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Antigen Discovery and Therapeutic Targeting in Hematologic Malignancies

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Abstract

Historically, immune-based therapies have played a leading role in the treatment of hematologic malignancies, with the efficacy of stem cell transplantation largely attributable to donor immunity against malignant cells. As new and more targeted immunotherapies have developed, their role in the treatment of hematologic malignancies is evolving and expanding. Herein, we discuss approaches for antigen discovery and review known and novel tumor antigens in hematological malignancies. We further explore the role of established and investigational immunotherapies in hematologic malignancies, with a focus on personalization of treatment modalities such as cancer vaccines and adoptive cell therapy. Finally, we identify areas of active investigation and development. Immunotherapy is at an exciting crossroads for the treatment of hematologic malignancies, with further investigation aimed at producing effective, targeted immune therapies that maximize anti-tumor effects while minimizing toxicity.

Keywords

Neo-antigens; antigens; cancer immunotherapy; mutation; genome sequencing; immunopeptidome; hematologic malignancies

Introduction

The recent successes of targeting immune checkpoint blockade for the treatment of solid tumors have led to the current broad adoption of immune-based therapy across diverse malignancies, with immunotherapy now anticipated to remain a steady part of the therapeutic armamentarium against cancer. Long before this current age, the effectiveness of immune-based therapy for the treatment of hematologic malignancies was widely

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demonstrated through decades of research and clinical experience. In particular, the curative experience of using allogeneic hematopoietic stem cell transplantation (HSCT) to treat leukemia demonstrated both the potent impact of the immune system to target malignant cells, but also indicated the possibility of developing significant immune-based toxicities. Indeed, over 25 years ago, Horowitz and colleagues elegantly showed that the presence of donor T cells during bone marrow transplantation for leukemia decreased the probability of relapse, providing early support for the use of competent immune elements to combat hematologic malignancies[1]. An immune basis for the anti-leukemic activity of donor allografts was further supported by the successful use of post-allograft infusions of lymphocytes from the original donor (DLI), which continues to provide an established means for effectively treating leukemic relapse after HSCT, often in the absence of further cytotoxic agents[2,3].

Identifying and characterizing the targets of the anti-leukemia responses induced by HSCT/DLI were amongst the earliest efforts to gain understanding of the mechanisms underlying these therapeutic responses, and continues to provide a rational path towards developing newer therapies. For DLI, although the precise mechanism by which anti-leukemia control is mediated has remained elusive, collective evidence has supported the idea that effective graft-versus-leukemia (GvL) responses relate to coordinated leukemia antigen-specific cellular and humoral immunity and to local reversal of $CD8^+$ T cell exhaustion within the bone marrow[4–11]. Thus, the process of antigen discovery has provided the means to dissect out the paths to therapeutic benefit. The demonstration of immune activity against leukemia from the HSCT/DLI experience has paved the way for the new area of cellular adoptive therapy with chimeric antigen receptor (CAR) T cells. At the same time, the concepts encompassed by HSCT of combinatorially incorporating immunologic help and focusing immune responses on cancer-specific antigens have foreshadowed the current active efforts in immune checkpoint blockade (CPB) and cancer vaccines in oncology. Characterization of antigen specificities has also provided insight into the mechanistic basis of the major immunologic complication of GvL, namely the donor immune responses against normal recipient cells, termed graft-versus-host disease (GvHD)[12,13]. The presentation and spectrum of targets of GvHD and its clinical management have likewise foreshadowed the severest complications of the new immune checkpoint inhibitors, namely autoimmune toxicities. In the current age, maximizing anti-tumor benefit (GvL) effect while minimizing toxicity (GvHD) remains an important goal, with these efforts extending to new CPB-based efforts[14,15].

Herein, we discuss prior and current methods for antigen discovery, including known tumor antigens in hematologic malignancies, with commentary on current immune-based therapies. In particular, we discuss known and proposed mechanisms for generating neo-antigens in hematologic malignancies, with a focus on identifying immunogenic neo-antigens for therapeutic targeting.

Identifying Tumor Antigens in Hematologic Malignancies

A major priority in cancer research has been the identification of tumor antigens, with the aim of targeting them through immune-based therapies. The methods used to identify such

antigens have evolved over decades (Figure 1). Overall, resource intensive cell-based and biochemical-based approaches have now led to higher throughput approaches based on systematic evaluation of DNA, RNA and protein to search for suitable antigens. Examples of some of the tumor antigens identified in acute myeloid leukemia (AML)[16–30], chronic myeloid leukemia (CML)[19,24,31–41], acute lymphoblastic leukemia (ALL)[19,30,42,43], chronic lymphocytic leukemia (CLL)[19,29,30,44–47], and multiple myeloma[21,22,27,30,48–52] are shown in Figure 2.

Experimental Approaches to Tumor Antigen Identification

The discovery of lineage-defining cell surface markers on human immune cells following the development of hybridoma technology[54], has been the starting point of much studies of human immunity. Although these findings were not specifically geared at discovering tumor antigens *per se*, these defining markers have become highly suitable antigen targets of current B and T cell-based immunotherapeutic approaches (described in the next section, and noted in Figure 2). For example, malignant B cells were found to express a unique variable region on cell surface immunoglobulin ("idiotype")[53], and monoclonal antibodies could be subsequently generated to therapeutically target these tumor idiotypes[55,56]. This type of technology was similarly used to identify lineage-defining cell surface markers on human immune cells, including CD19 and CD20, expressed on normal and malignant B cells[57]. Now, monoclonal antibodies directed against cell surface markers[29,58,59] expressed by lymphoma cells have become a standard approach in the treatment of a wide variety of lymphomas[60,6129,62] (i.e. rituximab, the monoclonal antibody targeting CD20[63]). More recently CD19 surface expression on certain ALL cells has been targeted effectively with CAR T cell therapy[64,65]. Ongoing investigative work to identify novel surface markers will likely continue to prove fruitful, as exemplified by the recent identification of restricted ROR1 surface expression on B-lineage ALL cells[66], and subsequent efforts to therapeutically target this surface antigen with CAR T cells[67,68].

Many investigative efforts have been focused on the identification of tumor antigens that could generate a classical T cell response. The earliest approach to bona fide tumor antigen discovery was through T cell-based screening of tumor cDNA expression libraries, pioneered by Boon and colleagues in the early 1980s, which led to the identification of the MAGE family of melanoma-associated antigens[69,70]. This time- and labor-intensive technique involves the generation of cDNA libraries from tumor cells, transfection into cells also expressing the appropriate MHC molecule, and then screening with tumor-reactive T cells, with cells transfected with an immunogenic antigen leading to T cell stimulation and cytokine release[69–76]. While this technique was initially successful in identifying melanoma antigens, subsequent application of this method has led to the identification of a number of leukemia-associated antigens, including minor histocompatibility antigens (mHAs) with leukemia-restricted expression[77–80]. Another early approach involved separating cell fractions (using reversed-phase liquid chromatography and gel electrophoresis), identification of fractions containing an immunogenic antigen and finally protein sequencing of the identified analyte[81]. Biochemical approaches like this were used to identify the first minor histocompatibility antigen HA-1 in hematopoietic cells[82]. Similarly, testing of HLA-bound peptides on tumor cells (isolated on the basis of immunoaffinity purification and

subsequent elution of HLA molecules[83–85]), pulsed on antigen-presenting cells against autologous lymphocytes, has led to the identification of antigens such as ADIR in multiple myeloma[86].

Humoral immunity may cooperative with T cell responses as part of a complex immune response, as demonstrated by the known protective effects of antibody responses in infectious immunity, and also through coordinated B cell and T cell responses identified in blood malignancies in settings of effective clinical response. For example, in patients with CML who received DLI, generation of high titer antibodies against CML antigens correlated with disease remission, suggesting that effective humoral immunity may serve as a positive biomarker for response to therapy[87]. To take advantage of higher serologic responses to tumors, Pfreundschuh and colleagues pioneered an alternative system for antigen identification, termed serological analysis of recombinant cDNA expression libraries or SEREX[88–90] in the 1990's. In this technique, a cDNA library is constructed from tumor cells, and transfected into prokaryotic cells. The recombinant proteins are then screened using the patient's serum, allowing for the detection of tumor antigens which generate a high-titer IgG antibody response in the patient. The clones that are identified can then have their DNA sequenced for identification of the tumor antigen. This technique has detected the antigens PRAME in AML[91], cTAGE-1 in cutaneous T cell lymphoma[92], and the cancer testis antigen NY-ESO-1[93] found in multiple myeloma[94], among others. More recently, this approach has been extended further with the use of high-density protein microarrays to identify antigens in CLL, CML, and multiple myeloma[95–97]. These serologic-based approaches have the advantage of providing a rapid method for identifying a broad array of potential tumor antigens, but also have the limitations that these antigens may be byproducts of tumor cytolysis but not tumor rejection antigens *per se*. In addition, this approach may fail to detect important tumor antigens that depend on post-translational modifications or conformational changes that do not occur in a prokaryote system[93,98,99].

More recently, antigens have been identified on the basis of differential gene expression profiling. Gene expression analysis seeks to identify differentially or aberrantly expressed genes in tumor cells compared to normal tissue[99,100]. These early studies began with cDNA microarray and SAGE (serial analysis of gene expression) platforms. These techniques have been used to successfully identify candidate tumor antigens in CLL (including ROR1)[101] and multiple myeloma (such as TEX14, PTPN20A/B, among others)[102]. While DNA microarray analysis typically requires *a priori* knowledge of transcript sequence, RNA-seq (and genome sequencing with computational prediction tools) allows for the identification of novel transcripts[103–106]. However, as gene expression may not correlate with protein expression, and does not take into account post-translational modifications that may contribute to immunogenicity.

Some of these limitations can be overcome with modern proteomic approaches. These approaches typically use mass spectrometry to identify and quantify peptide fragments[100,107]. Modifications to this technique include an initial immunoaffinity purification step to isolate HLA molecules and bound peptides, prior to mass spectrometry analysis. This technique allows for the identification of HLA-bound peptides, including mutated or tumor-specific HLA-bound peptides (such as a BCR-ABL peptide in CML[108]),

which constitute the “immunopeptidome” or “HLA ligandome” for a tumor[20,109,110]. A related approach can enrich for phosphorylated peptides, and analysis of the phosphoproteome of a tumor may similarly reveal novel antigens[111], and has led to the identification of MLL, LPP, and MEF2D, among others[112], in leukemias and lymphomas.

Overall, these and other approaches have identified unique tumor antigens, overexpressed or tumor-associated antigens, and cancer-testis antigens (which are, under normal circumstances, only expressed in an immune privileged environment)[113–115] across cancers[19]. Still another approach to tumor antigen discovery has been through “reverse immunology” techniques, where peptides are selected and synthesized based on a computationally predicted or experimentally determined ability to bind HLA molecules, and then are tested for their ability to elicit a T-cell response. In the hematologic malignancies[113], this strategy has led to the identification of leukemia-specific antigens linked to the GVL response, including proteinase 3 (PRTN3)[116,117], Wilms’ tumor protein 1 (WT1)[118], and the BCR-ABL fusion peptides[35]. As a further extension of this approach, exome-wide DNA sequencing data has been combined with computational prediction tools (such as NetMHC) to effectively predict a class of antigens called neo-antigens arising from tumor-specific genomic alterations. These somatic alterations include missense mutations (single nucleotide variants, or SNVs), or insertions or deletions leading to frameshift mutations (indels) and potential new open reading frames (neo-ORFs)[105,106,119,120].

For carcinogen-driven solid malignancies, such as melanoma[126–128], bladder cancer[129,130], and non-small cell lung cancer[131,132], where the somatic mutation loads (primarily from SNVs and indels) are high, more neoantigens have been predicted, and both spontaneous immunity and response to checkpoint blockade inhibition have been associated with increased neoantigen load, effective immune response (Figure 3A)[133].

In contrast, the somatic mutation burden for most hematologic malignancies is relatively low[134] and corresponding by lower numbers of neo-antigens have been predicted. Do alternative mechanisms for generating neo-antigens exist in hematologic malignancies (Figure 3B)? One possible source could be through the generation of neo-antigens through novel gene fusions. A canonical example is BCR-ABL, occurring in CML and some cases of ALL, which is known to be presented on certain HLA molecules and generate a T cell response[135–137], previously tested as a target of therapeutic peptide vaccines[138–140]. Another possibility involves abnormal splicing, with retention of introns leading to the generation of neo-antigens[141,142]. Spliceosome mutations are relatively common in AML (and myelodysplastic syndrome). Dvinge and colleagues demonstrated that AML cells have a higher number of retained introns (and, presumably, neo-antigens) than adjacent normal tissue (Figure 3B, adapted from ref. [142]). Therefore, even with a relatively low somatic mutation load, hematologic malignancies may employ alternate mechanisms for neo-antigen generation, and offer immunogenic tumor-specific targets for immune-based therapies.

Immunotherapies for Hematologic Malignancies

For hematologic malignancies, a number of therapeutic approaches are currently under investigation, that vary in the degree to which they specifically target an antigen (or

antigens), and to which they are “personalized” for each patient’s individual tumor (Figure 4).

Immune checkpoint blockade (CPB) represents a therapeutic strategy that potently enhance immunity in a non-antigen directed fashion nor personalized inhibits naturally occurring negative regulators of T cell activation and function, effectively “cutting the brakes” on T cells, leading to an antitumor response[143–147]. There have been several notable examples of success with this approach. In Hodgkin’s lymphoma, the *PDL1* and *PDL2* genes, located on chromosome 9p24.1, are frequently amplified, suggesting a possible susceptibility to PD-1 blockade. Impressively, in a cohort of patients with relapsed or refractory Hodgkin’s lymphoma (following autologous stem cell transplant and treatment with the antibody-drug conjugated brentuximab vedotin), treatment with the anti-PD-1 antibody nivolumab led to at least a partial response in the majority of patients[148,149], leading to FDA approval for this indication in 2016. For other relapsed or refractory hematologic malignancies (non-Hodgkin’s lymphoma, acute leukemias, and myelodysplastic syndrome), early trial data for nivolumab and for the anti-CTLA4 antibody ipilimumab have shown responses in at least some patients[150,151]. On the other hand, there are notable failures of this approach, including in multiple myeloma[152]. Further studies are needed to understand why certain malignancies fail to respond to these therapies. Although CPB is not an antigen-directed approach *per se*, response to checkpoint blockade has been shown to amplify the T cell response to personal neoantigens[153,154].

In a very different approach, exquisite antigen-specific targeting therapies directed at B and T cell responses have been devised for hematologic malignancies. Indeed, frequently used “off-the-shelf” antibody-based therapies targeting a specific tumor antigen were pioneered in the hematologic malignancies, with Levy and colleagues reporting in 1982 the case of a patient with a B cell lymphoma who had complete remission following administration of an anti-idiotype antibody[56]. Later, the anti-CD20 antibody rituximab became the first monoclonal antibody approved for cancer therapy, and remains a mainstay of treatment for many B cell lymphomas[60,63,155,156]. Rituximab functions primarily through activation of the complement cascade (i.e. complement-dependent cytotoxicity, or CDC) and by antibody-dependant cell-mediated cytotoxicity (ADCC). More recently approved anti-CD20 monoclonal antibodies, obinutuzumab and ofatumumab, have modified structures that increase programmed cell death (PCD) and ADCC, or increase CDC, respectively[157]. Other monoclonal antibodies targeting different surface antigens have been used a variety of hematologic malignancies, such as daratumumab (targeting CD38) in multiple myeloma[158,159], among others.

The modification of traditional monoclonal antibodies has led to further therapeutic opportunities. One such alteration involves the conjugation of a cytotoxic agent, with the goal of targeted delivery of the cytotoxic molecule to the target cells. The first antibody-drug conjugate (ADC), gemtuzumab ozogamicin, which combined an anti-CD33 (targeting a surface antigen on AML cells) with the cytotoxic agent calicheamicin, appeared effective in inducing complete remission in AML[160], but was later withdrawn from market over concerns about toxicity (specifically veno-occlusive disease)[161]. Currently, the anti-CD30 ADC brentuximab vedotin is available for relapsed CD30-positive lymphomas[162], and more

recently the anti-CD22 ADC inotuzumab ozogamicin has shown promising early results in relapsed ALL[163]. An alternative modification uses antibody engineering to combine the short peptide binding domains of two antibodies with different specificities, with the goal of bringing tumor cells into close proximity with T cells (termed bispecific T cell engagers, or BiTEs)[164]. Blinatumomab, which has specificity for both CD3 (found on T cells) and CD19 (found on ALL cells and some lymphomas), is the first FDA-approved BiTE, and has demonstrated efficacy in relapsed ALL[165,166].

On the T cell side, the field of adoptive antigen-specific T cell therapies has evolved greatly. Whereas initial adoptive cell therapies involved the *ex vivo* expansion of tumor-infiltrating lymphocytes using interleukin-2 (and thus, did not necessarily have a known target antigen), more recent efforts have focused on genetically modifying autologous T cells to express a chimeric antigen receptor (CAR) with specificity for a tumor antigen (such as CD19 for ALL)[167]. Current generation CAR constructs link an antigen-specific, extracellular single-chain variable fragment (ectodomain), with the intracellular signaling component of the T cell receptor CD3ζ (endodomain) and at least one stimulation domain (such as CD28 or 4-1BB) [58,59]. These constructs have shown great promise in the treatment of relapsed and refractory CLL[168], ALL[64,65], and multiple myeloma[169]. While this new therapy has generated considerable excitement, it has also had notable associated toxicity, and future generations of CAR constructs are being devised that attempt to balance efficacy and adverse effects[170–172].

Cancer vaccines provide an opportunity to focus the immune response in an antigen-specific fashion. Whole tumor cell vaccines represent a therapy that is personalized (by using the patient's individual tumor as a source of antigen), though the precise target antigen is typically not known. The aim of these therapies is to stimulate active immunity against tumor cells through presentation of tumor antigens by antigen presenting cells (APCs) and activation of the native immunity. In one therapeutic approach, autologous tumor cells are lethally irradiated and then either genetically engineered to secrete granulocyte-macrophage colony-stimulating factor (GM-CSF) or mixed with other GM-CSF secreting cells, and then re-administered to the patient, with the goal of recruiting APCs. This approach has been tested in AML and CLL, with some evidence of immunologic (and potentially clinical) responses[173,174]. An alternative whole tumor vaccine approaches involves the fusion of tumor cells with autologous dendritic cells (DCs). This DC/tumor cell fusion approach is under investigation for multiple myeloma[175,176], and has already shown some promising results in AML[177–179].

Neo-antigen directed therapeutic vaccines represent a truly personalized, antigen-specific therapeutic strategy. In this approach, targets of vaccination are identified on the basis of individual tumor-specific DNA sequence analysis of somatic mutations predicted to generate peptides that can bond to personal HLA molecules. As vaccines, this approach is anticipated to expand the breadth and repertoire of tumor-specific T cells that can participate in the anti-tumor immune response. This approach, while promising, is still in the early phases of investigation, with multiple clinical trials ongoing (see NCT00683670[103,180], NCT01970358[181], and NCT02035956[182] in melanoma). Combination of this approach with CPB is expected to synergize together, and active testing of this strategy is in progress.

Additional open questions include: How many neo-peptides must be administered to ensure an immune response? What immune adjuvant should be used? What is the optimal dosing and scheduling of these therapies? What toxicities will we observe, and will they be limiting? With multiple clinical trials ongoing, we will hopefully begin to answer some of these important questions, and be able to effectively direct a patient's immune response to maximize therapeutic benefit and minimize adverse outcomes.

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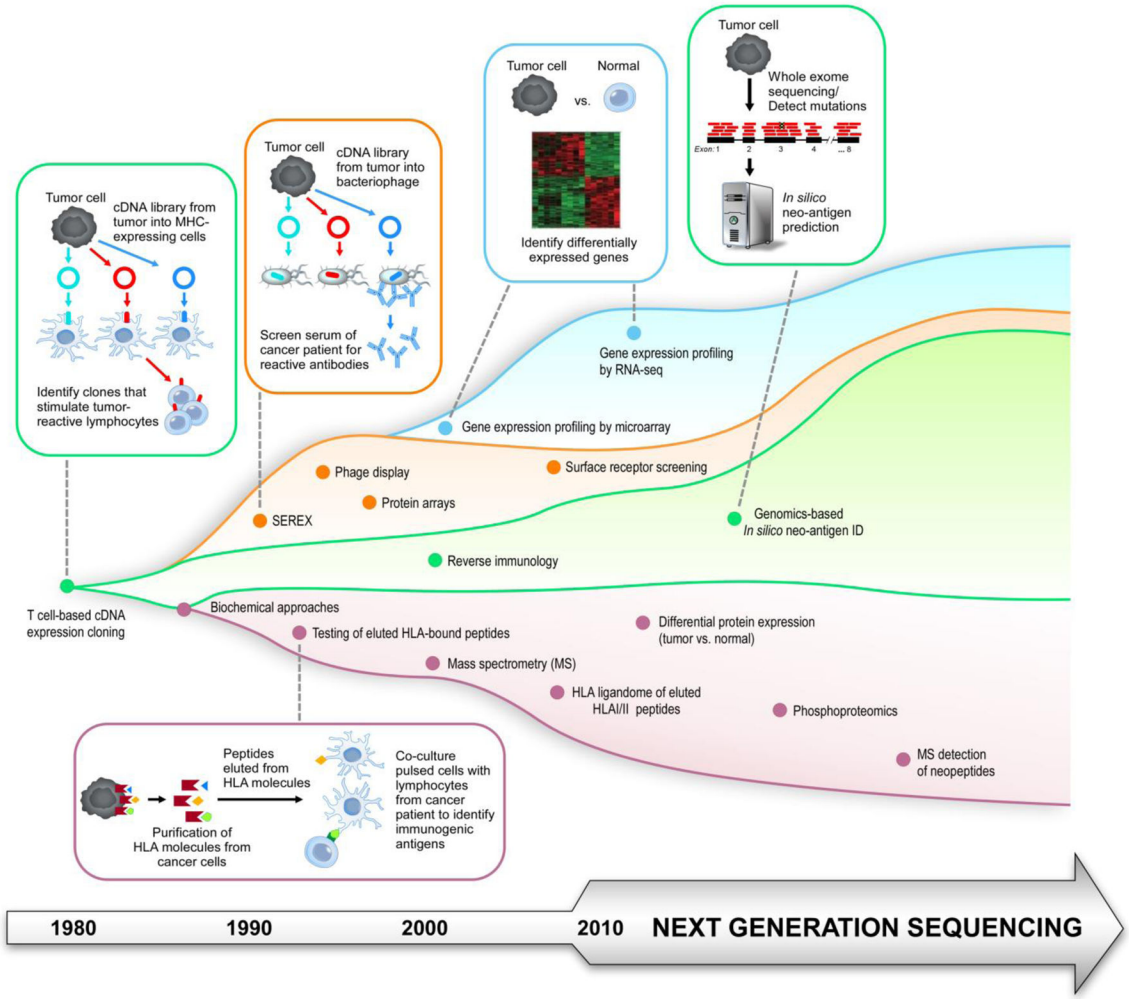

Figure 1. Evolution in the Methods of Tumor of Antigen Discovery

Historical and contemporary methods for tumor antigen identification, identifying T-cell based (green), serology-based (orange), gene expression based (blue) and biochemical/ proteomic-based (purple) approaches.

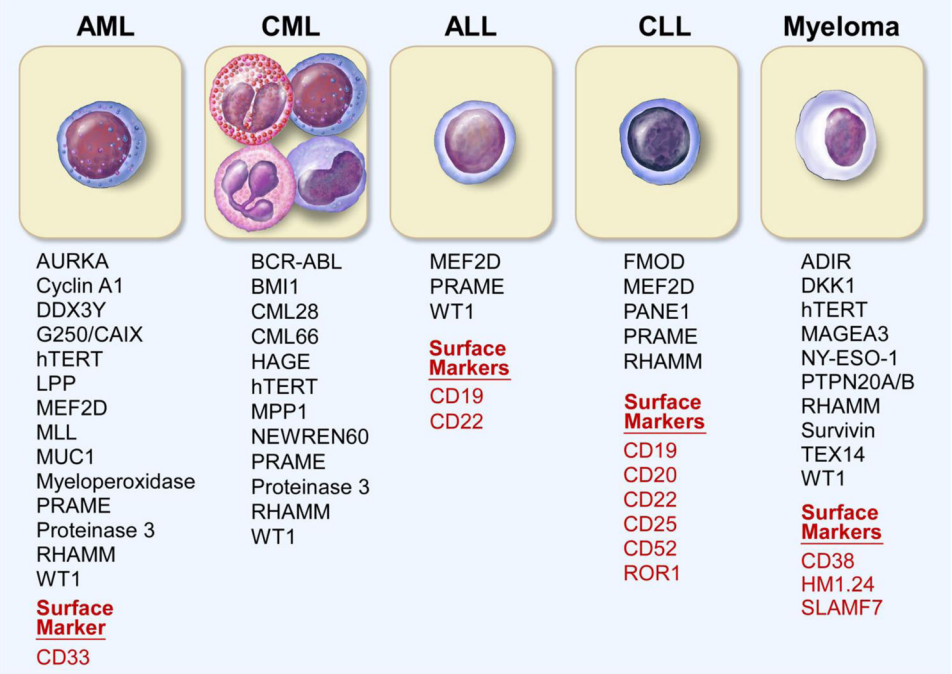

Figure 2. Examples of Tumor Antigens in Hematologic Malignancies

A selection (not exhaustive) of tumor antigens and cell surface markers in a variety of hematologic malignancies.

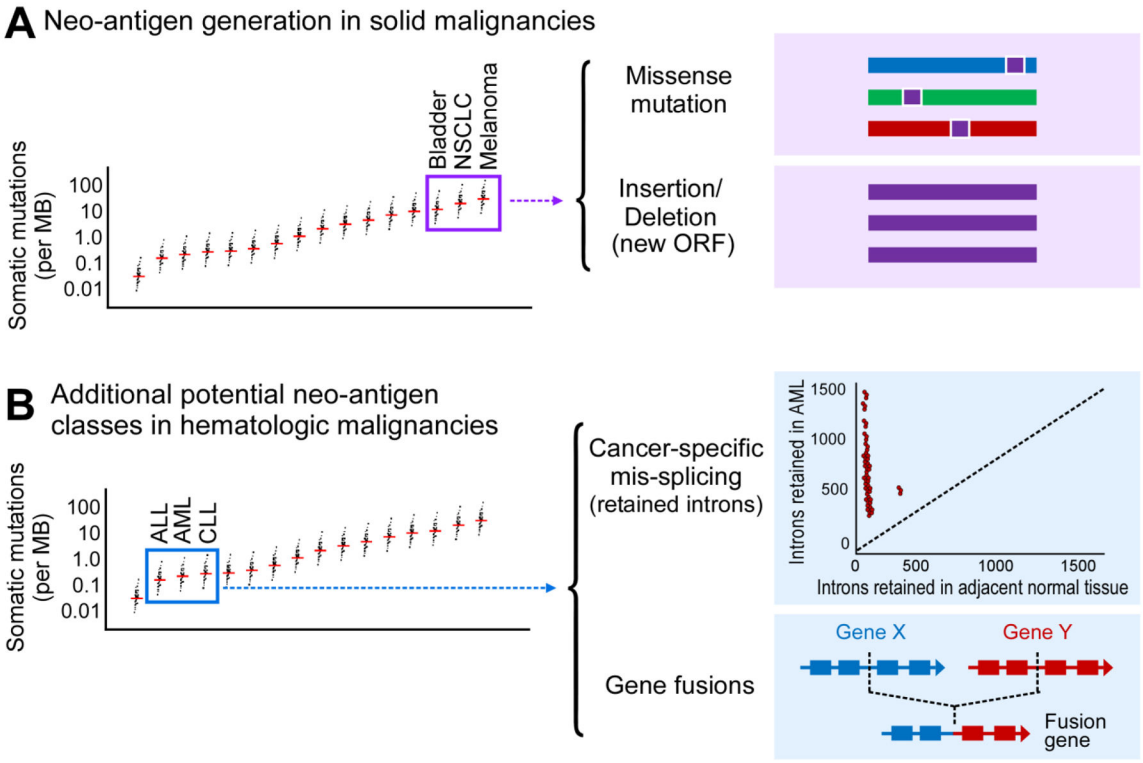

Figure 3. Potential sources of Neo-antigens in the Hematologic Malignancies

(A) Solid malignancies responsive to immunotherapies tend to have a higher mutational load, with more missense mutations and insertions/deletions, leading to a high number of neo-antigens. **(B)** Hematologic malignancies tend to have a lower number of somatic mutations, yet are often still able to generate immune responses. Other possible mechanisms for generating neo-antigens in the setting of low somatic mutation burden are gene fusions and alterations in RNA splicing leading to retain introns. Graph of somatic mutation number adapted from ref. [134].

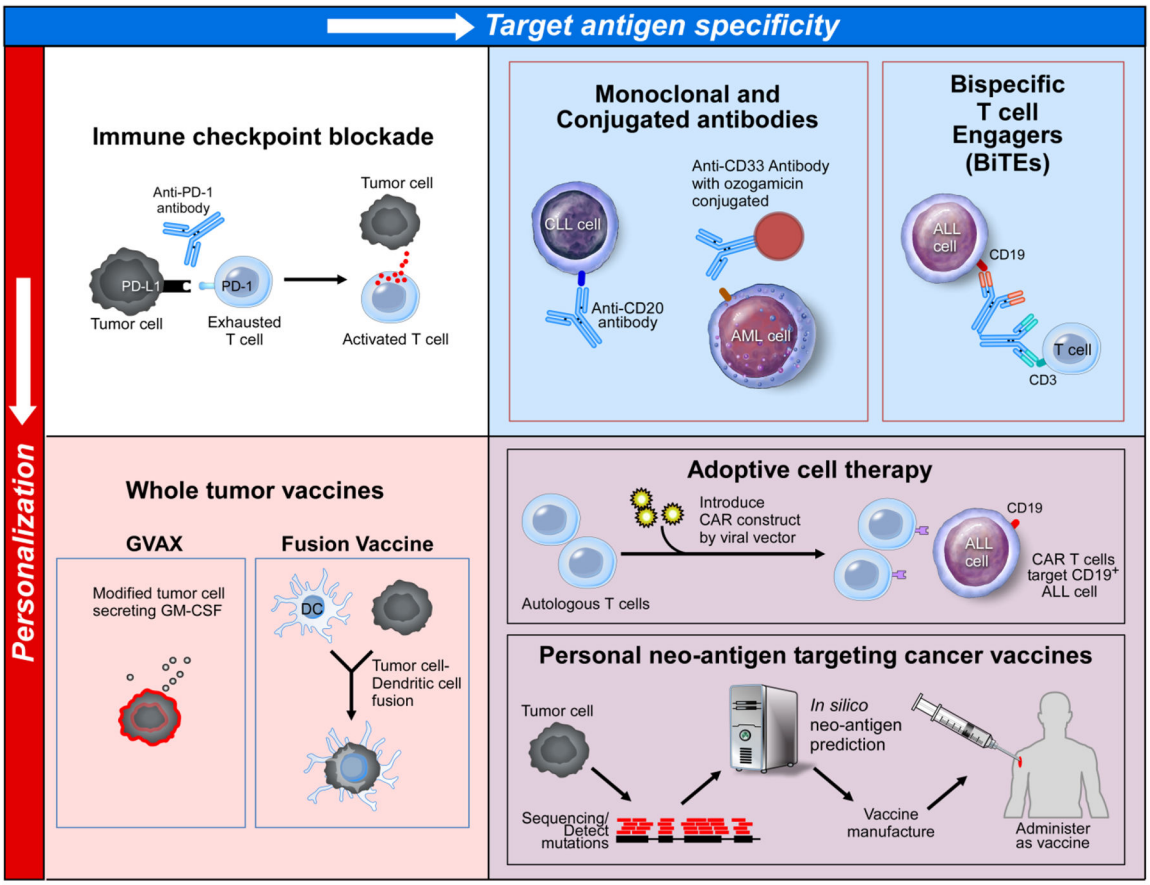

Figure 4. Immune based therapies in the Hematologic Malignancies vary in degree of antigen-targeting personalization

Immunotherapeutic strategies for hematologic malignancies can be categorized based on whether they are personalized for an individual patient/tumor (bottoms row), and whether they target antigen(s) are known/specified (right column). **In the top left panel**, immune checkpoint blockade with an anti-PD-1 antibody is depicted. Typically, tumor cells may express a ligand, PD-L1, which binds PD-1 on T cells and ultimately inhibits T cell effector function. Anti-PD-1 antibodies inhibit this effect, leading to T cell activation and effective tumor cell killing. This strategy is not personalized for an individual patient, and the specific target tumor antigen is not known. **In the bottom left panel**, whole tumor vaccines are depicted, including lethally irradiated tumor cells engineered to secrete GM-CSF to attract APCs (GVAX, left image), and DC/tumor cell fusions, which also leads to antigen presentation and activation of the native immune system. These strategies require personalized products, but the target tumor antigen is not known. **In the top right panel**, a variety of monoclonal antibody therapies are depicted, including conventional monoclonal antibody therapy against CD20, antibody-drug conjugate targeted against CD33-expressing cells, and the bispecific T cell engages blinatumomab which transiently cross-links T cells with CD19 expressing ALL cells. These strategies target specific antigens, but are not personalized for the individual patient. **In the top right panel**, CD19-targeting CAR-T cell therapy (bottom) and neo-antigen therapeutic peptide vaccine (top) strategies are depicted.

The therapeutic approaches require personalization for the individual patient/tumor, and are targeted against known tumor antigen(s).