suppression* in the tumor microenvironment. BTD, US FDA's breakthrough therapy designation; R/R, relapsed/refractory; CTL, cytotoxic T lymphocyte; ASCT, autologous stem cell transplantation.

Table 1

Promising clinical immunotherapeutics within hematologic malignancies

Therapeutic class	Agent	Study	Patients	Comments	Clinical approval
mAb	Obinutuzumab ⁵¹	Phase III	Untreated CLL (n=781)	Combo with chlorambucil versus rituximab combo: increased PFS, MRD-	In combination with chlorambucil for untreated CLL
mAb	Daratumumab ⁵⁹	Phase I/II	R/R MM (n=32)	31% ORR in all patients 67% ORR @ target PK dose-Median PFS not reached	Breakthrough therapy designation for R/R MM
Bispecific T cell engager	Blinatumomab ⁶¹⁻⁶³	Phase II Phase II Phase II	MRD ⁺ (n=21) Relapse (n=36) R/R (n=189)	80% MRD ⁻ 72% CR 43% CR/CRh	R/R Ph ⁺ B-ALL
Adoptive cellular therapy	CAR-T cells ⁶⁹⁻⁷²	Phase I Phase I Phase I	R/R CLL (n=3) R/R B-ALL (n=5) R/R B-ALL (n=2)	2 CR, 1 PR 5/5 MRD ⁻ 2/2 CR (1 CD19-relapse)	Breakthrough therapy designation for R/R B-ALL
Adoptive cellular therapy	LMP-CTLs ^{194,195}	Phase II	As adjuvant with high-risk disease (n=29) R/R EBV ⁺ NHL or HD (n=21)	28/29 with NED at 3 yrs 13/21 ORR; 11 CR's	–
In situ vaccination	Intratumoral TLR 9 agonist + low dose XRT ¹⁴⁵	Phase I/II	Indolent NHL (n=15)	1 CR; 3 PR; 2 SD (but continually regressing)	–
Multi-epitope vaccination	Whole tumor cell + GM-CSF vaccination post RIC allo-HSCT ^{147,150}	Phase I Phase I	HR MDS/AML (n=28) Advanced CLL (n=22)	9/15 in CR at 2 yrs 88% OS at 2 yrs (for 18 pts)	–
Checkpoint blockade	Pdilizumab, nivolumab ^{162,163,176}	Phase II Phase II Phase I	R/R DLBCL s/p ASCT (n=66) +rituximab in R/R FL (n=32) R/R cHL s/p ASCT (n=23)	RR=51%; CR=34% CR=52% ORR=87%; CR=17%	Breakthrough therapy designation for R/R HL s/p ASCT and brentuximab (nivolumab)